Investigating the Association between Socio-economic Position and Stillbirth in Brazil and the UK

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Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other university. This dissertation is my own work and contains nothing which is the outcome of work done in collaboration with others.

Abbie Jones
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Abstract

Stillbirths are under-researched in comparison to other child health outcomes. They rarely appear in national health targets or commitments, despite being an immense global burden with 2.6 million cases annually. Using routine national datasets, this thesis compares the social disparities in stillbirth rates within and between the UK and Brazil as a high-income and middle-income country, respectively.

The role of socio-economic position (SEP) in the likelihood of stillbirth, and how it is mediated through behavioural, health and pregnancy-related factors, is clarified comprehensively reviewed and a new conceptual model constructed. A comprehensive review of perinatal health policies in the UK and Brazil showcases Brazil's evolution as a major emerging economy from a public health perspective, in relation to the UK.

Analysis of the UK required two separate datasets; aggregated birth counts from ONS for England and Wales, and Scotland's Maternity and Neonatal Linked Database (MNLD). In England and Wales, higher stillbirth rates were associated with areas containing higher proportions of ethnic minority babies, after accounting for maternal age and other confounders. Whilst the data for England and Wales was limited to an aggregate analysis, the comprehensive Scottish data allowed a mediation analysis which was applied to the MNLD to investigate more fully the causal pathways between SEP and stillbirth. While socio-demographic factors such as maternal age, ethnicity, and marital status were found to have no *direct* effect on stillbirth risk, their mediating influence on gestational age and birth weight played a vital role in the cause of stillbirth.

Brazil's National Household Sample Survey (PNAD) was analysed to determine the primary socio-economic risk factors associated with stillbirth. The main challenge presented by the data was that the birth outcomes were presented as counts - the numbers of live births and stillbirths had by each woman. By converting the observed live birth and stillbirth counts for each woman into lists of possible birth sequences, and deriving the appropriate likelihood function, this thesis was able to perform regression on a new binary outcome for live birth verses stillbirth. Women with lower levels of education and inadequate household goods and services had a higher risk of stillbirth. Analysis of stillbirth rates based on women's lifetime birth histories revealed some counter-intuitive relationships between geographic and social factors and stillbirth, which were distorted by high parity among disadvantaged women.

Data and methodologies were too different to compare the magnitudes of variable effects between countries. Whilst our new methodological approaches have allowed more sophisticated analyses than have been previously possible, ultimately, this thesis has highlighted the strengths and limitations that different data sources allow in describing stillbirths globally. Without more comprehensive monitoring and better defined outcomes, countries will struggle to see the full picture. As we have shown aggregate level data are inadequate for public health monitoring in England and Wales, and restrictions on data availability prohibit informative individual-level analyses. Looking to the future the Scottish data has shown that the gold standard of data linkage is both viable and recommended for 21st century public health management.

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Abbreviations

BMI: Body Mass Index

CMACE: Centre for Maternal and Child Enquiries

GAP: Growth Assessment Protocol

HDI: Human Development Index

MBRRACE-UK: Mothers and Babies Reducing Risk through Audits and Confidential Enquiries (UK)

MDGs: Millennium Development Goals

MNLD: Maternal and Neonatal Linked Database (Scotland)

NHS: National Health Service (UK)

NS-SeC: National Statistics for Socio-economic Classification

ONS: Office for National Statistics (England and Wales)

PNAD: Pesquisa Nacional por Amostra de Domicílios (National Household Sample Survey - Brazil)

RCOG: Royal College of Obstetricians and Gynaecology

Sands: the Stillbirth and Neonatal Death charity

SDGs: Sustainable Development Goals

SEM: Structural Equation Model

SEP: Socio-economic Position

SeS: Brazil Socio-economic Status

SUS: Sistema Único de Saúde (National Health Service - Brazil)

UNICEF: United Nations Children's Fund

WHO: World Health Organisation

Glossary

As this thesis focuses on the impact of socio-economic variables, it will not delve into too much detail regarding specific biological conditions or medical interventions. However, the list below presents some broad definitions and acronyms for pregnancy-related terms that will be referred to in the literature.

Primiparous: having had one birth or is currently pregnant for the first time.

Multiparous: having experienced more than one birth. This could refer to multiple pregnancies or having had more than one birth in a single pregnancy.

Small for gestational age (SGA): a newborn smaller in size than normal for the gestational age, most commonly defined as a weight below the 10th percentile for that gestational age.

Large for gestational age (LGA): a newborn larger in size than normal for the gestational age, most commonly defined as a weight above the 90th percentile for that gestational age.

Intrauterine growth restriction (IUGR) or fetal growth restriction: poor or delayed growth of the fetus during pregnancy. Although IUGR and SGA are often sometimes used interchangeably, SGA refers to a weight at a given time point, while IUGR refers to the rate of growth over time.

Congenital anomaly: a structural or functional anomaly (e.g. metabolic disorder) that occurs during pregnancy and can be identified prenatally, at birth or later in life. These can be caused by single gene defects, chromosomal disorders, multi-factorial inheritance, environmental factors and micronutrient deficiencies (WHO, 2018).

Chapter 1

Introduction

1.1 Stillbirth in Brazil and the UK

As part of the country's rapid economic and social development, Brazil has made impressive strides towards achieving the Millennium Development Goals (MDGs), a series of eight goals set by the United Nations (UN) in 2000 that address world issues such as poverty, disease, discrimination and illiteracy. Notable progress has been made in reducing child mortality; Brazil met its MDG4 goal of reducing under-five mortality by two-thirds in 2015. Despite continuing social inequalities in health between regions (Victora et al., 2011b), there were significant additional decreases in infant mortality across all regions (IPEA, 2014). National infant and neonatal mortality rates fell by 66% and 57% respectively between 1990 and 2010 (UNICEF et al., 2011).

Despite this success, the decline in the stillbirth rate - 28.9% - has not been so dramatic (Blencowe et al., 2016). Although Brazil no longer ranks in the ten countries with the highest stillbirth counts (Lawn et al., 2016), data on stillbirth in Brazil is still not as extensively collected and studied in comparison to child and infant mortality. According to a Lancet review (Victora et al., 2011b), stillbirth rates in Brazil have been steadily declining since 1979, when rates were higher than 20 per 1,000 births. Compared with the 2015 rate of 10.8 (calculated with birth counts obtained from DATSUS), the stillbirth rate has halved in thirty-five years. The reduction is encouraging, but if similar attention was paid to stillbirth as has been paid to infant and child mortality, reductions in stillbirth rates could be even greater.

Health inequalities between regions of the UK are not as extreme as in Brazil, although they are still prevalent between social groups; while national health outcomes are improving, there is a widening gap between the outcomes of the most and least deprived communities (RCN, 2012).

The UK stillbirth rate has decreased by 32% in twelve years, from 5.7 per 1,000 births in 2003 to 3.87 in 2015 (MBRRACE-UK Collaboration, 2015, 2017). Yet the UK has relatively high rates when compared to other high-income countries. A 2011 Lancet study showed that while the late gestation stillbirth rate (twenty-eight weeks or more) fell significantly throughout the 1990s and early 2000s for many high-income countries, the UK's rate remained relatively stable and so still requires close monitoring (Flenady et al., 2011b).

1.2 The Underlying Problem

For international comparison, the World Health Organisation (WHO) defines stillbirth as a baby born with no signs of life at or after 28 weeks gestation (WHO, 2015). While there has been much effort to reduce child and maternal mortality through the MDGs and the subsequent Sustainable Development Goals (SDGs), consistent global monitoring of stillbirth seems to be sadly lacking. The overall stillbirth rate declined by approximately 1.1% per year between 1995 and 2010. Though encouraging, this lags behind the 2.3% reduction in child mortality (Cousens et al., 2011; Rajaratnam et al., 2010). More attention to this topic is needed; some bereaved parents have never even heard the term stillbirth (Sands, 2012). It rarely appears in key international or national health targets and commitments, despite being an immense global burden with 2.6 million cases estimated in 2015 alone (Lawn et al., 2016). Only in 2015 did the World Health Organization bring stillbirth to the forefront by including the stillbirth rate in its "100 Core Health Indicators" (WHO, a).

Stillbirths affect women across all social classes, but disproportionately affect women in poverty. Suggested demographic and socio-economic risk factors for stillbirth include ethnicity, education, socio-economic status, marital status, deprivation and living environment (Parsons et al., 1990; de Almeida et al., 2007; Seaton et al., 2012; Aminu et al., 2014). Efforts to address these inequalities in perinatal mortality are as vital as the medical interventions themselves.

Stillbirth can be a shattering experience for families. For real progress to be made, it should be included in future discussions, targets and interventions regarding maternal and child health. A detailed synthesis of information concerning the potential risk factors in both countries will give valuable insights into the relationship between socio-economic factors and stillbirth. Additionally, a comparison between Brazil and the UK of national health provision and government policy in caring for expectant mothers will provide a helpful contrast by which the understanding of both systems can be improved.

Furthermore, perinatal mortality rates have been used as a measure of maternal health and, on a broader scale, as a core indicator of public health and quality of care, reportedly because they are receptive to social and health inequalities (Justino et al., 2004; Richardus et al., 1998). Therefore, research into stillbirth events could have more extensive applications to public health outside of the immediate health of the mother and child.

1.2.1 International Comparison

The relationship between a given health outcome and a socio-economic position (SEP) indicator might differ internationally due to the cultural context surrounding the SEP indicator in each country. An understanding of the cause of health inequalities might be gained by comparing this relationship in high and middle-income countries (Matijasevich et al., 2012).

Regarding stillbirth in high-income countries, the UK does not fare well; it ranks among the top five developed countries for the number of annual stillbirths (Flenady et al., 2016). By investigating the causal pathways that lead to stillbirth in the UK, areas of improvement may be highlighted.

Brazil is of particular interest as a BRICS nation — one of the five major emerging economies (Brazil, Russia, India, China and South Africa). Notably, it briefly overtook the UK as the world's sixth largest economy in 2012 and has since remained in the top ten (The World Bank, 2017a). However this figure hides enormous wealth disparity between regions and between urban and rural areas; hence Brazil is still considered a middle-income country (The World Bank, 2017c). It appears 79th in the Human Development Index (HDI) 2016 rankings while the UK holds 16th place, which correlates with the countries' most recent public international rankings by ascending stillbirth rates (2009) in which Brazil places 79th, and the UK 33rd (WHO, 2011).

For the investigation of stillbirth, the UK and Brazil make interesting case studies as representatives of high-income and middle-income countries, respectively. Comparisons of health outcomes between Brazil and the UK have been conducted before (Matijasevich et al., 2009; Lima-Costa et al., 2012; Howe et al., 2014), including city-wide cohort studies of maternal and perinatal health (Matijasevich et al., 2008, 2012). Matijasevich et al. defended their choice of cohorts (in Pelotas Southern Brazil, and Bristol, South West England) as a reflection of populations with different levels of wealth and social inequality. Howe et al. cited that comparing cohorts from very different settings was a key strength of their study as it allowed for greater strength of inference than using just one cohort.

In this research, we will be comparing Brazil with the UK through the use of large-scale social survey data (Brazil) and linked hospital/administrative data (Scotland) that contain rich sources of socio-economic information.

1.2.2 Research Gaps

An extensive review of the literature (Chapter 2) has highlighted potential gaps in the current knowledge that we would like to address.

Unknown causal pathways to stillbirth
Social and behavioural factors appear to influence the risk of stillbirth through multiple causal pathways, but these relationships between social, behavioural and biological factors are rarely explored (Yakoob et al., 2009). Sometimes, studies focusing on biological risk acknowledge the contribution of social and behavioural factors to stillbirth risk, but are unable to quantify these risks due to a lack of available data (Lawn et al., 2016). We hope to bridge this gap in our UK analysis with the use of linked data for Scotland which contains socio-economic, behavioural, health and pregnancy-related factors. The interplay of these factors will be explored with mediation.

A country-wide study of stillbirth in Brazil, particularly with regard to socio-economic factors
Coverage of stillbirth data collection is increasing in Brazil, but not much has been published using national-scale information. One historical series paper described stillbirth rates across Brazil throughout 1996-2012 with an ecological analysis but criticised the lack of published studies on stillbirth in Brazil (Vieira et al., 2016). The Brazilian Ministry of Health remarked that the absence of analyses for birth statistics in the Brazilian literature reflect the lack of awareness, information and understanding that fetal mortality is largely preventable through access to health services (BRASIL. Ministério da Saúde, 2009).
In particular, the association between stillbirth and socio-economic or behavioural factors in Brazil requires more exploration. As of 2016, Brazil ranks 79th on the Sphere of Health Human Development Index (HDI) while having the ninth largest gross domestic product (GDP) in the world; therefore socio-economic inequalities undoubtedly have an impact on health outcomes such as stillbirth (The World Bank, 2017a).

A standard measure of socio-economic position in Brazil comparable to other developed countries
Identifying a single measure for such a multifaceted concept as socio-economic position (SEP) is complicated; various indicators such as education, occupation, income and household conditions are often used to represent and rank individuals (Matijasevich et al., 2012). In the UK, the Office for National Statistics uses routinely collected information on occupation to derive a National Statistics Socio-economic Classification (NS-SeC) which is used widely in research. Brazil has no such standard measure (V. Guerra, personal communication, April 17, 2017), making comparison difficult within Brazil, and internationally.

1.3 Objectives

This thesis aims, using routine national datasets, to determine the primary socio-economic risk factors associated with stillbirth in Brazil and the UK, and to compare relative magnitudes of these associations between and within the two countries. A secondary aim is to review and assess the datasets and associated resources available for investigating stillbirth (along with socio-economic factors) in Brazil and the UK. Ultimately, we aim to devise recommendations for policy change to reduce the occurrence of stillbirths in both countries.

1.3.1 Research Questions

The research questions that will be addressed are:

- What is the role of socio-economic risk factors in the likelihood of stillbirth, and how are they mediated through more proximate birth-related factors?
- In relation to health and social policy, what are the current practices in monitoring stillbirth rates in Brazil and the UK, and how do these compare with past government initiatives? In particular, how has Brazil's commitment to the UN's Millennium Development Goals resulted in policy change that could affect stillbirth rates?
- What national, routinely collected datasets are available for the purpose of investigating the relationships between socio-economic factors and stillbirth in Brazil and the UK?
- To what extent do inequalities in stillbirth rates exist across areas in Brazil and the UK? What are the social factors associated with stillbirth in both Brazil and the UK? How does the impact of these factors differ between the two countries?

1.3.2 A Note on Comparing Different Types of Data

This thesis intends to compare birth outcomes between Brazil and the UK. Due to restrictions upon data sources and availability, however, we found the need to split the UK analysis into two studies using separate datasets; one for England and Wales, and another for Scotland. A third study specifically for Northern Ireland was also considered, but attempting four analyses was outside the scope of this thesis in terms of data access, cost and time.

Each of the datasets is structured very differently. For example, in the England and Wales study, we were only able to obtain aggregate-level data, whereas the remaining two datasets are available at individual-level. Each contained differing variables of interest and requires specific methods to make valid inferences from the separate analyses. Comparing the results between countries was therefore very difficult, but the analyses provide a contrast of what can be achieved with different levels of data. In principle, we expected the study of Scotland, with the most accessible individual-level data, to provide the most valuable results in comparison to our aggregate study of stillbirth counts in England and Wales. For Brazil too, we studied individual-level data, but it contained a less well-defined outcome of stillbirth.

We acknowledge that initial data handling decisions had to be made to allow comparison between countries. Therefore some data handling choices may be different to choices made if the analyses were done in isolation.

1.3.3 Thesis Structure

In Chapter 2, we will introduce stillbirth as a global health issue, as well as establish our key interest in Brazil as a rapidly developing nation. We have expressed our intention to compare its evolving position concerning stillbirth with that of the UK, a comparatively "developed" country. A literature review will be conducted to address the first research question and to determine the key socio-demographic factors associated with stillbirth, particularly in these two countries.

Chapter 3 addresses the second research question (Section 1.3.1) by conducting a review of health and social policies in the countries of interest. It shall explore the UK and Brazil's efforts to reduce stillbirth rates, which will give our research a broader context and highlight the need to place additional attention on reducing stillbirth in both Brazil and the UK.

Chapter 4 will address the third research question with a brief overview of the available routine data concerning stillbirth and socio-economic position in these countries. It will explore the difficulties for researchers in accessing and analysing stillbirth data, and highlight the need for comprehensive and accessible administrative data.

We introduce the three datasets that are used in this thesis: aggregated information from the General Registration Office (GRO) Birth Records for England and Wales, then Scotland's Linked Maternity and Neonatal Database (LMND), and finally Brazil's National Household Sample Survey (PNAD – Pesquisa Nacional por Amostra de Domicílios). It will specify the variables used in each analysis and call attention to issues with the data that will need to be faced in the methodology. The aggregated stillbirth counts for England and Wales, for example, contain a large proportion of suppressed values. A notable amount of missing data also exists in Scotland's LMND. Limitations of the Brazil study's outcome variables require some extensive data manipulation. It also includes the conception and creation of a variable for socio-economic position to match the UK's NS-SeC grades.

The following three chapters will then comprise the methodology and results for each of the three studies: first England and Wales, secondly Scotland, and finally Brazil. They are ordered by complexity, adopting relatively simple methodology for the aggregate data for England and Wales, while Brazil's PNAD requires a somewhat novel approach. Each chapter will attempt to answer the fourth research question; to determine the association between socio-economic factors and stillbirth in each population.

Chapter 5 proposes a method for handling the suppressed values in the England and Wales dataset, involving a specialised likelihood function. This model will be compared against a standard ecological model.

Chapter 6 first details the multiple imputation methods used to account for missingness in the linked data for Scotland. From here, a mediation model will be considered, with a proposed causal link between socio-economic factors and stillbirth via other birth-related factors.

Chapter 7 will encompass the analysis of Brazil's household survey (PNAD). A method to overcome the limitations outlined in Chapter Four will be proposed. This method uses a specially created likelihood function and requires the data to be transformed into a long format, with each observation (row) detailing individual births (instead of individual women). Model selection methods will also be considered to reduce the model from the twenty-five variables considered to a significant subset. The results compare this model across age groups.

Finally, Chapter Eight will draw together and discuss the main findings from each study, comparing internationally between Brazil and the UK. It will critique the value of findings from each of the datasets, and outline the strengths and limitations of each study as well as the overall comparison. The chapter will re-address the research questions and draw the main conclusion from this work.

Summary

What is already known on this topic?

- Although Brazil has made impressive reductions in child mortality as part of the Millennium Development Goals, the decline in stillbirth rates has been less dramatic.
- The UK has a relatively high number of annual stillbirths within the developed world.
- Vast social and health inequalities in stillbirth rates continue to exist globally in low, middle, and high-income countries.

What does this study add?

- A new conceptual model for the causal pathways from SEP to stillbirth through environmental, behavioural and health factors.
- A comprehensive review of national policies regarding the reduction of stillbirth in the UK and Brazil, with comparisons between the two as a high-income and middle-income country, respectively.
- A comparison of national routine data concerning stillbirth between a high-income and middle-income country (at the expense of not having matching outcomes).
- The creation of a SEP measure for Brazil that is comparable with the UK National Statistic for Socio-economic Classification (NS-SeC).
- An investigation into the causal pathways for stillbirth using national data for Scotland.

Chapter 2

Definitions and Literature Review

In this chapter, we shall define stillbirth and place it in context as a global health issue as well as in the context of Brazil and the UK. We also briefly define the latent concept of socio-economic position (SEP) and how to measure it.

The main portion of this chapter comprises of a literature review aiming to clarify the role of socio-economic risk factors in the likelihood of stillbirth, and how are they mediated through more immediate birth-related variables. It is likely that there is no single route between SEP and stillbirth, instead that there are multiple causal links through various risk factors. For this, we introduce a conceptual model for stillbirth in an effort to disentangle some of these complex pathways. From this, we shall home in on the specific socio-demographic factors associated with stillbirth in Brazil and the UK.

2.1 Measuring Stillbirths in Brazil, the UK and Globally

2.1.1 Defining Stillbirth

The definition for *stillbirth* varies worldwide. For international comparison, the World Health Organisation (WHO) defines stillbirth as a baby born with no signs of life at or after 28 weeks gestation (WHO, 2015). Although the threshold for inclusion in routine country-specific statistics varies from 20 weeks (such as in the USA, Australia and New Zealand) to 28 weeks (such as in Nigeria, India and Pakistan), restricting the gestational age to 28 weeks aids international comparability. In low- and middle-income countries where most stillbirths occur, even these more advanced deaths can often go unrecorded thus leaving rates underestimated (Lawn et al., 2010). Some countries, including Brazil, use birth weight as a secondary or even primary criteria in defining stillbirth, usually with a cut-off point of

500-1,000g. WHO recommends prioritising the gestational definition for international comparison, since gestational age is more widely recorded than birth weight and the two measures do not necessarily give equivalent figures (Lawn et al., 2016). However, in some high-income countries with more advanced neonatal intensive care, including the UK, the viable age at which a baby can survive has decreased, and so the threshold gestational age for recording such births and stillbirths has been reduced (Lawn et al., 2009).

In 1992, the UK revised their definition from the 28-week start point to include births from 24 weeks gestation. In Brazil, stillbirth is commonly referred to as fetal death and is defined as a baby born with no signs of life after 22 weeks or more in gestation, or weighing at least 500g (BRASIL. Ministério da Saúde, 2010).

This terminology calls attention to the fact that some papers, and some countries, conflate the term *stillbirth* with *fetal death*, while others consider stillbirth, or "late fetal death", to be a subset of fetal death which refers to any death in the womb. Deaths that occur before the designated cut-off week are defined as miscarriages or spontaneous abortions. In the literature review, care has been taken to ensure that all sources referring to fetal death, in fact, signify "late fetal deaths": deaths that have occurred after at least 22 weeks of gestation.

2.1.2 The Global Context

About 100 countries collect vital registration data on stillbirths. However, only about half of these have data that is considered high-quality, and even fewer collect data using the WHO international definition (WHO, 2014). According to a more recent global estimation by *The Lancet* (Blencowe et al., 2016), the number of annual stillbirth remains at 2.6 million in 2015. Only one set of official WHO country-specific estimates exist, for the year 2009 (Cousens et al., 2011).

Despite its encouraging gradual decline in stillbirth rates, Brazil's rates are still double that of other developed countries (Vieira et al., 2016). As of 2009, it placed 79th in the world for ascending stillbirth rates (WHO, 2011).

In 2009, the UK had the highest stillbirth rate in a study of some of the highest-income countries (compared with Australia, New Zealand, the USA, Canada, Norway, Sweden, Denmark, France, Spain, Italy and Tuscan County) (Flenady et al., 2011b). It ranks 33rd in the 2009 WHO estimates 2011. Stillbirth is still described as a "major public health issue" among high-income countries; Flenady et al. (2016) argue that observed socio-economic disparities in stillbirth rates in high-income countries imply that they are avoidable and therefore further reductions are possible.

2.1.3 Brazil: A Rising Power

Brazil, like other Latin American countries, is undergoing intense population growth and development. Its 'megacities' are fast becoming the dominant consumers of resources and propagators of vast social inequalities in health between rich and poor (Canton, 2011). The social and public health implications are dramatic, and considerable regional variations exist (Victora et al., 2011a). National and regional counts for live births and stillbirths for the years 1996-2016 are available from DATASUS, a Ministry of Health organisation responsible for gathering data from official sources. From this, stillbirth rates for this period are shown in Figure 2.1. These values adhere to the 22-week definition, with on average 18% of stillbirths per year occurring in the 22-28 week window.

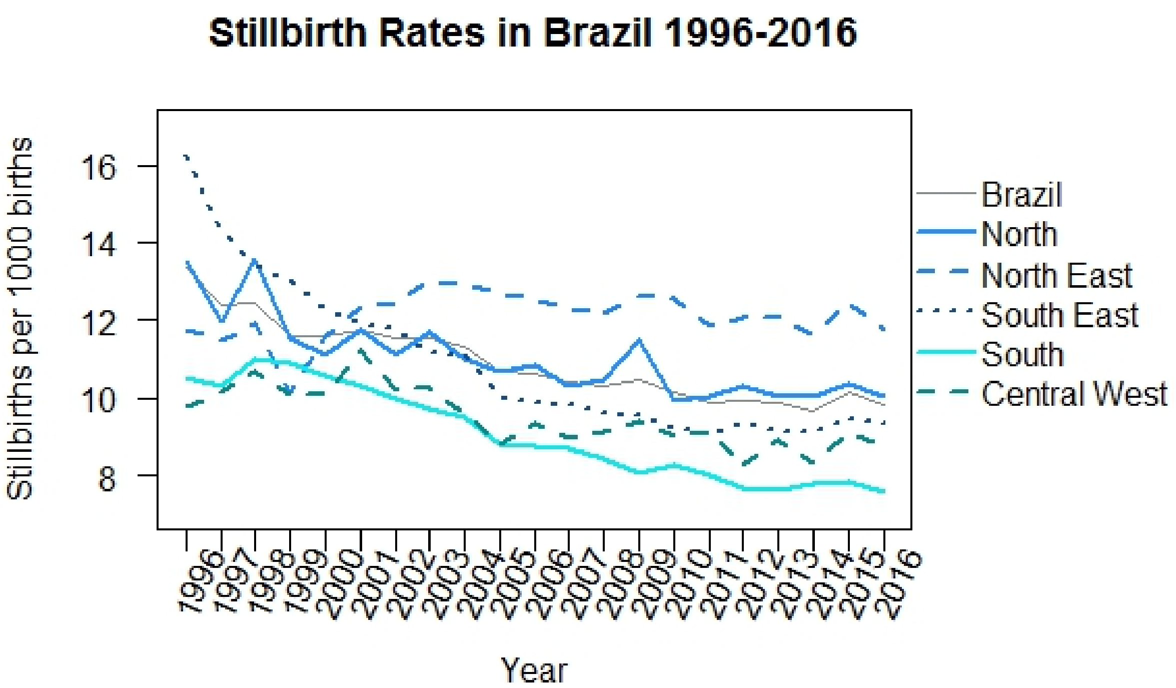


Figure 2.1: Stillbirth rates by region in Brazil 1996-2016
Data Source: DATASUS

The national rate has steadily declined over the last two decades to the most recently published figure of 9.82 per 1,000 births in 2016. In some ways, Brazil is considered a success story in stillbirth reduction; it no longer ranks in the top 10 for stillbirth counts world-wide (Flenady et al., 2016). However, the contrast between the southern and northern regions is stark. The 2016 rate for the North Eastern region (11.8 per 1,000 births) is 50% larger than for the Southern region (7.4 per 1,000). These national figures may disguise lower-level heterogeneity; inequality within and across states has been noted

(Landmann-szwarcwald and Macinko, 2016). The stillbirth rate for São Paulo is 7.9 per 1,000 births, but within its 645 municipalities, rates vary from 0 to 28.4 per 1,000 (Andrews et al., 2017).

Brazil's national health system is founded on the basis of universal access. Currently, 90% of women have access to prenatal care and attend appointments, and 98% of births occur in hospitals (Vieira et al., 2016). Therefore, there must be more multifaceted reasons to explain this inequality. Although studies on stillbirth have been published in recent years (Barbeiro et al., 2015), their numbers pale in comparison to the amount dedicated to other birth outcomes (Vieira et al., 2016).

2.1.4 The UK: A Surprising Struggle

Throughout the 20th century, the stillbirth rate in the UK had generally been declining until the threshold for defining stillbirth was amended from 28 weeks to 24 weeks gestation in 1992. Due to the definition change, the current situation regarding stillbirths can only be compared with data from 1993 onwards. National Records Scotland (NRS) still publishes the counts for "28+ weeks" alongside the values for the current definition; from this, it can be calculated that approximately 23% of stillbirths in Scotland occur in the 24-28 week window each year. Given that 89% of total UK births since 1993 occurred in England, the trends for England matches that of the UK almost identically, while the lines for Scotland and Northern Ireland, based on much lower counts, are more sporadic (Figure 2.2).

Since the definition change, there was a slow and steady decline in the stillbirth rate followed by a plateau in the late nineties at around 5.4 stillbirths per 1,000 births. Then, in 2002, an increase was observed across all four countries, with an escalation of 6% in England and Wales compared to 2001 (rate ratio 1.06; 95% CI 1.02–1.12) (CEMACH, 2005).

Until recently, there has been a scarcity of research focusing on stillbirth at a national scale. A 2012 meta-analysis (Weightman et al., 2012) explored social inequality and infant health in the UK but included only two papers on stillbirth. Since 2013, the government-commissioned programme Mother and Babies: Reducing Risk through Audits and Maternal Enquiries (MRRACE-UK) has been conducting annual national reports on perinatal mortality (see Section 3.3).

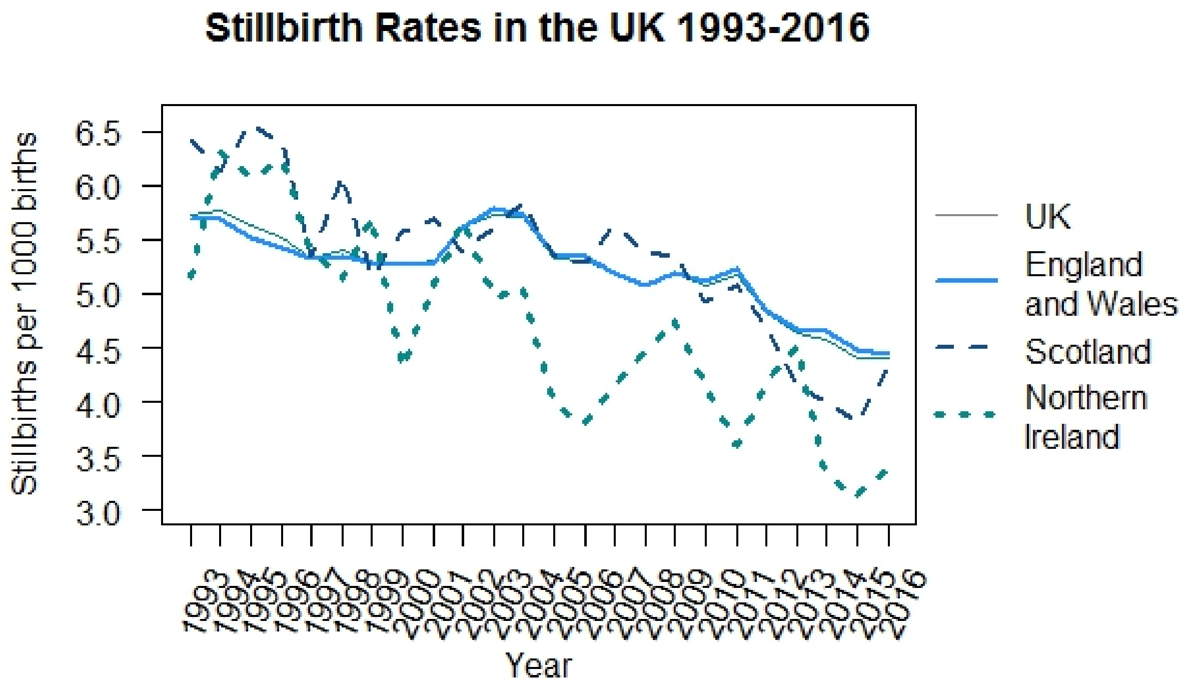


Figure 2.2: Stillbirth rates in the UK 1993-2016
Data Source: Office for National Statistics (ONS), National Records Scotland (NRS), Northern Ireland Statistics and Research Agency (NISRA)

2.2 Defining and Measuring Socio-economic Position

Socio-economic position (SEP) refers to social and economic factors that influence a person's status within the structure of a society (Galobardes et al., 2006). This study has already suggested a link between SEP and stillbirth. This section briefly outlines why it is important to measure SEP and how it might be quantified.

2.2.1 Why Compare Socio-economic Factors in Stillbirth?

Indicators of SEP have been linked to various health outcomes; within this, pregnancy can be an especially vulnerable period (Matijasevich et al., 2012). As shall be seen in the literature review, research regarding the sizeable socio-economic disparities in pregnancy outcomes such as preterm birth and intrauterine growth restriction are very consistent. Consequently, SEP must play a role in the cause of stillbirth. A biological cause can only be confirmed (or refuted) by accounting for social disparity, though the magnitude of its influence is less well reported (Spong et al., 2011).

Health inequalities expose within-country social and structural divisions which in turn may lead to divisions in quality of healthcare and access to medical facilities. Therefore to tackle such disparities, some measure of socio-economic position must be recorded and monitored in all vital statistics (Flenady et al., 2016).

2.2.2 Quantifying Socio-economic Position

Socio-economic position is a theoretical construct that cannot be directly observed, and the numerous ways of measuring it reflects its complexity (Galobardes et al., 2006). There is no universally agreed upon measure of social disadvantage, and often the choice of measure depends on the outcome. Education and income are frequently used as generic indicators of SEP, perhaps because they are relatively easy to categorise; education can be measured by years of schooling or level of qualification, and income is inherently quantifiable, although often poorly reported. In many studies, occupation forms the operational basis for defining SEP, although the creation of such a measure is more intensive than for education and income. Starting with a register of all occupations within a population - from the census, for example - these occupations are categorised into a manageable and exhaustive list of measures relevant to the researchers' needs (Alves and Soares, 2009).

For investigating childhood-related outcomes, the parents' education, income and occupation are appropriate measures of SEP, along with household conditions (e.g. quality of infrastructure or overcrowding within the house) (Galobardes et al., 2006). There is no single best measure of SEP to suit all demographics. While it is helpful when such indicators are included in vital statistics, different countries tend to base SEP on different factors which can make international comparison difficult.

In previous studies comparing health outcomes between the UK and Brazil, education and income have been used to represent SEP (Matijasevich et al., 2012; Lima-Costa et al., 2012). The UK tends to categorise education by qualifications while Brazil measures years of schooling.

Within the UK, area-level deprivation scores are popular in research, such as the Index of Multiple Deprivation and the Carstairs deprivation scores (Smeeton et al., 2004; Sutan et al., 2010; Wood et al., 2012; Seaton et al., 2012). These are derived from factors in the census (including income, employment, education, health, living environment, crime and car ownership) and are available at the aggregate level for small areas. Joyce et al. (2000) compared three common deprivation indicators – Jarman score, Townsend score and percentage of male unemployment – at the local authority level and concluded that are all suitable predictors of fetal mortality.

However, other argue that individual-level measures of disadvantage are preferred to area-level indicators for assessing adverse birth outcomes (Sloggett and Joshi, 1998). Perhaps the most commonly used individual-level measure of socio-economic position in the UK is the National Statistics Socio-economic

Classification (NS-SeC). It is recorded in administrative data alongside various outcomes, including birth statistics (derived from parents' occupations as recorded on birth certificates). The NS-SeC is a flexible measure that can be expanded or reduced from eight to five or three classes while preserving the underlying conceptual model of employment relations (ONS, 2005).

Table 2.1: Possible structures of the NS-SeC

Eight classes	Five classes	Three classes
1 Higher managerial and professional occupations 2 Lower managerial and professional occupations	1 Managerial and professional occupations	1 Managerial and professional occupations
3 Intermediate occupations 4 Small employers and own account workers	2 Intermediate occupations 3 Small employers and own account workers	2 Intermediate occupations
5 Lower supervisory and technical occupations 6 Semi-routine occupations 7 Routine occupations	4 Lower supervisory and technical occupations 5 Semi-routine and routine occupations	3 Routine and manual occupations
8 Never worked and long-term unemployed	Never worked and long-term unemployed	Never worked and long-term unemployed

Brazil has no such official measure of SEP recorded in its administrative data (V. Guerra, personal communication, April 17, 2017). Instead, for studies exploring child-related outcomes, education and family income are the most popular measures (Matijasevich et al., 2012; Ribeiro et al., 2009; Habermann and Gouveia, 2014). Maternal education is almost always quantified as years of schooling, and family/household income is either represented through quintiles of raw income or relative to minimum wage (per capita) (e.g. <1, 1-2, >2 times the minimum wage). Education and income data from household surveys have even been used in one study to create a "concentration index" which mapped the cumulative proportion of the health variable (infant death) against the cumulative proportion of the population stratified by SEP (according to maternal schooling and household income) (Garcia and Santana, 2011).

Alongside education and income, other SEP measures have included occupation (Nyarko et al., 2015) marital status (Goldani et al., 2004), ethnicity, employment status (Fonseca and Coutinho, 2010), ownership of consumer goods and overcrowding in the household (de Almeida et al., 2007). These choices generally seem to be based on what measures were available in the data that contained the outcome of interest.

Alves and Soares (2009) constructed a specific measure for SEP using survey data. Item Response Theory was used to create a hierarchical scale that measured the Socio-economic Level (Portuguese acronym: NSE) from a weighted combination of education, occupation and income. Using data from an educational survey, the NSE was based on information about the student's mother's schooling, the highest occupational stratum of the parents and the family's income (also considering average income of families in the same area). It was concluded to be a well-defined appropriate measure and, although challenging to construct, showed that it was possible to use variables in survey studies (even with self-administered questionnaires). In practice, its use seems to have been restricted to studies on education.

Santos (2006) also created a new socio-economic classification for Brazil. Using data from the 2002 household survey, the article presents "the relative distribution of the class categories in the Brazilian society and its income gaps". Inspiration for its layout was taken from the UK's NS-SeC system and other European measures, but Santos expanded on some levels, separating large and small employers, and expanding the "self-employed" category to distinguish between self-employed experts, agricultural self-employed and precarious self-employed (those with virtually no monetary income but who produce for their own consumption). It also includes a category for domestic employees, which made up 8% of the population in 2002, and numerous categories for agriculture as an important sector of Brazil's economy – currently accounting for 10% of its employment (The World Bank, 2017b).

2.3 The Role of Socio-economic Position in Stillbirth: a Literature Review

This review aims to answer research questions one and four, using the literature. Firstly, what is the role of socio-economic risk factors in the likelihood of stillbirth, and how are they mediated through more immediate birth-related variables? Secondly, which factors pose a particular risk in Brazil and the UK?

The majority of the literature in this review was obtained from the PubMed database which contains many respected public health journals including (but not limited to) the British Medical Journal (BMJ), the Journal of Clinical Epidemiology, *The Lancet*, American Journal of Public Health and BJOG: an International Journal of Obstetrics. The Scientific Electronic Online Library (Scielo), originally established in Brazil, was used to source Brazilian and other Latin American health journals such as the Revista de Saúde Pública and the Revista Ciência e Saúde Coletiva.

The main outcome of interest was stillbirth and its alternative terminology fetal death. Multiple risk factors for stillbirth were considered, loosely grouped into the following categories; socio-economic position, environment, maternal behaviour, maternal health, prenatal care, fetal characteristics and obstetric events. The review sought papers that examined the relationship between these factors and stillbirth, as well as papers investigating relationships between the factors themselves in order to understand the pathways between such factors and stillbirth. While the populations of many studies assessing the link between factors not related to pregnancy (e.g. between social and environmental factors) included males, only studies that at least included, if not comprised wholly of, women of child-bearing age (approximately 15 to 50 years) were included in the review. A full search string for the PubMed database can be found in the appendix (Section A).

The search was limited to articles dated from 1985 to present (30 years prior to the beginning of the search) and restricted to articles written in English and/or Portuguese. A Portuguese translation of the search string was also used in the Scielo database. Regarding study design, there were very few randomised controlled trials available due to the relatively rare nature of stillbirth; the review consists mostly of observational studies. However, special attention was paid to any studies attempting to investigate *causal* links between factors. Regarding the summary measures in these studies, odds ratios (ORs) were the primary measure of association with stillbirth, although studies with risk ratios and risk differences as their primary measure were also considered. ORs are popular summary measures in case-control studies and are commonly used in cross-sectional and cohort study designs, although their interpretation is a little trickier than for other common measures. The OR represents the odds that an outcome will occur given a particular risk factor, compared to the odds of the outcome in the absence of that risk factor. An OR larger than one submits that the risk factor is associated with higher odds of the outcome, while an OR less than one suggests an association with lower odds of the outcome. For example, an OR of 1.2 suggests that the exposed group has 20% higher odds of stillbirth than the reference group, whereas an OR of 0.8 suggests that the exposed group has 20% lower odds of stillbirth than the reference group. An OR of 1 suggests that the risk factor does not affect the odds of the outcome. Odds ratios differ from relative risk (RR) which is instead a ratio of *probabilities* that compares the risk of an event among those with a specific risk factor with those not exposed to the risk factor (reference group). With rare events such as stillbirth, the OR and RR can be near-identical; in these cases, some studies may consider the OR to be a sufficient surrogate for the RR.

Figure 2.3 shows flow diagram for the identification of suitable studies from the aforementioned databases. A small number of additional articles were obtained from other sources, chiefly ResearchGate and Lancaster University's literature database, Onesearch.

The review starts by proposing a conceptual model that highlights the causal mechanisms that may connect SEP to stillbirth. It then reviews literature specific to Brazil and the UK to determine the most prominent risk factors in each country. We note upfront that this review includes numerous systematic reviews and meta-analyses, which precludes this review from being classed as a systematic review in its own right.

Definition Inconsistencies. Much of the literature on stillbirth adheres to the "international comparison" definition of stillbirth (with the 28-week cut-off). However, studies using alternative national definitions for their respective countries were also considered. For example, the UK defines stillbirth at 24-weeks while Brazil often uses a 22-week limit. Moreover, some Brazilian literature (including official documents from the Ministry of Health) seems to conflate the terms *stillbirth* and *fetal death* as synonymous, whereas

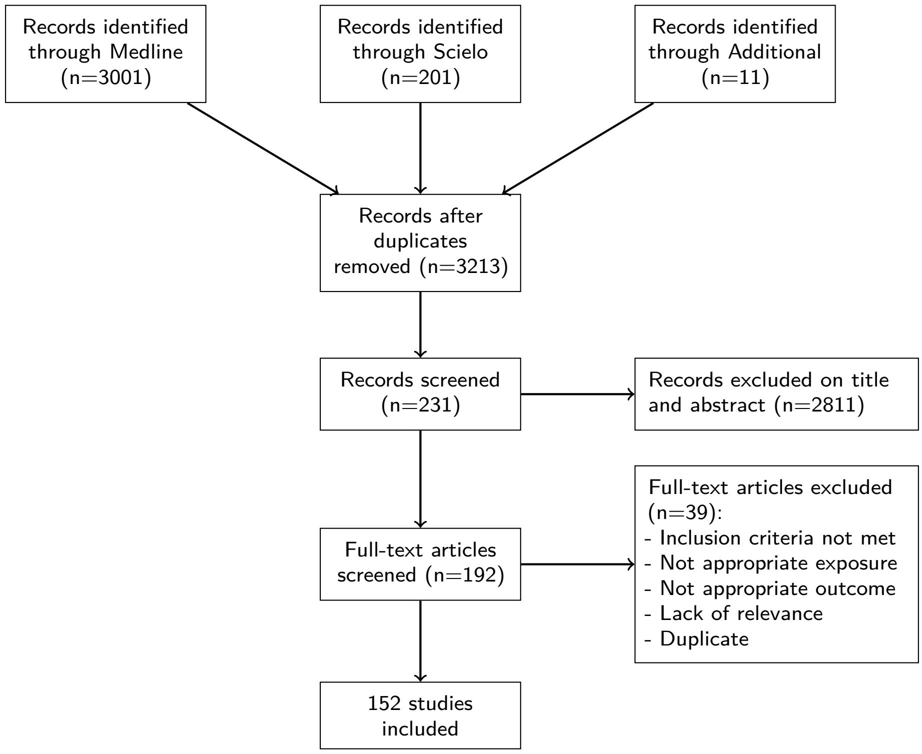


Figure 2.3: PRISMA flowchart for the identification of suitable studies

in the WHO definition, one is a subset of the other. An effort has been made to ensure that the literature below refers only to stillbirth.

2.3.1 Conceptual Model for Causal Pathways to Stillbirth

The cause of stillbirth is multi-factorial, and the relationships between stillbirth and its many risk factors are complex. Many systematic reviews and conceptual models already highlight biological factors in great detail (Menezes et al., 2009; Reinebrant et al., 2017). While these proximal biological factors are direct causes of stillbirth, distal factors – social, behavioural and environmental – also contribute to the risk of stillbirth through multiple causal pathways. Such factors may have a direct effect, be mediated by other factors or act as a proxy for some other unknown influence. For example, “inadequate antenatal care” could be measuring insufficient screening for preventable conditions, a lack of funding/resources, or acting as a proxy for social inequalities that affect healthcare access. However, these more distal factors (and their related interventions) attract less attention from researchers (Yakoob et al., 2009). Often, data for these distal determinants, such as poverty and inequity, are not available to quantify the risk (Lawn et al., 2016).

The conceptual model (Figure 2.4) is built on theoretical assumptions and practical observations in the literature. It is heavily influenced by Vandresse (2006) whose conceptual model for feto-infant mortality is more comprehensive than most, mainly because it is not restricted to available study variables but attempts to consider all possible pathways. Other influences for the conceptual model were Felisbino-Mendes et al. (2014) as well as studies using structured or multilevel models (Andrade et al., 2009; Fonseca and Coutinho, 2010; Oliveira et al., 2010; Warland and Mitchell, 2014), each of which treated stillbirth or perinatal mortality as a primary outcome.

The conceptual model includes nine broad determinants which have a direct or an indirect impact (or both) on stillbirth. The presence of a solid arrow denotes evidence in the literature of a causal link from one factor to another. A dotted arrow displays a proposed causal link; situations where there is a strong, well-known statistical association between the determinants, and the suggestion of a causal link, but it has not been confirmed. Recognising this distinction between cause and association is vital. The absence of a directed arrow suggests that taking into account the accumulated knowledge in the field, no causal relation is suggested.

Socio-economic position (SEP) and demographic characteristics include factors often used to define SEP; education, occupation, and income. They also feature ethnicity, mother's country of birth, marital status of the parents and area deprivation. Maternal age is represented by its own distinct box as it is more directly involved than the other demographic factors in the biological mechanisms that lead to stillbirth. Birth history refers to the parity of the mother as well as any adverse pregnancy outcomes experienced (previous stillbirth, miscarriage, etc.). Behavioural characteristics bring together aspects of the mothers' lifestyle during pregnancy: smoking and drinking habits, nutrition, physical activity, and psychosocial or physical stress. Environmental characteristics describe the immediate area with housing conditions, climate, air pollution, sanitation, urban/rural classification and remoteness – for instance, how far from the nearest hospital/antenatal care services. Prenatal and obstetric care denotes the access, availability and quality of care given before and during pregnancy and labour. Maternal health includes conditions such as obesity, hypertension and diabetes that are particularly relevant during pregnancy. Fetal characteristics include the weight, gestational age, and sex of the fetus, as well as whether the pregnancy has multiple births and the presence of health issues such as congenital anomalies, fetal growth restriction and perinatal asphyxia. Finally, obstetric complications denote any delivery complications.

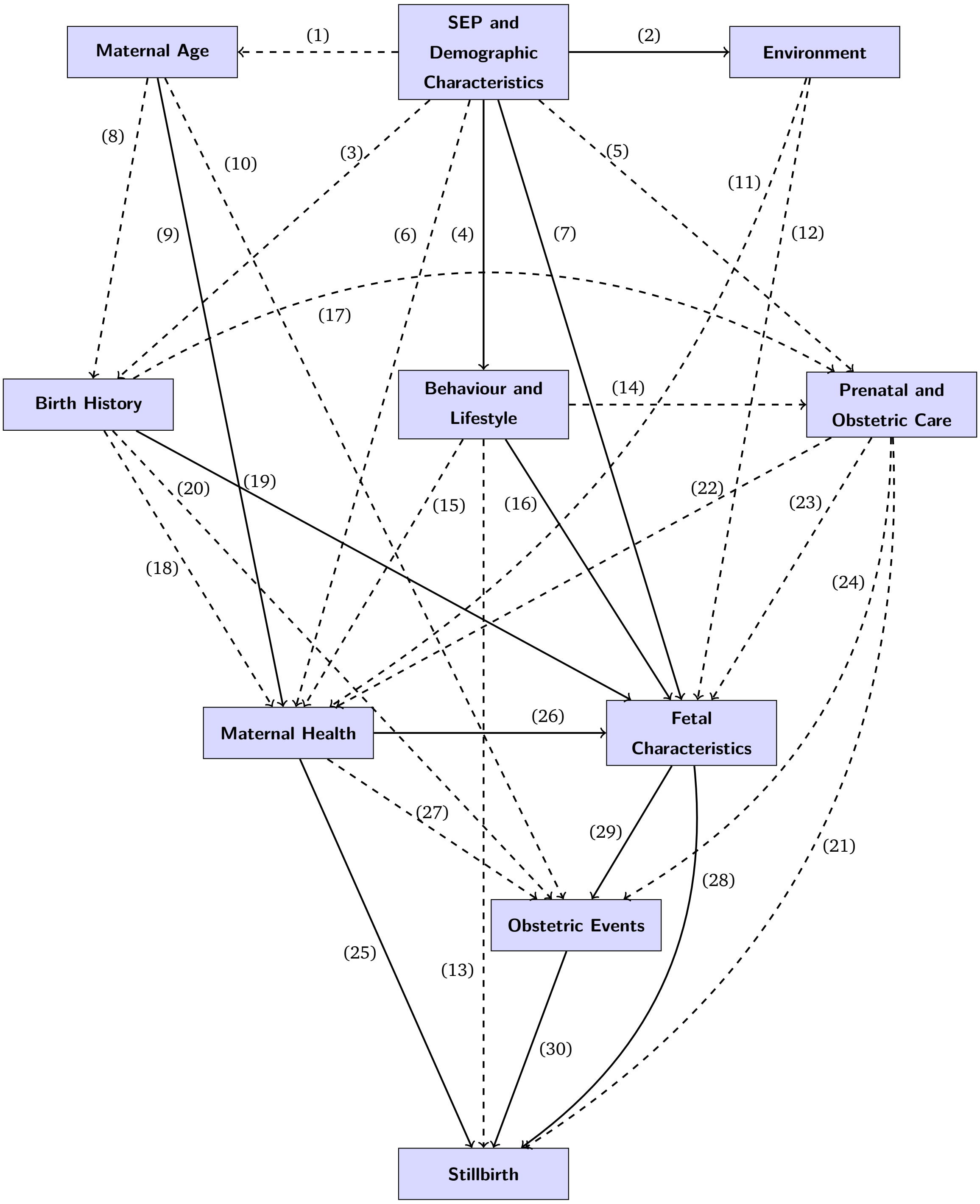


Figure 2.4: Conceptual model for pathways to stillbirth

Socio-economic Position (SEP) and Demographic Characteristics

Education. In addition to acting as a proxy for socio-economic position, a higher level of maternal education allows for better comprehension of health practices and the advice given by healthcare staff. In some developing countries, having less than five years of education has been significantly linked to an increased risk of stillbirth (KC et al., 2015; Löfwander, 2012). In high-income countries, mothers who have not finished high school had an amplified risk of experiencing a stillbirth compared to mothers with some higher education (Luo et al., 2010; Luque-Fernández et al., 2012). Despite decreasing stillbirth rates, the relative educational inequality between stillbirths has not improved in recent decades – even in high-income countries such as Canada (Savard et al., 2013). An international study of 19 countries showed that 1606 of 6447 stillbirths would not have occurred in 2010 if rates for all women matched those for women with post-secondary education (Zeitlin et al., 2016).

Education is almost certainly on the causal pathway for stillbirth but is unlikely to have a direct effect. A hierarchical model using Brazilian data (Oliveira et al., 2010) showed that although education exhibited a protective effect from fetal death in teenage pregnancies, it was mediated by other variables after the inclusion of levels hierarchically closer to the outcome such as birth history, maternal health and fetal characteristics.

Occupation/Employment. Occupation is another measure of SEP that may be a risk factor for stillbirth. A literature review of stillbirth studies in Brazil found that work stability had a protective effect against fetal death (Fonseca and Coutinho, 2010). After adjusting for prenatal care attendance, reproductive history, maternal diseases, and pregnancy-related disorders, a Swedish study found that compared to high-level "white-collar" working women, the risks of stillbirth for both skilled and unskilled "blue-collar" workers more than doubled (Stephansson et al., 2001).

Ethnicity. There are numerous studies indicating inequalities in the risk of stillbirth for different ethnic groups. In Canada and Australia, the native indigenous populations display a significantly higher risk than non-indigenous women (Li et al., 2013; Luo et al., 2010; Farrant and Shepherd, 2016). On the other hand, a New Zealand study found that Pacific ethnicity was no longer significant after accounting for maternal obesity and high parity as confounders (Stacey et al., 2011). In the Netherlands, an increased fetal mortality risk of 30%-80% for different minority groups was found (Ravelli et al., 2011). Similar observations have been made for minority groups in Brazil (Oliveira et al., 2010) and the UK (Parsons et al., 1990; Smeeton et al., 2004; Balchin et al., 2007).

Complex interactions between ethnicity and other variables have been observed in some studies. Penn et al. (2014) found moderate evidence of obesity being a particularly strong risk factor for South Asian women compared to white women in the UK. Balchin et al. (2007) found a significant interaction between ethnicity and gestational age on stillbirth. Compared to white women, after adjusting for various maternal and fetal characteristics, the risk of excess antepartum stillbirth increased by 80% for South Asian women, while it became insignificant for black women. These interactions could imply differing main aetiologies of stillbirth for different ethnic groups; the most important factors associated with antepartum stillbirth in Balchin et al.'s study were placental abruption for white women and low birth weight(below 2000g) for black and South Asian women.

These suggestions were somewhat echoed in a mediation analysis by Lorch et al. (2012) which sought to determine factors that mediated disparity in fetal death rates for different ethnic groups in a cohort of over 7 million women across three US states (California, Missouri, and Pennsylvania). Similar to the results from Balchin et al., birth weight and gestational age mediated the largest percentage of the disparity in fetal deaths for black women (49.6%: 95% CI: 42.7, 54.7) compared to non-Hispanic white women. Among Asian women, antepartum and intrapartum pregnancy complications such as eclampsia, cord abnormalities, hypertension and preterm labour mediated the largest percentage of the disparity (62.2%: 95% CI: 62.2, 100). Finally, for Hispanic women, socioeconomic factors mediated 35.8% of the disparity in fetal deaths (95% CI = 25.8%, 46.2%) compared to non-Hispanic white women. These findings suggest differing causal pathways to stillbirth for different ethnic groups.

Country of Birth. There is some evidence that migrant mothers from specific backgrounds, particularly humanitarian source countries, have an increased risk of stillbirth compared to women from the host country, for example, African mothers in Spain and Turkish mothers in Northern Europe (Villadsen et al., 2010; Luque-Fernández et al., 2012). In the case of Gibson-Helm et al. (2015) however, these disparities disappear when adjusting for age, parity, socio-economic status and body mass index, suggesting that the influence of country of birth on stillbirth may not be as strong as other factors considered in this review.

Marital Status. A stable marital or (cohabiting) status has been found to have a protective association with stillbirth in multilevel studies in Brazil (de Almeida et al., 2007; Fonseca and Coutinho, 2010). While most UK studies account for marital status as a risk factor, its association with stillbirth is usually not significant when accounting for other variables.

Deprivation. Deprivation, or neighbourhood deprivation, is another measure for SEP that characterises a neighbourhood or area by combining a few wide-ranging factors such as employment and income. Stillbirth rates tend to be higher in more deprived areas (Guildea et al., 2001; Gray et al., 2009). An international meta-analysis of studies in seven countries found that compared with the least deprived quintile, odds ratios for stillbirth rates were significantly increased in the most deprived neighbourhood quintile (OR 1.33, 95% CI 1.21–1.45) (Vos et al., 2014).

Post-code-level indicators of deprivation are popular in the UK, where measures such as Townsend, Carstairs or Jarman score are popular in research. Inequalities in socio-economic deprivation appear to have the most significant impact on antepartum stillbirths, as opposed to intrapartum deaths (Seaton et al., 2012) especially after adjusting for maternal age, height, smoking, parity, and marital status (Wood et al., 2012). These studies observed no comparable changes in the relationship between deprivation and stillbirth risk between 1985 and 2008. Other papers in the UK, however, have found no direct evidence of an effect of social deprivation on stillbirth (Smeeton et al., 2004) or more specifically unexplained antepartum stillbirth (Sutan et al., 2010) after adjusting for other factors such as maternal age, smoking, parity, birth history, gestational age, and birthweight.

Of the six UK studies mentioned, both of the ecological or otherwise aggregate studies (Guildea et al. and Seaton et al.) found significant association between neighbourhood deprivation and stillbirth. These studies were limited in that individual-level confounding variables, such as parity or smoking status, were not available to be accounted for.

The remaining four studies were individual-level studies using an aggregate area-level exposure variable for deprivation. Three of these studies (Gray et al., Wood et al., and Sutan et al.) use the same source of data investigating the population of Scotland (albeit for differing time periods), comparing categories of the Carstairs deprivation score. The study by Sutan et al. differs by focussing on the subset of *unexplained antepartum stillbirths*; they included all other stillbirth cases (explained and intrapartum) alongside live births in the control group. This perhaps somewhat explains why the study did not find a significant association between unexplained antepartum stillbirth and deprivation, while the other two Scottish studies did find an association for their *stillbirth vs live birth* outcomes.

Most of these six studies are population studies and are therefore at virtually no risk selection bias or small sample bias. The only exception comes from Smeeton et al., a smaller case-control study of 342 stillbirths and 1,368 live births for one health authority in London. This population is particularly deprived in relation to the rest of the UK; if the area is also more homogeneously deprived relative to the UK overall, this may explain why deprivation score did not have a significant impact on stillbirth in this area after accounting for various maternal and pregnancy-related factors.

A general issue with area-level deprivation scores, even in individual-level studies, is that they do not always correspond to individually measured socioeconomic position, as some women who would be categorised in lower social classes live in affluent areas and many women who would be categorised in higher social classes live in deprived areas. While these measures are still suitable for research and more easily available than individual indicators of deprivation, care must be taken when interpreting the findings of such analysis.

Pathways from SEP and Demographic Characteristics

Maternal age is separate in the conceptual model from other demographic variables, partly due to its more direct link to the biological factors along the causal chain, but also to acknowledge how the age at which a woman conceives is influenced by her socio-economic position (Path 1). In recent decades, particularly in developed countries, women have been postponing having children for various reasons: the rise of effective contraception, gender equity and increases in women's education and labour market participation to name a few (Mills et al., 2011). Women with higher levels of education tend to delay their time of conception, perhaps due to the prolonged absence of income during education, or the difficulties of combining family and education, compared to women with fewer education (Vandresse, 2006).

There is evidence of a causal link between SEP and birth outcomes via environmental factors (Path 2). Through causal pathway analysis, Amegah et al. (2013) show in a Ghanaian study that exposure to indoor air pollution from cooking with biomass fuel during pregnancy mediates 31-52% of the observed effects of socio-economic deprivation on the risk of low birth weight in live births (adjusting for maternal age, parity and sex of newborn). Thus, this connects *SEP* to *fetal characteristics* (**Path 7**) through *environmental factors* (**Path 2** $\rightarrow$ **Path 12**).

The same methods are used to demonstrate that the use of such biomass fuels and unsafe water consumption mediate 18% and 8%, respectively, of the observed increased risk of stillbirth for women with lower educational attainment (Amegah et al., 2017), adjusting for age, marital status, area and ethnicity. Obtaining these findings from a nationally representative population-based maternal health survey, the authors suggest that a lack of education could lead to a woman delaying access to prenatal care services, or being less able to apply the nutritional and health guidelines received during care. As the first to explore the mediating role of environmental elements in the education–stillbirth relationship, the authors suggest these factors could be important pathways through which SEP leads to stillbirths in Ghana and comparable developing countries. We acknowledge that this idea is not so extendable to developed countries and that this causal link is perhaps less relevant to these nations. While the study was able to account for lots of confounding factors with information from the large survey, the birth outcome information in the questionnaire referred to births that could have happened at any point in the mother's history. The household's water or fuel source could have changed since (or between) pregnancy(ies). Assuming these changes would be biased towards *improving* water/fuel source over time, this would *underestimate* the true effect of unsafe sources.

The evidence causally relating SEP to health is convincing, though most likely indirect (DHSS, 1980). This relation to health could arrive via a diverse range of social and economic resources which make it easier for those in more advantaged circumstances to avoid/negate poor health or health behaviours (**Path 4**) (Sloggett and Joshi, 1998; Green, 2014). For example, smoking has been associated with structural, material and perceived socio-economic disadvantage (Laaksonen et al., 2005; Hiscock et al., 2012) while there is less (but some) evidence for a link between SEP and excessive drinking in women in random sample surveys (Van Oers, 1999).

Another idea linking SEP to health is stress. Those in more disadvantaged circumstances will be more likely to suffer from external stressors such as social isolation, adverse life events, or financial difficulties; unhealthy behaviours such as smoking and excessive drinking could be seen as coping mechanisms for such stress (Green, 2014). Sperlich et al. (2013) show that single mothers – who are likely to be more socio-economically disadvantaged than partnered mothers – are twice as likely to be daily smokers. Heavy smoking in particular (and to a lesser extent moderate smoking) seems to be mediated by perceived psychosocial stress, with financial worries being the leading cause of this stress.

In a household survey of 857 adults in 6 low resource communities in Connecticut, Rosenthal et al. (2012) found that stress significantly mediated the association between full-time employment and health behaviours such as frequency of physical activity, unhealthy eating, cigarette smoking and alcohol consumption. Furthermore, depression was found to significantly mediate the relationship between full-time employment and healthy eating. While a causal relationship could not be confirmed in this cross-sectional study, their comparison of a reverse model offered further evidence for the hypothesised direction providing the best fit.

Narrowing in on maternal health behaviours during pregnancy, a large US longitudinal study of over 7,000 pregnancies between 1979 and 1999 (Margerison-Zilko, 2014) explored the effect of sudden economic contraction, or recession, on unhealthy behaviours during pregnancy. While there was no overall association found between economic contraction and maternal smoking or gestational weight gain, an interaction with ethnicity was found; non-Hispanic black women exposed to financial contraction during the first and second trimester were significantly associated with a 42% and 33% increased risk of alcohol use, respectively. However, the prevalence of smoking and alcohol use in this sample is higher than more recent estimates due to a decrease in maternal smoking/drinking, and so these findings may not be as relevant to current pregnancies.

A more recent path analysis of a smaller sample of 370 pregnancies in two US clinics indicated that chronic stressors, depressive symptoms, and the quality of the primary intimate relationship completely mediated the relationship between socio-economic status and prenatal smoking status (in third trimester), with no direct pathway between socio-economic status and prenatal smoking status present once mediators were added to the model (Yang et al., 2017). Socio-economic status was appropriately measured as a composite of household income, education and employment status. Stress, depression and relationship quality were assessed on multi-item scales in the form of questionnaires.
Conversely, the national longitudinal cohort study of 453 pregnancies by Gilman et al. (2008) instead claimed low educational attainment and nicotine dependence as the main predictors of maternal smoking, while the presence of diagnosed mood, anxiety and other substance-use disorders (along with other measures of SEP) were not significant once these factors were included. This result could occur because women with less education are less likely to quit when they become pregnant, or have less access to smoking cessation resources.
These contrasting findings could be attributed to the choice of measure for stress and depression in either study. Yang et al. measured “everyday stress” and pre/post-natal depression as evaluated on multi-item scales. Gilman et al. performed more specific diagnoses of 9 precise disorders with a structured interview.

Since 2008, four international systematic reviews have been conducted exploring the factors that influence the use of prenatal care (Simkhada et al., 2008; Boerleider et al., 2013; Hajizadeh et al., 2016; Roozbeh et al., 2016). Socio-economic status and maternal education overwhelmingly appear among the most important factors (**Path 5**), which could relate to the three most common barriers; financial (service cost), individual (awareness and attitude of the mother) and structural (distance and transportation) (Roozbeh et al., 2016). Poverty limits a woman's access, through either the cost of treatment or cost of transportation if they live far from a prenatal clinic, whereas even if she is employed, her work hours may not allow sufficient time to travel such distance. Regarding individual barriers, education may influence a woman's awareness of or attitude toward prenatal resources. More highly educated women may have increased awareness and understanding of warning signs during pregnancy. In developed and developing countries alike, highly educated women are more likely to access care – and moreover, tend to access it earlier in pregnancy – even when prenatal care is freely and readily accessible (Hajizadeh et al., 2016). A large mediation analysis of the Ghana Maternal Health Survey found that that urban residence was positively associated with receiving a higher quality of prenatal care, but that about half of the effect of a woman's urban/rural residence on quality of prenatal care was explained by social factors education and wealth (Afulani, 2015).

Social and cultural barriers are also significant in accessing prenatal care. Boerleider et al. (2013) looked specifically at non-western women's use of care in industrialised western countries; a lack of understanding of the western healthcare system and language difficulties were the most hindering factors, along with feelings of social exclusion and religious differences. These findings are corroborated in the previously mentioned reviews.

A study exploring the causal effect of women's education on maternal health in Peru – adjusting for various aspects of SEP – found that the effect was mediated through two causal pathways; fertility practices (birth spacing and increased use of contraception, thus avoiding unsafe abortions) and prenatal healthcare use (increased prenatal healthcare visits and deliveries in formal healthcare centres) (Weitzman, 2017). These chains are represented by **Path 3** $\rightarrow$ **Path 19** and **Path 5** $\rightarrow$ **Path 23** in the conceptual model.

Maternal health additionally acts as a mediator along the causal chain (Path 6). Through causal pathway analysis, Amegah et al. (2013) show in a Ghanaian cross-sectional study that malaria infection and poor nutrition mediate 10–21% and 16-44% of the observed effects of socio-economic disadvantage (a measure derived from education, income and area of residence) on the risk of low birth weight (adjusting for maternal age, parity and sex of the new-born). This further connects SEP to fetal characteristics (Path 7) through maternal health **Path 6** $\rightarrow$ **Path 26**.

A prospective study in London found that social and psychological factors have little or no direct effect on fetal growth after accounting for smoking, which was the most important single factor affecting low birth weight (Brooke et al., 1989). More recently, a systematic review and meta-analysis by Vos et al. (2014) found that, compared with the least deprived quintile, odds ratios were significantly increased for preterm delivery and small-for-gestational-age (adjusted ORs 1.23 and 1.31, respectively) in the most deprived neighbourhood quintile. However, the study singles out ethnicity as an important confounder and likely underlying mechanism influencing perinatal outcomes. Another meta-analysis by Kramer (1987) identified ethnicity to have a direct causal effect on fetal growth (**Path 7**) but ruled out a direct effect on gestational age. The indirect effect of ethnicity on both of these outcomes has been established in Brazil via socio-economic status which in turn was partially mediated by prenatal care (Nyarko et al., 2015).

This relationship between ethnicity and fetal characteristics (birth weight and gestational age) likely mediates the ethnic disparities in stillbirth rates. A mediation analysis by Gold et al. (2010) of 1.6 million singleton birth events evaluated the risk of fetal death for mixed-race couples, comparing white/white, black/black and black/white couples and adjusting for demographic, social, biological, genetic, congenital, and fetal risk factors. However, virtually all of the observed higher risk of fetal death for black/black and black/white couples was explainable by higher rates of low birth weight and prematurity.

Maternal Age

The increased risk of stillbirth with advanced maternal age is well documented, even after adjusting for factors such as higher parity, socio-economic status and certain fetal conditions (Nybo Andersen et al., 2000; Andrade et al., 2009; Kenny et al., 2013). Worldwide, a recent Lancet review declared that 6.7% (95% bootstrapped uncertainty range: 6.3–7.3%) of stillbirths could be attributed to older maternal age (Lawn et al., 2016). A systematic review containing 37 studies found that greater maternal age was significantly associated with an increased risk of stillbirth in 77% of studies (relative risks differed between 1.20 and 4.53). When adjusted for confounders, the relative risk did not considerably change (Huang et al., 2008). In the review, and the general literature, the most commonly used cut-off point to define advanced maternal age is 35 years or more, with age less than 35 years or 20–34 years used as the reference group.

Adolescent pregnancies too are associated with higher risk, perhaps due to adverse social and behavioural conditions surrounding pregnant teenagers, although biological factors may also play a role (Nybo Andersen et al., 2000; Lawn et al., 2016).

We do not presume maternal age to have a direct causal effect on stillbirth; rather it has an indirect effect via one or more causal pathways. In the aforementioned systematic review, 21 (57%) of the studies adjusted for potential confounders, most frequently relating to socio-demographic characteristics, behavioural factors, parity, prenatal care and maternal health. However, two hierarchical studies in Brazil found no significant association between maternal age and stillbirth, once intermediated by other variables (Oliveira et al., 2010; Fonseca and Coutinho, 2010). Similarly, despite statistical associations

(Kenny et al., 2013), Kramer's thorough meta-analysis summarised that maternal age was not a direct determinant of fetal characteristics such as intrauterine growth or gestational duration (Kramer, 1987).

Pathways from Maternal Age

It is evident that maternal age has a causal effect on parity and thus other elements of birth history (**Path 8**). Less obvious are the interactions observed between maternal age and parity on birth outcomes, suggesting that primiparous (or first-time) mothers aged 30–39 years were less likely to deliver very large-for-gestational-age (LGA) babies compared to multiparous women, and more likely to deliver small-for-gestational-age (SGA) (35+ years) or preterm babies (30-39 years). (Lisonkova et al., 2010; Kenny et al., 2013). An interaction between teenage pregnancy and parity observed by (Smith and Pell, 2001) found that primiparous women aged 15-19 were not at increased (adjusted) risk of adverse birth outcomes compared with women aged 20-29, but that women aged 15-19 having a second birth were at significantly increased risk of premature delivery and stillbirth. These results do not include smokers to avoid the major confounder of young women being more likely to smoke during pregnancy. The separate effects of parity on birth outcomes will be discussed later in the review.

Maternal health has been highlighted as an important mediator of the association between age and perinatal mortality (**Path 9**) (Fonseca and Coutinho, 2010). Generally, a mother's health status decreases with age, and those above 40 years are particularly more at risk of more severe life-threatening maternal morbidities such as renal failure, shock and acute cardiac morbidity, along with events such as obstetric interventions (**Path 10**) and intensive care admission (Lisonkova et al., 2017). A systematic review by (Lawn et al., 2009) asserts that teenage mothers alternatively face an increased risk of pregnancy-induced hypertension and obstructed labour as a probable mechanism leading to stillbirth.

Environmental Factors

Evidence for whether ambient air pollution and stillbirth are significantly associated is inconsistent. One systematic review summarised the evidence for this relationship with meta-analysis of 13 studies, two studies assessing the effects of short-term air pollution exposure with the remaining studies focusing on long-term exposure. The results did suggest that such exposure increases the risk of stillbirth; all the summary effect estimates for the risk of stillbirth were systematically elevated in relation to mean prenatal exposure to nitrogen dioxide, carbon monoxide, sulphur dioxide and particulate matter. However, none of these estimates reached statistical significance. Further research is needed to strengthen or refute the evidence.

A case-control study in São Paulo, Brazil, showed that traffic-related air pollution was not significantly related to stillbirth (de Medeiros et al., 2009). In this study, air pollution was quantified with a distance-weighted traffic density measure using geo-coded traffic data on roads surrounding each mother's address.

On the other hand, a large cohort study covering 244,758 births over 38 years in Cumbria, UK found that while stillbirth rates fell substantially over the study period, there was a consistent significantly increased risk of stillbirth in populations living close to crematoriums (OR: 1.04; 95% CI: 1.01 to 1.07) after adjustment for social class, year of birth, birth order, and multiple births (Dummer et al., 2003). Mercury was the main pollutant emitted from crematoriums. The study also observed populations near incinerators (for which pollutants included mixtures of particulates and heavy metals), but no such evidence was found for increased stillbirth risk. A limit of this study was that the actual pollution levels around each site was unknown, with *distance* serving as a proxy for exposure to pollution. Additionally, the authors acknowledged that due to medical advances and the subsequent reduction in stillbirths over time, the clinical characteristics of the cases might have changed over the years of the study. However, all analyses were adjusted for year of birth, ensuring that the stillbirth risk was effectively compared with that of other mothers giving birth around the same time.

There is more agreement on the risk of indoor air pollution from the household combustion of solid fuels (often relied upon for cooking in developing countries). A meta-analysis of 19 studies showed that constant exposure to the fumes could result in a 29% increased risk (summary effect estimate 95% CI: 1.18-1.41) of stillbirth ((Amegah et al., 2014)). Focus has been placed on developing interventions to reduce this risk across low- and middle-income countries (Yakoob et al., 2009).

Sanitation and access to clean water sources could also be an issue in developing countries. A population-based cross-sectional study in Afghanistan estimated that households with unimproved water access (without a piped water system or protected spring/rainwater collection) had a 91% increased adjusted odds of maternal mortality (aOR: 1.91; 95% CI: 1.11-3.30). There was also an association found between inferior toilet facilities and stillbirth risk, but it was not statistically significant (Gon et al., 2014). This study acknowledged a small possibility of bias from households' under-reporting of pregnancy-related deaths, but for such bias to lead to a spurious association between water and pregnancy-related mortality, households with improved water sources would have had to under-report deaths more than households with poorer water sources; this does not seem plausible.

In a prospective cohort study of 670 pregnant women in Odisha, India, the risk of adverse pregnancy outcomes, including stillbirth, more than doubled for women who practised open defecation compared to those with access to a latrine (Adjusted Odds Ratio (aOR): 2.38; 95% CI: 1.49–3.80) (Padhi et al., 2015).

Even in a high-income country such as the UK, a significant association with stillbirth was found for mothers living in areas with high levels of trihalomethane in the water supply (a chemical by-product produced after disinfecting water with chlorine) (Toledano et al., 2005). Individuals' post-codes from birth and stillbirth records were linked to routinely collected data on water samples in three northern regions of the UK. This relationship between stillbirth and exposure remained after adjusting for maternal age and small-area level socio-economic deprivation (OR: 1.11; 95% CI: 1.00–1.23).

It should be noted that all of these findings are associations found in observational (mostly cross-sectional) studies, with heterogeneous measures of exposure and no evidence of direct causal effects. Many large-scale individual-level studies use area-level exposures; for example, with the aforementioned study by Tolendo et al., it would not have been feasible to obtain tap water samples at each maternal address for a direct measure of individual exposure. There is an inevitable compromise between specificity of the exposure and study power. Potential pathways to stillbirth are presented below.

Pathways from Environmental Factors

In a large scoping review of systematic reviews and meta-analyses, Campbell et al. (2015) built a detailed conceptual framework identifying 77 risk mechanisms linking water, sanitation and hygiene practices to maternal health (**Path 11**) as well as perinatal health outcomes. These consisted of 67 chemical or biological factors (via ingestion, inhalation or contact with "contaminated" water) and ten factors relating to the practice and logistics of sanitation (poor hygiene and remote/dangerous water sources leading to, for example, hookworm, malaria, influenza and mental distress). The authors concluded that much of the evidence, based on observational studies and anecdotal evidence, is weak with relatively few systematic reviews.

One meta-analysis examining both sanitation facilities and water availability indicated that women in households with poor sanitation had three times the adjusted odds of maternal mortality citepBenova2014. Regarding water availability, the only individual-level study found a significant association between poor water availability and higher maternal mortality (aOR: 1.50; 95% CI: 1.10–2.10), while four out of six ecological studies also found an association. The systematic review was assessed for potential bias with the Newcastle Ottawa quality scale, scoring a low risk for selection bias but a potentially higher risk of bias for a lack of controlling for confounders such as socio-economic status, access to prenatal health services or quality of care, which in turn may cause maternal mortality.

In other systematic reviews and meta-analyses, exposure to environmental toxins and cooking with biomass fuels are associated with an increased risk of congenital abnormalities, fetal hypoxia and reduced fetal growth/low birth rate (Lawn et al., 2009; Amegah et al., 2014). The Lancet systematic review by Lawn et al. cites these fetal characteristics (**Path 12**) as probable mechanisms for stillbirth.
Not all of the literature agrees with this. After adjusting for socio-economic confounders, some studies see the association between environmental exposures or sanitation practices and low birth weight disappear (Elliott et al.; Padhi et al., 2015). On the other hand, in the latter study, the adjusted (and doubled) odds of preterm birth remained.

Evidence appears insufficient to confirm a direct causal relationship between environmental exposure and fetal characteristics, but there is at least an indirect link via maternal morbidity.

Behavioural and Lifestyle Factors

Ample research and large meta-analyses show the association between mothers' smoking habits and adverse pregnancy outcomes such as stillbirth (Flenady et al., 2011a; Marufu et al., 2015). A Swedish population prospective cohort study by Högberg and Cnattingius (2007) revealed that, compared with non-smokers, women who smoked during their first pregnancy but not during their second showed no increase in stillbirth risk in the second birth, while the odds ratio among women who continued to smoke during both pregnancies was 1.35 (95% CI 1.15–1.58). This result supports a causal association between smoking during pregnancy and an increased stillbirth risk (**Path 13**).

Smoking also seems to mediate the social inequalities in stillbirth. In their population-based retrospective cohort study of singleton births in Scotland, Gray et al. (2009) found that the risk of stillbirth was 56% higher in the most deprived areas compared with the least deprived areas, and that smoking accounted for 38% of these inequalities in stillbirths. The study included a non-responder "unknown" category for smoking status, which in the analysis showed a similar risk profile to the category of smokers. In a small way, this strengthened the study by tackling the misclassification of smoking status. However, the study was limited by its area-based outcome in the form of stillbirth rates by post-code deprivation quintiles; such a score does not always reflect individual socio-economic position as some women who would be categorised in higher social classes live in lower-income areas and vice versa.

Additionally, alcohol and other social drugs have been detected as a risk factor for stillbirth. In their population-based retrospective cohort analysis of births in Missouri, Aliyu et al. (2008) observed a dose-response relationship between maternal alcohol intake in pregnancy and the risk of early stillbirth. Compared to non-drinking mothers, women who consumed alcohol while pregnant had a 40% higher risk of stillbirth, and pregnant women who consumed five or more drinks per week experienced a 70% higher risk. However, the data for mothers' alcohol intake was collected *after* delivery, which could lead to systematic recall bias based on the pregnancy outcome.

In a US case-control study by Varner et al. of social (and more illicit) drugs (2015), the most common individual drug used (cannabis) increased the risk of stillbirth with an odds ratio of 2.34 (95% CI 1.13-4.81). However, this effect was reduced by 10% when adjusting for tobacco smoking, while adjusting for cannabis did not affect the risk for tobacco smokers. This finding suggests that the association between cannabis and stillbirth is at least partially due to confounding by tobacco smoke. Unlike the other studies of smoking included in this review, Varner et al. confirmed the self-reported exposure to tobacco and illicit drugs in more than half of the women via maternal blood samples and toxicology testing of the umbilical cord. This objective measure protects the findings somewhat against recall bias. On the other hand, the very small number of cases testing positive for individual drugs may be a source of bias via small sample size.

An elevated risk of stillbirth has also been observed among heroin and cocaine users in a literature review by (Keegan et al., 2010).

Dumith et al. (2012) suggested exercise to be a protective risk factor for stillbirth. Women who performed physical activity during pregnancy were less likely to have a stillbirth; there was no association between exercise and preterm birth or low birth weight. However, when adjusting for potential socio-economic confounders, the association almost disappears. The authors acknowledge a potential reverse causality bias; women who were more “at risk” may have been medically advised to avoid exercise.

Domestic or partner violence has been found in some studies to increase the risk of low birth weight or fetal death (Murphy et al., 2001; Fonseca and Coutinho, 2010). However, data on partner violence is challenging to collect and prone to reporting bias (Heazell et al., 2015); mothers may feel unable or unwilling to discuss it with health professionals. Further data collection on this issue of abuse during pregnancy is called for (Campbell, 2001).

Pathways from Behavioural and Lifestyle Factors

In Brazil and a global systematic review (Ribeiro et al., 2009; Hajizadeh et al., 2016), smokers were less likely to access and slower to access prenatal care. They may be reluctant to access care for fear of judgment from health professionals. A similar argument may be made for other unhealthy behaviours such as alcohol and illicit drug use during pregnancy (**Path 14**). Such behaviours do lead to poor health (DHSS, 1980) and therefore to poor maternal health (**Path 15**).

Regarding fetal health, a meta-analysis by Kramer (1987) deduced cigarette smoking, alcohol consumption, and tobacco chewing to have a direct causal impact on fetal growth (**Path 16**). Furthermore, in developing countries, smoking was the most important single modifiable factor of intrauterine growth restriction (IUGR). The same result was found for a large prospective cohort study in a UK hospital, even after accounting for numerous social, psychosocial, and behavioural factors (Brooke et al., 1989). Furthermore, among those in the same cohort who smoked during pregnancy, high alcohol and caffeine consumption disproportionately exacerbated the risk of fetal growth restriction (Peacock et al., 1991).

Another prospective study of this London hospital cohort, this time investigating preterm birth, found an association between smoking and delivery before 32 weeks, with no excess risk from smoking after 32 weeks’ gestation (Peacock et al., 1995). Kramer (1987) also determined that smoking directly impacts gestational duration. As well as the aforementioned fetal characteristics, den Draak (2003) found smoking during pregnancy to contribute to several other adverse outcomes including abruption placentae, placenta praevia, preterm birth, spontaneous abortion, and stillbirth. There even appeared to be a dose-response relationship between the number of cigarettes smoked and the occurrence of such complications.

Alcohol has been found to have a much more significant association with early stillbirth (24-28 weeks) than with later stillbirths (Aliyu et al., 2008). Aliyu et al. acknowledge that the exact pathway linking alcohol to stillbirth was unknown, but examines possible intermediate mechanisms from the literature, including decreased blood flow in the placenta and placental abruption. A review by den Draak (2003) inferred that alcohol was suspected to cause congenital anomalies and that more than one drink per day (particularly more than three drinks per day) has been associated with fetal growth retardation.

Returning finally to the effect of more illicit drugs, an association has been observed between maternal history of psychiatric alcohol/drug-related disorder and a doubled risk of stillbirth due to congenital malformations or delivery complications (King-Hele et al., 2009). Additionally, an increased risk of low birth weight new-borns has been noted amongst mothers who used cocaine during pregnancy (Keegan et al., 2010).

Criticism of self-reported health measures. The measurement of health behaviours is not straightforward. Studies often rely on self-reporting by the participant of their habits/lifestyles/life events. Pregnant women might lie about their drinking or smoking habits due to social stigma, which could lead to under-reporting of perceived unhealthy behaviours. Women may be hesitant to report cases of domestic violence due to perceived repercussions for themselves or their baby.

In an ideal world, studies would accurately verify the exposure with objective testing just as salivary cotinine testing for smoking. These measures have been achieved in some longitudinal studies, but collecting this information routinely on a large scale is not practical. Of the observed studies, only Varner et al. (2015) measured drug intake via testing of the mother's blood and umbilical cord alongside the self-reported intake from the mother.

Additional problems of bias can occur if the mother's history was recorded in retrospect *after* the delivery. Mothers with poor pregnancy outcomes may systematically underreport poor health behaviour to a greater extent than mothers with better outcomes due to the social stigma; they might be afraid to admit to any behaviours that could have contributed to a stillbirth. All but one of the studies in this section (Aliyu et al., 2008), however, recorded such information early in the pregnancy before the outcome of the birth was known.

Still, in the case of such under-reporting of unhealthy behaviours, then the effect estimate would be biased towards the null, i.e., the results would suggest a weaker relationship between these behaviours and stillbirth. Despite this, the review shows overwhelming evidence of a strong (and in some studies, casual) association between these factors.

Birth History

In a hierarchical model where each variable was adjusted for preceding variables in the proposed causal chain, a previous birth with low birth weight was significantly associated with antepartum stillbirth (de Almeida et al., 2007). In a meta-analysis of 17 studies, the risk of stillbirth was elevated in women with a prior preterm birth or SGA (aOR 1.70; 95% CI 1.34–2.16) and (aOR 1.98; 95% CI 1.70–2.31), respectively, but more than doubled (aOR 4.47; 95% CI 2.58–7.76) when two prior adverse outcomes were combined (Malacova et al., 2017). A different meta-analysis found that a previous caesarean delivery could increase the risk of subsequent stillbirth by 23% (O'Neill et al., 2013).

Not only are previous adverse pregnancy outcomes important, but so is the time since one occurred; a systematic review found an increased risk of stillbirth for those with a shortened inter-pregnancy interval after an adverse birth outcome (Yakoob et al., 2009).

Pathways from Birth History

Multiparity is associated with inadequate use of prenatal care services (**Path 17**) (Ribeiro et al., 2009; Chiavarini et al., 2014; Melo et al., 2015). In two systematic reviews, one of which was specific to developing countries, high parity was associated with reduced use of prenatal care. The opposite was observed for women with histories of preterm birth, fetal loss or obstetric complications who were more likely to use prenatal care services (Simkhada et al., 2008; Hajizadeh et al., 2016).

Regarding the link between birth history and maternal health (**Path 18**), another systematic review found that grand multiparous women (more than four births) were at an increased risk of gestational diabetes and chronic hypertension, but at a reduced risk of preeclampsia (Jacquemyn et al., 2006; Al-Shaikh et al., 2017). Lawn et al. (2009) in particular cites this pathway through gestational diabetes as a probable mechanism for stillbirth.

The aforementioned systematic review (Jacquemyn et al., 2006) also links birth history to fetal characteristics (**Path 19**), with grand multiparous women having an increased placenta previa (where the placenta partially or fully blocks the cervix from the foetus). However, findings suggest grand parity poses no significant impact on placental abruption or fetal death. The comprehensive meta-analysis by Kramer (1987) states that parity and history of low-birth-weight infants have a direct causal impact on fetal growth (while ruling out prior miscarriage, abortion, stillbirth or neonatal death as having only indirect effects). On the other hand, he deduces that a history of prematurity or miscarriage instead has a causal effect on gestational duration (while ruling out parity as indirect only).

Finally, Kenny et al. (2013) and Al-Shaikh et al. (2017) observed that first time mothers were more likely to have an emergency or elective Caesarean section (**Path 20**).

Prenatal and Obstetric Care

A lack of prenatal care attendance is one of the strongest modifiable risk factors for antepartum stillbirth (**Path 21**). Attending prenatal visits provides an opportunity to screen for and receive advice on other potential risk factors for stillbirth. Access to (and use of) adequate prenatal care has a protective effect against stillbirth, even when adjusting for maternal age, race, parity, previous stillbirth and various socio-economic and biological factors (Fonseca and Coutinho, 2010; Partridge et al., 2012; KC et al., 2015). Furthermore, in low/middle-income countries, women not delivered by a skilled attendant were more likely to have a stillbirth (relative risk (RR) 2.8, 95% CI 2.2-3.5) (Mcclure et al., 2015). However, a study of stillbirth in Ghana submitted that the timing of a woman's first prenatal care visit may not be an essential determinant of stillbirth, compared to other factors (Beauclair et al., 2014).

Four structural or hierarchical models examining fetal death in Brazil identified adequate prenatal care as an important determinant of stillbirth (de Almeida et al., 2007; Andrade et al., 2009; Oliveira et al., 2010; Fonseca and Coutinho, 2010). The multi-level model by Andrade et al. specified that attending less than six prenatal appointments quadrupled the risk of fetal death (OR 4.4; 95% CI 2.5-7.5). Fonseca and Coutinho identified that having a companion during admission (perhaps a proxy for social support) had a protective effect against fetal death.

Pathways from Prenatal and Obstetric Care

The effect of poor access to health services on maternal health, through increased risk of infection and undiagnosed/untreated infections, has been listed as a probable mechanism for stillbirth (**Path 22**) (Lawn et al., 2009). In a meta-analysis of 4 studies, a significant reduction in maternal morbidity was observed for maternities receiving community-based antenatal intervention (average RR 0.75; 95% CI 0.61 to 0.92) (Lassi et al., 2010).

With respects to fetal characteristics (**Path 23**), a study in Portugal determined that – adjusting for ten socio-economic, behavioural and biological factors – receiving adequate or intermediate care had a protective effect on the risk of preterm delivery and low birth weight. The adequacy of care was measured with Kessner's Adequacy of Prenatal Care Index, which is derived from the date of the first prenatal care visit, the total number of visits and gestational duration. Coria-Soto et al. (1996) found that while the number of visits were associated with preterm birth and IUGR, the content of the visits differed in impact; women with insufficient content had 76% greater odds of preterm delivery, while the content of prenatal visits showed no significant effect on IUGR. Conversely, Beeckman et al. (2013) argued that the number of visits alone had no impact on preterm birth, but their new derived tool measuring Content and Timing of care in Pregnancy (CTP tool) provided a better assessment of the risk of preterm birth. We note that these three studies took place in countries with free access to prenatal care, and thus these interpretations might not be generalisable world-wide.

Finally, poor access to healthcare services during labour, perhaps due to distance or financial barriers, could lead to increased risk of obstetric complications (**Path 24**). This could occur through increased delays in accessing care, a lack of quality emergency obstetric care even when care is accessed (e.g. no caesarean section possible or need for additional payments), or increased risk of obstetric complications when delivering outside of a hospital setting. The above-mentioned systematic review by Lawn et al. (2009) also describes these links as probable mechanisms for stillbirth.

Overall, good quality prenatal care will positively affect the risk of stillbirth through various causal pathways, since numerous modifiable health issues for the mother and foetus can be controlled throughout pregnancy.

Maternal Health

There is ample evidence that maternal health status has a direct effect on stillbirth (**Path 25**). Three systematic reviews – two focusing on low-middle income countries – evaluated that maternal factors are the most frequently reported cause of stillbirth (attributing to 8-50% of stillbirths) (Aminu et al., 2014). These factors are often split into two categories: maternal infections in pregnancy (with syphilis, positive HIV status and malaria among the most common) and maternal disorders (in particular diabetes, hypertension and maternal malnutrition) (Bhutta et al., 2011). Lawn et al. (2016) argue that maternal infections could be particularly targeted as preventable factors; malaria in pregnancy is estimated to be attributable for about 20% of stillbirths in sub-Saharan Africa, while data on HIV/AIDS is too scarcely collected to calculate. Multiple structural or hierarchical models examining fetal death in Brazil each indicate maternal morbidity as an important determinant of fetal death (Andrade et al., 2009; Oliveira et al., 2010; Fonseca and Coutinho, 2010). In particular, in a hierarchical model where each variable was adjusted for preceding variables in the proposed causal chain, mothers with hypertension, diabetes, or bleeding during pregnancy were significantly associated with antepartum stillbirth (de Almeida et al., 2007).

For high-income countries, a meta-analysis by Flenady et al. (2011a) for *The Lancet* Stillbirth Series concluded that maternal obesity was the highest ranking modifiable risk factor for stillbirth, beating advanced maternal age and maternal smoking. A meta-analysis of 18 cohort studies (most from high-income countries) found a dose-response relationship with pooled adjusted relative risk of 1.24 per 5-unit increase in maternal BMI for stillbirth (95% CI 1.18-1.30) (Aune et al., 2014).

Aune et al. also noted that BMI is more strongly associated with fetal deaths later in pregnancy, rather than earlier. A US cohort study of two million women found that after 39 weeks, the risk increased more rapidly for those with the largest BMI values. The risk for women with BMI greater than 50kg/m2 was almost six times that of "normal" weight women at 39 weeks gestation and over 13 times greater at 41 weeks. Obesity was associated with almost a quarter of the stillbirths that occurred in that 37-42 week period (Yao et al., 2014). The authors recommended that optimal times for labour inductions should be considered for each BMI band. Lindam et al. (2016) accounted for familiar confounding by using sisters of obese women who had also given birth as controls. Compared with the control population of women in the "normal" BMI class, the stillbirth risk increased for increasing BMI values, inferring that obesity in pregnancy is associated with stillbirth independently of genetic and early environmental factors.

These results, along with the magnitude and consistency of the association and the improvement in fetal survival after a decrease in inter-pregnancy BMI for obese mothers, provide compelling evidence of a causal relationship between obesity and stillbirth (Salihu, 2011).

A less studied but notable factor is psychological stress during pregnancy. A study in Denmark found that women with a high level of psychological stress had an 80% increased risk of stillbirth compared to those with intermediate stress levels. The results remained unchanged after adjusting for multiple SEP and behavioural factors, restricting the cohort to first-time mothers and excluding those health complications during pregnancy such as diabetes, hypertension and vaginal bleeding (Wisborg et al., 2008).

Pathways from Maternal Health

Many of the maternal factors mentioned previously have causal links through fetal characteristics (**Path 26**) including infections (e.g. syphilis, herpes and rubella) as well as other maternal disorders (diabetes, hyperthermia and malnutrition) which are strongly suspected or proven to cause congenital anomalies (den Draak, 2003). Malaria, general morbidity and episodic illness along with gestational weight gain and caloric intake have been shown to have direct causal impacts on intrauterine growth (Kramer, 1987). Kramer's meta-analysis cites gestational nutrition and low pre-pregnancy weight as the most important modifiable factors after smoking. Hypertension is also suspected to cause reduced fetal growth and placental dysfunction, including abruption (Lawn et al., 2009).

Evidence for the existence of a genetic predisposition to preterm births is persuasive, including increased recurrence risks for preterm birth for women with prior preterm birth or who were themselves born preterm, and observed increased risks for women with sisters who have had a preterm birth (Gravett et al., 2010). However, we must – where possible when analysing data – recognise the difference between elective and spontaneous preterm birth. Elective preterm labour induction is sometimes beneficial for mothers with severe maternal hypertensive disorders (e.g. pre-eclampsia, eclampsia), maternal diabetes or placental problems (e.g. placenta praevia), or foetuses with IUGR (den Draak, 2003). It may also be used to combat the higher risk of stillbirth for term/post-term births in obese women (seen above with Yao et al. (2014)). Therefore some statistical association observed could be due to an induced preterm birth to mitigate further complications from maternal disorders, rather than the disorders directly causing preterm birth.

Maternal disorders, such as diabetes hypertension, are frequently associated with obstetric issues such as birth asphyxia and obstructed labour (**Path 27**) (den Draak, 2003; Lawn et al., 2009). Another "probable mechanism" for stillbirth presented in the systematic review by Lawn et al. includes an increased risk of feto-pelvic disproportion in women who were malnourished in childhood.

Fetal Characteristics

The link between fetal characteristics and stillbirth (**Path 28**) is undoubtedly causal. Multiple systematic reviews state congenital abnormalities are one of the five major causes of stillbirth amongst low-middle income countries; the risk for infants with congenital anomalies is nine times that of those without (RR 9.1, 95% CI 7.3, 11.4) (Mcclure et al., 2015; Bhutta et al., 2011; Aminu et al., 2014).

Preterm birth and fetal growth restriction are often at the end of the causal pathway to stillbirth (Lawn et al., 2016). Fetal growth restriction has been associated with stillbirth in both Brazil and UK specific studies (Fonseca and Coutinho, 2010; Gardosi et al., 2014; Norman et al., 2009) after adjusting for various confounders. There are risk factors associated not only with preterm gestational age, but post-term. *The Lancet*'s Stillbirth Series review stated that pregnancies lasting longer than 42 weeks pose an increased risk of stillbirth and accounts for an estimated 14% of stillbirths worldwide (Lawn et al., 2016).

There are some fetal demographic characteristics with causal effects on other fetal characteristics. The meta-analysis by Kramer (1987) deduced that infant sex directly affected intrauterine growth, with a 19% increased risk for females versus males.

Most studies restrict singleton births, since observations from multiple birth sets are not statistically independent, but multiple births in pregnancy have been shown to pose an increased risk of prematurity, IUGR and stillbirth (Smith et al., 2014; Alencar et al., 2015).

Pathways from Fetal Characteristics

Regarding a causal link to obstetric events (**Path 29**), a recent study showed that major congenital malformation accounted for the largest proportion of intrapartum deaths (36/81) in Ireland (McNamara et al., 2018). Foetal infection has also been attributed as a risk factor for birth and perinatal asphyxia (restriction of oxygen in the womb) (den Draak, 2003).

Obstetric Events

The final causal pathway links obstetric events to stillbirth (**Path 30**). Multiple systematic reviews attribute delivery complications as one of the five major causes of stillbirth amongst low-middle income countries; these include asphyxia and birth trauma (accounting for 3.1-25% of stillbirths) and umbilical problems (2.9-33.3%). Breech delivery is also associated with a tripled risk of stillbirth (RR 3.0, 95% CI 2.6, 3.5) (Mcclure et al., 2015).

In an English case-control study, breech presentation, spontaneous breech delivery and emergency caesarean delivery has highly increased odds of stillbirth (OR 6.55 (95% CI 3.65- 11.76), OR 22.43 (95% CI 2.70- 184.53) and OR 19.43 (CI 2.31-163.59) respectively) (Smeeton et al., 2004). Women with a previous caesarean delivery also had increased odds of stillbirth in subsequent pregnancies (Keag et al., 2018), particularly antepartum stillbirth (O'Neill et al., 2013).

We must note the difference between emergency caesarean and the use of planned caesarean section as an intervention. Planned caesarean deliveries have shown, for each 1% increase in the proportion of planned caesarean deliveries (up to 8%), a decrease of 1.61 intrapartum stillbirths per 1,000 births (Goldenberg et al., 2007). A systematic review by Darmstadt et al. (2009) corroborated these findings, particularly noting the impact of reducing stillbirths in cases of term breech presentation.

2.3.2 Factors of Interest in Brazil and the UK

Risk factors specific to Brazil

Considerable variation in stillbirth rates exist between regions in Brazil, with significantly higher risk in the North and North East. However, variation in socio-economic position does not explain these findings; the differences persist after accounting for deprivation level, urban/rural classification, and various SEP factors (Carvalho et al., 2017). Instead, access to (and use of) prenatal care could explain these regional differences. The northern and southern regions have different healthcare needs (Vieira et al., 2016), yet limited supplies and low availability of national healthcare (SUS) services are barriers to adequate healthcare in the North and Northeast (Andrade et al., 2009).

A systematic review of 11 studies by Barbeiro et al. (2015) evaluated that the main factors associated with fetal death are inadequate prenatal care or the lack of it entirely, low levels of education, maternal morbidity and adverse reproductive history. Education, in this case, may be acting as a proxy for SEP or financial independence.

The review included four hierarchical or structural models of city-specific data. Variables found to be significant in these analyses were consistent across different studies from various cities and regions, although it is noteworthy that most of these studies used urban city populations and, therefore, there may be variation from rural populations that is unaccounted for. A later study (Lima et al., 2016) was consistent with the findings from the systematic review, but also noted the protective effect of caesarean delivery.

Brazil has an unusually high number of births delivered via caesarian section. Over 55% of all births in 2016 were caesarian deliveries (DATASUS, 2018), the second highest rate worldwide after the Dominican Republic (56%). Caesarian deliveries seem to be perceived as a social trend rather than medical need (Victora et al., 2011a). While they can be life-saving when dealing with pregnancy complications, undergoing such a major abdominal surgery unnecessarily poses long-term risks for the mother and subsequent pregnancies (Keag et al., 2018).

The modifiable factors of obesity and young maternal age were also picked out as relevant in recent studies (Felisbino-Mendes et al., 2014; Carvalho et al., 2017).

A note on the Zika virus: In November 2015, Brazil's Ministry of Health declared a national public health emergency after an outbreak of the Zika virus, a virus spread by Aedes mosquitoes, was reported in North East Brazil. In areas affected by the virus, there had been a sudden increase in reports of microcephaly in newborns – an otherwise rare condition associated with incomplete brain development. The World Health Organization declared the virus a public health emergency of international concern in February 2016 (Lowe et al., 2018), and an association between Zika virus infection in pregnancy and microcephaly was confirmed by de Araújo et al. (2017).

Soon after the outbreak, a case study in which a stillborn fetus was found to have the virus (Sarno et al.) prompted further investigation; the virus was found to be associated with adverse birth outcomes (Brasil et al., 2016).

Brazil has since lifted the state of emergency, and while there has been a significant decline in overall births, no significant change to rates of fetal death were observed. The authors suggested that postponement of pregnancy was responsible for the decreased fertility rates (Castro et al., 2018).

Risk factors specific to the UK

The majority of research output on the relationship between socio-economic risk factors and birth outcomes are set in Scotland, using their high-quality linked maternal data, but coverage across the rest of the UK also exists.

There appears to be much less regional variation in stillbirth rates in the UK compared Brazil; instead the focus in on much smaller pockets of deprivation throughout the country. Weightman et al. (2012)

conducted a systematic review of UK studies, exploring the effect of deprivation quintiles on various birth outcomes. However, as mentioned in Section 2.1.4, there were only two papers on stillbirth that fit the inclusion criteria; one was unpublished and untraceable, the other by Gray et al. (2009). The pooled odds of stillbirth in the most deprived quintiles compared to the least deprived were 1.54 (95% CI 1.39-1.72).

There appears to be plentiful evidence of deprivation impacting stillbirth in the UK (Guildea et al., 2001; Gray et al., 2009; Wood et al., 2012; Seaton et al., 2012). Others, however, have found no direct evidence of an effect of social deprivation on stillbirth after adjusting for various factors such as maternal age, smoking, parity, birth history, gestational age, and birthweight (Sutan et al., 2010; Smeeton et al., 2004). Seaton et al. claimed that unexplained antepartum stillbirths accounted for 50% of the observed deprivation gap. Wood et al. (2012) encountered mixed results; after adjusting for maternal characteristics, they found an association between socio-economic deprivation and an increased risk of antepartum stillbirth (from a congenital anomaly), but that intrapartum death had no such significance.

Rather than deprivation, Smeeton et al. (2004) argued that ethnicity plays a vital role in stillbirth risk, with higher odds for black (aOR 1.59; 95% CI 1.10 to 2.31) and South-east Asian (aOR 3.03; 95% CI 1.40 to 6.59) women compared to white women. Additionally, the adjusted risk of antepartum stillbirth increased earlier in pregnancy for South Asian women (Balchin et al., 2007). Balchin et al. also found that the most important observed factor related to antepartum stillbirth for white women was placental abruption, but for black and South Asian women it was low birth weight, suggesting that there could be different pathways to stillbirth for specific ethnicities. There was also an interaction found between obesity and ethnicity in the UK, with obesity presenting a particularly strong risk factor for stillbirth in South Asian women (aOR 4.64, 95% CI 1.84-11.70) (Penn et al., 2014). Although some targeted interventions for black and minority ethnic (BAME) women have been helpful, they are not nationally available to the vast majority of BAME women (Garcia et al., 2015).

A multivariate analysis in England identified ethnicity (African, African-Caribbean, Indian, and Pakistani), parity (first-time birth and third or later birth), smoking, maternal obesity (BMI $\geqslant 30$), pre-existing diabetes, history of mental health problems, antepartum haemorrhage, and fetal growth restriction as risk factors for stillbirth (Gardosi et al., 2013b). The potentially modifiable risk factors – maternal obesity, smoking during pregnancy and fetal growth restriction – in combination accounted for more than half of the stillbirths. Fetal growth restriction presented the highest risk, occurring in pregnancies regardless of smoking behaviour. If unrecognised, this risk of stillbirth was five times that of births for which growth restriction was diagnosed at the antenatal stage.

The Lancet series' systematic review of high-income countries found the highest ranking modifiable risk factors to be advanced maternal age, obesity and smoking (Flenady et al., 2011a). Vais and Kean (2015) called for effective interventions regarding weight management, smoking cessation and timing the optimal age for childbearing in the UK. The UK also has one of the highest teenage pregnancy rates among these high-income countries, which too presents an increased risk of stillbirth.

There has been significant progress regarding smoking following the July 2007 national comprehensive smoke-free legislation in the UK, when smoking was prohibited in enclosed public spaces and workspaces. A time series analysis found an immediate 7.8% reduction in stillbirth associated with this change (95%CI 3.5–11.8; $p < 0.001$) (Been et al., 2015). The authors estimated that in the first four years following the legislation, 991 stillbirths were prevented.

There have also been numerous studies in the UK exploring the relationship between previous birth outcomes, for example, previous stillbirth or caesarean delivery, and risk of stillbirth in subsequent pregnancies (Smith and Pell, 2001; Bhattacharya et al., 2010; Moraitis et al., 2015). These studies have been made possible through Scotland's comprehensive linked maternity data which allows for birth events to be investigated in the context of the mother's entire reproductive history.

2.3.3 Summary

Earlier in the chapter, we defined stillbirth and placed it in a global context, as well as in the context of Brazil and the UK. We also discussed the latent concept of socio-economic position (SEP) and how to measure it.

This review aimed to clarify the role of socio-economic risk factors in the likelihood of stillbirth, and how are they mediated through more immediate birth-related variables. Evidence demonstrates that there is no single pathway to explain stillbirth. Most research has identified multiple risk factors with adjusted odds of high magnitude, suggesting that there is no single cause of stillbirth; instead there exists an intricate web of additive or interactive effects between these risk factors resulting in stillbirth. We created a conceptual model for stillbirth in an effort to disentangle some of these complex pathways. At the top of the chain, demographic and socio-economic factors may be distant but nevertheless vital for effectively reducing stillbirth. Even in high-income countries, disparities among factors such as ethnicity account for a substantial burden on public health; the convoluted relationships between factors hinder the construction of effective interventions to narrow the gap in stillbirth rates (Spong et al., 2011).

This complex system of mechanisms might be simplified by considering stillbirth at different stages, following evidence of different etiological factors affecting early versus late stillbirth (Sharma et al., 2007). Separate conceptual frameworks for antepartum and intrapartum stillbirth might be helpful, but that is not within the scope of this thesis.

We acknowledge that the majority of studies reviewed in this chapter are observational and retrospective – commonly cross-sectional or population-based cohort studies – and thus cannot confirm a causal association in the way that a randomised control trial could. However, the outcomes of interest (namely stillbirth) are relatively rare, making it very difficult and expensive to conduct longitudinal or randomised control trials large enough to collect sufficient numbers of cases to analyse. Nevertheless, while the observational studies in our review cannot properly confirm causal inference, we have been careful to note when studies have attempted to investigate causal associations through mediation or other forms of path analysis.

Secondly, the review aimed to determine which factors pose a particular risk of stillbirth in Brazil and the UK. Brazil is a large and diverse country, with notable social, economic, and regional inequalities. A frequent determinant of stillbirth, the country faces a problem of ensuring that sufficient prenatal care is accessible to every expectant mother, including in the more rural North and North East regions. The UK, like many high-income countries, faces advanced maternal age, obesity and smoking as major preventable risk factors.

With a new understanding of the causes of stillbirth and the role of SEP as the “causes of the causes”, the next chapter explores how Brazil and the UK have tackled the reduction of stillbirth in recent years.

Chapter 3

Policy Review: Practices in Reducing Stillbirth in Brazil and the UK

This chapter addresses the first research question: *In relation to health and social policy what are the current practices in monitoring stillbirth rates in Brazil and the UK, and how do these compare with past government initiatives? In particular, how has Brazil's commitment to the UN's Millennium Development Goals resulted in policy change that could affect stillbirth rates?*

This chapter will explore government legislation for both countries and, where possible, determine its impact on stillbirth rates and the wider world of maternal health. Additionally, it will compare Brazil's evolving healthcare with that of the UK, a comparatively "developed" country. Ultimately, this review gives our research a broader context and highlights the need to place further attention on reducing stillbirth in both Brazil and the UK.

3.1 Global Efforts

3.1.1 The Millennium Development Goals

The Millennium Development Goals (MDGs) were signed into effect in September 2000 by the 191 United Nations (UN) states, committing world leaders to combat global issues through 8 specific goals including the reduction of child mortality (MDG 4) and improving maternal health (MDG 5) (United Nations, 2001). Quantifiable targets were set for each goal to measure progress, each taking baseline figures from 1990 and setting a deadline for 2015. For MDGs 4 and 5, the targets were:

Target 4.A. Reduce the under-five mortality rate by 2/3 between 1990 and 2015

Target 5.A. Reduce the maternal mortality ratio by 3/4 between 1990 and 2015

Target 5.B. Achieve universal access to reproductive health by 2015

Stillbirths, although not included in MDG tracking, are related to measures in MDG 4 and 5 concerning child and maternal mortality, and with the care received during pregnancy and delivery. In the case of Brazil, where stillbirth is often not explicitly mentioned in policy, initiatives related to these MDG targets and similar outcomes (e.g. infant and neonatal mortality) can be used to observe how policy may affect the stillbirth rate.

Assessing the MDG 2015 Targets

According to the UN's MDG 2015 report, the global under-five mortality rate more than halved from 90 to 43 deaths per 1,000 live births between 1990 and 2015. Although this did not quite meet the target 2/3 reduction (Target 4.A), it is still noteworthy progress. Globally, the rate of reduction in under-five mortality has more than tripled since the early 1990s; continuing at this momentum, it is expected to reach this 2/3 reduction target in the next few years.

Improvements in maternal health have been less successful. The UN summary reports a reduction of 45% in the maternal mortality ratio between 1990 and 2015, considerably below the target of 75% (Target 5.A). This average even masks an increase in some countries (The Lancet Editorial, 2014). Regarding access to reproductive health (Target 5.B), the global percentage of births that were assisted by skilled health professionals increased from 59% in 1990 to 71% in 2015, and the prevalsence of contraception use among women aged 15-59, married or in a union, increased from 55% to 64%. However, only half of pregnant women are estimated to receive the recommended amount of antenatal care (United Nations, 2015).

Still, all progress is encouraging. The Lancet Editorial (2014) praised the coming together of advocates of newborn, child and maternal health to combine their focus with global programmes such as the *Every Newborn Action Plan*, the *Every Woman, Every Child Initiative*, and the *Partnership for Maternal, Newborn, and Child Health*, and their commitment to women and children remaining at the forefront of global health.

Worldwide, the estimated stillbirth rate reduced by 25.5% (24.7 to 18.4 per 1,000 births) between 2000 and 2015. However there is considerable uncertainty around this estimate (range 6·6 - 41·5%), due to the lack of registration for stillbirths in many low- and middle-income countries, where an estimated 98% of stillbirths occur (Blencowe et al., 2016; Morisaki et al., 2017).

3.1.2 The Post-2015 Agenda

The Sustainable Development Goals (SDGs)

With the end of the MDGs, the UN has continued to commit to jointly addressing world issues with the new Sustainable Development Goals (SDGs) (United Nations, 2015). Sadly, while child and maternal mortality continue to be monitored (with the addition of neonatal mortality), stillbirth remains absent from the new goals. This absence has caused some contention from health professionals who had urged the inclusion of stillbirth in the global targets (Lawn, 2014; The Lancet Editorial, 2014). (Qureshi et al., 2015) argue that stillbirth should have equal footing on the global health agenda with neonatal mortality; as demonstrated by the MDGs, governments are more likely to invest in policies and monitoring of outcomes for which they are publicly accountable. Routinely reporting data and setting explicit national and international targets would help to engage global leaders and encourage government action to reduce national stillbirth rates.

Every Newborn Action Plan

Launched in 2014 and led by WHO and UNICEF, the Every Newborn Action Plan focused on newborn survival and the prevention of stillbirths. It prioritises the intrapartum/neonatal period, where the most lives can be saved; globally, 44% (1.2 million) of stillbirths occur during labour (WHO, 2014).

Targets specific to stillbirth in the action plan are;

Intermediate Target: By 2030, all countries will reach the target of 12 or fewer stillbirths per 1,000 total births.

Final Target: By 2035, all countries will reach the target of 10 or fewer stillbirths per 1,000 total births and continue to close the equity gap.

Reaching this target would achieve an average global stillbirth rate of 8 per 1,000 births and would require an average annual rate of reduction of 3.5%.

The plan outlines five Strategic Objectives to achieve its goals. The objectives relating to stillbirth are to strengthen investment in care during labour, birth and the first week of life, and to count every newborn through measurement, programme-tracking and accountability.

The plan was developed from the findings of the Millennium Development Goals, in which stillbirths were not included and consequently received less attention and investment, resulting in slower progress. Given that a large proportion of under-5 deaths occur in the neonatal period, the commitment to reduce child mortality would not be fulfilled without specific attention to stillbirth and neonatal mortality.

Unfortunately, while a target for reducing neonatal mortality is included in the Sustainable Development Goals, stillbirth is not explicitly mentioned (United Nations, 2015).

Since 2014, many countries have responded to the Every Newborn Action Plan and have begun to implement targets, programmes and interventions. However in most countries, implementation is low, and funding allocations for such development are scarce or non-existent (Frøen et al., 2016). As one of the top 20 countries for the number of neonatal deaths, Brazil was one of 33 countries targeted for the Action Plan's "Tracking Tool" which monitors the national targets being set. However, it is one of few countries not to complete the Tool (WHO, c).

3.1.3 Other Key Global Players

The International Stillbirth Alliance The International Stillbirth Alliance (ISA) is a worldwide coalition of parents, researchers and healthcare professionals who are dedicated to raising awareness of stillbirth and promoting global collaboration in stillbirth prevention and provision of appropriate care for bereaved parents (ISA, 2015). Many projects have collaborated with the UK stillbirth charity Sands (Section 3.3.1), and members of ISA were the lead authors on the highly influential Lancet's Stillbirth Series (Frøen et al., 2011).

The Lancet Stillbirth Series The international medical journal *The Lancet* devoted a series of six papers to uncovering the worldwide issue of stillbirth. Published in April 2011, the series consolidated research about the estimated global burden of 3 million annual stillbirths and provided evidence for cost-effective interventions that could save more than a million babies annually (Frøen et al., 2016). The series recommended priority areas for going forward around the topics of leadership, elevating women's voices, investment in and implementation of interventions; standardised indicators to measure the effect of interventions, and research into current knowledge gaps (Bernis et al., 2016). It included recommendations for change in high-, middle- and low-income countries, and highlighted in detail the impact of stillbirth on parents (Sands, 2012a).

The series was very widely received, placing stillbirth in the global spotlight; an editorial in the Lancet commented: "these papers, like no other Lancet Series before, have triggered a remarkable response not just from academia and organisations, but also from the public" (The Lancet Editorial, 2011). Stillbirth consequently appeared in discussions for the post-2015 agenda (Frøen et al., 2016).

A second Lancet series, "Ending Preventable Stillbirths", was published in 2016. It followed up from the 2011 articles with updated stillbirth estimates, a review on the extent to which their recommendations had been implemented, and a renewed call to action for the post-2015 era (Bernis et al., 2016). It reported that despite the improved global visibility of stillbirth, many recommended interventions were not yet standard and progress was slow (Frøen et al., 2016). Encouragingly, though, the monitoring of stillbirths through national civil registration and health management information systems increased dramatically, and in 2015 WHO named stillbirth rate as one of its 100 Core Health Indicators (WHO, a).

3.2 Social and Health Policy in Brazil

Stillbirths have been included in the national registry since 1973 (BRASIL. Ministério da Justiça, 1973), although a decade passed before the social acknowledgement of stillbirth caught up. In some areas of Brazil in the 1980's, stillborn babies were routinely placed in the "next available" coffin to be buried with an adult; this led to severe under-reporting (Kelley and Rubens, 2010). As of 2000, it has been made compulsory for doctors to submit death certificates for fetal deaths with gestations of 20 weeks or more (CFM, 2000).

After the fall of its military dictatorship in 1985, the newly democratised Brazilian government drew up the Federal Constitution of 1988 which, among many aims of social development, outlined equal access to healthcare as "a right of all and an obligation of the State" (BRASIL. National Constituent Assembly, 1988).

With this goal, Brazil's national health service (Sistema Único de Saúde - SUS), was established in 1990, which granted universal health coverage, free at the point of access (BRASIL. Congresso Nacional, 1990). Before this, only those who contributed to social security were eligible to receive healthcare, and half of the population had no health coverage at all. By 2010, 75% of the population depended entirely on the SUS for healthcare, while the rest chose to pay for private insurance within Brazil's two-tier health system (WHO, b).

As part of the reforms, Brazil implemented various programmes and policies aimed at maternal and child healthcare. We discuss such programmes below and observe the changes in the stillbirth rates across the country following their implementation. There is little direct mention of stillbirth in Brazil's health policies. However, as mentioned previously, initiatives aimed at reducing infant and maternal mortality by targeting antenatal and delivery care can be assumed to contribute to Brazil's stillbirth rates (and other birth outcomes) (Barros et al., 2010).

3.2.1 1980-1999: The Arrival of the SUS

1983 Programa de Atenção Integral à Saúde da Mulher (PAISM)

Comprehensive Programme of Action for Women's Health

This unprecedented public policy was put forward by the Ministry of Health as part of its restructuring of the whole national health system. PAISM aimed to reduce morbidity and mortality rates among mothers and infants as well as to transform women's reproductive rights with full and equal access to family planning and contraception (BRASIL. Ministério da Saúde, 1985). On top of maternal health, PAISM tackled women's health as a whole, including contraception, teen care, menopause, and the prevention of sexually transmitted infections (Almeida, 2005).

In the years that followed, it was observed that the policy, although revolutionary in content, was not effectively installed throughout the country. Funding logistics limited actions in many areas and issues remained (Neto et al., 2008): access in some regions; the quality of care; the quality and humanisation of care; and the unacceptable maternal and perinatal mortality rates (Serruya et al., 2004).

1991 Programa de Agentes Comunitários de Saúde (PACS)

Programme of Community Health Agents

The PACS aimed to link communities with primary health services, via the employment of an Agente Comunitário de Saúde (ACS), or Community Health Agent, chosen within each community. After a successful trial implementation in the North-eastern state of Ceara in 1991, the programme was nationally launched and regulated in 1997 by the SUS (Neto et al., 2008). The ACS conducted monthly home visits with each family in their community to monitor health, provide education on basic nutrition, and safety and promote healthy activities. Children and pregnant women received special attention and more frequent visits. Responsibilities of the ACS included identifying pregnant women and referring them to prenatal care, monitoring the vaccination period during pregnancy, providing education on family planning, and even promoting meetings between pregnant women in the community.

The programme was an important strategy in improving the scope of SUS care; Brazil's Ministry of Health acknowledged the "tireless work" of Community Health Agents as instrumental to the progress made in the health of millions of women and children (BRASIL. Ministério da Saúde, 2001a). Between 1994 and 2000, the number of Community Health Agents increased from 29,098 to 118,980, which paralleled a colossal increase in service coverage from 16.7 million to 68.4 million residents (BRASIL. Ministério da Saúde, 2001b). In particular, by 2000, over 20.2 million residents were part of a specific stratum, the Programme to Reduce Infant Mortality, which was introduced in 1995 and focussed mainly on North-eastern municipalities with basic actions – for example, sanitation, nutritional education, and immunisation – in order to reduce infant mortality rates in the country's most deprived areas (Victora, 2001). The programme was additionally praised for its assistance in providing more coverage and higher quality of information on births and deaths (including stillbirths) in regions with high rates of under-reporting (BRASIL. Ministério da Saúde, 2009).

1994 Programa de Saúde da Família/ Estratégia de Saúde da Família (PSF/ESF)

Family Health Programme

Soon after the launch of the PACS, The Family Health Programme (PSF) was implemented in 1994 (renamed the Family Health Strategy in 2003). As health facilities were concentrated in urban and wealthy areas, the PSF, similarly to the PACS, aimed to reorganise primary health care by deploying teams of doctors, nurses, and community health workers in the country's poorest areas to deliver a range of primary care services, including women's and child health. Considerable salary incentives attracted professionals to the programme (Victora et al., 2011a). The programme expanded rapidly, reaching 50.7% of the population by 2010 (Barros et al., 2010). In just November of 2009, the PSF logged 664,612 prenatal care appointments throughout Brazil, and almost half of those took place in the north-east region, where such care had been severely lacking before the 1990's (Campanha Saúde para as Crianças Primiero, 2011).

Measuring the impact of the PSF on infant mortality in Brazil, a longitudinal ecological analysis conducted from 1990-2002 saw the overall infant mortality rate fall from 49.7 to 28.9 per 1,000 live births (Macinko et al., 2006). A 10% increase in PSF coverage was associated with a 4.5% reduction in infant mortality, controlling for all other health determinants. Furthermore, the PSF had a greater impact in municipalities with lower human development and a higher infant mortality rate at the beginning of the study period, suggesting that the PSF had contributed towards reducing health inequalities (Aquino et al., 2009).

1997 Universal civil birth registration is free of charge: Decreto n^o 9534

This law amends Law No. 6,015 (1973) on birth registration, now making it universally free to register births. Prior to this, registering a birth and obtaining a birth certificate cost a fee, and although it was free for very low-income families, the bureaucracy and perceived humiliation of claiming poverty dissuaded people from registering (da Silva Santos, 2012). Removing this financial and social barrier could potentially result in more registrations of births and stillbirths alike, and therefore more reliable statistics for the Ministry of Health to use when creating health policy.

3.2.2 2000-2016: Working Towards the Millennium Development Goals

After the release of the Millennium Development Goals, more public policies emerged in Brazil regarding prenatal care and mortality rates. While some may not have been introduced as a direct response to the MDGs, their principal aims incorporated those same goals of reducing infant and maternal mortality.

2000 Regulations for provision of death certificate: Decreto n^o 1601

This law officially sets forth that doctors must submit death certificates for fetal deaths with gestations of 20 weeks or more, birthweight of 500g or more, or length 25cm or more (CFM, 2000).

This amended previous legislature regarding death certificates (CFM, 1989) which did not mention fetal deaths.

The death certificates contained information to be used as vital statistics for monitoring socio-economic disparities as well as the cause of stillbirth. However, even after registration was made mandatory, the content of these stillbirth registrations were lacking. During 2001-2003, the most frequently registered variables were sex (98%), place of residence (83%) and parity (70%), while other important variables were not recorded, such as mother's age (20%) and schooling (17%) (Beringhs et al., 2008).

2000 Programa de Humanização do Pré-natal e Nascimento: Decreto n^o 569

National Programme for Humanization of Prenatal and Birth: Decree n^o 569

This national programme was created by the Ministry of Health and included the goal of reducing Brazil's high rates of maternal, perinatal, and neonatal mortality. The policy echoed the message of the PAISM, proclaiming that access to pre-natal, delivery, and post-natal care through adequate health services is an irrefutable right for all pregnant women and their new-borns (Almeida and Tanaka, 2009).

The main universal actions included receiving a minimum of 6 prenatal consultations throughout the pregnancy, various laboratory tests at the first consultation and again at 30 weeks of pregnancy, HIV testing and a tetanus vaccine, classification of gestational risk, and specific care for high-risk pregnancies. Additionally, the PHPN set out to standardise the quality of healthcare facilities and equipment so that even the smallest and most rural facilities adhered to a set of standard requirements. Requirements for each health unit included:

- Sufficient and appropriate materials and equipment, including a gynaecological table, clinical stethoscopes, blood pressure measuring device, and a set inventory of "essential medicines"
- Patient privacy during the consultation
- A professional team to attend each birth
- Specific record keeping for monitoring and systematically assessing care with health indicators provided by the Ministry of Health

(BRASIL. Ministério da Saúde, 2000)

Some success was observed; the percentage of pregnant women who could attend seven or more prenatal consultations increased from 30% in 1996 to almost 50% in 2005. However, the proportion of pregnant women unable to access any prenatal care remained stable during that time (Neto et al., 2008). Despite an increase in the quantity of prenatal appointments, no significant improvement in the quality of care was observed (Cassiano et al., 2014). Disparities in quality still persisted after the programme's implementation, with a lack of basic services for lower income families even in the country's most developed regions.

2004 Pacto Nacional pela Redução da Mortalidade Maternal e Neonatal

National Pact to Reduce Maternal and Neonatal Mortality

The National Pact to Reduce Maternal and Neonatal Mortality set out to reduce maternal and neonatal mortality rates by 5% annually to meet the targets for the Millennium Development Goals (BRASIL. Ministério da Saúde, 2007). Published by the Ministry of Health, the pact acknowledged that many existing national and state programmes had failed to sufficiently improve obstetric and neonatal care services, and that maternal mortality rates remained particularly high compared to other countries. It implored that cooperation between relevant institutions and social sectors was essential to fully implement changes. Actions included redirecting resources to projects such as the Community Health Agents Programme, expanding the Family Health Strategy, increasing the number of intensive care unit beds and monitoring ethnic and social inequalities (BRASIL. Ministério da Saúde, 2004). Of particular concern was Brazil's high rate of caesarean sections which, when performed unnecessarily, could cause infection, bleeding, or anaesthetic complications in labour, increasing the risk of mortality for the mother, and baby during and after delivery (Cassiano et al., 2014). The pact attempted to combat this by encouraging natural childbirth.

2010 Vigilância do Óbito Infantil e Fetal: Portaria n^o 72

Surveillance of Infant and Fetal Death: Law n^o 72

Despite registration for stillbirths being official since 1973, persistent under-reporting of fetal and infant deaths prevented health professionals from implementing effective interventions. Law 72 made the surveillance of infant and fetal death mandatory in both public and private health services within the Unified Health System (SUS). It declared that death certificates must be properly completed in all fields and submitted a maximum of thirty days from the date of occurrence (BRASIL. Ministério da Saúde, 2010). In this document, fetal death was defined as a fetus born dead weighing at least 500g or after 22 weeks gestation.

2011 Rede Cegonha: Portaria n^o 1459

The Stork Network: Law n^o 1459

The Stork Network tried to implement a new, more comprehensive, model of maternal and child health, focusing on the pre-natal period, delivery, child growth and development. It aimed to restructure the existing network to ensure universal access and reduce maternal and neonatal mortality rates. Actions were to be executed gradually throughout the country according to epidemiological criteria such as infant and maternal mortality rates and population density. These actions were categorised into four structural components: prenatal care; labour and birth; post-labour recovery and child health; and logistics, transport and health regulation (BRASIL. Ministério da Saúde, 2011).

Many actions echoed those from previous policies, for example, rapid pregnancy tests along with clinical and lab testing for infections such as HIV and syphilis, providing a minimum of six prenatal consultations, and prompt access for high-risk pregnancies to pre-natal care (Cassiano et al., 2014). The policy also included new or expanded actions. Several tests were added to the previous list of prenatal lab tests. New initiatives included setting up sufficient obstetric and neonatal beds in Intensive Care Units and standardising delivery practices based on scientific evidence, in accordance with WHO regulations. The policy promoted an overhaul in logistics to facilitate, in emergency situations, safe transport for pregnant or post-partum women and infants at high risk via the Mobile Emergency Care System - SAMU Stork - in advanced support ambulances equipped with incubators and neonatal fans (BRASIL. Ministério da Saúde, 2011).

Legislation for the Stork Network was considered to be the most comprehensive Maternal and Child Health programme to be drawn up by the Federal Government (Cassiano et al., 2014). Compared with previous legislation on maternal and child healthcare, the Stork Network included specific strategies to achieve goals that were only proposals in other programmes, and its plans regarding funding were praised for being comprehensive, realistic, and achievable (da Silva et al., 2011). However, the policy was criticised for sometimes reiterating predecessors such as PAISM and PHPN; Silva et al. suggested that instead of creating a new law with the same promises, policy makers need to assess what was effective in previous programmes and work to improve it.

As a consequence of the Stork Network, improved access to prenatal care has allowed early identification of teenage pregnancies, thus minimising the risk of preventable complications (de Barros et al., 2017). However, recent evaluations of the programme have classified the general *quality* of prenatal care as unsatisfactory for all indicators (Maia et al., 2017). This shortfall in quality was especially true for women of lower income, those reliant on Community Health Agents (through PACS), and residents of rural areas (Martinelli et al., 2014).

2015 Projeto Parto Adequado

Adequate Childbirth Project

Rates of births delivered through caesarean section are unusually high in Brazil, and increased from 37.9% to 53.9% between 2000 and 2011, with the most affluent municipalities having the highest rates - some up to 96%. Caesareans were more frequent among women with higher education, white skin colour, older age, and in first-time mothers (Barros et al., 2015). These effects were weakened when accounting for whether public or private healthcare was used, with higher caesarean rates among those using private healthcare (Hopkins et al., 2014). While caesarean deliveries can be life-saving when dealing with pregnancy complications (as noted in the literature review in Section 2.3), undergoing such a major abdominal surgery unnecessarily can have long-term risks for the mother in subsequent pregnancies (Keag et al., 2018). Numerous programmes have tried to counteract this trend, including the National Pact to Reduce Maternal and Neonatal Mortality and the Stork Network, but virtually no impact has been made.

The Adequate Childbirth project, developed by the National Agency for Supplementary Health (ANS) and with support from the Ministry of Health, aimed to promote innovative and feasible obstetric care via vaginal delivery and reduce the percentage of caesarean sections. The initiative additionally aimed to offer women appropriate personalised care, considering evidence-based medicine and the sociocultural circumstances of the woman and her family.

An 18-month pilot project (Phase 1) worked with 35 hospitals, achieving transformational results; vaginal deliveries increased from 20% to 37.5%, avoiding 10,000 unnecessary caesarean sections (ANS, 2016). Nearly 90% of individual hospitals were able to increase the percentage of vaginal deliveries, and more than half of them exceeded the target of 40%.

The Adequate Childbirth project is now in Phase 2 (until 2019), expanding its coverage to nearly 150 voluntarily participating hospitals and operators from all over the country (Leal, 2018).

2016 Restriction on Caesarian Sections: Resolução n^{o} 2144

Under resolution 2144, each woman still has the right to opt for a caesarean section, provided that she has received all of the information – clarifying the benefits and risks of both vaginal and caesarean delivery – and can make an informed choice. However, to guarantee the safety of the foetus, the caesarean section can only be performed from the 39th week of gestation (CFM, 2016). Births at 37 and 38 weeks gestation are thought to be at increased risk of adverse outcomes (Leal et al., 2017).

3.2.3 A Holistic Approach: Social and Environmental Policy

Social and environmental policies also play a role in improving maternal health and therefore reducing stillbirth rates and other adverse pregnancy outcomes. The 1988 Federal Constitution lists the "protection of motherhood and childhood" as a critical civil right. It reprises regulations set out in the Consolidation of Labour Laws (1943) stating that pregnant women in the workplace are entitled to:

- Employment stability - from the confirmation of pregnancy up to five months after delivery, she cannot be fired without cause
- Exemption from working hours if necessary to attend pre-natal appointments
- Maternity leave of 120 days (from the 8th month of pregnancy), without loss of job or salary

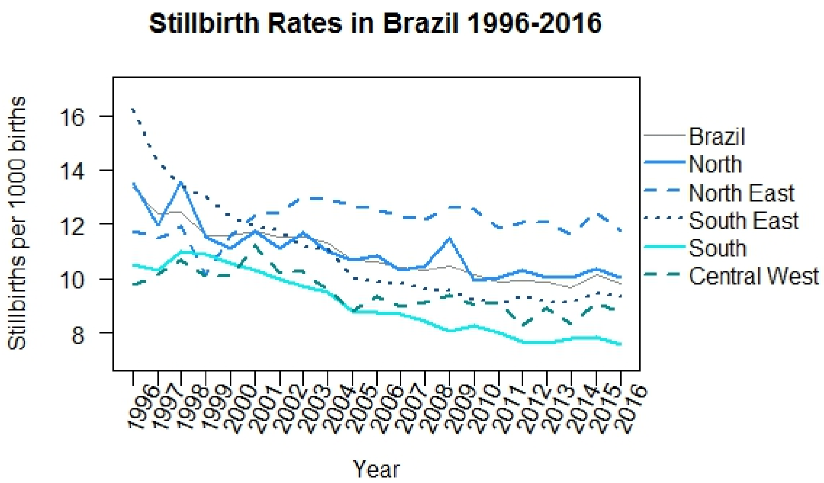
(BRASIL. National Constituent Assembly, 1988)

These policies, while not directly responsible for better pregnancy outcomes, provide income stability for pregnant women and enable the aforementioned health policies to work more effectively.

As noted in the literature review, environmental factors are also associated with maternal and fetal health. In 2007, the government introduced a "Basic Sanitation" Law 11445, with a guiding principle of granting universal access to a clean water supply and sewage/waste management, taking public health and environmental protection into consideration. It promoted collaboration with policies for urban and regional development to combat poverty and improve health, for which basic sanitation is a determining factor. Special objectives were made to prioritise areas of low-income populations and to provide for indigenous populations via projects compatible with their socio-cultural structure (BRASIL, 2007). Returning briefly to the Millennium Development Goals, Brazil met its MDG 7 targets; the population percentage without sustainable access to safe drinking water and basic sanitation has been halved (IPEA, 2014).

3.2.4 Summary of Changes in Stillbirth Rates in Brazil

We return to Figure 2.1 from the previous chapter to assist us in observing the changes in stillbirth rates over the last two decades in the context of the policies presented.



The graph shows that although rates have declined slightly, progress appears glacially slow and some regional rates have remained stable or even increased - the North and North-east regions rates are consistently higher in comparison to the southern regions. It is difficult to discern whether there has been a concrete increase in stillbirths in this time, however, as increased reporting could contribute to this upwards spike in the graph at the turn of the millennium, especially in the northern regions.

Reporting and Registration Under-reporting of deaths in Brazil was a major issue, especially in the North and North-east, with the under-reporting of stillbirths often proportionally larger than for neonatal and infant deaths (RIPSA, 1998). Since 2000, Brazil's death registry - the Mortality Information System

(Sistema de Informações sobre Mortalidade - SIM) - has been steadily increasing in coverage and quality of birth and stillbirth information in these regions (BRASIL. Ministério da Saúde, 2009). This coincided with the national roll-out of outreach initiatives such as the Family Health Strategy and Community Health Agents, and could explain the increase in the stillbirth rate for northern regions in the early twenty-first century.

In the North-eastern state of Maranhão in 2008, a study comparing data from the SIM with the Hospital Inform System (SIH) discovered that 165 stillbirths, 9.7%, were unaccounted for in the official SIM. With these additional cases, the stillbirth rate was corrected from 12 to 13.3 (Rafael et al., 2011). Nevertheless, this is a monumental improvement; the estimated stillbirth rate from SIH data for Maranhão in 1995 was six times larger than found in the SIM.

A recent systematic review found that the quantity and quality of data registrations are still lacking. Despite the 2010 legislation making completion of all fields in the death certificate compulsory, the level of completeness of fetal death certificates was deficient, both in the completion of variables, particularly socio-demographic variables, and in defining the underlying causes of death (Barbeiro et al., 2015). Rafael et al. (2011) suggested that health professionals were more likely to neglect registering a stillbirth due to an instilled indifference towards and assumed inevitability of fetal death. The omission of stillbirth registrations – whether due to difficulties of access, training of health professionals, or cultural attitudes – compromises the analysis of birth data and holds up progress in implementing actions to reduce mortality rates (BRASIL. Ministério da Saúde, 2009).

Antepartum vs Intrapartum Stillbirth Both antepartum (before labour) and intrapartum (during labour) stillbirth rates have improved. One study based in the southern city of Pelotas showed that intrapartum rates decreased by 72% to 0.7 per 1,000 births between 1982 and 2004 while antepartum rates fell by 36% to 8.4 per 1,000 births (Matijasevich et al., 2008). In a municipality-level study across all of São Paulo, the percentage of intrapartum stillbirths ranged between 0-4% of stillbirths (Andrews et al., 2017). As seen in the literature review in Chapter 2, antepartum rates are strongly associated with certain social factors (deprivation and ethnicity), maternal health factors (diabetes and hypertension), birth history (previous caesareans and low birth weight births), and a lack of prenatal care, while intrapartum stillbirths are generally linked to the quality of delivery care. Of note, 98% of births occur in hospital in Brazil (Vieira et al., 2016). Given that 90% of pregnant women attend at least the minimum recommended amount of prenatal visits (França et al., 2016), there is an opportunity for facility-based interventions to reduce antepartum stillbirth risk.

How have Policies Helped? With the overlapping of implementation of initiatives throughout the last two decades, it would be almost impossible to attribute observed outcomes to a specific policy. Changes that could affect stillbirth are mostly measured in the coverage of prenatal care. Matijasevich et al. (2012)

compared socio-economic inequalities in pregnancy-related health outcomes between birth cohorts in the south-eastern city of Pelotas from 1982 to 2004. The long time scale allowed the study to showcase the great reduction in income-inequalities since the introduction of the national health service (SUS); before this, most services were inaccessible or unaffordable for women from low-income backgrounds. More recently, França et al. (2016) evaluated the coverage and equity of selected reproductive and maternal interventions in Brazil between 1986 and 2013. Interventions included the frequency and timing of prenatal care visits, institutional delivery, and caesarean sections. Coverage of all indicators displayed a steady increase over time, with coverage of institutional delivery and the attendance of at least four prenatal visits exceeding 90% in 2013. With the exception of caesarean sections, there were significant reductions in income inequalities for all measures, with near universal coverage by 2013 for even the poorest 20% of women and those living in rural or remote areas. The authors praised the Family Health Programme and the introduction of Community Health Agents as large contributors to this success.

The epidemic of unnecessary caesarean sections are a present concern, but initial results from the Adequate Childbirth Project are very promising, with selected hospitals almost doubling the proportion of vaginal births in just 18 months (ANS, 2016). It is too early to determine the success of the project's recent expansion, or how this might affect the risk of stillbirth; caesarean deliveries tend to affect stillbirth risk in subsequent pregnancies, so there may be a few years before the effects of this policy, if any, become apparent.

Reaching the Millennium Development Goals The MDG targets specific to reducing child mortality (MDG 4) and improving maternal health (MDG 5) were:

Target 4.A. Reduce the under-five mortality rate by 2/3 between 1990 and 2015

Target 5.A. Reduce the maternal mortality ratio by 3/4 between 1990 and 2015

Target 5.B. Achieve universal access to reproductive health by 2015

Brazil's child mortality rate fell from 59 to 19 between 1990 and 2010, surpassing the target of 20 (UNICEF and Ministério da Saúde, 2011). Within this, its infant and neonatal mortality rates fell by 66% and 57%, respectively, placing Brazil in the top five fastest progressing countries in neonatal mortality rates since the 1990 MDG baseline (Lawn et al., 2014). Regional-level disparities in infant mortality are still concerning, ranging from 10 per 1,000 births in the South region to 15.5 per 1,000 births in the North in 2016, but this is an improvement on the range two decades prior (19.2 to 29.9 for the same regions in 1996) (DATASUS, 2018).

MDG Target 5.A was not quite reached in Brazil; the maternal mortality ratio fell from 141 to 68 deaths per 100,000 live births between 1990 and 2010, only a 50% decrease (Souza et al., 2013). The government tackled this by implementing the Stork Network in 2011 to increase access and quality of prenatal care and the investigation of maternal deaths. The official 2015 measure for this target for Brazil has not yet been published. Progress for Target 5.B - universal access to reproductive health - has been much more successful, with 99% of births taking place in hospitals and 90% of pregnant women attending at least four prenatal visits in 2011 (IPEA, 2014).

Over this period, Brazil's stillbirth rate declined from 13.36 per 1,000 births in 1996 (using the earliest available counts from DATASUS) to 10.16 per 1,000 births in 2015, a 24% reduction. In some populations, the neonatal death rate is decreasing so rapidly that it has fallen under the stillbirth rate. Between 2010-2014 in the state of São Paulo, 42% of its 645 municipalities had a higher stillbirth rate than neonatal mortality rate and, following patterns, this figure could reach 60% in the next 20 years (Andrews et al., 2017). This trend highlights an issue of visibility for stillbirths and the need for a shift in policy.

3.2.5 Conclusion (Brazil)

Stillbirth rates in Brazil appear to have decreased while reporting has increased, although coverage is not yet universal and the quality of the data recorded is still lacking (Barbeiro et al., 2015). While counting stillbirths is a necessary first step, collecting socio-economic and health information is crucial for identifying gaps in care and levels of inequality across areas.

The decreasing rate over the last 25 years coincides with the implementation of aforementioned health programs and social policies. Despite some shortcomings, coverage of essential resources have increased, and equity has improved considerably, although further assessment of care quality is needed (França et al., 2016). The role of the Family Health Programme and Community Health Agents have been fundamental to the early identification and monitoring of pregnant women, as well as the carrying out of consultations, examinations, and health interventions (Campanha Saúde para as Crianças Primiero, 2011).

Thanks to improved coverage in delivery interventions, Brazil's small proportion of intrapartum stillbirths reflects that of other developed countries, where an estimated 10% of stillbirths are intrapartum (Blencowe et al., 2016). Changes in antepartum stillbirth rates may take longer to emerge, as interventions must tackle more ingrained social, behavioural and health risk factors that led to antepartum stillbirth.

Despite being considered largely preventable, stillbirths have been neglected by health services and policy (BRASIL. Ministério da Saúde, 2009), instead being overshadowed by the efforts to meet the Millennium Development Goals. Although the Ministry of Health has collected information on fetal deaths for more than 25 years, it has not been regularly evaluated (Lima et al., 2006). Weighed against infant and neonatal mortality, there have been very few studies concerning stillbirth in the Brazilian literature and official statistics. While a number of studies relating to stillbirth have been published since 2000, many consider it only as part of a broader outcome such as perinatal mortality (the combination of stillbirths and neonatal deaths); most are district-level cohort studies based in the South-east region with only a handful exploring the more vulnerable northern regions (Barbeiro et al., 2015). The overwhelming conclusion to be made is that stillbirths in Brazil need to be focussed on as a public health issue and explicitly acknowledged in policy in order for it to accomplish the same progress as other birth outcomes.

3.3 Social and Health Policy in the UK

The registration of stillbirths has been a legal requirement in England and Wales since 1927 and in Scotland since 1939. In Northern Ireland, registering a stillbirth is optional to parents (NIDirect and Department of Finance and Personnel (Northern Ireland), 2014). The 1953 Births and Deaths Registration Act defined a stillbirth as "a child which has issued forth from its mother after the twenty-eighth week of pregnancy and which did not at any time after being completely expelled from its mother breathe or show any other signs of life".

The UK's National Health Service has been providing universal healthcare for all UK residents, free at the point of service, since 1948. One of its core principles is that good healthcare should be available to all, regardless of wealth Its comprehensive reference website, NHS Choices, provides information and resources regarding stillbirths including support for families and advice on monitoring pregnancies and reducing risk (NHS England, 2013).

While Brazil's initiatives are mostly carried out by the government through their ministry of health or the SUS, the UK has many organisations and charities, governmental and non-governmental, dedicated to reducing adverse pregnancy outcomes. Before discussing the important policies and initiatives in the UK that aim to reduce stillbirth rates, we shall introduce the main parties involved.

3.3.1 Key Players for Change: Organisations and Charities

Royal College of Obstetricians and Gynaecologists (RCOG)

The Royal College of Obstetricians and Gynaecologists, founded in September 1929, is a registered charity that works to improve women's healthcare across the world. They work in every aspect of women's health; developing the education, training and exams for prospective O&G specialists, collaborating internationally to improve maternal morbidity and mortality rates worldwide, and publishing clinical guidelines for high quality healthcare and patient information leaflets explaining medical conditions in lay terms, among many other actions.

Sands – Stillbirth and Neonatal Death Charity

Sands is a registered charity, founded in 1978, whose main goal is to provide support for families affected by stillbirth or neonatal death, and to work with health professionals to establish protocols to ensure that bereaved parents receive compassionate care. They also fund research into preventing fetal and neonatal mortality. Sands has made some impressive strides in recent years, lobbying the UK governments to acknowledge stillbirth as a national tragedy and to implement preventative initiatives (Sands, 2015b).

Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE-UK)

The MBRRACE-UK programme was commissioned in 2012 on behalf of NHS England, NHS Wales, the Scottish Government Health and Social Care Directorate and the Northern Ireland Department of Health. The programme monitors all perinatal deaths in the UK, aiming to support the NHS in improving quality of services to pregnant women and their children (MBRRACE-UK Collaboration, 2015).

Similar programmes have existed in the UK since the 1990s. The Confidential Enquiry into Stillbirth and Deaths in Infancy (CESDI) was established in 1993 following the legal change in the definition of stillbirth (The Stillbirth Definition Act 1992; see below). Due to funding restructuring, the programme was closed and replaced twice, first as the Confidential Enquiries into Maternal and Child Health (CEMACH) in 2003, then as an independent charity in 2009, the Centre for Maternal and Child Enquiries (CMACE), commissioned by the National Patient Safety Agency. From 2010 there was a halt in data collection while the various national health departments within the UK reviewed the need for such surveillance (Kurinczuk et al., 2014). MBRRACE-UK was eventually launched in 2012.

MBRRACE-UK collect information on pre-natal care, delivery, the post-mortem examination, and the cause of death for each stillbirth and neonatal death, along with information on the mother's health, lifestyle, and pregnancy history. Findings from analysis of this data are compiled into an annual report that has "the potential to substantially improve our understanding of the rates and variations in perinatal mortality rates across the UK and thus the identification of preventive measures" (MBRRACE-UK Collaboration, 2015, pg. ii).

Perinatal Institute for Maternal and Child Health

Beginning as the West Midlands Perinatal Institute in 2000, this national not-for-profit organisation was set up with the primary focus of understanding the causes of adverse perinatal outcomes and developing prevention strategies. They acknowledge that addressing social inequalities would reduce a significant proportion of avoidable perinatal mortality (Perinatal Institute for Maternal and Child Health, 2011). Best known for putting together the highly successful Growth Assessment Protocol (GAP) programme in 2013, the institute also creates custom growth charts and resources for pregnant mothers to monitor their pregnancy. With the GAP programme's success, the group expanded its initiatives to a national scale, becoming the Perinatal Institute in 2013 and winning multiple awards for patient care (Perinatal Institute for Maternal and Child Health, 2013, 2014, 2015). Now self-funded through education and training workshops, the team provides support services to maternity care professionals with training in standardised maternity records, fetal growth assessment and perinatal audits.

3.3.2 1992-2016: Key Initiatives

Since the 1953 Registration Act, there was no significant legislation or actions from the government concerning stillbirth until the 1990s.

1992 The Stillbirth (Definition) Act

The Definition Act amended the previous 1953 law regarding the definition of stillbirth, changing the "twenty-eighth week" gestational cut-off point to the "twenty-fourth week". This change was based on a unanimous agreement of medical professionals after improvements in neonatal care had brought about increased survival rates of babies born at 24-27 weeks gestation (Sands, 2015a).

Increased survival of these very preterm births in a 1993 birth cohort justified the change and highlighted the necessity of including these births in perinatal mortality rates (Cartlidge and Stewart, 1995). However, it was noted that a better measure would be also to discount infants weighing below 500g, a group for which the survival rate is so low that the deaths are seen as inevitable. Including them would reduce the specificity of the perinatal mortality rate as a measure of effectiveness for prenatal care.

1999 Towards Safer Childbirth Report

This report from the Royal College of Obstetrics and Gynaecology (RCOG) resulted from growing concerns about the quality of care that women and babies received during labour and birth. Evidence that some consultant obstetricians did not see labour as part of their regular duties suggested that potentially high-risk women fell under the radar in terms of quality of care.

The report outlined recommendations including the explicit redefinition of consultants' responsibilities, the creation of the Labour Ward Forum with patient representatives, and staff training on the subject. Of the units involved, many had achieved most of the target actions in the report, although staffing levels remained an issue (RCOG and RCM, 2007).

2008 Why17? Campaign

The charity Sands launched this national public awareness campaign based on the unchanging statistic that 17 babies died each day as a result of stillbirth and neonatal death (Sands, 2009). The campaign aimed to instigate public debate and place the issue on political agendas, to raise funds for research and to work with key parties, researchers and policymakers to develop a national strategy to reduce stillbirth and neonatal death rates (Sands, 2015d).

The campaign ran until 2014 when it was announced that the number of babies dying in the UK each day had fallen to 16 in 2013 (MBRRACE-UK Collaboration, 2015).

2009 *Saving Babies Lives* Report

Published by Sands alongside the "Why17?" campaign, the report cited suboptimal pre-natal care and under-resourced maternity services as factors contributing to stillbirth and stated that a lack of funding for scientific research was hindering progress in reducing the numbers of deaths. Sands wanted perinatal deaths to receive at least the same attention as the hugely successful campaign to reduce cot death had received decades earlier (Sands, 2009).

The report was introduced to each of the four UK governments consolidating the essential issues surrounding stillbirth and neonatal mortality and lobbying each government to act on reducing perinatal mortality rates (Sands, 2010). Recommended actions included: acknowledgement of stillbirth as a health issue at a national level; research funding to match the £3 million Sands intended to invest over five years; actions to increase knowledge and evidence needed to provide effective antenatal detection of higher-risk babies; standardised data collection on all pregnancies to include information about the mother, baby, antenatal, and delivery care; a comprehensive review of every stillbirth which features the parental view of care given; and public health information on stillbirth risks so that prospective parents can make informed choices (Sands, 2009).

The impact of the report and Sands' subsequent lobbying was impressive. Within the next four years, each of the four UK governments set up groups specifically to address the issues of stillbirth and neonatal mortality: the Scottish Stillbirth Group in 2010; the Welsh Initiative for Stillbirth Reduction in 2012; the Department of Health Stillbirth "Task and Finish" groups for England in 2013; and the Northern Ireland Maternal and Infant Loss steering group in 2013 (Sands, 2015c). The manifestos of many of these groups contain recommendations from the *Saving Babies Lives* report.

2011 Lancet Stillbirth Series

The hugely influential series of articles made a worldwide impact and brought global attention to stillbirth. Although the series praised the UK's perinatal auditing with CMACE, one article revealed that the UK had the highest stillbirth rate of 12 peer high-income countries (Flenady et al., 2011b). Such public exposure may have influenced the UK in the rapid turnover of policies and actions in the following years.

2011 The Stillbirth Clinical Studies Group and the first Stillbirth Seminar

Sands and the Royal College of Obstetrics and Gynaecology combined their resources to collaborate on various projects:

The Clinical Studies Group (CSG) brought together research specialists from different fields, including public health, biostatistics and molecular biology, to develop new research and review potential stillbirth-related projects (Sands, 2012a). The CSG meets biannually to identify priorities for stillbirth research, propose and design studies as well as considering studies, and to offer advice to investigators (RCOG, 2015).

The Stillbirth Seminar, on the other hand, aimed to educate medical staff involved in maternity care through discussing clinical issues surrounding stillbirth and sensitive management after death (Sands, 2012b).

2012 *Preventing Babies' Deaths: what needs to be done?* Report

Sands published another report, observing that although infant mortality rates had fallen dramatically in the previous decade, to the lowest ever levels in the UK, stillbirth rates had not significantly changed since the late 1990s (Sands, 2012a). Despite evidence that research and audits have improved stillbirth rates in other countries (Flenady et al., 2011b), funding for CMACE to collect perinatal mortality data in regions of the UK had been suspended since April 2011, pending review for the continuation of the programme. Sands argued that without information on where and why the deaths occur, the potential to address the problem disappears.

The *Preventing Babies' Deaths* report urged the UK governments to re-implement a properly funded standardised programme of national confidential enquiries into perinatal deaths. The auditing of hospital-level mortality to review quality and effectiveness was also vital.

In the document Sands additionally advocated for: new research to understand social inequalities in perinatal death; funding for the research development of reliable diagnostic tests for use during routine antenatal care to detect risks; urgent action to address the minimum staffing requirements that weren't being met; and medical training of doctors and midwives to include a module on perinatal death in order to improve awareness and understanding of its risks and impact.

The contract for perinatal auditing was taken up by MBRRACE-UK in May 2012, a year after the suspension of CMACE. MBRRACE-UK began a thorough data collection and review of perinatal deaths in 2013, along with a review of the mortality rates across NHS units to assess performance (MBRRACE-UK Collaboration, 2015).

2013 Growth Assessment Protocol (GAP)

The West Midlands Perinatal Institute, observing that the primary contributor to avoidable stillbirth in the UK was a lack of antenatal recognition of fetal growth problems, launched a programme of training and implementation of protocols in fetal growth assessment (Clifford et al., 2013). Their research began in three selected NHS regions throughout 2008-2011, resulting in reductions of stillbirths to their lowest levels in each region since the 1992 definition change. Despite the three regions covering less than a quarter of all maternities in England, and that the stillbirth rate in the rest of England and Wales saw no significant change, the study resulted in an overall drop in stillbirth rates in England and Wales to 4.81/1,000 births, the lowest rate in 20 years (Gardosi et al., 2013a, 2014). Evidence suggested a causal relationship between the intervention and the reduction in stillbirth rates (Gardosi et al., 2013a).

The project was expanded and made accessible to all UK maternity units in 2013 as the 'Growth Assessment Protocol' (GAP). The GAP aimed to address fetal growth problems through comprehensive staff training, regular monitoring for intrauterine growth restriction, audits of missed cases to identify training needs and surveillance system failures, and evidence-based protocols to standardise practice (Clifford et al., 2013).

Gardosi et al. (2013a). estimated that if the GAP programme could replicate the success of the West Midlands study – a 22% reduction in the stillbirth rate – then extrapolated to the rest of the UK, the programme could potentially save 1,000 babies a year. Since implementation, the downward trend in stillbirth rates has been mirrored in the regions with high uptake of the GAP and a causal protective effect of the intervention on stillbirth rates has been confirmed (Gardosi et al., 2014). As of May 2018, 78% of trusts and health boards in the UK had implemented the GAP.

2014/2015 NHS England makes reducing stillbirth rates a priority

In 2013, for the first time, reducing stillbirth and neonatal death rates became a mandated objective from the government to NHS England (Department of Health, 2013), and consequently, that aim was included in the NHS England Business plan 2014-2015. Similarly, it appeared as a key indicator in the NHS Outcomes Framework for 2015/2016 (NHS England, 2016). The goal of reducing perinatal mortality had been present in previous versions of the Outcomes Framework since 2011 (Sands, 2012a), but with a much smaller focus; in this updated edition, it was a headlining item.

2015 Each Baby Counts

The primary goal of this initiative, headed by the Royal College of Obstetricians and Gynaecologists (RCOG), was to reduce the number of stillbirths, neonatal deaths and brain injuries as result of incidents during labour by 50% by 2020. According to Sands' *Saving Babies Lives* report (2009), the risk of intrapartum-related deaths – all for labours which had begun with a live and seemingly healthy baby – had essentially plateaued since 2000. RCOG argued that stillbirths could follow the UK's dramatic reduction in maternal mortality partly thanks to lessons learned from reviewing and auditing cases (RCOG, 2014).

The project focussed on intrapartum events; reasoning that an estimated 500 babies die or are left severely disabled every year in the UK, not due to being born too small, too soon, or having a congenital abnormality, but because something goes wrong during labour (RCOG, 2015).

The plan to pool together results from local inquiries of intrapartum events had never been done before. Data for 2015 – the baseline year – was collected by MBRRACE-UK and reviewed by RCOG. After conducting more than 2,500 evaluations of local reports, RCOG have observed a significant variation between the qualities of perinatal death reviews between different NHS institutions. One quarter were found to provide insufficient information to determine the actions and quality of care provided (RCOG, 2017a). Recommended actions are being implemented to improve the quality of reviews and antenatal/neonatal monitoring (RCOG, 2017b).

2015 Department of Health announces ambition to halve the rate of stillbirths, neonatal, and maternal deaths in England

In November 2015, the health secretary committed to reducing the rate of stillbirths, neonatal and maternal deaths in England by 50% by 2030, with a part-way target reduction of 20% by 2020. The department promised to invest £4 million into NHS trusts to provide training and buy high-tech digital equipment, and a further £500,000 into developing a new system for reviewing stillbirth and neonatal cases (DHSC, 2015).

The UK is currently on track to meet the part-way target reduction of 20% by 2020. In 2017, with further funding and support promised, the government brought forward the final target deadline to 2025, which – according to the Royal College of Midwives – could potentially save a further 4000 lives (DHSC, 2017; Ewers, 2017).

2016 *Saving Babies Lives* Care Bundle to Reduce Stillbirth

Following the 2015 commitment, NHS England published the "Care Bundle" - new guidelines for maternity units in reducing stillbirth. Launched in March 2016, the four key initiatives in the Bundle are:

1. Reducing smoking in pregnancy
2. Risk assessment and surveillance for fetal growth restriction
3. Raising awareness of reduced fetal movements
4. Effective fetal monitoring during labour

These issues had been selected as having the greatest potential to impact stillbirth rates (NHS England, 2016).

Based on recent evaluations of early adopters in the phases March-June 2016 and July-Sept 2016, the majority of service providers have begun to implement all four elements of the Bundle. For each of the four elements respectively, 48%, 18%, 41% and 51% of providers have fully implemented the element (Widdows et al., 2018).

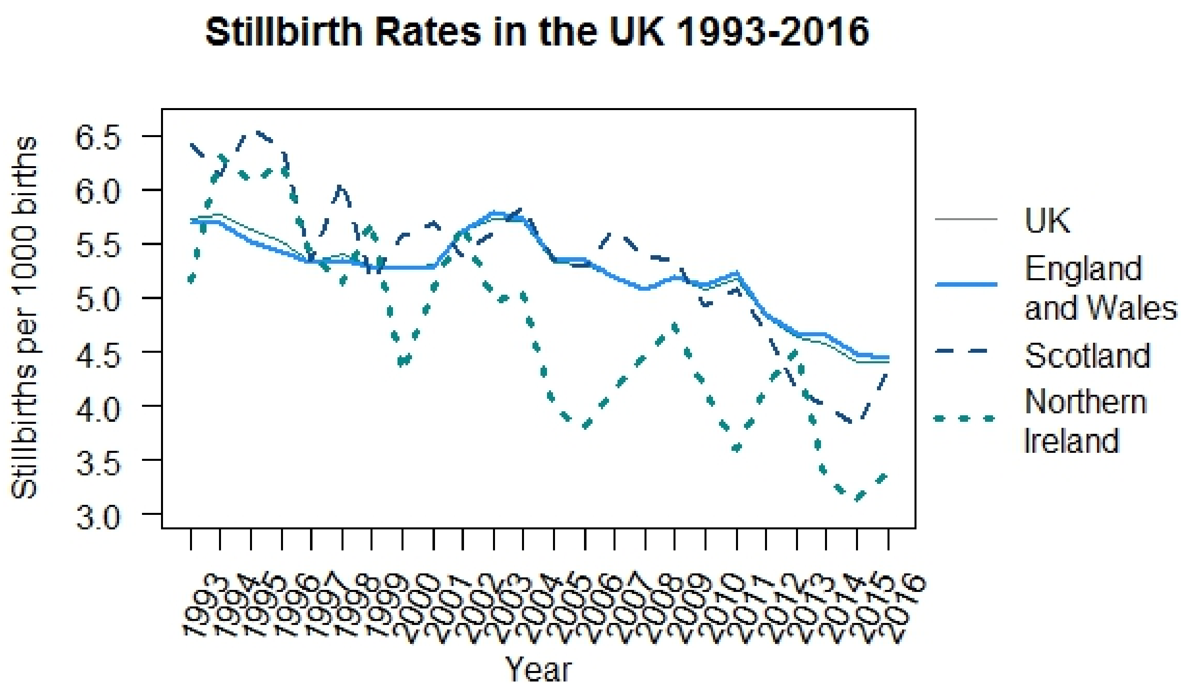
3.3.3 The UK's Role in the Millennium Development Goals

The UK signed the Millennium Declaration in 2000, along with 189 countries. As a comparatively developed "donor" country, the UK's responsibility mainly focussed on Goal 8, global partnership, by facilitating developing regions to achieve the goals for themselves. The UK pledged to meet the MDGs by assisting developing countries both in terms of aid (it was the largest single donor in Africa) and as an influence on international policy and action (Crisp, 2007). From the beginning, the UK laid out a set of specific actions to reduce child poverty (MDG1) (Short and Brown, 2001) and in 2004, the Chancellor of the Exchequer committed to UK government increasing expenditure on aid to reach 0.7% of gross national income by 2013 at the latest (Haines and Cassels, 2004). Health goals were tackled via partnerships with countries in Sub-Saharan Africa, where the under-five mortality rate in 2005 was 179 per 1,000, compared to 6 per 1,000 in the UK (Crisp, 2007).

Following the G8 summit in 2010, in which the progress of the MDGs was discussed, the UK committed to addressing the most off-track Millennium Development Goal: to improve maternal health (MDG 5). There were still persistently high numbers of maternal deaths during pregnancy or childbirth in developing countries, which subsequently increased the risk of mortality for the foetus. Proposals for UK action included expanding access to family planning, addressing unsafe abortion and lack of skilled care at delivery (DID, 2010).

3.3.4 Summary of Changes in Stillbirth Rates in the UK

We return to Figure 2.2 from the previous chapter to assist us in observing the changes in stillbirth rates over the last two decades in the context of the policies presented. Since the definition change, there



Stillbirth Rates in the UK 1993-2016
Data Source:Office for National Statistics (ONS), National Records Scotland (NRS), Northern Ireland Statistics and Research Agency (NISRA)

was a slow and steady decline in the stillbirth rate, followed by a plateau in the late nineties at around

5.4 stillbirths per 1,000 births. Then in 2002, an increase was observed in England and Wales, with an escalation of 6% compared to 2001 (rate ratio 1.06; 95% CI 1.02–1.12) (CEMACH, 2005).

ONS investigated this increase though trends in the stillbirth rate by known risk factors between 1993 and 2002. No strong evidence was found to suggest that any particular subgroup of sex, birth weight, gestation, maternal age, region of maternal residence, or mother's country of birth might account for the observed increase; all subgroups had increased stillbirth rates in 2002, and many also showed small increases prior to this. Cause of death was also considered, but similarly, no particular cause of stillbirth seemed to be responsible for the increased rate.

Marital status, however, did have an association; a significant 24% increase in the stillbirth rate was observed for births outside marriage. The rise in stillbirth rates among singleton births was also higher than among multiple births. However, without further evidence this could not be explained, and ONS refrained from making any conclusions without more data (ONS, 2015). The stillbirth rate for England and Wales rose again in 2003 to 5.8 per 1,000 births, the highest since the definition changed, and high rates throughout the UK continued to be observed until 2004.

From there, the overall stillbirth rate returned to its pre-2002 rate and has since steadily decreased. The number of stillbirths fell from 4,116 in 2004 to 3,430 in 2016 despite the number of total births growing by 8% in the same period. The rate did briefly rise again in 2009 and 2011, but not so dramatically or significantly as in 2002.

Regarding the devolved nations, rates are based on lower birth counts and are therefore generally more changeable. However, for both Scotland and Northern Ireland, the stillbirth rate has been consistently lower than England and Wales since 2010.

Surveillance and Auditing The greatest reduction in stillbirth rate occurred between 2011 (5.2 per 1,000 births) and 2013 (4.6 per 1,000 births). It was during this period that surveillance of perinatal deaths by CMACE was suspended, and so details about the cause of this reduction are lacking. Much of the reduction has been attributed to the implementation of Growth Assessment Protocol (GAP) by the West Midlands Perinatal Institute in their pilot study of three NHS regions. However, during this time, projects instigated by Sands and RCOG were also taking shape, and therefore more surveillance data might have been useful to explain the impact of the different programmes on the observed downward trend. MBRRACE-UK has since taken on the mantle of CMACE to collect, analyse and report national surveillance data on maternal and perinatal outcomes. The RCOG initiative, Each Baby Counts, further assesses individual post-mortem reviews and is in the process of developing both recommendations to improve the quality of audits and interventions to reduce adverse perinatal outcomes.

Antepartum vs Intrapartum Stillbirth Of the four target actions outlined in the Department of Health's "Care Bundle", three appear to prioritise reducing risks for antepartum stillbirth, with interventions for antenatal care and lifestyle changes for the mother. The other focuses on care during delivery. This balance appropriately reflects the statistic that 86% of stillbirths in the UK occur in the antepartum period, while 10% are intrapartum and 4% have unknown timing (MBRRACE-UK Collaboration, 2017). Meanwhile, RCOG's Each Baby Counts concentrates exclusively on intrapartum stillbirths along with neonatal deaths. The two types of stillbirth have been suggested to have different aetiologies and risk factors (see Section 2.3) and so treating them somewhat separately in two initiatives has some logic to it.

How have Policies Helped? In recent years, the improvement of maternity services in the UK has been in the spotlight with the publication of various national recommendations and initiatives, notably the GAP, Each Baby Counts and the *Saving Babies Lives* Care Bundle. After years of stagnation (and increases) in the stillbirth rate, the post-2011 drop correlates with the increased attention to stillbirth in UK policy, which in turn correlates with the publication of the Lancet Stillbirth Series (2011) which publicised the UK's relatively high stillbirth rates.

As mentioned in Section 3.1.2 regarding the Sustainable Development Goals, governments are more likely to invest in policies and monitoring of outcomes for which they are publicly accountable (Qureshi et al., 2015). Therefore the setting of a deadline to reduce stillbirth, neonatal and maternal death rates in England by the Department of Health will likely make a tremendous difference.

Section 2.3.2 cites intermediate risk factors such as the extremes of maternal age, smoking, and obesity as particularly relevant in the UK. While the primary focus is on more immediate risk factors such as fetal growth restriction, the Care Bundle acknowledges the pathways from these demographic and behavioural factors in its protocols. Element 1 targets maternal smoking explicitly, while the action plan for Element 2 includes an "algorithm and risk assessment tool" which outlines the protocol for monitoring women with increased risk of fetal growth restriction. The list of characteristics for at-risk women includes advanced maternal age, smoking, drug misuse, previous adverse birth outcomes, diabetes, hypertension, and obesity.

Comparison with High-income Countries Despite falling to its lowest rates since the definition changed, the UK's stillbirth rate is double that of the best performing nation – Iceland's 1.3 per 1,000 births compared to the UK's 2.9 in 2015 using the international definition ($\geq$ 28 weeks) – and its annual rate of reduction since 2000 is mediocre compared to other high-income countries such as Norway, Denmark, Finland, Germany and the Netherlands (Flenady et al., 2016). One suggested justification for this higher rate is the UK's particularly high rate of teenage pregnancy; women who are generally more at risk of stillbirth due to their age, lower BMI, and social deprivation. An effective national programme to combat this has yet to be found (Vais and Kean, 2015).

The fact that other high-income countries have achieved significant reductions demonstrates that more can be done. If, for example, the UK could meet the mortality rates of Norway and Sweden, 1,000 babies could be saved each year (MBRRACE-UK Collaboration, 2015).

3.3.5 Conclusion (UK)

Stillbirth rates have generally been improving since 2004, with a recent accelerated reduction coinciding with the influx of government policies and actions introduced over the last five years. Measurable targets and specific interventions that will make the biggest impact have been rolled out with the *Saving Babies Lives* Care Bundle, and its coverage across NHS trusts throughout the country is increasing. It is safe to say that this attention to stillbirths, brought on partly by the Lancet Stillbirth Series and dedicated lobbying from Sands, has had a positive impact.

In section 3.2.5, we stated that the first step to reducing stillbirth was reporting and registration. The second, it seems, is rigorous auditing and reviewing of these reports. The UK has been commended for its perinatal auditing system (Flenady et al., 2016), and after an unfortunate hiatus between 2010 and 2012, the UK's commitment to learning from every perinatal death has been solidified in the efforts of MBRRACE-UK, RCOG and the Each Baby Counts programme.

However, issues remain. None of the recent policies have explicitly addressed socio-economic disparities in stillbirth rates. While such differences are acknowledged and adjusted for in annual surveillance reports by MBRRACE-UK, no actions have been taken to decrease the gap. Social, racial and geographical inequalities in perinatal outcomes endure. There is still a 25% difference in stillbirth rates between regions (NHS England, 2016). The latest MBRRACE-UK report (2017) found that babies of Asian/Asian British and Black/Black British ethnicity had significantly higher risk of stillbirth compared to white babies in 2015 (Risk Ratio (RR) 1.66; 95% CI 1.49-1.84 and RR 2.30; 95% CI 2.03-2.61 respectively). The gap between black and white babies has even widened over the last three recorded years. Similarly, while a small but steady decline in stillbirth rates has been observed for all levels of deprivation, the gap between the most deprived and least deprived mothers remains unchanged in the three years since MBRRACE began collecting data. Those from the most deprived quintile are at a 68% increased risk of stillbirth compared to the most affluent quintile (95% CI 1.50-1.89) (MBRRACE-UK Collaboration, 2017). There is a possibility that these socio-economic differences will reduce as a by-product of changes to other factors - for example, via a reduction in maternal smoking which is more prominent among disadvantaged women. However, with no explicit plans to monitor socio-economic disparities, it will be difficult to determine the causes of such “side-effects”.

Nonetheless, the recent reduction in stillbirth rates is commendable and has been successful enough for the Department of Health to bring forward the current target deadline 2030 to 2025. With a rate reduction of 1/1,000 births representing 700 fewer deaths in England each year (Perinatal Institute for Maternal and Child Health, 2018), this means that thousands of lives will be saved.

3.4 Summary

The table below briefly summarises the observations made from this policy review, comparing Brazil and the UK side by side. Unless otherwise specified, statistics for Brazil are calculated via data obtained from DATASUS, and UK statistics are combined from ONS, NRS and NISRA.

	UK	**Brazil**
Stillbirth Definition	Baby born with no signs of life after 24 weeks gestation	Baby born with no signs of life after 22 weeks gestation or weighing at least 500g
Stillbirth Rates (National Definition)	4.4 per 1,000 births in 2016 5.2 per 1,000 births in 2000 (16% reduction). 86% antepartum, 10% intrapartum, 4% unknown timing - for 2015 (MBRRACE-UK, 2017).	9.8 per 1,000 births in 2016 11.6 per 1,000 births in 2000 (15% reduction). 91% antepartum, 4% intrapartum, 5% unknown timing – for 2016.
Stillbirth Rates (International Definition: >28 weeks)	England and Wales (ONS): 3.2 per 1,000 births in 2016 Scotland (NRS): 3.1 per 1,000 births in 2016 *(NI figures for >28 weeks unavailable)* **33rd in the world** - 2009 figures ranked lowest to highest (WHO, 2011).	8.8 per 1,000 births in 2016 **79th in the world** - 2009 figures ranked lowest to highest (WHO, 2011).
Stillbirth Registration	Collected by: Office for National Statistics (England and Wales), National Records of Scotland, and Northern Ireland Statistics and Research Agency. Universal coverage of live and stillbirth registration.	Collected by: Mortality Information System (Sistema de Informações sobre Mortalidade – SIM). Coverage has increased rapidly in recent years, but there exists some under-reporting of births and deaths - especially fetal and infant death – in remote rural areas.

Table 3.1 continued from previous page

	UK	Brazil
Monitoring and Audits	Reviewed by: MBRRACE-UK. Government-funded organisation continuously assesses stillbirth data and produces annual reports on rates, trends and risk factors. The key objective is determining which deaths were avoidable and recommend interventions for future avoidance. Intrapartum stillbirth cases are further reviewed by Each Baby Counts. Some issues remain with incomplete information on stillbirth reports.	No routine national review system exists. Data is collected via the SIM, but little is done with it at a national level. Issues remain with incomplete information on stillbirth certificates, particularly socio-economic information.
Social Inequalities and Risk Factors	Evidence for significant deprivation gap in antepartum stillbirth risk. The main modifiable lifestyle risk factors are the extremes of maternal age (<20 and >40 years), smoking and obesity.	Regional variation with increased stillbirth risk in the North and North East. The main risk factors are quality and quantity of prenatal care and level of education.
Policy Focus	Stillbirth has been a primary outcome measure of many policies and initiatives; Why17 (2008), GAP (2013), Each Baby Counts (2015) and Care Bundle (2016). Each Baby Counts, focusses solely on intrapartum events, while the Care Bundle initiatives mostly prioritise antepartum stillbirths. Government initiatives have mostly addressed biological risk factors (e.g. GAP (2013)), with little attention to social inequalities.	Very little government policy is specific to stillbirth. Current policies focus on achieving universal coverage of adequate prenatal care and equalising care given. Expanded rapidly in recent years – 90% coverage of prenatal care and 98% of labours take place in health facilities. Recent focus also on reducing caesarean rates.
International Rankings	"High Income" Country (World Bank, 2017) Human Development Index classification: "Very High" – 16th worldwide as of 2015 (UNDP, 2016)	"Upper-middle Income" Country (World Bank, 2017) Human Development Index classification: "High" – 79th worldwide as of 2015 (UNDP, 2016)

Using the definition for international comparison recommended by WHO, Brazil's stillbirth rates are more than double that of the UK. However, Brazil's low proportion of intrapartum stillbirths rivals that of "more developed" countries including the UK (Blencowe et al., 2016).

It is evident that the two countries are at different stages of their journey, from a public health perspective, to eradicating preventable stillbirths. Brazil is still working on achieving universal coverage of birth and stillbirth registration, whereas the UK has moved on to creating programmes to review this data and learn how to prevent future cases. Similarly, policies in Brazil are working towards providing universal prenatal and intrapartum care, and succeeding, while the UK is targeting stillbirth more specifically through fetal growth monitoring and interventions.

As noted in Section 2.3.2 of the literature review, significant social inequalities in stillbirth rates still exist in both countries – the UK seems not to be addressing this as much as it could be – and there is much to be done. However, since 2000, both countries are progressing in overall stillbirth rate reductions at a similar rate.

The next chapter will describe the datasets for Brazil and the UK that will be analysed in this thesis.

Chapter 4

Data Comparison

This chapter addresses the second research question; *What national, routinely collected datasets are available for the purpose of investigating the relationships between socio-economic factors and stillbirth in Brazil and the UK?* After introducing the three datasets used in this thesis, a brief overview of data sources concerning stillbirth and socio-economic position is presented. It explores the difficulties for researchers in accessing and analysing stillbirth data and highlights the need for comprehensive and accessible administrative data.

There are multiple additional advantages to analysing national routine data over other secondary sources for researchers and health policy makers. Routine datasets are likely to be more up-to-date than one-off secondary sources, which is valuable to policy makers needing to make timely yet informed decisions. The comprehensiveness of routine data not only facilitates the generalisability of the findings to reflect a real-world situation (Morrato et al., 2007), but such large samples are particularly beneficial for investigating rare events such as stillbirth. There is an opportunity for analysis of trends across years of collection, and comparisons with other datasets; a single national collection of a given measure ensures consistency, and different national routine datasets tend to contain similar standard measures which enable meaningful comparisons (Kane et al., 2000).

The first of the three datasets used in the thesis is aggregated information from the Office for National Statistics (ONS) birth registrations for England and Wales. The second dataset comes from Scotland's Maternity and Neonatal Linked Database (MNLD).The third is Brazil's National Household Sample Survey (PNAD – Pesquisa Nacional por Amostra de Domicílios). Variables used in each analysis are specified and issues with the data to be addressed in the methodology are outlined.

The chapter ends with a summary table of the three datasets, outlining the similarities and differences in the variables of interest and overall structure.

It should be noted that decisions regarding the choice and structure of variables are not made in isolation. With the intention to compare between Brazil and the UK, attempts were made to match similar variables between datasets and to categorise the data as closely as possible across datasets, particularly the two individual-level datasets for Scotland and Brazil.

4.1 England and Wales: Aggregated Birth and Stillbirth Counts from the Office for National Statistics (ONS)

4.1.1 Origin of the Data

The information within this dataset was requested and obtained from the Office for National Statistics (ONS) birth and stillbirth registration datasets. Details from all birth events in England and Wales are registered by the General Register Office (GRO) and passed onto the ONS who are responsible for the disclosure of the data. ONS birth registration data has been used for various research purposes including estimating populations and exploring historical trends in birth and health patterns.

4.1.2 The Aggregate Dataset

The dataset was provided in comma-separated values (CSV) format and contains information on live and stillbirth counts for all recorded births between 2006 and 2014. The outcomes of interest are the aggregated live and stillbirth counts for each of the 348 Local Authority (LA) districts in England and Wales, further stratified by six age groups; < 20, 20-24, 25-29, 30-34, 35-39, and 40+ years.

Suppressed data. Stillbirth counts below three within any age/LA stratum were considered disclosive, with some individuals being potentially identifiable. Therefore, 286 counts of zero, one or two (14% of the stillbirth counts) were suppressed. An initial challenge shall be to handle this suppression within the outcome variable in the analysis.

Exclusions from the sample. Of the 348 Local Authority (LA) districts in England and Wales, two were eliminated from the analysis due to insufficient information; the stillbirth counts in these areas were entirely suppressed. Through excluding the Isles of Scilly and the City of London, 183 and 581 live births were removed respectively ($<$0.0001% of live births).

4.1.3 Variables of Interest

After exclusion of the two districts with very small counts, the sample consisted of 6,360,631 recorded birth events, of which 6,329,402 (99.5%) were live born and 31,229 (0.05%) were stillborn, resulting in a crude stillbirth rate of 4.91 per 1,000 births. This does not account for suppressed data, and given that there remained 274 suppressed stillbirth counts, each representing 0-2 stillbirths, there could be up to 548 additional stillbirths that are suppressed in the dataset.

Outcome variables. The live birth and stillbirth counts are aggregated by the 346 LA districts and six age groups, with an average of 18,383 births per district. The LA districts can be in turn amalgamated into 112 counties or ten regions. These grouped live birth and stillbirth counts are the primary outcome variables in this study.

Table 4.1 shows the total counts of live and stillbirths in the sample by age group, along with the number of suppressed cell values. The majority of suppression occurs for the youngest and oldest age groups due to smaller birth counts (and consequently smaller stillbirth counts) in these demographics.

Table 4.1: Live and stillbirths in England and Wales (2006-2014) by age group

Age Group (years)	<20	20-24	25-29	30-34	35-39	40+
Number of live births	343,612	1,165,011	1,733,695	1,813,794	1,026,418	246,872
(%)	(5.43)	(18.41)	(27.39)	(28.66)	(16.22)	(3.9)
Number of stillbirths	1,899	6,008	8,031	8,192	5,413	1,686
(%)	(6.08)	(19.24)	(25.72)	(26.23)	(17.33)	(5.4)
Suppressed cells	106	15	7	5	14	127
(%)	(38.69)	(5.47)	(2.55)	(1.82)	(5.11)	(46.35)

The primary challenge in analysing this data will be handling the notable suppression of the stillbirth counts, particularly for the extreme age groups. Methods to address this, involving the creation of a specialised likelihood function with which to perform regression, are explained in Chapter 5.

Exploratory variables. The remaining five exploratory variables considered were the baby's ethnicity, mother's country of birth, mother's socio-economic status, mother's marital status and whether the pregnancy resulted in multiple births or a singleton. In the aggregate dataset, these are represented as the percentage of mothers in the age/LA stratum that correspond to that individual-level binary characteristic. Table 4.2 presents summaries of these covariates.

Ethnicity was grouped into the percentage of white and non-white babies in each age/LA stratum, while the mother's country of birth variable was divided into those born in the UK and those born outside of the UK.

Table 4.2: Risk factors for stillbirth from the ONS in England and Wales (2006-2014).
Percentage of mothers in the age/LA stratum with given characteristic

Exploratory Variables	**Range**	**Mean**	**Median**	**Number of Suppressed Values**
Ethnicity: Percentage non-white	0-82	14.7	7.9	0
Country of Birth: Percentage not UK-born	0-80	16.91	12	0
NS-SeC Status: Percentage Level 2/3	8.8-100	56.65	52	0
Marital Status: Percentage unmarried	13.3-99	52.98	42.4	1
Multiple Births: Percentage multiple birth cases	0.4-10.8	3.36	3.1	60

Socioeconomic status is measured with the National Statistic for Socio-economic Classification (NS-SeC). An individual's NS-SeC status is derived from their occupation and their level of responsibility within that role. The NS-SeC is a flexible measure that can be expanded or reduced to three, five or eight levels. This data uses the three-level system, with the levels defined as:

Level 1 Higher managerial, administrative and professional occupations

Level 2 Intermediate occupations

Level 3 Routine and manual occupations

In the aggregate data, however, groups two and three are combined to create a binary variable for Level 1 and Level 2/3. Note that the NS-SeC was collected for only 10% of birth records, but the aggregate variable – the percentage of women in Level 2/3 amongst those with known NS-SeC status – is still usable.

Marital status is grouped into the percentage of married and unmarried mothers in each age/LA aggregate stratum. The unmarried group combines all marital status categories of women that aren't married at the time of birth, whether they are divorced, separated, widowed or never married. Finally, the pregnancy events are grouped into multiple (twins, triplets or more) and singleton births.

Binary variables. It would be ideal to separate the exploratory variables (Table 4.2) further into multiple categories so as to explore the demographic diversity of the population in more detail. However, dividing the data further would result in more suppression of smaller counts and a further loss of information. For example, treating the three NS-SeC groups as three separate levels would lead to almost half of that information being suppressed. A balance had to be struck between more data categories and the statistical power of the analysis.

Suppression in exploratory variables. The marital status and multiple birth percentages are suppressed in one and 60 age/LA strata, respectively, for being potentially disclosive. Such confidentiality-related suppression would occur if these missing percentages were very small and the corresponding birth counts were also small. In all of these groups, the live birth count is less than 1,000, and the stillbirth count is less than 8 (or suppressed). All but two groups contain women from the youngest age bracket (< 20 years). Since the missingness within these covariates is practically negligible ($< 0.01\%$ and 3% for marital status and multiple birth respectively) the missing values were imputed with the covariate's minimum known percentage value for the relevant age group.

4.2 Scotland: Maternity and Neonatal Linked Database (MNLD)

4.2.1 Origin of the Data

Although suitable individual-level data is not available for the whole of the UK, Scotland has been making great strides in linking routine health and social data for academic and analytical purposes, boasting some of the most impressive linkages of national routine data in Europe (Delnord et al., 2016).

One such initiative is the Maternity and Neonatal Linked Database (MNLD), which contains obstetric histories for mothers giving birth in Scotland from 1981 onwards together with linked records relating to all of her offspring. It collects approximately 55,000 recorded births per year. The database can link the UK national birth records in Scotland with the more specific National Record of Scotland (NRS) and the episode-level Maternity Inpatient and Day Case Record (SMRO2) dataset, alongside other records and surveys. The NRS achieves complete coverage of births in Scotland, while the SMR02 achieves approximately 98%, with most of the missingness attributed to home births (for which providing SMR02 information is optional but not mandatory) (ISD Scotland, 2010). The exclusion of home births from data collection is unlikely to be a source of significant error (NMAHP Research Unit, 2013).

The MNLD, particularly the SMR02, has been used to investigate changing patterns of obstetric care, the contribution of smoking to perinatal death and various social inequalities in adverse birth outcomes in Scotland (Norman et al., 2009; Gray et al., 2009; Wood et al., 2012). A study researching risk factors for unexplained antepartum stillbirths in Scotland, 1994 to 2003 was conducted by Sutan et al. (2010) using variables from the MNLD. It compared unexplained antepartum stillbirth with other outcomes (live births, explained antepartum and intrapartum stillbirths). It included a socio-economic factor in the form of a deprivation score based on the mother's postcode. Our investigation uses more recent data and focuses more deeply on the associations between socio-economic position and stillbirth in Scotland with individual level social factors.

For this study, linked information from the NRS live and stillbirth records and the SMR02 for 2011-2013 was specially granted by the Farr Institute Scotland via the electronic Data Research and Innovation Service (eDRIS).

4.2.2 The Dataset

The original dataset was provided in CSV form via the Farr Institutes' Safehaven. It contains all linked information for hospital births to women aged 18-45 during the period 2011-2013 and contains records for 165,206 births from 151,832 mothers. The age restriction closely matches the age restrictions in the

England and Wales dataset studied in Section 4.1.3. The pregnancy-related, health-related, demographic and socio-economic exploratory variables under consideration are discussed in Section 4.2.3.

Exclusions from the sample Live births with gestations less than 24 weeks were excluded, to be more comparable with the stillbirths (which by UK definition must all have gestations of 24 weeks or more). Two live birth observations of unknown sex were excluded.

4750 observations (3% of the sample) were part of a multiple birth event (twins, triplets, etc.). Due to issues of correlation and small counts, it was decided to restrict the analysis to singleton births, and so all multiple birth cases were removed from the sample. It is worth noting, however, that the stillbirth percentage among births that were part of a multiple birth event was 0.8%, compared to 0.4% of total births in the data being stillborn; this warrants further analysis.

The finalised sample for analysis consists of 149,501 women with 160,120 recorded births.

Collapsed and derived variables In exploration, numerical predictors were checked for linearity with the outcome, and any predictors with a non-linear relationship were categorized. Some categorical levels were collapsed when the amount of detail was deemed superfluous or the stillbirth counts within each level were too small to analyse. Some variable transformations were made to match similar variables in the datasets for Brazil or England and Wales. These variables and others are described in more detail in the following section.

4.2.3 Variables of Interest

Primary Outcome Variable

The binary response measure was the outcome observed at each recorded birth: live birth or stillborn. The sample consists of 160,120 recorded births of which 159,485 (99.6%) were live and 675 (0.4%) were stillborn, resulting in crude stillbirth rate of 3.97 per 1,000 births.

Explanatory Variables

The linked datasets contain dozens of variables potentially associated with stillbirth. Based on our literature review, twenty-one predictors were selected which are displayed in Table 4.3, grouped into birth-related, demographic, socio-economic and health-related variables. Categorical variables are presented as counts and percentages while means and standard deviations are provided for the continuous variables.

Birth-related variables The mode of birth, originally a categorical variable with 14 levels detailing various medical methods of delivery, was collapsed to a more manageable yet still informative six levels. The birth weight was measured in grams. Extreme values (birth weights outside 0100-5500g range) were queried and values deemed impossible were deleted (ISD Scotland, 2018a). Gestational age at delivery (in weeks) was judged by the clinician (doctor or midwife), usually by an ultrasound measurement.

The total number of previous pregnancies (prior to the observed pregnancy) was categorised into 0, 1, 2, 3 and 4 or more. Subsequent variables relating to previous births counts (previous stillbirths, neonatal deaths and spontaneous abortions) were similarly dichotomised into a yes/no variable for previous history of stillbirth, neonatal death or spontaneous abortion (miscarriage).

Demographic variables The mother's age at delivery (in years) was categorised into six 5-year age groups; the percentage breakdown of births in each group closely matches that of the England and Wales data in Table 4.1. The variable for mother's ethnicity originally had 42 levels, partly due to labelling errors in the linkage process). These groups were collapsed into four levels. Despite the very small counts for non-white ethnic groups, it was decided to allocate separate categories to black and South Asian women, as the literature review suggested that black and South Asian mothers in the UK were at particular risk with differing risk factors. Information from the dataset on mother's country of birth was dichotomised into a binary (UK-born/ Not-UK-born) variable to match the corresponding information from the England/Wales dataset.

Marital status, referring to the legal marital or civil status of the mother, initially had seventeen categories due to labelling errors, similarly to the variable for ethnicity. These were collapsed into five groups. The "parents married" indicator differs slightly from legal marital status; this specifies not only whether the baby's parents are married, but for unmarried mothers, it states whether the birth is a single registration or a joint registration and if so, whether the parents live together.

The urban/rural code, developed by the Scottish Household Survey and derived from population (settlement size) and remoteness (measured by drive times), was collapsed from six categories into a binary urban/rural variable. The Local Authority district or council area is based on the 2011 definition.

Socio-economic variables An individual's socio-economic status is measured with the National Statistic for Socio-economic Classification (NS-SeC), derived from their occupation. A flexible measure that can be expanded or reduced to three, five or eight levels, this study uses the five-level system. Deprivation is measured with the Carstairs 2011 Scotland deprivation score, a postcode-level measure constructed from four elements found in the 2011 Census (household density, employment, social class and car ownership). The scores are grouped into quintiles.

Health-related variables The mother's body mass index was derived from her given height and weight at booking (approximately 12 weeks into pregnancy) using the standard transformation BMI = $\text{weight}_{kg}/\text{height}_{m}^{2}$. Some extreme values of height (outside the range 138-185cm) and weight (outside the range 32-127kg) in the dataset were queried as potential errors, and impossible values were deleted. The diabetes variable indicates if a woman has diabetes and whether its diagnosed was pre-pregnancy or gestational (diagnosed during pregnancy).

The dataset contained two variables related to smoking; one for smoking history (before the pregnancy) and another for smoking during pregnancy. These were combined to form one variable concerning smoking with the levels "never smoked", "former smoker" and "smoked during pregnancy". A woman is considered to have smoked during pregnancy even if she stopped once the pregnancy was confirmed but had been a smoker between her last menstrual period and the confirmation of pregnancy. Similarly, the drug misuse variable records whether the mother had misused drugs at any time during the observed pregnancy.

The number of alcoholic units consumed (in a typical week) was categorised into "none", "1-3 units" and "4 or more units". One unit was defined as half a pint of normal beer, one pub measure of spirits or one small glass of wine (ISD Scotland, 2018b). This question was asked of women at their midwife maternity booking (typically at 8-12 weeks of pregnancy) and referred to typical intake over the previous three months, therefore capturing both pre-pregnancy and during-pregnancy drinking habits.

Table 4.3: Risk factors for stillbirth in the MNLD for Scotland (2011-2013)

	Live births		Stillbirths	
Risk Factor	**Num.**	**%**	**Num.**	**%**
Total	159485		635	
Birth-related factors				
Mode of birth				
Normal	64231	40.3%	406	63.9%
Forceps	20264	12.7%	31	4.9%
Breech	314	0.2%	117	18.4%
Elective caesarian	19523	12.2%	16	2.5%
Emergency casesarian/Other	25153	15.7%	65	10.2%
Birth weight				
Normal (≥2500g)	150994	94.7%	240	37.8%
Low (1500-2499g)	6899	4.3%	151	23.8%
Very low (<1500g)	1133	0.7%	241	38.0%
NA: 117				
Gestational age (continuous)				
Weeks: mean (sd)	39.2 (1.8)		33.4 (5.5)	
Parity				

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Table 4.3 continued from previous page

Risk Factor	Live births Num.	%	Stillbirths Num.	%
0	52280	32.8%	245	38.6%
1	51121	32.1%	149	23.5%
2	27615	17.3%	113	17.8%
3	14099	8.8%	57	9.0%
4 or more	13471	8.4%	70	11.0%
NA: 900				
Previous stillbirth				
No	157476	98.7%	625	98.4%
Yes	1111	0.7%	9	1.4%
NA: 900				
Previous neonatal deaths				
No	157907	99.0%	630	99.2%
Yes	678	0.4%	5	0.6%
NA: 900				
Previous spontaneous abortion				
No	120038	75.3%	484	76.2%
Yes	38426	24.1%	149	23.5%
NA: 1023				
Sex of baby				
Male	82013	51.4%	312	49.1%
Female	77572	48.6%	323	50.9%
Socio-economic and demographic factors				
Socio-economic status				
Managerial and professional	48791	30.6%	175	27.6%
Intermediate	22595	14.2%	88	13.9%
Smaller employer and self-employed	8623	5.4%	23	3.6%
Supervisors/ craft related	10974	6.9%	41	6.5%
Routine occupations	44382	27.8%	181	28.5%
Long term unemployed	397	0.2%	8	1.3%
Students, not stated or not classifiable	23723	14.9%	119	18.7%
Deprivation quintile				
1 – least deprived (or not a resident)	38469	23.9%	175	27.2%
2	33594	21.1%	131	20.6%
3	32087	20.1%	115	18.1%
4	27623	17.3%	103	16.2%
5 – most deprived	27712	17.4%	111	17.5%
Urban/rural code				
Urban areas	117964	74.0%	482	75.9%
Small towns	18856	11.8%	63	9.9%
Rural areas	22128	13.9%	86	13.5%
NA: 541				
Ethnicity				
White	102760	64.4%	403	63.5%

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Table 4.3 continued from previous page

	Live births		Stillbirths	
Risk Factor	**Num.**	**%**	**Num.**	**%**
Black	2020	1.3%	17	2.7%
South Asian	3237	2.0%	20	3.1%
Other	2747	1.7%	10	1.6%
NA: 48906				
UK born				
Yes	134344	84.2%	530	83.5%
No	25126	15.8%	105	16.5%
NA: 15				
Parents marital status				
Married – to each other	78272	49.1%	277	43.6%
Joint registration – Same address	55023	34.5%	224	35.3%
Joint registration – Different address	18531	11.6%	95	15.0%
Sole registration	7659	4.8%	39	6.1%
Maternal age				
18-19 years	6368	4.0%	25	3.9%
20-24 years	29292	18.4%	199	31.3%
25-29 years	44554	27.9%	174	27.4%
30-34 years	47808	30.0%	177	27.9%
35-39 years	25465	16.0%	103	16.2%
40-45 years	5998	3.8%	37	5.8%
Health and behavioural factors				
Smoking Status				
Never	102255	64.1%	350	55.1%
Smoker during pregnancy	31475	19.7%	180	28.3%
Former smoker	18593	11.7%	69	10.9%
NA: 7198				
Drug Misuse During Pregnancy				
No	134812	84.5%	520	81.9%
Yes	2777	1.7%	17	2.7%
NA: 21994				
Alcohol Consumption				
None	132057	82.8%	527	83.0%
1 to 3 units per week	3504	2.2%	9	1.4%
4 or more units per week	2988	1.9%	9	1.4%
NA: 21026				
Body Mass Index (continuous)				
BMI: mean (sd)	26.1 (5.7)		27.3 (6.2)	
NA	17900	11.2%	155	24.4%
Diabetes				
No	151856	95.2%	557	87.7%
Yes – pre-existing	950	0.6%	13	2.0%
Yes – gestational (or unknown)	2826	1.8%	6	0.9%
NA: 3912				

Dealing with Missing Data

Although the non-response rate for the majority of individual variables in the linked data was very low, missing values were dispersed throughout the data haphazardly. The complete-case subset of the singleton births dataset contained 42,484 observations, 27% of the original 160,120 observations. A more sophisticated approach to handling missing data than list-wise deletion is required, and will be addressed in Section 6.1.1.

Due to either non-response or recording error, the percentage of missing data was largest for the measure for marital status with 49.7% missingness. It was decided to drop this variable from the analysis as it accounted for 35% of missing values overall and some of the methods used to tackle missing data become unstable with such elevated missingness (Wulff and Ejlskov, 2017). Instead, the variable for whether the newborn's parents were married is used. Although it is a slightly different measure, indicating parents' cohabiting status as well as their marital status, it is complete and provides more information about the mother's living situation.

After marital status, the measure for ethnicity had the largest percentage of missing data (31%). 13 other variables had missing values ranging from less than 0.01% to 14%, the breakdown of which can be seen in table 4.4. There was a slight pattern of correlated missingness in behaviour-related predictors (e.g. smoking, drugs, alcohol, BMI). This information was usually collected at the first antenatal visit (at approximately 12 week gestation), and so missingness within these variables are unlikely to be related to the outcome of stillbirth.

Table 4.4: Variables with missing data in the MNLD, Scotland

Variable	**Number of missing values**
Birth weight	117 (<1%)
Parity	900 (<1%)
Previous stillbirths	899 (<1%)
Previous neonatal deaths	900 (<1%)
Previous abortions	1,023 (<1%)
Ethnicity	48,906 (31%)
UK born	15 (<1%)
Urban/rural code	541 (<1%)
Smoking status	8,729 (5%)
Drug misuse	21,994 (14%)
Alcohol	21,026 (13%)
Body mass index	18,015 (11%)
Diabetes	3,912 (2%)

4.3 Brazil: National Household Sample Survey (PNAD)

Routine national data for Brazil was not available for use in this thesis; instead we examine a national cross-sectional survey that includes information on stillbirth cases. This section will first summarise the construction of the sample survey before going on to describe the subset used to investigate stillbirth.

4.3.1 Origin of the Data

Brazil's National Household Sample Survey (Pesquisa Nacional por Amostra de Domicílios – PNAD) is an annual cross-sectional survey conducted by the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE). Since its inception in 1967, the objective of the PNAD has been to produce basic information for analysing Brazil's socio-economic development. Permanent topics include demographic characteristics, education, employment, income, fertility and housing. Each year, in addition to the main topics, a supplementary survey is produced providing more detailed information on a chosen theme. In the last decade, these themes have included: access to social programs (2006, 2014), education (2007), health (2008), access to technology (2008, 2011, 2013-2015), food safety (2009, 2013), access to justice (2009) and socio-occupational mobility (2014).

These statistics act as an essential tool for the formulation and evaluation of policies addressing the socio-economic development and improvement of living conditions in Brazil. The anonymised PNAD data is freely available to download from IBGE's website (IBGE, 2017).

Sample Plan of the PNAD

The complex sampling plan aims to provide a representative sample of the population within the five major regions and, within these, the twenty-seven Federative Units (UFs) (IBGE, 2015). The PNAD 2013 contains information on 362,555 people within 14,897 households throughout the country.

The sampling plan (illustrated in Figure 4.1) has three stages: municipalities (primary units), census tracts (secondary units) and households (tertiary units). Households include private households and housing units within collective households. The municipalities were grouped into two categories: "self-representative" (autorrepresentativas – AR) and "not self-representative" (NAR).

AR: municipalities located in metropolitan regions along with other larger municipalities (in terms of population). All municipalities in the AR category are included in the sample with certainty.

NAR: the remaining smaller municipalities. These are stratified and selected with replacement from each stratum with probability proportional to the resident population acquired from the 2010 Population Census.

From here, census tracts are selected with replacement from all of the chosen municipalities. This time they are sampled with probability proportional to the number of households also obtained from the 2010 Population Census. Finally, the households are selected with equal probability from each census tract and each member of the household is surveyed.

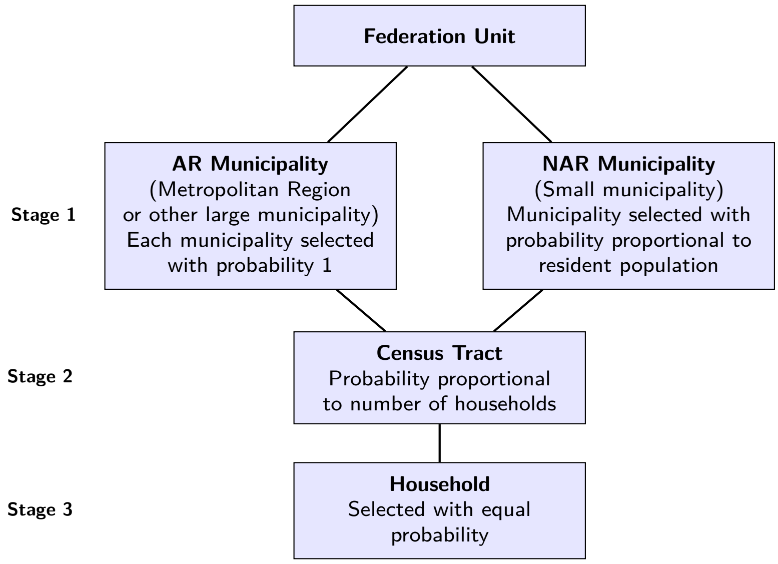

Figure 4.1: Sampling plan for the PNAD

Hierarchical Structure of the PNAD

The PNAD has a hierarchical structure, collecting data at both household- and individual-level. This structure makes it possible to account for the effects of variation within and between households. Multiple members of each house are surveyed, and it is natural to assume that many would have similar characteristics within their group, thus suggesting the existence of dependence of within-group observations.

However, this thesis study focuses on the subset of women who have given birth and so, for the most part, can avoid this issue. For the majority (95%) of households in the final subset (detailed in Section 4.3.2) there is only one woman who has given birth; thus the group-level information essentially becomes individual-level and we shall treat it as such.

Measuring Stillbirth with the PNAD

The PNAD questionnaire has two questions regarding stillbirth:

1. Until the reference date, has [the individual] had any child who was stillborn?
2. How many stillbirths did [the individual] have up to the reference date?

Equivalent data is collected for live births. In the survey, the numbers of live births and stillbirths are further divided into the counts for males and females, but this study focuses on the total number. The questionnaire defines stillbirth as a baby born dead after seven months gestation, which closely matches the 28 week limit in the WHO's definition international comparison.

Although information from the first question forms a binary variable, note that it is not equivalent to observing whether a given birth is stillborn or live born. This PNAD variable measures only whether the observed woman has *ever* had a stillbirth. Logistic regression with this outcome would be unsuitable, as "having had a stillbirth" may well be just a proxy for high parity, or for have given birth at all. Any results derived from this model would be challenging to interpret meaningfully. Therefore, the binary measure shall be retained for data checking and cleaning but the analysis will instead focus on the PNAD's aggregate birth counts as outcomes of interest. Chapter 7 will explain the methodology employed to utilise these variables.

4.3.2 The Dataset

The original data was provided in SAS and text files, as two separate datasets for household- and individual-level information. These were converted for use in R software and merged into one CSV file for data cleaning and subsequent analysis. The merged PNAD dataset contained information regarding 362,555 individuals within 116,543 households. The data was individual-level with each row relating to one person. The following sections will discuss the steps taken before analysis began.

The subset of interest is women aged 15-49 who have given birth. Since the mother's age at the time of birth is unknown (see Section 4.3.3), the subset was restricted to those of childbearing age at the time of survey in an attempt to capture only the more recent births.

Exclusions from the sample Women outside of the 15-49 age range, women who had not given birth and all men were excluded from the dataset. 1,190 women born outside of Brazil were also excluded to similarly restrict the sample to more relevant births; since the dates of birth and the women's dates of entry to Brazil are unknown, these births could have occurred out of the country. A negligible 16 individuals who were listed as employed but with no defined occupation were discounted as a measure for socio-economic status could not be derived for them.

In order to use the household data, the subset was restricted to households classified as permanent private residences. This excluded any collective housing, including hotels, hostels, elderly care homes and student accommodation, as well as improvised housing within bars, offices, etc (IBGE, 2015). Household-level information was not available for these collective and improvised units.

The final sample contains 61,748 mothers within 58,622 households.

Data cleaning A small number of inconsistencies between outcome variables were addressed. Seventy women answered "yes" to having had a stillbirth but had neglected to answer the follow-up question concerning the number of stillbirths; this count was recoded to "1". Equivalent data cleaning was conducted for 116 women with live births.

Dealing with missing data Almost all of the missing data in the dataset was systematic; sections within the questionnaire were directed at a sub-group of the sample. For example, work-related information was collected solely for the 41,469 women (63%) who were classified as employed in the last year. In these cases, the remaining 20,279 women with no work information were included in the variable as an "unemployed" category.

Collapsing variables In exploration, numerical predictors were checked for linearity with the outcome, and any predictors with a non-linear relationship were categorised. Some categorical levels were collapsed when the amount of detail was deemed superfluous, or the stillbirth counts within each level were too small for a meaningful analysis. Some variable transformations were made to match similar variables in the datasets for Scotland. These exploratory variables and others are described in more detail in Section 4.3.5.

4.3.3 Primary Outcome Variables

The primary response variables were the numbers of live births and stillbirths had by each woman in her lifetime. Of the 61,748 women in the sample, 61,550 had at least one live birth, and 2,416 had at least one stillbirth; 2,218 women had experienced at least one of each. The average number of births per woman was 2.37 births, with 2.32 live births and 0.05 stillbirths. Ninety-five percent of the sample had five births or less, but some had many more, with seven women having 20-23 births in their lifetime. The highest number of stillbirths was six.

The total number of live births and stillbirths in the sample were 143,236 and 2,785 births respectively, resulting in a crude overall stillbirth rate of 19.1 per 1,000 births, or approximately 2% of total births.

This rate initially seems very high, given that the 2016 national stillbirth rate for Brazil was 9.8 per 1,000 births. A likely explanation for this high rate, in part, is that the year – or even decade – of any given birth in this sample is unknown. Some births within the observed counts could have occurred as early as 1979, when the stillbirth rate was more than 20 per 1,000 births (Victora et al., 2011).

The rates in this sample are also heavily affected by parity i.e. the total number of births up to the survey date. To explain this difference, note that the national stillbirth rate is based on the number of stillbirths and live births for a given year. However, the sample's rate is based on each woman's total number of live births and stillbirths in her lifetime (up to the survey date). These counts produce what we shall call *lifetime* stillbirth rates.

To illustrate this, Table 4.5 displays stillbirth counts and rates by the number of total births had up to the survey. For example, the subset of women who have each had three births had a total of 688 stillbirths and 32,054 live births respectively. Therefore, the stillbirth rate for women that have had exactly three births is 21.01 per thousand births. Observe that among women with only one birth the rate is 8.9 per 1,000 births, much closer to the 2016 national rate 9.8 per 1,000 births, but from there the rate increases as the number of births increase.

Table 4.5: Stillbirth rates (per 1,000 births) by total births delivered in the PNAD, Brazil

	Total	**1 Birth**	**2 Births**	**3 Births**	**4 Births**	**5 Births**	**6 Births**	**7+ Births**
Total Still.	*2787*	178	442	688	515	339	230	393
Total Live	*143236*	19748	41292	32054	20049	10151	7738	12204
Stillbirth Rate	*19.07*	***8.93***	***10.59***	***21.01***	***25.04***	***32.32***	***28.87***	***31.2***
Stillbirth rates (per 1,000 births) by total births and age group								
Age 18-24	*16.15*	10.16	15.35	26.61	32.20	20.00	31.75	86.9
Age 25-39	*17.11*	7.87	11.03	20.04	23.70	31.88	23.93	23.7
Age 40-49	*21.84*	10.31	8.91	21.57	26.06	32.89	33.05	34.1

The table also shows stillbirth rates stratified by age group. The increase of stillbirth rate with increased parity is consistent over all age groups. The rate is also generally higher for the younger and the older age groups compared to this middle group of 25-39 years. The extreme rate for the youngest subset with seven or more total births is due to the very small number of women; it contains only eleven women with ninety-two births and eight stillbirths between them, hence the high stillbirth rate of over one in twelve births.

"Retroactive" analysis. These outcome variables are less than ideal. One established problem is that although the PNAD records the number of births for a woman, the actual year of any given birth is unknown. Our study accounts for this, in part, by restricting the sample to women aged 15-49 at the time of the survey, i.e. women currently of potential child-bearing age. This cut-off should narrow down the observations somewhat to the most recent births.

An additional issue with these outcomes is that the other variables in the data reflect the woman's SEP at the time of the survey, which is not necessarily the same as at her (unknown) time(s) of birth. Analysis of this data must assume that, for the most part, each mother's socio-economic situation has remained constant, or at least not meaningfully changed, since her first birth. This may be an unreasonable assumption considering that people generally become wealthier as they get older, which could introduce bias or dilute effects in the results, particularly for older women in the sample. Inference regarding the effects of socio-economic factors on stillbirth will be challenging.

This phenomenon in which we must use *current* information to predict potentially *past* events shall be referred to as "retroactive" analysis as a shorthand in further discussion.

Handling age as a predictor. The literature review affirmed that the mother's age at delivery is undoubtedly an important predictor of both parity and risk of stillbirth. Figure 4.2 shows the range and frequency of ages in the sample of women who have given birth, where each bar refers to one year of age. The average age of the sample is 35.4 years (SD = 8.37). For women who have had a stillbirth, the average age is 37.7 years (SD=7.83). Naturally, the number of women who have given birth begins very low for the teenage women in the sample and increases with age until levelling off (and decreasing slightly) from around age 35.

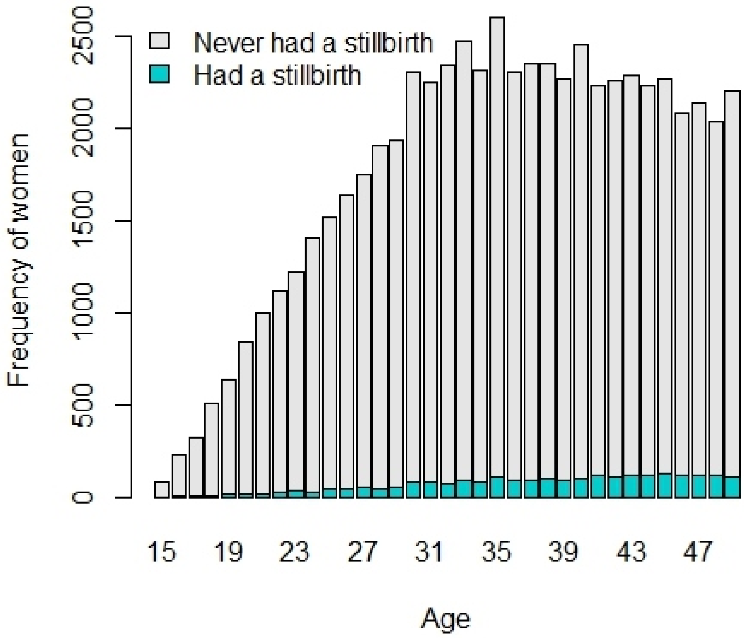

Figure 4.2: Frequency of women with births by ages in the PNAD sample

Of course, this variable depicts the woman's current age, not age at delivery, and therein lies an issue of interpretation since the mother's age at delivery – the maternal age – for any given birth is unknown. To combat this somewhat, the study investigates age as a cohort effect of women stratified by their current age; it aims to interpret the pattern of births over the lifetimes of, for example, women who were in their 40s during the PNAD 2013 survey (i.e. born 1963-1973) compared to younger women. The cohorts are as listed in Table 4.5; 18-24 years, 25-39 years and 40-49 years. The cohorts of women would have been born in the periods 1989-1998, 1974-1988 and 1964-1973 respectively, with their reproductive years beginning around 2004, 1989 and 1979.

Novel use of the aggregate birth data An aggregated outcome for birth counts makes analysis difficult not least because it masks potential variation in stillbirth risk between a woman's individual births, perhaps due to parity and previous adverse birth outcomes. Parity is clearly important, as observed in the literature review and Table 4.5 where the observed stillbirth rate increases for women with higher parity. Moreover, this increasing rate suggests that using a standard binomial or Poisson model to analyse these counts would be inappropriate; a required assumption for these models is that the proportion of stillbirths would remain constant as the total number of births for a woman increases.

Instead, a novel approach is outlined in Section 7.1.1, in which pseudo orderings of live and stillbirths for each woman are simulated from this aggregated outcome data, and regression is performed on each binary birth outcome in that pseudo-sequence.

4.3.4 Derived Variables

The PNAD 2013 contains over 400 variables, many relating to living conditions, which have the potential to impact a maternal health. Influenced by previous studies, numerous variables were combined to derive measures of socio-economic position. Breakdowns of the original variables can be found in the PNAD 2013 variable dictionaries freely available from IBGE.

Derived Variables: Brazil's Living Standards Survey (PPV)

The following five variable derivations were influenced by Brazil's Living Standards Survey 1996-1997 (Pesquisa sobre Padrões de Vida - PPV) which, using questions similar to the PNAD, derived measures for the quality of household construction, household services, household occupancy, basic household goods and status household goods.

Household construction. Using three categorical variables from the PNAD which detail the main materials of the household's wall, roof and floor, the PPV assigns given materials as either adequate or inadequate. However, the PPV but does not specify how it derives one overall indicator for construction quality for these binary indicators.

The PNAD 2013 data does not include information about the material of the floor, but the measure was closely replicate using available data on the walls and roof. An indicator score for household construction was defined as adequate only if *both* the walls and roof were deemed adequate, and inadequate if one or neither variable did.

Household services. The PPV uses five categorical PNAD variables to measure the quality of household services: existence of a bathroom, the type of sewage/sanitation system, existence of piped water in at least one room, the destination of household waste and the form of house lighting (electricity, gas lamps, etc.). Similar to the construction variable, the PPV assigns elements within these variables as either adequate or inadequate but does not specify how it derives an overall measure for household services.

For this study, an ordinal variable was created with scores of Adequate (if 4-5 of the services were adequate), Semi-adequate (if 2-3 of the services were adequate) and Inadequate (if one or none of the services were adequate).

Household occupancy. The PPV ascribes household density as adequate if it contains less than three residents per habitable room and inadequate otherwise. "Habitable" rooms are defined as any rooms apart from a kitchen or bathroom. The PNAD 2013 replicated this measure using the number of bedrooms.

Basic goods. The PNAD contains many yes/no questions on whether each household includes certain appliances. The PPV declares a household to have adequate basic goods if it contained a cooker, a fridge, a television and a radio. Various studies and literature use the PPV's classification of whether a household contains certain "basic goods" as an indicator of socio-economic status (Moraes, 2015).

For this study, the 1999 definition was updated to also include owning a phone (mobile or landline) as a basic good, due to the notable increase in phone ownership in the last decade; 96% of individuals in the 2013 data have a phone in their households, compared to 73% that have a radio. A binary indicator was created for basic household goods with scores of Adequate (if the household contained 3-5 of the basic goods) and Inadequate (0-2 basic goods).

Status goods. The PPV considers other household items in the PNAD as more expensive or rare, labelling them "status goods". Many are included in this study along with new additions (such as having an internet connection) that were not available in the PNAD at the time of the PPV definition. Conversely, some of the PPV's status goods no longer appear in PNAD 2013, such as the ownership of a video cassette player.

This study considers eight household items as status goods; a freezer, a water filter, a washing machine, a digital TV, a paid TV service, a personal computer (including laptop), internet access and a car. An ordinal variable with scores of Adequate (if the household contained 6-8 of the status goods), Semi-adequate (2-5 goods) and Inadequate (0-1 status goods) was created.

Other Derived Variables

Socio-economic status. As mentioned in the descriptions of the UK datasets, many UK social studies measure SEP with the National Standard Socio-economic Classification (NS-SeC), derived by the ONS. The NS-SeC is popular due to its flexibility; it can be aggregated from 9 down to 3 class categories while preserving its underlying conceptual framework (Santos, 2006).

Brazil has no such official measure (V. Guerra, personal communication, April 17, 2017). This study aimed to create a comparable measure for socio-economic status in Brazil using variables from the PNAD. The UK measure is derived from two pieces of information; the individual's occupation code (from the Standard Occupation Classification (SOC) 2010 list) and their employment status (whether they are employed, self-employed, or an employer and how many employees are in the organisation).

The PNAD has two variables that can be used to approximately replicate this measure; the individual's occupational group and their employment status. Following the steps provided in the ONS document "Deriving the NS-SeC: self-coded method", Table 4.6 attempts to approximately replicate the 5-level NS-SeC variable (Table 6 in the aforementioned ONS document), this time using the two PNAD variables for occupational group and employment status. For use in the study, we shall refer to this measure as the Brazil Socio-economic Status (SeS).

Table 4.6: Derivation of Brazil Socio-economic Status (SeS) variable to match the UK's NS-SeC measure

	Occupational Group							
Occupational status	General managers	Arts and sciences professionals	Middle level technicians	Admin service workers	Service, sales, production	Agricultural workers	Armed, auxiliary forces	Unemployed (NA)
Employee	1	1	4	2	5	5	4	-
Domestic worker	-	-	5	-	5	-	-	-
Self-employed	3	3	3	3	3	3	-	-
Employer	1	1	3	3	3	3	-	-
Unpaid	4	4	5	5	5	5	-	-
Work for self	-	-	5	-	5	5	-	-
Unemployed (NA)	-	-	-	-	-	-	-	10

Class 1	Managerial, administrative and professional occupations
Class 2	Intermediate occupations
Class 3	Small employers and self-employed
Class 4	Lower supervisory and technical occupations
Class 5	Semi-routine, routine, agriculture occupations
Class 10	Long term unemployed

The occupational group "armed and auxiliary forces" were allocated to the NS-SeC category "technical occupation" as suggested by an ONS user manual (ONS, 2005). Note that these variables refer to an individual's primary job and do not account for any additional employment that the individual may hold.

Food security. PNAD 2013 contains a supplemental questionnaire on nutrition and food security. It contains eight questions for all household members and six additional questions related to children in the household, if applicable. IBGE derive the Brazilian Food Insecurity Scale (Escala Brasileira de Inseguraną Alimentar - EBIA). The EBIA classifies a household's food security into four levels; secure, light insecurity, moderate insecurity and serious insecurity. This classification is outlined in Table 4.7. Note that it has two separate definitions for adult-only households and family-with-kids households.

The EBIA is considered a sensitive indicator of food deprivation, considering both objective and subjective aspects, e.g. the current or recent availability of food as well as the family's concern for the future availability of food (Russano, 2015).

Table 4.7: Classification of the level of food insecurity, considering the presence or absence of children under 18 in the household

	Number of "yes" responses	
Level of food insecurity	Households with children under 18	Households without children under 18
Secure	0	0
Light insecurity	1-5	1-3
Moderate insecurity	6-9	4-5
Serious insecurity	10-14	6-8

4.3.5 Exploratory Variables of Interest

The PNAD contains dozens of variables potentially associated with health outcomes and more specifically stillbirth. Based on our literature review, twenty-one predictors were selected which are displayed in the tables below, grouped into individual-level and household-level information. Variable breakdowns by age cohort can be found in B.3 of the Appendix. Also included are the stillbirth rates for each category level, i.e. the sum of the stillbirths divided by the sum of the live births had by all women with the given characteristic (multiplied by 1,000). As showcased in Section 4.5, these stillbirth rates are affected by parity, and so stillbirth rates are also provided for the subset of women with only one birth to get a clearer picture. This subset, containing 19226 births, resulted in very small stillbirth counts for some category levels. Rates based on stillbirth counts less than 10 are denoted as *, while ** denotes rates based on less than 5 stillbirths.

Individual-related Characteristics

Table 4.8 displays the twelve individual-related explanatory variables being considered, with counts divided between women that have had at least one stillbirth and those with no history of stillbirth.

Age is categorised and collapsed into the three cohorts explored in the previous section. The mother's ethnicity is categorised into four groups; white, black, and brown/mixed are defined in the PNAD, while the very small amount of remaining women (1%) are combined into an "other" group. Categories for marital status were collapsed to match the equivalent variables in the individual-level data for Scotland. Similarly to the Scottish variable in Section 4.2.3, there were a large proportion of missing values for those that did not disclose their marital status.

Socio-economic status (SeS) was derived to match the UK's NS-SeC measure (as described in Section 4.3.4). It distinguishes the long-term unemployed between those who are unemployed and seeking work, and those who are not economically active, e.g. students or home-makers. Education was measured as the highest level of education achieved was collapsed from fourteen levels to three – primary (or below), secondary and tertiary (or above) education.

Location of work was collapsed from eight levels to three; a fixed establishment (e.g. an office, shop, school, warehouse, factory), other locations (outdoors, in a vehicle, in the household or an employer's household) and those who did not disclose their location of work or were unemployed. The remaining employment-related variables were similarly collapsed due to small counts in some levels. Although multiple employment-related variables will be highly correlated and overlap in meaning, the model selection process will determine which employment-based measure is the most important in predicting to stillbirth. It would be interesting to see if any of these factors, such as location or hours worked, provide additional detail on top of the derived variable for socio-economic status.

Table 4.8: Individual socio-economic risk factors for stillbirth in the PNAD 2013, Brazil

	History of stillbirth				**Stillbirth rate**	
	No (%)		**Yes** (%)		*All*	*Women with*
Characteristic	59332 women		2416 women		*women*	*1 birth*
Age						
15-24 years	7179	98%	159	2%	16.2	10.2
25-39 years	31137	97%	1120	3%	17.1	7.9
40-49 years	21016	95%	1137	5%	21.8	10.3
Ethnicity						
White	24097	97%	785	3%	16.7	7.8
Black	5204	95%	271	5%	23.2	10.9
Brown/mixed	29505	96%	1340	4%	20.0	9.6
Other	526	96%	20	4%	17.0	12.8**
Marital status						
Married	3058	95%	149	5%	20.9	8.5*
Single	27649	96%	1175	4%	19.8	10.8
Separated/divorced/widowed	5634	96%	353	4%	20.1	8.8
Not disclosed	22991	96%	839	4%	17.6	6.2
Socio-economic status						
1: Managerial, administrative, professional	5368	97%	144	3%	15.7	4.6
2: Intermediate	4985	97%	153	3%	19.4	11.1
3: Small employers, self employed	6170	96%	285	4%	21.7	11.4
4: Supervisory, technical	2610	97%	78	3%	17.0	12.0
5: Routine, semi-routine, agricultural	20739	96%	937	4%	19.2	9.4
Long term unemployed - seeking work	2903	95%	143	5%	25.5	11.4
Economically inactive	16557	96%	676	4%	17.9	6.9
Highest education level						
Primary and below	28362	95%	1422	5%	20.0	12.4
Secondary	23271	97%	768	3%	18.4	7.1
Tertiary and above	7699	97%	226	3%	16.3	7.0
Work history						
Has worked	48681	96%	1986	4%	19.3	9.3
Never worked	10651	96%	430	4%	18.3	7.2
Age began working						
$\leq$ 9 yrs	12603	95%	619	5%	21.1	11.2

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Table 4.8 – continued from previous page

Characteristic	History of stillbirth **No** (%) 59332 women		**Yes** (%) 2416 women		Stillbirth rate *All women*	*Women with 1 birth*
10-14 yrs	11524	97%	415	3%	18.3	9.1
15-19 yrs	15745	97%	563	3%	17.9	8.7
Not employed	19460	96%	819	4%	19.0	7.8
Location of work						
Fixed establishment	22615	97%	727	3%	17.1	8.6
Outdoors, home, employer's home	12060	95%	582	5%	20.5	10.7
Not disclosed or not employed	24657	96%	1107	4%	19.8	8.6
Hours/week spent working						
$\leq$ 14 hrs	2983	95%	159	5%	21.1	7.8*
15-39 hrs	9958	96%	432	4%	19.2	8.8
40-44 hrs	15550	97%	501	3%	16.5	8.9
45+ hrs	7828	96%	328	4%	21.3	10.6
Unemployed/unknown	23013	96%	996	4%	19.5	8.5
Household income range (per capita)						
No wage or $\leq$ 1/2 min. wage	19515	95%	939	5%	18.6	6.9
$>$ 1/2 to 1 min. wage	17866	96%	701	4%	19.2	8.0
$>$ 1 to 2 times min. wage	12601	97%	439	3%	19.0	9.9
$>$ 2 times min. wage	6681	97%	227	3%	20.6	13.6
Not disclosed	2669	96%	110	4%	19.7	5.4*

Household-related Characteristics

Table 4.9 displays information on the nine household-related explanatory variables being considered, including two geographic variables about the household location. Formulations of these following derived variables were explained in Section 4.3.4: household construction, household services, household density, basic goods, status goods, food security.

The urban/rural indicator was collapsed from 8 levels detailing the types of urban and rural areas, while the region of residence was derived from the state-level geographic variable "Federation Unit", reducing the number of levels from 27 states to a more manageable six regions.

Stillbirth rates for some of the variable levels appear counter intuitive or contradictory to the literature. In Table 4.8, a smaller percentage of women in the higher wage range bracket had a stillbirth compared to those in lower wage range brackets, but the stillbirth rate was still higher in the affluent groups. For the full sample, the urban/rural indicator in Table 4.9 shows lower rates for rural areas than for urban areas, as well as relatively lower rates for the North East region, which in reality has the highest of the regions (Figure 2.1). These lifetime rates appear to be particularly skewed by trends in parity for these groups; women in rural areas and the northern regions tended to have higher parity than their urban and southern counterparts. Looking at the corresponding rates for women with just one birth, the disparities between urban and rural areas disappear, while the North/South regional disparities become more pronounced.

Shifting focus from the births to the mothers, we see, for example, that 4.3% from Table 4.9) of women living in the North and North East from the sample have had at least one stillbirth, compared to 3.1% and 3.7% from the South and South East, respectively. However, since women in the northern states regions also tend to have many more births generally, the denominator value in the stillbirth rate can become inflated, causing the rates for the North East, in particular, to appear lower than other regions. Analysis of this data shall need to account for differences in parity among these groups.

Subset of single births. We are able to explore this relationship between these social factors, parity and stillbirth thanks to the novel method laid out in Chapter 7. Additionally, a sensitivity analysis will also be conducted using the subset of women with exactly one birth.

It would be tempting to use this subset for the main analysis. An advantage would be that births in the subset would tend to be more recent. However, this sample would be too selective. While, for most of the explanatory variables, the demographics of the women with one birth versus the full sample are not too different, the demographics for age cohort, education level and income range differ greatly. As shown in Table 4.10, the women with one birth are disproportionately younger, more educated and have a higher household income (per capita). This *single birth* subset includes women who chose to only have one child, which could be confounding. An additional issue that, since the subset comprises only 32% of the main sample, some variable level counts end up being extremely small.

Importantly, we cannot explore the effect of parity (or the number of previous stillbirths) on stillbirth if this subset is relied upon for the main analysis. Therefore, we call upon it only for a sensitivity analysis after exploring parity and previous stillbirth with the full sample.

Table 4.9: Household socio-economic characteristics for stillbirth in the PNAD 2013, Brazil

	History of stillbirth				**Stillbirth rate**	
	No (%)		**Yes** (%)		*All*	*Women with*
Characteristic	59332 women		2416 women		*women*	*1 birth*
Household construction						
Adequate	58448	96%	2359	3.9%	19.0	8.9
Inadequate	884	94%	57	6.1%	21.4	16.9**
Household services						
Adequate	50192	96%	1965	3.8%	19.1	9.2
Semi-adequate	7947	95%	383	4.6%	19.3	7.4
Inadequate	1193	95%	68	5.4%	17.8	3.8**
Household density						
Adequate	49173	96%	1984	3.9%	19.5	10.0
Inadequate	10159	96%	432	4.1%	17.3	4.4
Household basic goods						
Adequate	56934	96%	2266	3.8%	18.9	8.4
Inadequate	2398	94%	150	5.9%	21.9	25.0
Household status goods						
Adequate	12214	97%	388	3.1%	17.2	7.3
Semi-adequate	22293	96%	819	3.5%	18.5	8.0
Inadequate	24825	95%	1209	4.6%	20.2	11.0
Food security						
Secure	42176	97%	1500	3.4%	17.8	8.6
Light food insecurity	11838	96%	539	4.4%	19.7	7.6
Moderate food insecurity	3136	93%	230	6.8%	25.6	19.5
Severe food insecurity	2182	94%	147	6.3%	23.0	11.7*
Urban/rural code						
Urban	50978	96%	2043	3.9%	19.5	9.0
Rural	8354	96%	373	4.3%	17.1	8.7
Region						
North East	9937	96%	446	4.3%	18.2	9.9
North	17538	96%	790	4.3%	20.4	10.0
Central West	4894	96%	198	3.9%	19.7	12.3
South East	16463	96%	637	3.7%	19.3	8.1
South	8885	97%	284	3.1%	16.4	6.5
Federal District	1615	96%	61	4.3%	19.1	7.2**

Table 4.10: Selected demographics for the full sample of women with at least one birth and the subset of women with exactly one birth in the PNAD 2013

Demographics	**All women**	**Women with one birth**
Age		
15-24 years	12%	25%
25-39 years	52%	45%
40-49 years	36%	30%
Highest education level		
Primary and below	48%	35%
Secondary	39%	49%
Tertiary and above	13%	16%
Household income range (p.c.)		
No wage or <=1/2 min wage	33%	24%
More than 1/2 to 1 min wage	30%	31%
More than 1 to 3 times min wage	21%	25%
More than 3 to 5 times min wage	11%	15%
Did Not Declare	5%	5%

4.4 Other Data Sources Considered

This section presents a brief overview of other national routine data sources concerning stillbirth that were considered for this study and details why they were ultimately not suitable.

4.4.1 Stillbirth Data Sources in the UK

Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is a database containing details of all admissions and appointments at NHS hospitals in England, including birth events. Maternity records are split into "delivery episode" specific to the mother and "birth episodes" specific to each baby. These records contains delivery and maternity information for live and stillbirth events, including birthweight, gestational age, mode of birth, number of births in the pregnancy and parity, as well as the socio-demographic factors maternal age, Index of Multiple Deprivation (IMD) score and the baby's ethnicity.

HES data has been used in the past to investigate the effect of specific surgical or obstetric interventions on pregnancy outcomes (Aylin et al., 2016; Knight et al., 2017). HES was once combined with NHS Workforce Statistics and NHS reference costs to investigate the relationship between workforce staffing, cost and the quality of care received (Sandall et al., 2014). However, while HES contains rich information unavailable elsewhere, it is currently tremendously underused for research (Ghosh et al., 2016). Despite its suitability, no research into the wider causes of stillbirth using the data has been published. This is likely due to the difficulty of accessing HES and other individual-level birth event data in England, which shall be elaborated upon in the next section.

Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE-UK)

MBRRACE-UK is a national collaborative programme involving the surveillance and investigation of maternal deaths, stillbirths and infant deaths. The aim of the programme is to provide robust national information to support the delivery of safe, equitable, high quality, maternal, newborn and infant health services (NPEU, 2018). MBRRACE-UK has taken the role from equivalent past programmes Confidential Enquiry into Maternity and Child Health (CEMACH) and the Centre for Maternity and Child Enquiries (CMACE). Information on socio-economic position is recorded in the form of the Index of Multiple Deprivation (IMD), a neighbourhood-level measure of deprivation that combines information on income, employment, education, health, crime and living environment in the area.

However, MBRRACE-UK only collects such robust information for cases of stillbirths, infant deaths and maternal mortalities. Their data is therefore not useful to this thesis as it requires equivalent information regarding live births to make comparisons.

ONS Longitudinal Study (LS)

The Longitudinal Study for England and Wales links census and life events data for a 1% sample of the population. It contains records on over 500,000 people at each point in time, and it is generally representative of the whole population (ONS, 2018). Alongside a wealth of socio-economic indicators, the LS does record information on live and stillbirths to female LS members. However, only approximately 25-45 stillbirths per year have been recorded in the last decade. Consequently, when stillbirth cases are grouped by socio-economic measures in the analysis, counts will rapidly become very small, leading to issues of suppression.

4.4.2 Stillbirth Data Sources in Brazil

Mortality Information System (SIM)

Brazil's routinely collected stillbirth and live birth data – collected through the Mortality Information System (Sistema de Informação sobre Mortalidade – SIM) and Live Birth Information System (Sistema de Informações Sobre Nascidos Vivos – SINASC), respectively – compiles microdata for the mother's place of residence, age, ethnicity, marital status, education, and parity, along with the baby's sex, gestational age, birth weight, delivery type, pregnancy type, and cause of death. The SIM defines stillbirth as the death of a fetus before or during delivery, occurring from 22 weeks or weighing more than 500g.

Aggregate tabulations, graphs and maps using this data can be easily and freely generated online through the platform DATASUS; descriptive studies of stillbirth using these tabulations have been performed (Vieira et al., 2016). Access to the individual-level data itself is very restricted, similar to the aforementioned ONS data. Gaining permission for both the SIM and SINASC at an individual level was outside the realm of this thesis.

National Health Survey (PNS)

The new Pesquisa Nacional de Saúde (PNS) 2013, released by IBGE in 2015, is a new sample survey on Brazilians' health that contained questions surrounding a woman's most recent birth. These questions aim to provide individual birth-level information on live and stillbirths that occurred in the period 2011-2013. The survey replaces the health supplement of the PNAD that was recorded every five years until 2008 and covers many of the same topics, including many indicators of socio-economic position. This dataset, in theory, would be ideal for the current thesis' aims. However, data from the stillbirth-related questions were not sufficiently collected and consequently not released in this first edition of the survey. Therefore, we moved to explore more novel methods with information from the PNAD.

Non-routine data. There exist smaller, one-off or irregular studies of stillbirth in both countries that have been previously used to study socio-economic factors and stillbirth: the Pelotas cohorts in southern Brazil and the ALPSAC study in Avon, UK. However, we have chosen to focus on national, routinely collected data at the expense of detailed variables in one-off cohort studies because we wished to review the potential resources for both countries' governments to tackle stillbirth at a national level.

4.5 Summary

It is clear, through programmes such as HES and MBRRACE in the UK and SIM in Brazil, that sufficient routine national information on stillbirth exists. However, making this comprehensive data accessible to researchers and comparable with equivalent information on live births is another challenge.

Access to individual-level routine birth data in England. The studies of Scotland and Brazil in this thesis use individual-level information. However, obtaining individual-level data on births and stillbirths in England, from the ONS and NHS, is a slow process and requires several conditions to be met:

- Governance approval from the Confidential Advisory Group at the Health Research Authority (HRA) under section 251 of the NHS Act 2006 to receive individually identifiable data without the consent of individuals involved.
- Research ethical approval from the HRA; permission from a university ethics committee would not be sufficient.
- Data provider approval through NHS Digital including permission from the Data Access Advisory Group's (DAAG), who consider whether the research will sufficiently benefit the health and social care system (HRA, 2017). DAAG sometimes considers PhD projects sponsored by an organisation such as a medical charity with a clear interest in the outcome or supported by a relevant group in health and social care [as of 2018, this service has been replaced with the Data Access Request Service (DARS) (NHS Digital, 2018)].

These processes of approval can be prohibitive to many researchers, particularly PhD projects, in that they take years to complete; as we were unable to meet these requirements in the given time frame, we compromised with aggregate-level data for the study of England and Wales. The limitations of analysing aggregate data, primarily the ecological fallacy (in which population-level association erroneously implies individual-level association) are discussed further in Chapter 5.

Data linkage. The key to effectively examining the connection between socio-economic position and stillbirth is the linkage of routine data systems. A systematic review by Delnord et al. (2016) demonstrated how this valuable research tool allows understanding of not only birth-related health indicators but also the aetiology and consequences of observed events.

The review also identified specific obstacles in the research of linked data, including high costs and missing data. These were certainly experienced in accessing Scotland's linked data. Protection of potentially identifiable data is paramount, but it can also be an obstacle; the time and funding required to approve a researcher and make the data available to them is outside the budget and time-frame of some researchers or organisations.

The data used within this thesis may not be the optimal choice for our research purpose. They are, however, the best available within the budget restrictions and time-frame of a PhD study. This thesis will explore what analysis is possible with different levels of data and suggest methods by which useful findings can still be gained from these data.

Summary of Datasets

Table 4.11 displays a summary of the three datasets used in this thesis, describing their different structures and variables. The ONS data for England and Wales is provided at aggregate-level by LA and age. Scotland's MNLD has individual-level data for each birth. Brazil's PNAD has individual-level data for each mother. However, the outcome measure is the aggregate of birth events for each woman (Chapter 7 will show how this is transformed to consider individual birth events).

The definitions for stillbirth vary between the UK and Brazil. Both of the UK studies include births from 24 weeks of gestation, following the UK definition. The PNAD defines stillbirth with a cut-off of seven months gestation, approximately 28 weeks, in line with WHO's definition for international comparison.

The stillbirth rates for each population are also presented. The rates for Scotland are slightly lower than for England and Wales, although the UK rates are not directly comparable as the data encompasses different years. The total *lifetime* stillbirth rate for Brazil is not comparable with the UK rates, as they do not measure the same thing (as explained in Section 4.3). However, the rate for the subset of women in the PNAD sample with only one previous birth gives a more comparable figure, showing a stillbirth rate almost double that of either UK figure.

The exploratory variables in the ONS dataset are very limited with only five potential predictors: baby's ethnicity, mother's country of birth, socio-economic status (NS-SeC), marital status and for birth-related predictors, only multiple birth status.

Many of these predictors are present in some form in the other datasets. All three have some indicator of ethnic group, although due to the countries' demographics the breakdown of categories differs. The ONS gives a binary white/non-white split, the MNLD specifies white, black, South Asian and other, while the PNAD details white, black, mixed/brown and other for Brazil. All three also contain an indicator for marital status, grouped as three levels (married, never married and divorced/separated/widowed) for both the MNLD and PNAD, and as a binary indicator (married/unmarried) for the ONS data. It is reasonable to assume that the majority of women in the "unmarried" category on the ONS data have never married; in the MNLD for Scotland, 57% of mothers in Scotland in 2011-2013 had never married while 7% were divorced, separated or widowed (excluding those with unknown marital status).

The final predictor that appears in all three datasets is socio-economic status. The NS-SeC measure is used in both UK datasets (the three-level and five-level version for England and Wales and Scotland respectively). The PNAD contains a measure equivalent to the five-level NS-SeC measure, derived in Section 4.3.4.

Scotland's MNLD contains a relatively even proportion of socio-economic and demographic variables, health indicators and information specific to the observed birth. Brazil's PNAD contains approximately the same number of explanatory variables, but almost all are indicators of socio-economic position and potential deprivation with no health or birth-related indicators.

The linked dataset for Scotland, boasting a wealth of individual-level health and administrative data for its population, is the most ideal of the three datasets for our research aims. In principle, it will be the most straightforward to analyse and provide intriguing results. It will provide a contrast with the aggregate data for England and Wales for what findings are achievable with different levels of data.

Table 4.11: Comparison of the three datasets used in this thesis

	England/Wales (ONS)	Scotland (MNLD)	Brazil (PNAD)
Aim	Examine associations between socio-economic factors and stillbirth in England and Wales at an aggregate level.	Determine socio-economic risk factors associated with stillbirth in Scotland.	Determine socio-economic risk factors associated with stillbirth in Brazil.
Data	Aggregated birth counts from the ONS for 2006-2014. Birth counts for 348 Local Authority (LA) districts in England and Wales, further stratified by six age groups; <20, 20-24, 25-29, 30-34, 35-39, and 40+ years. 6,329,402 births including 31,229 stillbirths.	Maternity and Neonatal Linked Database (MNLD) for 2011-2013. Individual-level information combines NRS (National Records for Scotland) birth records and SMR02 episode-level data on maternity discharge forms. 149 mothers with 160,120 births, including 675 stillbirths.	National Household Sample Survey (PNAD) 2013 Individual-level annual cross-sectional national survey. 61,550 women, 2,416 of whom have had a stillbirth. 146,021 total births including 2,785 stillbirths.
Outcome Measure	Number of live births and stillbirths in each age/LA stratum. **Rate:** 4.91 per 1,000 births	Binary outcome of each birth – live or still. **Rate:** 3.97 per 1,000 births	Lifetime number of live births and stillbirths for each woman **Rate:** 19.1 (total), 8.93 (1 birth)
Explan-atory Variables	For each age/LA stratum: ***Demographic and Socio-economic*** Baby's ethnicity – % non-white babies Mother's country of birth – % non-UK Socio-economic status – % mothers of NS-SeC level 2/3 Marital status – % unmarried mothers Multiple births – % birth events that were multiple births	***Demographic and Socio-economic*** Mother's age Mother's ethnicity Mother's country of birth Parents married indicator Socio-economic status Deprivation score Urban/rural code ***Health*** Body mass index Diabetes Smoking status Weekly alcohol consumption Drug misuse during pregnancy ***Birth-related variables*** Mode of delivery Birth weight Gestational Age Number of previous pregnancies Number of previous stillbirths Number of previous neonatal deaths Number of previous spontaneous abortions	***Demographic and Socio-economic*** Mother's age Mother's ethnicity Mother's marital status Socio-economic status Highest level of education Location of work Hours per week spent working Age began working Work history Household income range (per capita) ***Household characteristics*** Household construction Household services Household density Household basic goods Household status goods Food security Urban/rural code Region

Comparing the results between countries will, therefore, be very challenging, but is guaranteed to provide a contrast of what can be achieved with different levels of data. In principle, we expect the study of Scotland, with the most accessible individual-level data, to provide the most comprehensive results in comparison to our aggregate study of stillbirth counts in England and Wales.

The following three chapters describe the methods and results for each of the three separate studies. All statistical analyses are conducted using R version 3.1.1. Findings from each study will be compared in Chapter 8.

Chapter 5

Associations Between Socio-economic Factors and Stillbirth in England and Wales

This chapter examines associations between socio-economic factors and stillbirth in England and Wales at an aggregate level, using data provided by the ONS. As described in Section 4.1 of the previous chapter, the outcomes for this analysis are counts of live births and stillbirths for each local authority (LA) district, stratified further by age group. This aggregate analysis of birth counts serves as a proxy analysis, since national individual-level data was unavailable. The data includes demographic and socio-economic information for each LA/age stratum in the form of percentages, i.e. ethnicity is represented as the percentage of babies in the stratum that were non-white.

An initial challenge provided by the data is the suppression of stillbirth counts observed in any stratum with fewer than three stillbirths. To overcome this, the likelihood function for a binomial generalised linear model (GLM) was adapted to account for the missing outcomes taking the values 0, 1 or 2. We also wished to determine whether there was additional area-level variation in stillbirth risk across areas of England and Wales after accounting for the socio-economic covariates, and so random effects for the local authority districts were added to the model.

The socio-economic covariates are expressed as the percentage of mothers in the age/LA stratum that correspond to an individual-level binary characteristic. Potential non-linear relationships between these continuous covariates and stillbirth were explored with spline functions. Finally, interaction terms between covariates were considered to determine whether the value of one variable influenced the effect of another variable on the risk of stillbirth.

This chapter presents and compares the various models constructed with these methods and selects the most favourable.

5.1 Methods Used in the Analysis of Stillbirth Data in England and Wales

This section specifies the methods used to analyse the ONS data for England and Wales. It starts by outlining the modified likelihood function that accounts for the suppressed outcome values. The second section describes how random effects can be approximated in this function using Gaussian Quadrature.

Section 5.1.3 then illustrates how non-linear relationships between the outcome and covariates can be explored with piecewise linear spline functions. Finally we describe the AIC function which is used during the model selection process.

5.1.1 Likelihood Function Accounting for Suppressed Data

With the outcomes of interest being the birth and stillbirth counts for each age/LA stratum, binomial logistic regression is an appropriate starting point for this analysis. McCullagh and Nedler (1989, pg. 101) provide a general overview.

Let n_i denote the overall number of births (live or stillborn) in each group i and let y_i be the number of stillbirths observed for group i. We view y_i as a realisation of a random variable Y_i that takes values 0, 1, ..., n_i. We assume the n_i births in each group are independent and have the same probability π_i of "success", which in this case is stillbirth. Then the distribution of Y_i is binomial with parameters π_i and n_i. The probability distribution is given by

$$\mathbb{P}\{Y_i = y_i\} = \binom{n_i}{y_i} \pi_i^{y_i} (1-\pi_i)^{n_i - y_i}.$$

The probability π_i of stillbirth for those in group i can be expressed as a linear function of K observed covariates $\mathbf{x_k}$ and parameters $\boldsymbol{\beta}_k$, through the transformation of the logit function

$$\text{logit}(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \sum_{k=1}^{K} x_{ik}\beta_k \tag{5.1}$$

$$\pi_i = \frac{\exp(\sum_{k=1}^{K} x_{ik}\beta_k)}{1+\exp(\sum_{k=1}^{K} x_{ik}\beta_k)}. \tag{5.2}$$

The difficulty arises at this point when we consider that some of the stillbirth counts y_i in our data are unknown due to suppression. The simplest method of handling the suppressed values would be to fix all missing stillbirth counts equal to either 0, 1 or 2 before conducting a standard binomial GLM regression analysis. A more sophisticated approach would be to construct a likelihood function that accounts for the three possible values of the missing outcomes, hereafter referred to as the Exact Likelihood function.

Firstly, we create an indicator function to distinguish between the known and suppressed values of y_i. For each observed stillbirth count i,

$$1_{sup}(y_i) = \begin{cases} 1, & \text{if } y_i \text{ is suppressed} \\ 0, & \text{if } y_i \text{ is not suppressed.} \end{cases} \tag{5.3}$$

For the non-suppressed values, the standard binomial likelihood of the observed y_i can be calculated:

$$L_i(\beta|y) = \binom{n_i}{y_i} \pi_i^{y_i} (1-\pi_i)^{n_i - y_i}. \tag{5.4}$$

The likelihood for the suppressed stillbirth observations is the sum of the probabilities that the suppressed stillbirth count is 0, 1 and 2. Here, we do not know the total number of births n_i in group i, since we do not know the number of stillbirths. Instead, we use the known number of live births l_i to calculated the probabilities

$$L_i(\beta|y) = \binom{l_i}{0} \pi_i^0 (1-\pi_i)^{l_i} + \binom{l_i+1}{1} \pi_i^1 (1-\pi_i)^{(l_i+1)-1} + \binom{l_i+2}{2} \pi_i^2 (1-\pi_i)^{(l_i+2)-2}. \tag{5.5}$$

Combining Equations 5.3, 5.4 and 5.5, the likelihood for each of the observed counts is:

$$\begin{aligned} L(\beta|y) = & \left[\prod_{i=1}^{N} \binom{n_i}{y_i} \pi_i^{y_i} (1-\pi_i)^{n_i - y_i} \right]^{(1-1_{sup}(y_i))} \\ & + \left[\prod_{i=1}^{N} \binom{l_i}{0} \pi_i^0 (1-\pi_i)^{l_i} + \prod_{i=1}^{N} \binom{l_i+1}{1} \pi_i^1 (1-\pi_i)^{l_i+1} + \prod_{i=1}^{N} \binom{l_i+2}{2} \pi_i^2 (1-\pi_i)^{l_i} \right]^{1_{sup}(y_i)}. \end{aligned}$$

The logs of these likelihoods are summed to obtain the overall log-likelihood. This likelihood contribution can then be optimised to estimate the model's covariate coefficients.

Interpreting odds ratio results as probabilities

5.1.2 Geographic Variation with Random Effects

We wish to determine whether there is any additional area-level variation in stillbirth risk across areas of England and Wales after accounting for the socio-economic covariates. The data contains a variable denoting the Local Authority district for each observed birth count. Accounting for the district as a fixed effect would require an unrealistic number of parameters, as well as giving poor estimates for districts with low birth counts. Including geographic area in some way as a random effect may be more appropriate.

An advantage of treating area in this way is that, unlike fixed effects, random effects are estimated with partial pooling. This is helpful in cases where there are few observations in an area; partial pooling means that the area's effect estimate will be partially based on the more plentiful data from other areas. This serves as a compromise between ignoring area as a variable (and thus masking any area-level variation) and estimating an effect for each separate area.

Generalised linear mixed models (GLMMs) are extensions of generalised linear models (GLMs) to consider both fixed and random effects (Agresti, 2007). Our mixed model, an extension of Equation 5.1, is represented as

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \sum_{k=0}^{K} x_{ijk}\beta_k + u_j \tag{5.6}$$

where y_{ij} and π_{ij} are respectively the response stillbirth count and stillbirth probability for observation group i in area j, and β_k is one of K fixed regression coefficients for predictor variable x_{ijk}. The new term u_j is the random effect for area j which explains some unobserved heterogeneity between geographic areas.

In generalised linear mixed models, the likelihood contribution for each area j can be expressed as

$$\begin{aligned} L_j(\beta,\sigma^2) &= \int_{\infty}^{-\infty} \mathbb{P}\{y_j|\beta,u\} f(u;\sigma^2)\,du \\ &= \int_{-\infty}^{\infty} \prod_i \mathbb{P}\{y_{ij}|\beta,u\} f(u;\sigma^2)\,du \end{aligned} \tag{5.7}$$

where $f(u;\sigma^2)$ is the distribution of the random effect u.

Since there is no closed form solution form this integral, various numerical approximation methods exist for obtaining the maximum likelihood estimates (Pinheiro and Bates, 1995). One such method is the Gaussian Quadrature approach which approximates the integral by a finite sum of nodes.

Quadrature refers to a numerical integral that incorporates a weighted sum such that

$$I = \int_b^a f(x)dx \approx \sum_i w_i f(x_i) \tag{5.8}$$

where x_i is a node (or quadrature point) and w_i an associated weight.

We wish to use Gaussian quadrature to approximate integrals with respect to the random effect $u \sim N(0, \omega^2)$ with a set of B nodes $\{u_1, ..., u_B\}$ that have associated probability weights $\{w_1, ..., w_B\}$.

In turn this approximates our continuous distribution with a discrete distribution that takes only B possible values with certain probabilities. Thus the likelihood in Equation 5.7 can be approximated as a sum over the likelihood given a particular value of the random effect;

$$L_j(\beta, \sigma^2) = \int_{-\infty}^{\infty} \prod_i \mathbb{P}\{y_{ij}|\beta, u\} f(u; \sigma^2)\, du \approx \sum_{b=1}^{B} \prod_i \mathbb{P}\{y_{ij}|\beta, u_b(\sigma^2)\} w_b \tag{5.9}$$

where B is the chosen number of nodes. The choice of B can be increased until the estimates and standard errors have stabilised to the desired degree of precision.

This calculation for the mixed model's likelihood function was incorporated into the Exact Likelihood function (Section 5.1.1) that accounts for the suppressed data.

Estimating the Random Effects

The probability that a random effect for area j takes the particular discrete value of node u_b $(b = 1, ..., B)$ can be expressed as

$$\mathbb{P}\{U_j = u_b\} \approx \frac{L_{jb} w_b}{\sum_{b=1}^{B} L_{jb} w_b} \tag{5.10}$$

where L_{jb} is the likelihood for area j if the random effect was equal to the node u_b, and w_b is the node's associated probability weight.

Therefore the expectation is

$$\mathbb{E}\{U_j\} = \sum_{b=1}^{B} u_b \mathbb{P}\{U_j = u_b\} = \sum_{b=1}^{B} \frac{L_{jb} w_b u_b}{\sum_{b=1}^{B} L_{jb} w_b} \tag{5.11}$$

The expected random effects for each area can be used to map the variability in stillbirth counts across England and Wales.

Along with local authority, random effects for the larger administrative areas of county and region were also considered. Although smaller areas are generally preferred to capture the more nuanced differences in risk, stillbirth counts in some local authorities may be too small to produce a powerful analysis; aggregating these small counts across larger areas may be necessary.

Technical note on mapping Mapping coordinates for Local Authority district boundary lines in England and Wales were acquired from the UK Data Service in shapefile format. These are used in Section 5.2.2 to display analysis results. Data cleaning was required to match labels in both datasets before merging the shapefiles with the birth data. The shapefile combines two very small districts with larger ones; the Isles of Scilly with Cornwall and City of London with Westminster. This merging was already accounted for in the birth data by excluding the Isles of Scilly and City of London due to their heavily suppressed information. Both deleted districts had all-censored stillbirth counts and very small live birth counts compared to the other districts; therefore we can justify treating the shapefile's combined districts as Cornwall and Westminster, respectively.

5.1.3 Exploring Non-linear Relationships through Splines

In the aggregate dataset of local authorities (stratified by age), the socio-economic covariates are continuous, expressed as the percentage of mothers in the age/LA stratum that correspond to an individual-level binary characteristic i.e. white/non-white ethnicity or married/unmarried status. We wish to explore the existence of a non-linear relationship between stillbirth and the covariates. For example, is there a threshold value beyond which the any covariate's relationship to stillbirth changes? Spline regression provides a flexible way of modelling this by dividing the data's range into smaller segments and fitting simple models to each. This method is attractive because its basis functions (described below) can be treated as ordinary covariates in regression (Kagerer, 2013).

Advantageously, spline regression fits within the class of linear regressions and so is generally less computationally intensive than other semi-parametric methods. de Boor (2001) provides a detailed overview of the method.

The Truncated Power Basis

Piecewise linear splines The simplest spline (of degree 1) is formed by linking linear segments. The covariate data is split into sub-intervals and a linear function is fitted over each sub-interval. Each line may differ in gradient but must connect to the adjacent lines at the interval boundaries, known as knots. A spline with K interior knots divides the data into $K + 1$ sub-intervals. A linear spline regression function for a single covariate is

$$y = \beta_0 + \beta_1 x + \sum_{k=1}^{K} \alpha_k (x - \xi_k)_+ \tag{5.12}$$

with the K knots denoted ξ_k, $k = 1, ..., K$ and the truncation function $(x - \xi_k)_+$ defined as

$$(x-\xi_k)_+ = \begin{cases} 0 & x < \xi_k \\ x-\xi_k & x > \xi_k. \end{cases} \tag{5.13}$$

The truncation function affects only the fit of the spline to the right of knot ξ_k. For values of x in the first segment, the basis function is simply $y = \beta_0 + \beta_1 x$. In the next segment, the basis function is $y = \beta_0 + \beta_1 x + \alpha_1(x - \xi_1) = \beta_0 - \alpha_1\xi_1 + (\beta_1 + \alpha_1)x$, which continues from the end point of the previous segment with an additional gradient $(\beta_1 + \alpha_1)$. More generally, the gradient of the line between knots ξ_k and ξ_{k+1} is $\beta + \alpha_1 + ... + \alpha_k$. The parameters $\beta_0, \beta_1, \alpha_1, ..., \alpha_K$ can be estimated by maximum likelihood just like ordinary covariates.

Higher order splines Linear splines can fit data as well as, or even better than higher degree polynomials, but sometimes a smoother line is desired. We can achieve this by constructing the spline with segments of higher order. Using intervals of quadratic (or more commonly, cubic) polynomials allows the curve to remain relatively easy to interpret whilst achieving the smoother line of a higher order polynomial.

A spline of degree D is

$$y = \beta_0 + \beta_1 x + ... + \beta_D x^D + \sum_{k=1}^{K} \alpha_k (x - \xi_k)_+^D \tag{5.14}$$

with K knots and the same truncation function $(x - \xi_k)_+$ from Equation 5.13 raised to the power of D. The number of parameters is $D + K + 1$. Such a spline function is continuous along with its first $D - 1$ derivatives. The D^{th} derivative is continuous at the knot points.

Unfortunately, a common issue for the truncated power basis is that the fitting algorithm can become numerically unstable if the basis functions are correlated (Ruppert et al., 2003). An alternative approach is the use of a B-splines basis function, described below.

The B-spline Basis

B-spline basis functions can be used in the same circumstances as truncated polynomials. All splines are linear combinations of B-splines, which consist of connected polynomial pieces. However, they are not highly correlated and always take values between 0 and 1, thus the algorithms used to fit them are much more stable (Birk, 1994).

B-splines of degree 1 form the basis for linear piecewise fits. As a simple example, consider degree 1 B-splines on a domain x with four knots (x_0, x_1, x_2, x_3). It splits into three linear pieces; x_0 to x_1, x_1 to x_2 and x_2 to x_3. Figure 5.1 shows the three basis functions. Within each interval, the corresponding

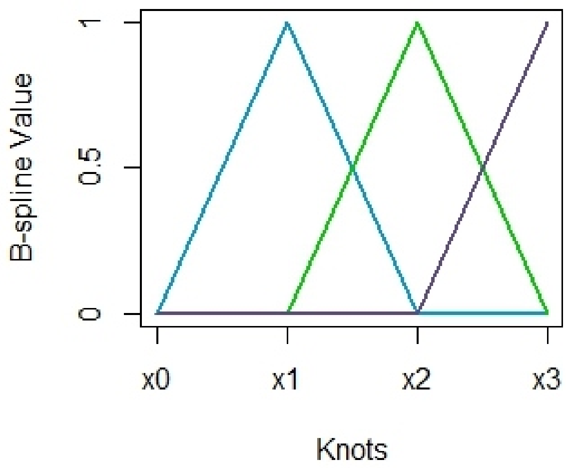


Figure 5.1: Degree 1 B-splines for linear piecewise fit with equidistant knots

B-spline function goes from 0 to 1 with a proportional slope, then declines to 0 at the following knot. On either side of the boundary knots x_0 and x_3, the B-splines are equal to 0. The B-spline values each form a column in a new predictor matrix for regression.

More generally, a B-spline of degree D has following properties:

- it consists of $D + 1$ polynomial pieces, each of degree D;
- at the knots, derivatives up to order $D - 1$ are continuous;
- it is positive on a domain spanned by $D + 2$ knots and zero elsewhere;
- at a given x, $D + 1$ B-splines are non-zero.

(Ellers and Marx, 1996)

Given a domain divided into $K - 1$ intervals by K knots (including the boundary knots at either side), the number of B-splines of degree D in the regression is $n = D + K - 1$.

Let $B_j(x; D)$ denote the value at x of the jth B-spline of degree D. Then the regression function $y(x)$ is

$$y(x) = \sum_{j=1}^{n} B_j(x; D)$$

with estimate parameters $\alpha_j, j = 1, \ldots, n$.

In R, the B-spline basis was constructed with the package `splines`.

Knot selection Decisions concerning the number and placement of knots are very important. In terms of which knot sequence would produce the best fitting regression model, Birk (1994, pg. 69) laments that “there is little or no formal theory to justify” the choice. A trivial starting point would be to use equidistant knots or have an equal number of observations between knots. Practically speaking, an examination of the data combined with knowledge of the subject matter may help determine appropriate knot selection.

The goal for this analysis is not necessarily to produce the smoothest fit but to determine where “breakpoints” in the continuous covariates might be - threshold values beyond which the a covariate’s association to stillbirth changes. We employ a manual yet systematic approach. Firstly, each of the continuous covariates will be investigated one at a time within the model, with the other covariates remaining linear. Beginning with splines of degree 1 (piecewise linear models), spline functions will be performed with evenly distributed segments, i.e. 1 knot at the median, 2 knots at the 33% and 66% centile, 3 knots (quantiles), 4 knots (quintiles) and 9 knots (deciles). From the patterns observed in these results, we systematically experiment with knot placement until an optimal selection is found, with the relative quality of each selection being compared via the models’ AIC values.

5.1.4 Model Fitting

Whether comparing models for the selection of variables or the placement of spline knots, their relative quality was compared with Akaike’s Information Criterion (AIC) (Akaike, 1974). The AIC is defined as

$$\text{AIC} = -2\log(\text{maximum likelihood}) + 2(\text{number of model parameters}).$$

The AIC measures the difference in fit between two (or more) models by comparing their maximum likelihood values. It also penalises for the number of parameters required to construct the model. Lower AIC values indicate a better fit. AIC is particularly flexible for our purposes as it was designed for testing non-nested models.

AIC is commonly used in the selection of mixed models, and to compare a GLMM with an equivalent GLM containing the same fixed effects (i.e. just missing the random component) (Bolker et al., 2008).The appropriateness of this approach has been questioned for linear mixed models for which the AIC was biased towards smaller models without random effects (Greven and Kneib, 2010). Such consensus has yet to be reached for generalised linear mixed models. AIC has also been used in the model fitting process for spline models (Ruppert et al., 2003; Kagerer, 2013; Montoya et al., 2014). Since the degree of the spline and the number of knots chosen affect the number of parameters, the AIC can account for these elements when penalising the number of parameters.

5.2 Results for the Analysis of Stillbirth Data in England and Wales

Exploration began with a standard binomial GLM. Singularly imputed data (in which suppressed stillbirth counts were fixed at a possible number) were compared with a specially constructed function that accounts for suppressed data, hereafter referred to as the Exact Likelihood function or with its associated Exact Likelihood model. Although appropriate, modelling with the Exact Likelihood function was computationally intensive, and so for the model selection process, singularly imputed data was used (with suppressed stillbirth counts fixed at 1). These standard analyses offered evidence of a potential geographic influence alongside socio-demographic effects. These results prompted a mixed effects analysis considering geographic area as a random effect.

Thirdly, analyses were aimed at the construction of B-spline functions to explore non-linear relationships between the five continuous explanatory variables and stillbirth. Piecewise linear functions, connected at a small number of knots, were formed that displayed such a non-linear relationship for many of the covariates. From there, the model was extended to include interactions to determine the existence of inter-covariate relationships that affected the stillbirth outcome.

All of these elements were combined for model selection, before finally returning to the Exact Likelihood function to construct the final model.

5.2.1 Singularly Imputed vs the Exact Likelihood Model

The simplest method of handling the suppressed data in the data was to fix all missing values equal to either 0, 1 or 2. Three sets of standard binomial models were performed to explore whether the parameter estimates differed under these three circumstances. Then the more sophisticated model with its Exact Likelihood function (explained in Section 5.1.1) was conducted and compared with the results of these singularly imputed data models.

First, the continuous covariates for ethnicity, country of birth, socio-economic status, marital status and multiple births were considered in their own model (A). From here, stratification for age group (B) and geographic area (C) was added.

Although the data contains information at a Local Authority level, it was impractical to consider fixed effects for each local authority as it would create an additional 346 parameters in the model. Instead, odds ratios at a regional level are reported here for exploration purposes. The East Midlands was chosen as the reference category for the 10 regions, as its stillbirth and live birth counts best reflected the national average (even when stratified by age group).

The estimated odds ratios, 95% confidence intervals and p-values from each model are displayed in Table 5.1, along with each model's AIC value and their number of parameters.

Table 5.1: Comparison between singularly imputed models (with suppressed values fixed at 0, 1 and 2) and the Exact Likelihood model for England and Wales

	Suppressed values set to 0			Suppressed values set to 1			Suppressed values set to 2			Exact Likelihood Model		
A: Covariates only												
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Baseline	1.00			1.00			1.00			1.00		
% non-white	1.010	(1.01, 1.01)	<0.001	1.010	(1.01, 1.01)	<0.001	1.010	(1.01, 1.01)	<0.001	1.010	(1.01, 1.01)	<0.001
% born outside UK	0.996	(1, 1)	<0.001	0.996	(1, 1)	<0.001	0.996	(0.99, 0.10)	<0.001	0.996	(0.99, 0.10)	<0.001
% NS-SeC group 2/3	1.005	(1, 1.01)	<0.001	1.006	(1, 1.01)	<0.001	1.006	(1.00, 1.01)	<0.001	1.005	(1.00, 1.01)	<0.001
% unmarried	1.002	(1, 1)	0.001	1.003	(1, 1)	<0.001	1.003	(1.00, 1.01)	<0.001	1.003	(1.001, 1.004)	<0.001
% multiple births	1.121	(1.11, 1.14)	<0.001	1.131	(1.12, 1.15)	<0.001	1.141	(1.13, 1.16)	<0.001	1.130	(1.112, 1.15)	<0.001
AIC (6 parameters)	11344			10943			10907			10389		
B: Stratifying for age groups												
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-val**
Baseline	1.00			1.00			1.00			1.00		
% non-white	1.008	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001	1.007	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001
% born outside UK	0.998	(1, 1)	0.003	0.998	(1, 1)	0.003	0.998	(1, 1)	0.004	0.998	(0.996, 0.999)	<0.001
% NS-SeC group 2/3	1.007	(1.01, 1.01)	<0.001	1.007	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001	1.007	(1.01, 1.01)	<0.001
% unmarried	1.004	(1, 1.01)	<0.001	1.003	(1, 1.01)	0.004	1.002	(1, 1)	0.026	1.002	(1, 1.01)	0.021
% multiple births	1.007	(0.99, 1.03)	0.499	1.002	(0.98, 1.02)	0.851	0.997	(0.98, 1.02)	0.779	0.998	(0.98, 1.02)	0.869
Age Group												
<20 yrs	0.846	(0.77, 0.93)	<0.001	0.901	(0.82, 0.99)	0.022	0.957	(0.88, 1.05)	0.334	0.940	(0.86, 1.03)	0.173
20-24 yrs	0.894	(0.85, 0.95)	<0.001	0.902	(0.85, 0.95)	<0.001	0.910	(0.86, 0.96)	<0.001	0.921	(0.871, 0.973)	0.004
30-34 yrs	1.181	(1.13, 1.23)	<0.001	1.180	(1.13, 1.23)	<0.001	1.178	(1.13, 1.23)	<0.001	1.166	(1.117, 1.217)	<0.001
35-39 yrs	1.425	(1.35, 1.51)	<0.001	1.435	(1.36, 1.52)	<0.001	1.443	(1.37, 1.53)	<0.001	1.422	(1.345, 1.504)	<0.001
40 yrs +	1.721	(1.58, 1.87)	<0.001	1.879	(1.73, 2.04)	<0.001	2.038	(1.88, 2.21)	<0.001	1.913	(1.76, 2.08)	<0.001
AIC (11 parameters)	11167			10708			10595			10145		

Table 5.1 continued from previous page

	Suppressed values set to 0			Suppressed values set to 1			Suppressed values set to 2			Exact Likelihood Model		
C: Stratifying for and area												
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-val**
Baseline	1.00			1.00			1.00			1.00		
% non-white	1.008	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001	1.008	(1.01, 1.01)	<0.001
% born outside UK	0.999	(1, 1)	0.178	0.998	(1, 1)	0.111	0.998	(1, 1)	0.066	0.998	(0.99, 1)	0.055
% NS-SeC group 2/3	1.006	(1, 1.01)	<0.001	1.007	(1.01, 1.01)	<0.001	1.007	(1.01, 1.01)	<0.001	1.006	(1.00, 1.01)	<0.001
% unmarried	1.003	(1, 1.01)	0.001	1.003	(1, 1.01)	0.010	1.002	(1, 1)	0.050	1.002	(1.00, 1.01)	0.047
% multiple births	1.012	(0.99, 1.03)	0.261	1.006	(0.99, 1.03)	0.542	1.001	(0.98, 1.02)	0.907	1.003	(0.98, 1.02)	0.805
Age Group												
<20 yrs	0.884	(0.8, 0.97)	0.011	0.934	(0.85, 1.03)	0.157	0.985	(0.9, 1.08)	0.753	0.976	(0.89, 1.07)	0.612
20-24 yrs	0.916	(0.86, 0.97)	0.003	0.920	(0.87, 0.98)	0.005	0.924	(0.87, 0.98)	0.008	0.940	(0.89, 1.00)	0.037
30-34 yrs	1.164	(1.11, 1.22)	<0.001	1.165	(1.12, 1.22)	<0.001	1.166	(1.12, 1.22)	<0.001	1.151	(1.101, 1.203)	<0.001
35-39 yrs	1.398	(1.32, 1.48)	<0.001	1.411	(1.33, 1.49)	<0.001	1.423	(1.35, 1.51)	<0.001	1.398	(1.32, 1.481)	<0.001
40 yrs +	1.684	(1.55, 1.83)	<0.001	1.843	(1.7, 2)	<0.001	2.005	(1.85, 2.17)	<0.001	1.877	(1.73, 2.04)	<0.001
Region												
East	0.948	(0.9, 1)	0.061	0.945	(0.89, 1)	0.045	0.942	(0.89, 1)	0.034	0.942	(0.89, 1.00)	0.037
London	0.970	(0.91, 1.04)	0.374	0.970	(0.91, 1.04)	0.364	0.970	(0.91, 1.04)	0.355	0.971	(0.91, 1.04)	0.377
North East	1.030	(0.96, 1.1)	0.393	1.012	(0.95, 1.08)	0.730	0.994	(0.93, 1.06)	0.874	1.012	(0.95, 1.08)	0.735
North West	1.042	(0.99, 1.1)	0.113	1.030	(0.98, 1.08)	0.255	1.018	(0.97, 1.07)	0.486	1.028	(0.98, 1.08)	0.285
South East	1.017	(0.97, 1.07)	0.532	1.011	(0.96, 1.07)	0.675	1.006	(0.96, 1.06)	0.829	1.006	(0.95, 1.06)	0.830
South West	0.965	(0.91, 1.02)	0.233	0.961	(0.91, 1.02)	0.187	0.958	(0.9, 1.02)	0.149	0.958	(0.90, 1.02)	0.151
Wales	1.049	(0.98, 1.12)	0.155	1.035	(0.97, 1.11)	0.296	1.022	(0.96, 1.09)	0.502	1.035	(0.97, 1.11)	0.305
West Midlands	0.953	(0.9, 1.01)	0.089	0.944	(0.89, 1)	0.039	0.935	(0.89, 0.99)	0.016	0.941	(0.89, 0.99)	0.031
Yorkshire and the Humber	1.080	(1.02, 1.14)	0.005	1.063	(1.01, 1.12)	0.026	1.046	(0.99, 1.1)	0.096	1.059	(1.00, 1.12)	0.037
AIC (20 parameters)	11138			10686			10577			10124		

Comparison Between the Singularly Imputed Models

The three simpler models with suppressed values fixed at either 0, 1 or 2 (columns 1 to 3 of Table 5.1) appear to have very similar results; covariates were largely consistent in their estimates and significance levels.

When the socio-demographic covariates were considered without age or area stratification (A), all estimates were statistically significant across the three models. Country of birth and marital status appear inconsequential with odds ratios of 1. Ethnicity shows a small incremental 1% increase in the odds for stillbirth as the percentage of non-white babies in the group increases. Similarly, a 1% increase in the percentage of mothers in NS-SeC groups 2 and 3 is associated with a 1% increase in stillbirth odds. Multiple births, however, have a much larger effect with odds increasing by approximately 13% incrementally as the percentage of multiple birth cases in the group increases.

Note that since they are effectively three different datasets, it would be ill-founded to compare AIC values between models than denote their suppressed values differently (i.e. comparing across the table). We can, however, compare AIC values for models using the same dataset (i.e. down the columns of the table)

All of the models were improved by stratifying for both age group and area according to their lower AIC values, despite the extra parameters added. However, when age groups are included (B), the effect of multiple births cases in the group is no longer significant. Moreover, when area (region) is considered (C), the covariate denoting the percentage of mothers born outside the UK also ceases to be significant.

Compared to the baseline age group of 25-29 years, younger groups had reduced odds of stillbirth and older groups increased odds. Most of the suppressed values occur for the youngest and eldest age groups, which could explain why their estimates are more varied between the three singularly imputed models (and in the case of the youngest group, are less statistically significant).

Comparison of the singularly Imputed Models with the Exact Likelihood Approach

Although the differences between three singularly imputed models are very small, it is worth exploring a more sophisticated way of dealing with suppressed values, i.e. by finding the exact likelihood of each suppressed count occurring.

Like the others, the Exact Likelihood model (column 4 of Table 5.1) was improved when accounting for age group and region (C). Although many of the regional categories appear largely insignificant at the 5% level, the model's AIC value is much lower when they are included. This provides evidence for a potential association between geographic area and stillbirth that could be pursued further with random effects.

Estimates from the Exact Likelihood model very closely resemble those of the singular imputed model with suppressed values fixed at 1 (column 2). When accounting for age and region (C), the two models were consistent in which variables were significant at the 5% level. The estimates for the socio-demographic covariates and the regional levels were identical between the two models to two decimal places. Within the age groups, the Exact Likelihood model produced higher odds ratios for the youngest and oldest groups compared to the simplified model. Compared to a baseline group (women aged 25-29 in the East Midlands who are white, born in the UK, married, in NS-SeC group 1 and had a single birth), the odds of stillbirth were 15%, 40% and 88% higher respectively for women aged 30-34, 35-39 and 40+ years.

The Exact Likelihood model undoubtedly handles the suppressed data more appropriately than when modelling with the singularly imputed data, and where possible we would prefer to use this more sophisticated approach. However, this method is more complicated and time-consuming, and so for further exploration into random effects, splines and interactions, the simpler singularly imputed data (with suppressed values fixed at 1) shall act as a suitable proxy. We shall return to construct our final model is Section 5.2.5 with the Exact Likelihood function.

5.2.2 Introducing Random Effects

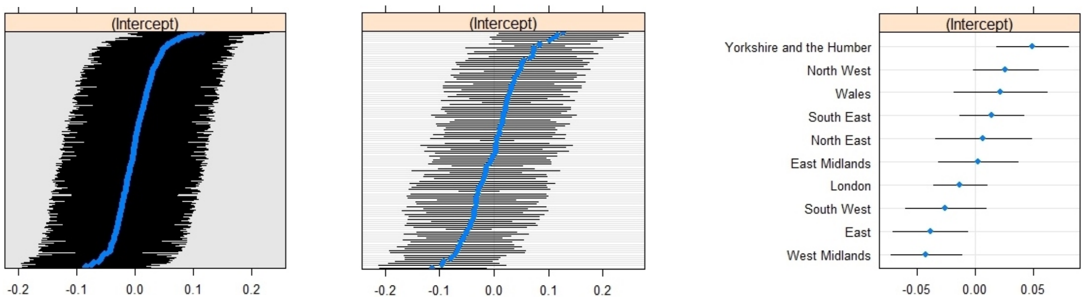
Three levels of geographic administrative boundaries were considered as random effects; local authorities (346 areas), counties (112) and regions (10 including Wales). Mixed-effects models were performed for each of these levels, considering the socio-demographic covariates and age groups, with results displayed in Table 5.2.

Fixed estimates and significance levels were near-identical between the three models, and remained consistent with the those from the fixed effects models in Table 5.1. The random effect variances, showing the among-area variability in each model, were near-zero which questioned the need for a random effect for area. When compared to the AIC values from the equivalent fixed effect model with no geographic variable (AIC = 10708 from Table 5.1), all of the mixed models had lower AIC values, implying a random effect for area was indeed suitable. Modelling geographic area at a county level gave the largest drop in deviance (AIC = 10671 from Table 5.1) and implies the best model fit.

Despite endorsement from the AIC comparison, the random effect variance seemed almost negligible. We further examined the random effect for each of the mixed models with caterpillar plots. The horizontal lines in these plots represent the 95% prediction intervals for each of the areas. Although the intervals for some areas comfortably overlapped zero, there were a sufficient number that do not to conclude that there was a need for a random effect for area within the model. This is most easily seen in Figure 5.2*c* displaying the regional random effect estimates; three out of the ten prediction intervals did not include zero.

Table 5.2: Comparison between models with local authority (LA), county and regional level random effects for England and Wales

	LA Level			County Level			Region Level		
Random Effects	**Variance**	**SD**	**Num. Groups**	**Variance**	**SD**	**Num. Groups**	**Variance**	**SD**	**Num. Groups**
	0.0046	0.068	346	0.0054	0.074	112	0.0011	0.033	10
Fixed Effects	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Baseline									
% non-white	1.01	(1.01, 1.01)	<0.001	1.01	(1.01, 1.01)	<0.001	1.01	(1.006, 1.01)	<0.001
% born outside UK	1.00	(1, 1)	0.016	1.00	(1, 1)	0.069	1.00	(0.99, 1)	0.034
% NS-SeC group 2/3	1.01	(1.01, 1.01)	<0.001	1.01	(1.01, 1.01)	<0.001	1.01	(1.01, 1.01)	<0.001
% unmarried	1.00	(1.00, 1.01)	0.015	1.00	(1.00, 1.01)	0.002	1.00	(1.00, 1.01)	0.009
% multiple births	1.00	(0.99, 1.01)	0.817	1.01	(0.99, 1.03)	0.565	1.01	(0.99, 1.03)	0.601
Age Group									
<20 yrs	0.91	(0.86, 0.96)	0.054	0.89	(0.81, 0.98)	0.021	0.92	(0.84, 1.01)	0.087
20-24 yrs	0.91	(0.87, 0.95)	0.001	0.90	(0.84, 0.95)	<0.001	0.91	(0.86, 0.97)	0.002
30-34 yrs	1.18	(1.14, 1.21)	<0.001	1.18	(1.13, 1.23)	<0.001	1.17	(1.12, 1.22)	<0.001
35-39 yrs	1.43	(1.37, 1.49)	<0.001	1.43	(1.35, 1.51)	<0.001	1.42	(1.34, 1.50)	<0.001
40 yrs +	1.87	(1.78, 1.98)	<0.001	1.86	(1.71, 2.01)	<0.001	1.85	(1.71, 2.01)	<0.001
AIC (12 parameters)	10681			10671			10694		



(a) Local Authority Districts (b) Counties (c) Regions

Figure 5.2: Caterpillar plots of random effects estimates for stillbirth rates within geographic areas within England and Wales

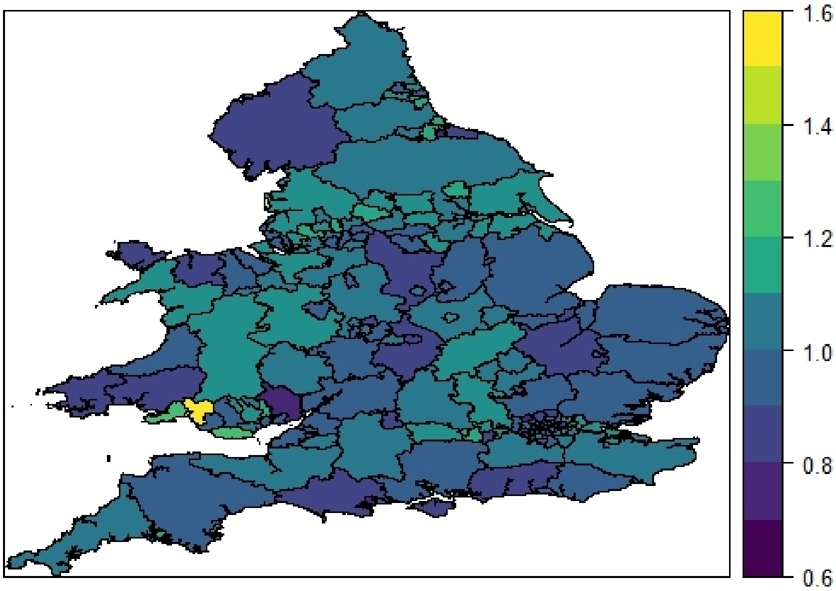
Maps Comparing Fixed and Random Estimates

We can examine the county-level random effects visually through maps. Figure 5.3*a* shows the counties colour-coded by the exponentiated estimates for their random effect. Figure 5.3*b* shows the counties colour-coded by odds ratio for an equivalent fixed model, considering county as a fixed effect. For the fixed model, Bedford was assigned as the baseline county, as its stillbirth and live birth counts best reflected the national average in each age group. The estimated random effect deviations in the mixed model were also adjusted to centre around Bedford for comparison.

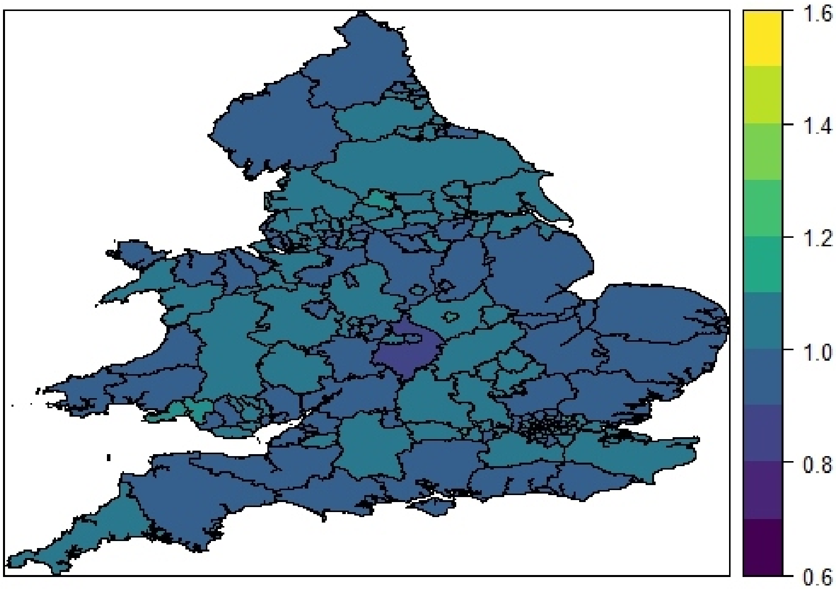
The maps appear very similar. The odds ratios in the fixed model range between 0.62 and 1.42 while the mixed model gives a more conservative estimate range of 0.76 to 1.39. This is because random estimates are calculated with partial pooling and therefore avoid the more extreme estimates that can be calculated when the group population is very low.

Summary of Mixed Effects Results

To summarise, we found that ethnicity, country of birth, socio-economic status and marital status have a significant association with stillbirth counts in England and Wales at the aggregate level, as does the mother's age. Our model improved when random effects for area were added, which suggests that there are important unmeasured explanatory variables for each area that influence stillbirth counts in a way that seems random because we do not know the value(s) of missing explanatory variable(s). The largest drop in model deviance occurred when the random effect was measured at a county level. Therefore, this county-level mixed effects model accounting for our known covariates and age groups was chosen for further analysis.



(a) Map of exponentiated random effect estimates



(b) Map of odds ratios for the fixed effect of county (baseline Bedford)

Figure 5.3: Comparison of fixed and random effects estimates for the effect of county on stillbirth rates in England and Wales

5.2.3 Introducing Splines

In all previous analysis of the dataset, the five socio-demographic covariates were considered to have a linear relationship with stillbirth rate. In this section, splines were used to explore whether a potential non-linear relationship existed.

Once more, a mixed model was considered, containing the fixed socio-demographic covariates and age groups in addition to a random effect for county. As in all preceding analyses using mixed models, the suppressed stillbirth counts are singularly imputed to be 1.

A systematic trial-and-error approach, described in Section 5.1.3, was used to determine the most appropriate knot placements for the spline model. Firstly, each continuous covariate was investigated one at a time within the model, with the other covariates remaining linear, to determine the optimal number and placement of knots for each covariate using B-splines.

For all covariates except country of birth, knots were found that improved the model fit and suggested a piecewise linear effect for that covariate. The most influential knot selections (according to AIC) are displayed in Table 5.3.

Table 5.3: Optimal knot placements for the piecewise splines model for England and Wales

Variable	Num. Interior Knots	Interior Knots	Boundary Knots
Ethnicity	1	3	0, 82
NS-SeC	2	36, 83	8.8, 100
Marital status	2	37, 86	13, 99
Multiple births	2	1.4, 2.6, 3.5	0.4, 11

Higher order splines (quadratic, cubic and higher polynomials) were then considered, but none improved the model fits.

Model Selection of Splines

The B-spline functions for each variable were then added to our existing mixed effects model one at a time in a bi-directional stepwise manner; beginning with the covariate that had the largest drop in AIC value from the spline functions. This covariate was NS-SeC, measuring the percentage of women in each stratum with a lower NS-SeC status. After that, the variable with the second largest spline effect was marital status, then the percentage of multiple birth cases, then ethnicity. Country of birth was considered both as a linear covariate and in piecewise segments, but neither brought improvement to the fit and so it was removed from the model entirely. This model selection process can be seen in Table 5.4, along with the step-wise AIC values.

Table 5.4: Model selection for piecewise spline functions on covariates for England and Wales

	AIC	**Parameters**
Model with linear covariates	10671	12
...+ NS-SeC spline...	10659	14
...+ marital status spline...	10658	16
...+ multiple births spline...	10654	19
...+ ethnicity spline...	10653	20
...remove country of birth entirely	10653	19

Optimal Model using Splines

Table 5.5 shows results for the final splines model with its piecewise linear splines (again, using the singularly imputed data with suppressed birth counts fixed to 1).

Table 5.5: Model selected splines model (singularly imputed data) for England and Wales

Random Effects	**Variance**	**SD**	**Num. Groups**
County	0.0058	0.07601	112
Fixed Effects	**OR**	**95% CI**	**p-value**
Baseline			
% non-white: 3%	1.258	(1.02, 1.56)	0.0331
% non-white: 82%	2.125	(1.69, 2.68)	<0.001
% NS-SeC group 2/3: 36%	1.354	(1.20, 1.53)	<0.001
% NS-SeC group 2/3: 83%	1.702	(1.45, 2.01)	<0.001
% NS-SeC group 2/3: 100%	1.490	(1.11, 2.01)	0.0084
% unmarried: 37%	1.147	(1.05, 1.26)	0.0037
% unmarried: 86%	1.305	(1.11, 1.54)	0.0017
% unmarried: 99%	1.619	(1.27, 2.07)	<0.001
% multiple births: 1.4%	1.208	(1.04, 1.40)	0.0117
% multiple births: 2.6%	1.165	(1.00, 1.36)	0.0474
% multiple births: 3.5%	1.258	(1.07, 1.48)	0.0052
% multiple births: 11%	1.185	(0.93, 1.51)	0.1689
Age Group			
<20 yrs	1.063	(0.87, 1.30)	0.5518
20-24 yrs	0.961	(0.89, 1.04)	0.3288
30-34 yrs	1.112	(1.04, 1.19)	0.0016
35-39 yrs	1.349	(1.25, 1.46)	<0.001
40 yrs +	1.789	(1.63, 1.96)	<0.001
AIC	10653	(20 parameters)	

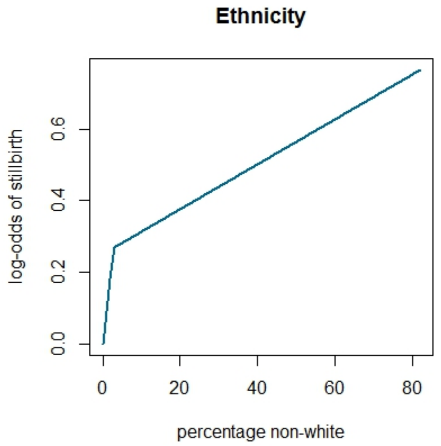
The intercept refers to a hypothetical baseline aggregate group of mothers aged 25-29 whose demographic corresponds to the minimum values for each covariate in the observed data (see Table 4.2 for these minimum values). All of the included socio-demographic variable estimates appear significant with the exception of one spline interval for multiple births.

Interpreting spline estimates The spline odds ratio estimates can be a little challenging to interpret (see Equation 5.12 in Section 5.1.3 for more detail). Figure 5.4 aids understanding with a plot of the log odds for the spline function for each covariate. The plots show the optimal knots for each covariate (where the lines connect) and their effect on the stillbirth log-odds as the percentage increases with each covariate. The observed minimum value for each covariate is treated as the baseline; the log-odds estimates are calculated only for the variable's range in the data.

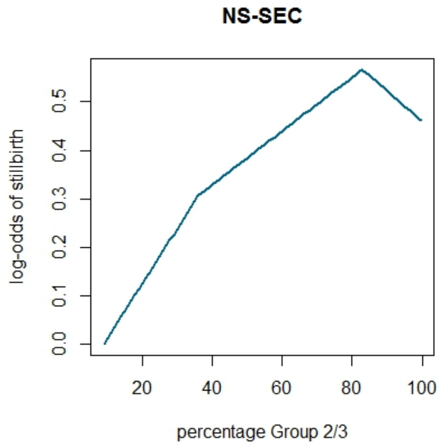
For an example using the baby's ethnicity, the log-odds for a group with 3% non-white babies compared to a baseline minimum 0% is 0.229 (corresponding to the odds ratio estimate 1.258 in Table 5.5). Since the effect is linear between 0-3% This suggests that the log-odds of stillbirth increase by 0.076 for each additional percentage of non-white babies in the group up to the knot at 3%, and so for covariate x values between 0 and 3, the log-odds are $0.076x$.

At the next knot, we see that the odds ratio for a group with 82% non-white babies is 2.215, and so the log-odds is 0.754. The linear rate of change between the knots at $x = 3$ and $x = 82$ must, therefore, be $(0.754 - (0.0764 \times 3))/(82 - 3) = 0.00665$, i.e. the log odds increase by 0.0066 for each additional percentage of non-white babies in the group after 3%. For example, a group with 70% non-white babies would have an odds ratio of $1.258 + 0.0066 \times 70 = 1.72$ for stillbirth compared to an all-white group.

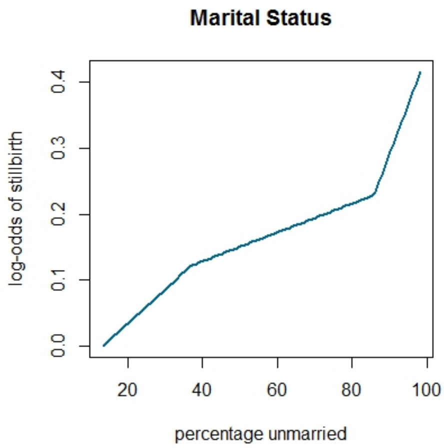
Looking at the overall variable effects in Figure 5.4, for ethnicity and marital status, the log-odds of stillbirth are monotonically increasing as the percentage of non-white babies and unmarried women increase, respectively. For socio-economic position, the log-odds generally increase as the percentage of mothers in NS-SeC Group 2/3 increase but reverse somewhat when the percentage of these groups go beyond 83%.



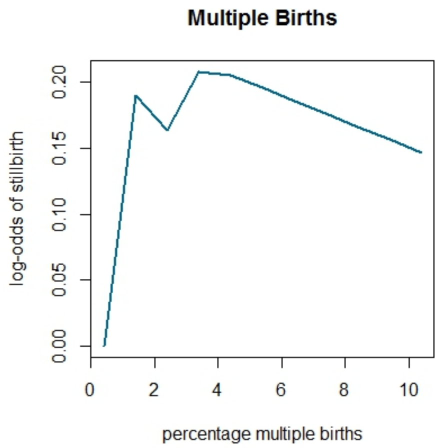
(a) Ethnicity and the log-odds of stillbirth
knot at 3%



(b) Socio-economic position and the log-odds of stillbirth
knots at 36% and 83%



(c) Marital Status and the log-odds of stillbirth
knots at 37% and 86%



(d) Multiple Births and the log-odds of stillbirth
knots at 1.4%, 2.6% and 3.5%

Figure 5.4: Effect of covariates' piece-wise linear spline functions on the log-odds of stillbirth

The effect of multiple births on stillbirth seems to be the most changeable as the percentage of multiple birth events increase in the group. Figure 5.4*d* shows that there are three turning points between 1.4% and 3.5% in which the log-odds shift from drastically increasing to decreasing effect. Practically speaking, they do not all seem necessary. A simplified version of this spline was investigated that removed the middle knot at 2.6% entirely, but this resulted in an increased AIC value and therefore a worse-fitting model. We note that almost half of the observed groups have multiple birth percentages that fall between 1.4 and 3.5, perhaps justifying this seemingly erratic behaviour of the piecewise splines.

There were no knots found in the covariate for country of birth that improved the model in comparison to its linear version.

It was possible that the non-linear relationships between stillbirth and the covariates discovered could be better explained by splitting the data into categories rather than segments of different linear functions. A version of the optimal model was constructed, this time treating each covariate at categorical with the categories divided at the same knot points. This resulted in a model with an AIC value 10892, much higher than the spline model's 10652. This suggests that the spline model with the segments of linear functions captures the non-linear relationships between variables more appropriately.

5.2.4 Introducing Interactions

Interactions between the socio-demographic variables were considered in a similar, systematic way to the splines. There were 15 potential interactions between ethnicity, NS-SeC level, marital status, multiple birth status and age.

A bi-directional stepwise selection procedure was applied to the full model including all potential interaction terms to determine which combination of these (if any) to include in the model, with model fit measured by AIC. The resulting optimal model included two interactions; between marital status and multiple birth status, as well as between marital status and socio-economic position. The estimates for this model are displayed in the first half of Table 5.6.

The positive coefficient for the interaction term between NS-SeC level and marital status implies that the higher the percentage of unmarried mothers in the observed group, the greater the effect of socio-economic status on stillbirth. This suggests that married women's socio-economic status does not impact their risk of stillbirth as much as unmarried women, potentially because they are more likely to have economic security from their spouse. Conversely, the interaction suggests that for women of higher socio-economic position, their marital status does not impact their risk of stillbirth as much as it does for disadvantaged women, whose risk might be more closely affected by whether there is a partner to help provide.

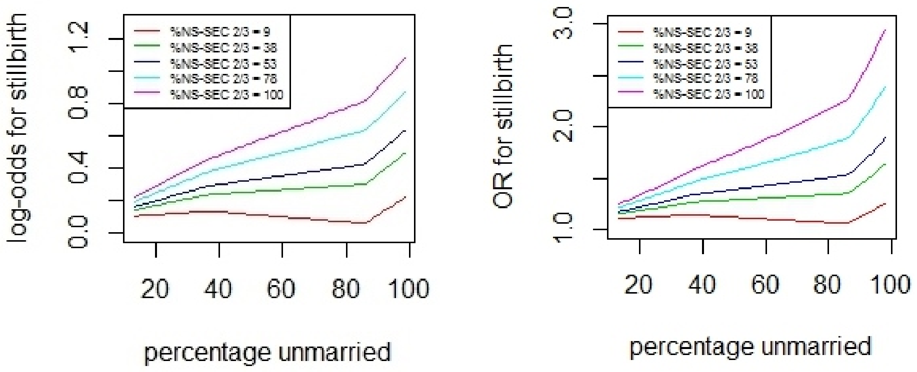
In the same way, the positive interaction coefficient between marital status and multiple births status suggests that the higher the percentage of unmarried mothers in the group, the greater the impact that multiple birth status has on stillbirth, and vice versa.

With the inclusion of the interaction estimates, many of the covariate estimates themselves vary greatly from the previous model (Table 5.5) and were no longer significant in terms of their p-values. The estimates for marital status and multiple birth status switch direction from an increasing to decreasing effect on the odds of stillbirth, mostly likely to "balance out" the interaction effects.

Table 5.6: Final selected model with splines and interactions (singularly imputed data) for England and Wales

Random Effects	**Variance**	**SD**	**Num. Groups**
	0.0058	0.07603	112
Fixed Effects	**OR**	**95% CI**	**p-value**
Baseline	1		
% non-white: 3%	1.266	(1.02, 1.56)	0.029
% non-white: 82%	2.142	(1.70, 2.70)	<0.001
% NS-SeC group 2/3: 36%	1.251	(1.09, 1.44)	0.001
% NS-SeC group 2/3: 83%	1.301	(0.93, 1.83)	0.127
% NS-SeC group 2/3: 100%	0.978	(0.54, 1.78)	0.941
% unmarried: 37%	0.851	(0.68, 1.07)	0.160
% unmarried: 86%	0.531	(0.25, 1.12)	0.097
% unmarried: 99%	0.565	(0.22, 1.42)	0.226
% multiple births: 1.4%	0.934	(0.75, 1.17)	0.546
% multiple births:2.6%	0.740	(0.53, 1.03)	0.074
% multiple births:3.5%	0.735	(0.50, 1.08)	0.116
% multiple births: 11%	0.393	(0.18, 0.84)	0.016
Age Group			
<20 yrs	1.022	(0.83, 1.25)	0.838
20-24 yrs	0.931	(0.85, 1.02)	0.111
30-34 yrs	1.113	(1.04, 1.19)	0.002
35-39 yrs	1.359	(1.26, 1.47)	<0.001
40 yrs +	1.765	(1.61, 1.94)	<0.001
Interactions			
NS-SeC*marital status	1.0001	(1, 1)	0.129
marital status*multiple births	1.002	(1.00, 1.01)	0.003
AIC	10646	21 parameters	

The combination of splines and interactions makes it difficult to interpret the covariates' overall impact on stillbirth. Take, for example, the effect of marital status. Figure 5.5a shows how the two interaction terms affect the log odds of stillbirth as the percentage of unmarried women in the area increases. These odds were explored at 5 evenly spaced values for the percentage of women of NS-SeC level 2 or 3 in the group. For simplicity, the multiple birth status in the interaction was fixed at its median 3%. The interaction coefficients may have seemed trivial, but for a group with the average percentage of unmarried mothers (42%), the odds ratio for stillbirth ranges from 1.13 to 1.63 depending on the NS-SeC demographic. for a group with 70% unmarried mothers, the odds ratio ranges between 1.09 and 1.99.



(a) Stillbirth log-odds for various % values of marital status and NS-SeC level

(b) Stillbirth odds ratios for various % values of marital status and NS-SeC level

Figure 5.5: Effect of covariates' piece-wise linear spline functions and their interactions on the log-odds and odds ratios for stillbirth *(Multiple Birth Status fixed at 3%)*

At this point, it was briefly considered to reintroduce the previously removed covariate for mother's country of birth. Although not significant to the model itself, it may have a significant interaction with another variable. However, with the covariate re-introduced, the stepwise model selection process did not find a model with a more improved fit that the current model in Table 5.6

A fixed effects version of the model (without the random effect for counties) was also conducted for comparison. Its AIC value (10691) being larger than the mixed model's (AIC = 10646) suggests that the random effect component is still worth including.

5.2.5 Final Model with Exact likelihood Function

Now that the model selection process has been streamlined using the singularly imputed data, we return to the more sophisticated Exact Likelihood function to model the suppressed data. Repeating the final mixed effects model with splines and interactions from Section 5.2.4, Table 5.7 shows the equivalent odds ratios, 95% confidence intervals, and p-values using the Exact Likelihood method. Random effects were estimated using the Gaussian Quadrature approach discussed in Section 5.1.2. A fixed effects version of the model was also conducted for comparison.

Table 5.7: Final model (with Exact Likelihood approach) for England and Wales, with interactions included

	Mixed Effects Model			Fixed Effects Model		
Random Effects	**Variance**	**SD**	**Num Groups**			
County	0.0055	0.0743	112			
Fixed Effects	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
% non-white: 3%	1.26	(1.019, 1.564)	0.039	1.48	(1.208, 1.821)	<0.001
% non-white: 82%	2.11	(1.673, 2.659)	<0.001	2.34	(1.898, 2.882)	<0.001
% NS-SeC group 2/3: 36%	1.34	(1.190, 1.514)	<0.001	1.42	(1.271, 1.587)	<0.001
% NS-SeC group 2/3: 83%	1.69	(1.428, 1.996)	<0.001	1.96	(1.694, 2.263)	<0.001
% NS-SeC group 2/3: 100%	1.48	(1.09, 2.01)	0.012	1.69	(1.27, 2.26)	<0.001
% unmarried: 37%	1.08	(0.91, 1.28)	0.473	1.39	(1.19, 1.62)	<0.001
% unmarried: 86%	1.14	(0.80, 1.61)	0.588	2.03	(1.48, 2.79)	<0.001
% unmarried: 99%	1.41	(0.93, 2.02)	0.137	2.63	(1.80, 3.85)	<0.001
% multiple births: 1.4%	1.14	(0.91, 1.43)	0.317	1.55	(1.26, 1.92)	<0.001
% multiple births: 2.6%	1.03	(0.74, 1.45)	0.978	1.82	(1.34, 2.48)	<0.001
% multiple births: 3.5%	1.09	(0.74, 1.61)	0.785	2.10	(1.48, 3.00)	<0.001
% multiple births: 11%	0.87	(0.41, 1.88)	0.565	3.59	(1.80, 7.16)	<0.001
Age Group						
<20 yrs	1.07	(0.87, 1.32)	0.505	1.03	(0.84, 1.25)	0.805
20-24 yrs	0.96	(0.89, 1.04)	0.341	0.93	(0.86, 1.00)	0.063
30-34 yrs	1.11	(1.04, 1.19)	0.001	1.12	(1.06, 1.20)	<0.001
35-39 yrs	1.36	(1.26, 1.47)	<0.001	1.38	(1.29, 1.49)	<0.001
40 yrs +	1.82	(1.66 2.00)	<0.001	1.94	(1.77, 2.12)	<0.001
Interactions						
NS-SeC*marital status	1.00	(1.00, 1.00)	1.000	1.00	(1.00, 1.00)	1.000
marital status*multiple births	1.00	(1.00, 1.00)	0.417	1.00	(1.00, 1.00)	<0.001
AIC	10090	21 parameters		10166	20 parameters	

There are some similarities between the mixed model and the singularly imputed version of the same model (Table 5.6); the estimates for ethnicity and the age groups follow similar patterns to their singularly imputed counterparts, and the interactions are the same, although they are no longer significant. The estimates for marital status and multiple birth status have switched again from a having a negative to a positive effect on the stillbirth log-odds, more closely resembling the estimates from the models without interactions.

Since the interaction terms appear trivial and not significant, the Exact Likelihood model was repeated, this time without interaction terms. Estimates for this model are displayed in Table 5.8. Once more, a fixed effects version of the model was also included for comparison. Note the AIC value of 10088 is slightly lower than the previous model, suggesting a better fit.

Number of Gaussian Quadrature points. To confirm that the effect estimates calculated with the Gaussian Quadrature approach had stabilised, the two models (with and without interaction terms) were computed with B = 20, 50, 100, 200, 300 and 500 quadrature points. The results displayed in this section are estimated from 500 quadrature points.

In the model without interactions (Table 5.8), the estimates and their standard errors had stabilised with 50 quadrature points. With interactions, however (Table 5.6), the model required up to 500 quadrature points before the estimated appeared to stabilise.

Therefore, due to its lower AIC value and more stable estimates, our final model is the Exact Likelihood model including splines but not interactions.

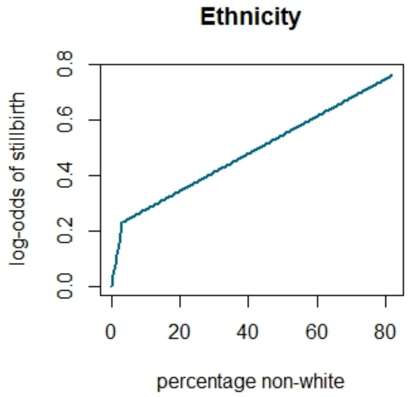
Table 5.8: Final Model (with Exact Likelihood approach) for England and Wales, with interactions removed

	Mixed Effects Model			Fixed Effects Model		
Random Effects	**Variance**	**SD**	**Num Groups**			
County	0.0055	0.0742	112			
Fixed Effects	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Baseline						
% non-white: 3%	1.26	(1.02, 1.56)	0.033	1.32	(1.08, 1.62)	0.007
% non-white: 82%	2.11	(1.68, 2.66)	<0.001	2.09	(1.70, 2.57)	<0.001
% NS-SeC group 2/3: 36%	1.35	(1.20, 1.53)	<0.001	1.38	(1.23, 1.54)	<0.001
% NS-SeC group 2/3: 83%	1.71	(1.45, 2.02)	<0.001	1.86	(1.61, 2.14)	<0.001
% NS-SeC group 2/3: 100%	1.49	(1.10, 2.02)	0.010	1.60	(1.20, 2.13)	0.001
% unmarried: 37%	1.14	(1.04, 1.25)	0.005	1.11	(1.02, 1.21)	0.015
% unmarried: 86%	1.29	(1.09, 1.52)	0.003	1.20	(1.03, 1.39)	0.016
% unmarried: 99%	1.61	(1.26, 2.06)	<0.001	1.48	(1.18, 1.85)	<0.001
% multiple births: 1.4%	1.22	(1.05, 1.42)	0.012	1.21	(1.04, 1.41)	0.013
% multiple births: 2.6%	1.17	(1.00, 1.37)	0.047	1.16	(1.00, 1.36)	0.057
% multiple births: 3.5%	1.26	(1.07, 1.49)	0.006	1.22	(1.04, 1.44)	0.015
% multiple births: 11%	1.18	(0.92, 1.51)	0.193	1.11	(0.87, 1.42)	0.388
Age Group						
<20 yrs	1.07	(0.86, 1.32)	0.496	1.09	(0.89, 1.32)	0.416
20-24 yrs	0.96	(0.89, 1.04)	0.346	0.96	(0.89, 1.03)	0.229
30-34 yrs	1.11	(1.04, 1.19)	0.002	1.14	(1.07, 1.21)	<0.001
35-39 yrs	1.35	(1.25, 1.46)	<0.001	1.39	(1.30, 1.50)	<0.001
40 yrs +	1.83	(1.66, 2.01)	<0.001	1.90	(1.74, 2.08)	<0.001
AIC	10088	19 parameters		10129	18 parameters	

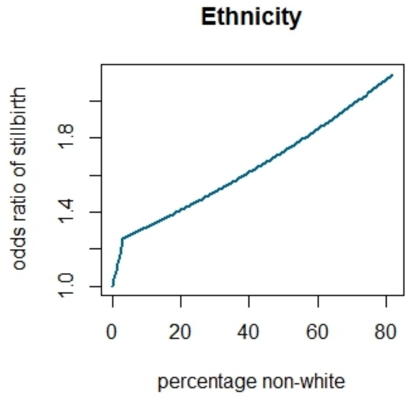
Final Model

The estimates for our final model were displayed previously in Table 5.8. Each odds ratio is compared to a hypothetical baseline aggregate group of mothers aged 25-29 whose demographic corresponds to the minimum values for each covariate in the observed data.

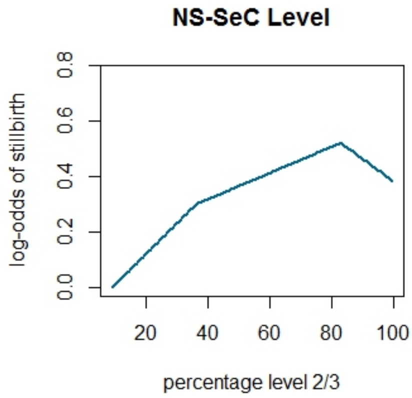
To aid interpretation of the table, Figure 5.6 displays the stillbirth log-odds and odds ratio estimates for the spline function of each covariate. The observed minimum value for each covariate is treated as the baseline; the log-odds estimates are calculated only for the variable's range in the data.



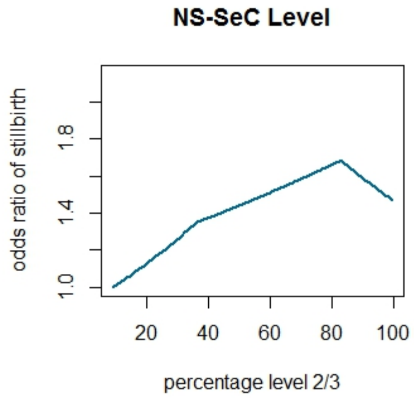
(a) Ethnicity and the
log-odds for stillbirth
knot at 3%



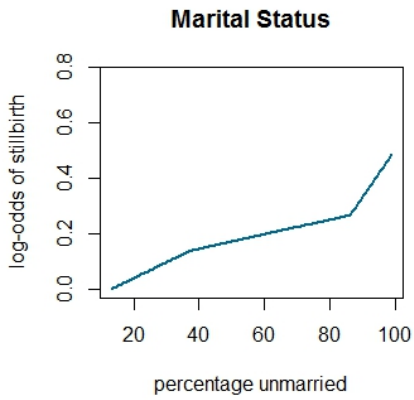
(b) Ethnicity and the
odds ratio for stillbirth
knot at 3%



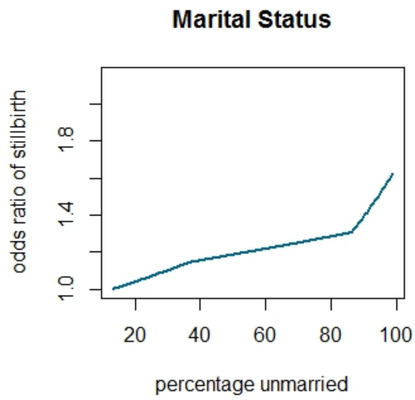
(c) Socio-economic position and the
log-odds for stillbirth
knots at 36% and 83%



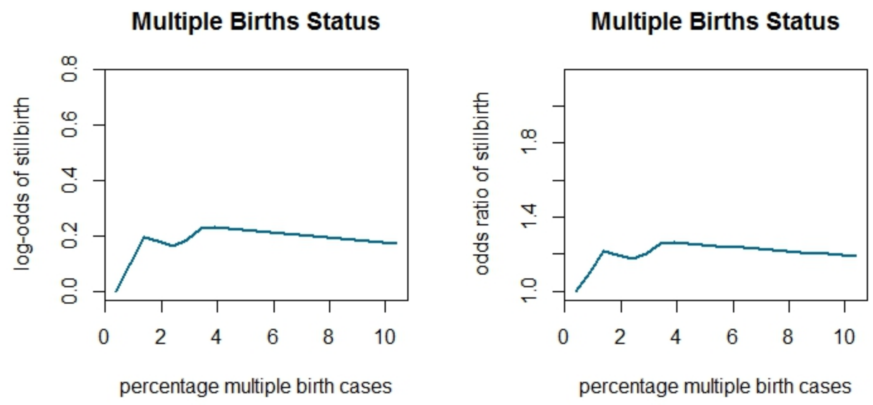
(d) Socio-economic position and the
odds ratios for stillbirth
knots at 36% and 83%



(e) Marital status and the
log-odds for stillbirth
knots at 37%, 86%



(f) Marital status and the
odds ratios for stillbirth
knots at 37%, 86%



(g) Multiple births and the log-odds for stillbirth
knots at 1.4%, 2.6% and 3.5%

(h) Multiple births and the odds ratios for stillbirth
knots at 1.4%, 2.6% and 3.5%

Figure 5.6: Effect of covariates' piece-wise linear spline functions on the log-odds of stillbirth in the final Exact Likelihood model

Fixed effects Compared to the baseline age group (25-29 years) in the mixed effects model, the odds for younger mothers were not significantly different. Older groups had increasingly worse odds of stillbirth with odds increasing by 11%, 35% and 83% compared to the baseline for women aged 30-34, 35-39 and 40+ respectively.

Looking to the socio-demographic covariates, the odds ratio for a group with 3% non-white babies compared to a baseline 0% was 1.26. Using the formula from Equation 5.12 in Section 5.1.3, we can calculate that the log-odds of stillbirth increased by 0.077 for each additional percentage of non-white babies in the group up to 3%. Given that the odds ratio for stillbirth for a group with 82% non-white babies was 2.11, we can further calculate that the log-odds increased by 0.007 for each additional percentage of non-white babies in the group between 3% and 82%. For example, a group with 30% non-white babies would have an odds ratio of $1.26 + 0.007 \times 30 = 1.53$ compared to an all-white group.

The patterns in these figures are consistent with the graphs for spline estimates from the singularly imputed model in Section 1.2.3. For ethnicity and marital status, the log-odds of stillbirth are monotonically increasing as the percentage of non-white babies and unmarried women increase respectively. Regarding socio-economic position, the log-odds generally increase as the percentage of mothers with lower NS-SeC levels increase but reverse somewhat when the percentage of these groups goes beyond 83%. The effect of multiple birth status is the most changeable, with three turning points between 1.4% and 3.5% in which the log-odds shift drastically from increasing to decreasing and back again before gradually decreasing as the percentage of multiple birth cases in the area exceeds 3.5%. All of the included socio-demographic variable estimates appear significant with the exception of one spline interval for multiple births.

Interpreting odds as probabilities and rates While odds ratios are informative, they are not directly or easily interpretable to non-researchers. With this in mind, we translated these study results from odds to probabilities and rates to better suit policy-relevant discussions. Our final model's log-odds estimates were input into the logit equation described in Methods Section 5.1.1 (Equation 5.1), which can in turn be transformed into a probability (Equation 5.2). The logit function for piecewise linear splines (Equation 5.12) was also incorporated. The resulting probabilities were relatively small and are perhaps more easily interpreted as stillbirth rates (per 1000 births).

Consider a hypothetical baseline aggregate group of mothers aged 25-29 whose demographic corresponds to the minimum values for each covariate in the observed data (see Table 4.2 for these minimum values). The probability of stillbirth for this baseline group is 0.00226, or 2.3 stillbirths per 1000 births. Keeping all other covariates the same as for the baseline group, the probabilities for age groups 30-34, 35-39 and 40+ years increase to 2.5, 3.1 and 4.1 stillbirths per 1000 births respectively.

Regarding ethnicity, mothers in groups with 5% non-white babies have probability 0.00290 of having a stillbirth, or a rate of 2.9 per 1000 births, while those in groups with 25%, 50% and 75% non-white babies have much higher rates of 3.5, 4.4 and 5.6 per 1000 births, respectively. Similarly, groups where 25% of mothers are in NS-SeC Levels 2 or 3 have stillbirth probability 0.00271 or 2.7 per 1000 births. This rate increases to 3.6, and then 4.8 per 1000 births for groups with 50% and 75% mothers in these NS-SeC levels.

Concerning marital status, groups with 25% unmarried mothers have stillbirth rates of 2.4 per 1000, while the rate for groups with 75% unmarried mothers is 3.1 per 1000 births. Finally, a group in which 2% of pregnancies result in multiple births (twins, etc) has a rate of 3.0 stillbirths per 1000 births, but for a group with 5% multiple birth pregnancies, the rate increases to 6.5 per 1000 birth.

Random effects The variance of the random effects is reasonably low at 0.06, suggesting a very small amount of heterogeneity between counties across all age groups and demographics. The largest estimated random effect was found for Blackpool, equating to a 14% increased odds stillbirth, but the majority of estimates were much smaller.

A fixed effects version of the model was also conducted since, on the surface, the random effects seem practically negligible. However, the smaller AIC value indicates that despite the small random effects variance, the mixed effects model is superior to the fixed effects model. This suggests that there are important unmeasured explanatory variables for each county that influence stillbirth counts in a way that seems random because we do not know the value(s) of such missing explanatory variable(s). The variability could also be explained by the unknown distribution of the aggregated covariates within the groups, for example, the proportions of stillbirths that were from unmarried mothers.

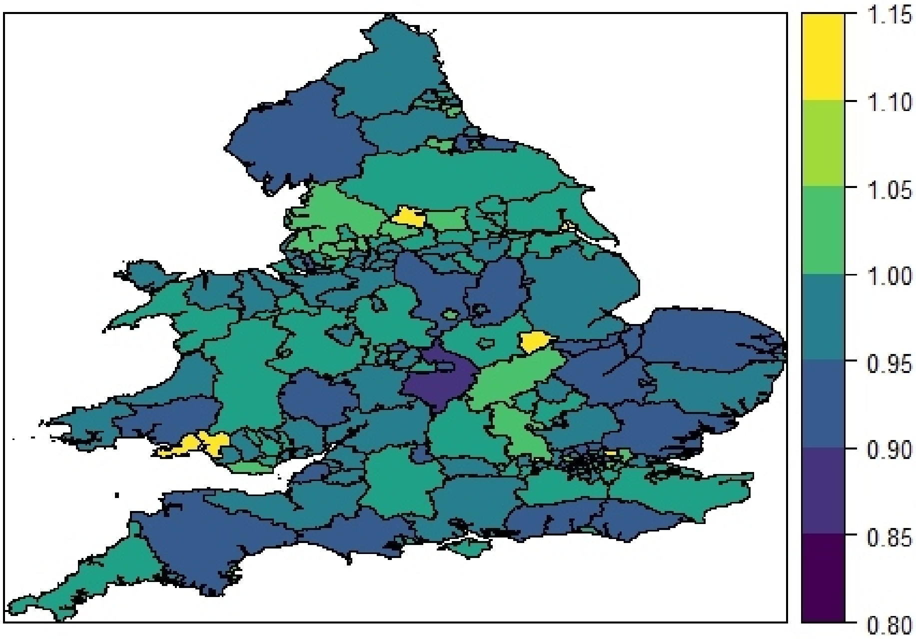


Figure 5.7: Random effects estimates for the effect of county on stillbirth rates in England and Wales

5.3 Discussion of the England and Wales Analysis

In this chapter, we have presented an analysis of aggregate birth data in England and Wales, where the observed birth and stillbirth counts are grouped by local authority (LA) district and are stratified by age. This section assesses the use of aggregate data, summarises the findings of this analysis and attempts to place them in the context of previous literature. It also reviews the strengths and limitations of the methods used.

5.3.1 Working with Aggregate Data

Individual-level birth data from the ONS has been obtained for research (MBRRACE-UK Collaboration, 2016), but access to this data requires lengthy processes of approval from the Confidential Advisory Group at the Health Research Authority (HRA), and the Data Access Advisory Group (DAAG) (HRA, 2017; NHS Digital, 2018). These processes provide no guarantee of permission for the use of data in PhD projects, and as we were unable to meet these requirements in the given time frame, we compromised with aggregate-level data.

The counts of births and stillbirths were broken down by local authority (LA) and age group. Smaller administrative areas, such as super output areas (SOAs) have been used for ecological research in the UK, but for a relatively rare event such as stillbirth, the counts per area would be too low for meaningful analysis; many would have no stillbirths at all in the given period. For the same motivation of obtaining large enough counts in each area, this study data covers the period 2006-2014. An analysis of stillbirth data by Seaton et al. (2012) used SOAs for two three-year intervals but could not account for ethnicity, lifestyle, health or even age. Our study compromises on area size but compensates with more detailed covariate information.

Investigating cross-level bias: As with many studies of aggregate data, this analysis may suffer from the well-known *ecological fallacy* (cross-level bias), in which population-level association erroneously implies individual-level association. Association at a population level does not necessarily reflect the magnitude, or even direction, of the effect at an individual level (Robinson, 1950), and so it is difficult to say anything causal about the relationships between variables. Cross-level bias could inflate parameter estimates, or even suggest a parameter estimate with a counter-intuitive relationship to stillbirth. There is a multitude of potential causes of cross-level bias in an aggregate analysis, many of which are demonstrated by **?** and some of which could apply to our study. There could be a group-level confounding risk factor, for example district-level care services that would influence individual stillbirths in that area. The LA districts themselves could be confounding, for example if the distribution of individual risk factors differs by LA (Weiss and Koepsell, 2014). We have tried to combat this potential bias by stratifying for age.

Advantageously, we did have a covariate value (%) for each age/LA stratum, which is not often available in ecological data where covariates may only be given by area. Care has been taken in interpretation to not infer an individual relationship for associations between variables at an aggregate level.

Variable availability: The data contained a very limited selection of explanatory variables with four socio-economic characteristics and one birth-related characteristic. Nominal categories were combined into binary indicators (e.g. white/non-white) and thus were not particularly detailed. However, detailed breakdowns of the categories would have resulted in even smaller cell counts and necessitated further suppression, hindering their usefulness. Including the variables as binary indicators was a compromise to prevent further loss of information.

5.3.2 Summary of Findings

Multivariate analysis showed all of the socio-demographic variables to be significant when accounting for age and region of residence, with the exception of mother's country of birth and multiple birth status (the percentage of birth events that resulted in twins, or more, in that group). Compared to a baseline group of white infants, the odds of stillbirth were seen to increase incrementally as the percentage of non-white infants in the observed group increased. Similar associations were found for increases in the percentage of unmarried mothers, multiple birth cases and women of lower/middle socio-economic classification (NS-SeC Level 2 or 3).

Compared to a baseline age group of 25-29 years, older mothers had increased odds of stillbirth while younger mothers had reduced odds. No significant difference was found for the youngest age group (<20 years), likely due to low birth counts and high suppression in this group.

Evidence of a significant geographic effect on stillbirth at the regional level prompted an investigation into random effects. Random effects were used due to the unrealistic number of parameters that a fixed effect for area would require. Three administrative levels of geography were considered: local authority, county and region. A very small but statistically significant amount of heterogeneity between areas was discovered for all levels of geography, with county-level random effects providing the best model fit.

B-spline functions – connected linear pieces – were used to transform each covariate into piecewise linear functions, connected at a small number of "knots", which exposed non-linear relationships between many of the covariates and stillbirth. In the presence of splines in the multivariate model, no significant association was found between stillbirth and the mother's country of birth (likely due to a high correlation with ethnicity), and so this variable was removed from the model.

Regarding ethnicity, compared to an all-white group, the odds of stillbirth were seen to increase dramatically as the percentage of non-white infants increased from 0% up to 3%, where such a group had a 26% increased odds of stillbirth. From there, the increase was less extreme but by no means diminished; the groups with the highest percentage of none-white babies had more than double the odds of stillbirth. Marital status had a similarly increasing effect, albeit less severe.

Socio-economic classification also had a considerable association with stillbirth. The odds generally increased as the percentage of low/ middle-class mothers (according to the NS-SeC) in the group increased. The risk peaked for groups with 86% low/ middle-class mothers, where the odds for stillbirth were nearly 70% higher than for a baseline group with the lowest proportion of these women. From there, however, the odds decreased slightly – groups with entirely low/ middle-class women had lower odds of stillbirth than some of the more socio-economically diverse groups. This occurrence of poorer health outcomes for disadvantaged people in relatively wealthy areas compared to more homogenously deprived areas has previously been observed in the UK (Sloggett and Joshi, 1998).

The effect on stillbirth of multiple birth cases in the group was the most changeable, but also the smallest in magnitude. Generally, age/LA groups with a higher percentage of multiple birth events had higher odds of stillbirth than the baseline group with no multiple births, but no significant association can be seen for any groups with more than 3.5% multiple birth events.

From there, the model was extended to include interactions to determine the existence of inter-covariate relationships that affected the stillbirth outcome. Despite the potential for a significant interaction in the singularly imputed data (where suppressed stillbirth counts were fixed at 1), the more sophisticated Exact Likelihood model did not necessitate them for the final model. It is probable that the singularly imputed models had more variability to account for, compared to the Exact Likelihood model, and therefore required more complicated terms to account for it.

Overall, these results suggest that the baby's ethnicity and the mother's age have the biggest influence on the odds of experiencing a stillbirth, but that socio-economic status, marital status and multiple births also play a considerable role. Nevertheless, there is still variation in stillbirth risk between counties that is unaccounted for in our observed variables.

Comparison with the literature

Reports from MBRRACE-UK, analysing national birth data annually since 2013, also investigate perinatal mortality at a local authority level. Using a multi-level analysis, they calculate stabilised and adjusted stillbirth rates for each area (adjusting for individual ethnicity, age, multiple birth status and area deprivation quintile). The goal of the reports is to identify particular areas in the UK where perinatal mortality rates are more than 10% higher than average. The ranking of these areas changes drastically year on year and thus are difficult to compare with our study, which encompasses the period 2006-2014. However, the map produced in Figure 5.7 is generally similar to those in the MBRRACE-UK reports.

Overall, the covariate effects agree with the findings from the MBRRACE-UK 2016 report on stillbirth, which calculated unadjusted rate ratios at an individual-level for all UK births in 2014 by age group, ethnicity, deprivation quintile, and multiple birth status.

Ethnicity has been suggested to play a vital role in stillbirth risk in UK studies, with distinctly higher odds for black and South-east Asian women compared to white women and different pathways to stillbirth for specific ethnicities (Smeeton et al., 2004; Balchin et al., 2007; MBRRACE-UK Collaboration, 2016). As mentioned previously, we were not able to capture this detail the different ethnic groups with the binary indicator for ethnicity.

The National Statistics Socio-economic Classification (NS-SeC) is not regularly used as a measure of SEP in birth-related studies, despite being recorded in administrative data alongside birth statistics (derived from parents' occupations as recorded on birth certificates). Instead, area-level deprivations scores are often used, such as the Index of Multiple Deprivation and the Carstairs Deprivation scores which are based on aggregate information at the level of super output area (SOA) (Smeeton et al., 2004; Sutan et al., 2010; Wood et al., 2012; Seaton et al., 2012). However, individual-level measures of disadvantage have been preferred to area-level indicators for assessing adverse birth outcomes (Sloggett and Joshi, 1998).

While most UK studies account for marital status as a risk factor, its association with stillbirth is usually not significant when accounting for other variables. Our findings are in keeping with the literature on stillbirths within multiple birth events; the stillbirth risk for multiple births in the UK has decreased over time but remains more than twice as high as for singletons (Smith et al., 2014; MBRRACE-UK Collaboration, 2016).

Advanced maternal age is one of the high ranking modifiable risk factors for high-income countries (Flenady et al., 2011a), and our findings support the UK literature in this regard (MBRRACE-UK Collaboration, 2016). The UK also has one of the highest teenage pregnancy rates among these countries, which too presents an increased risk of stillbirth (Vais and Kean, 2015). Our results do not suggest a significant difference in risk for teen births from the baseline age group (25-29 years), but this is likely due to very small birth counts in the teen LA/age strata.

Missing variables: This study only had access to four socio-economic variables and one birth-related variable (multiple births). We were unable to explore many of the pathways to stillbirth, as can be seen in Figure 5.8 which displays the components of the conceptual model for stillbirth from Chapter 2. The light grey boxes indicate variable topics that we were unable to account for in the study for England and Wales. For the UK and other high-income countries, behavioural factors such as smoking play an important role in perinatal outcomes (Vais and Kean, 2015). Other missing topics include parity, maternal health and morbidity, prenatal care, and obstetric events. One cohort study of births in the West Midlands found that the potentially modifiable risk factors maternal obesity, smoking during pregnancy and fetal growth restriction in combination accounted for more than half of the stillbirths observed (Gardosi et al., 2013a). These variables may be very informative if they were included in routine national birth data.

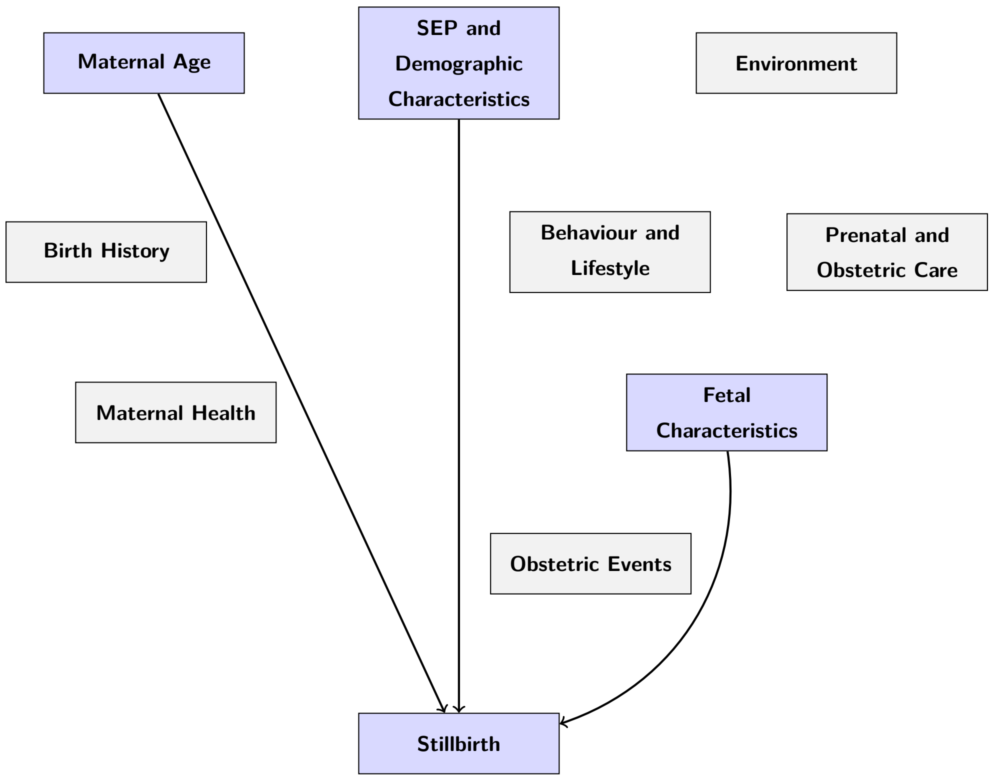


Figure 5.8: Pathways to stillbirth observed from available variables in the ONS for England and Wales. *Grey boxes indicate variable topics not covered in the data.*

5.3.3 Discussion of Methods

One method to both reduce bias and increase the number of available study variables would be to link up individual-level data (for example, census microdata) for the same (or a similar) population cross-tabulated by stratum, thus giving unique covariate values for each stratum (Lancaster et al., 2006). However, such data was unavailable for our population; the census microdata could provide information based on women in the population, but not specifically the subgroup of women who had given birth around this period which will likely have a different demographic. We did not pursue this method further.

Dealing with suppression. Stillbirth counts below three within any age/LA stratum were suppressed in the provided dataset. Data suppression of small counts, if ignored, will always underestimate outcome rates in groups with small populations, which in this case most frequently occur in the youngest age group.

There are various possible methods for dealing with suppressed values. Following the methods for handling general missingness by imputing missing cells with the average of non-missing values (Ohno-Machado et al., 2002), one could impute cells that are suppressed for their small values with the average of the possible small values (as we initially did when replacing the suppressed cells with 1). Another method would be to compute an expected stillbirth count for the suppressed cells by multiplying the corresponding total birth count by an applicable age-adjusted regional (or county-level) stillbirth rate (Tiwari et al., 2014).

Our final analysis accounted for the suppressed data by calculating the likelihood of each missing cell taking the possible values (0, 1 or 2). To our knowledge, this method has not been employed before. Calculating the exact likelihood of the unknown suppressed value appropriately accounts for the variability of the missing data and is relatively simple to implement in scenarios when the missing data can take only a limited number of values. The method is well suited to the analysis of aggregate data with suppressed small counts, which are particularly common with data that are freely available and may be useful to those without specialised access to individual-level confidential data.

Random effects. A very small but significant random effect was observed at the county level in this analysis. Since studies with aggregate data are less able than individual-level studies to correct for individual confounders, we might expect more heterogeneity and perhaps a higher magnitude or significance from the group-level random effects. Perhaps the same analysis with individual-level data would not find a significant area-level random effect.

The maps in Figure 5.3 show that the random effect estimates were less extreme than if the area-level effect had been treated as a fixed component. This smoothness is due to aforementioned partial pooling, which reduced the likelihood of an area being falsely identified as an outlier by chance alone.

Gaussian quadrature was used to calculate the random effects in the Exact Likelihood model, while for the singularly imputed models, Laplace approximations were used (the default method in R). Gaussian quadrature was chosen because it was relatively simple to incorporate into the Exact Likelihood function (Handayani et al., 2017). Integrals were approximated with respect to the random effect with B=500 nodes, which appeared sufficient for the likelihood to have stabilised for the model considering interactions. For the final model (without interactions), the likelihood stabilised with only B=50; the estimates remained consistent for any higher number of nodes.

Linear splines vs categorical level. For each of the continuous covariates, an alternative version of the model was constructed, treating the covariates as categorical with the levels split at the same intervals as the splines' knot points. However, this resulted in a poorer model fit each time, suggesting that the spline model captures the non-linear relationships between variables more appropriately by accounting for the "within-level" as well as the "between-level" variation in the relationship between the covariates and stillbirth rate.

5.3.4 Conclusion

Overall, these findings suggest that of the socio-economic factors available in the data, mother's age and baby's ethnicity have the biggest influence on the odds of experiencing a stillbirth, but that socio-economic status, marital status and multiple births also play a considerable role. A small amount of variation across counties in England and Wales is also detected that is unaccounted for in our observed variables. The scope and interpretations of this study were extremely limited by the aggregate nature of the data and the small number of available variables. A strength of the study lies in its handling of suppressed outcome data, through the creation of a function that calculates the likelihood of the unknown suppressed values alongside the known values. Despite the shortcomings of the data, these methods are relatively straightforward to undertake, and their results agree with similar literature for the UK (much of which uses individual-level data). Aggregate data is more easily available, less costly and quicker to produce than individual-level data, and so these methods may provide an accessible approach for health service planners to monitor up-to-date trends in stillbirths. The findings from this ecological analysis are not sufficient to infer any causal relationships, which shall be explored with Scottish data in the following chapter.

Chapter 6

Associations Between Socio-economic Factors and Stillbirth in Scotland

This chapter will examine the relationship between stillbirth and socio-economic, demographic, behavioural, health and birth-related factors at an individual level, using data from the Maternity and Neonatal Linked Database (MNLD), introduced in Section 4.2. The binary response measure was the outcome observed at each recorded birth, live birth or stillborn.

The initial challenge posed by the dataset is the missingness throughout many of the variables; this shall be accounted for by using Multiple Imputation (MI), which involves generating multiple complete "potential" versions of the dataset, running the desired analysis and pooling the results. Preliminary univariate and multivariate regression analysis will be conducted to identify the most significant variables.

From here, a mediation model will be considered to explore how birth-related factors bridge the connection between stillbirth and the more distal factors from the conceptual model in Section 2.3.1 (socio-economic, behavioural and health factors). This shall be addressed through Structural Equation Modelling (SEM). The methods for applying structural equation models to multiply-imputed data are described in Section 6.1.5. Results for the two types of analysis, standard multivariate regression and structural equation modelling, will be discussed and compared.

6.1 Methods Used in the Analysis of Stillbirth Data in Scotland

Fourteen of the twenty-one variables in the MNLD sample had missing values, the breakdown of which can be seen in Table 4.4 in the chapter on introducing the datasets (Section 4.2.3). The variable for ethnicity has the largest percentage of missing data (31%) while the remaining variables had missing values ranging from 0% to 14%.

The simplest method for dealing with missing data is to omit any subjects with missing values on any of the variables, analysing only the subjects with information on all variables in the model, i.e. the complete cases. This is known as "listwise" deletion or complete case analysis. However, this can lead to a loss of information and therefore less accurate estimates. Although the non-response rate for the majority of individual variables in the MNLD was very low, missing values were dispersed throughout the data haphazardly. Of the 160,120 observations in this study, 42,484 (27%) had complete information. Furthermore, if the data is not missing completely at random (MCAR), i.e. there are systematic differences between people that respond to a particular question and those that do not, then the analysis results may be biased (Leeuw and Hox, 2008). Therefore, a more sophisticated approach for handling missing data was required.

This section explores an alternative imputation technique for handling missing data in which missing values are replaced by "plausible" values.

6.1.1 Handling Missing Data with Multiple Imputation (MI)

Multivariate Imputation (MI), proposed by Rubin (1987), accounts for the uncertainty in missing values by generating several different plausible data sets, analysing each separately, and combining the results.

The MI procedure assumes that the missing data is missing at random (MAR), i.e. the probability that a value is missing depends only on observed values and can be predicted using them. It handles missing data in three stages:

Stage 1: Imputation. M copies of the dataset are created, with missing values in each dataset replaced by plausible imputed values. These plausible values are predicted using variables correlated with the missing data. The differences between the imputed values across datasets reflect the uncertainty surrounding the missing data.

Stage 2: Analysis. Standard statistical methods can be used to model each imputed dataset. Estimates in each dataset will be different due to the variation introduced in the imputation process.

Stage 3: Pooling Results. The M estimates for each parameter are averaged together to produce one overall unbiased estimate $\bar{\theta} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_m$ for each parameter in the model. The parameter's standard error, σ, is pooled from the M imputed data sets using Rubin's Rules (1987) which account for this variability between imputed datasets. For each pooled parameter estimate θ, the standard error is

$$\sigma_{\bar{\theta}} = \sqrt{\frac{1}{M}\sum_{m=1}^{M}\sigma_m^2 + (1+\frac{1}{M})(\frac{1}{M-1})\sum_{m=1}^{M}(\hat{\theta}_m - \bar{\theta})^2}$$

where $\frac{1}{M}\sum_{m=1}^{M}\sigma_m^2$ is the average variance across imputations (within-imputation variance), $(\frac{1}{M-1})\sum_{m=1}^{M}(\hat{\theta}_m - \bar{\theta})^2$ is the variance of parameter estimates across imputations (between-imputation variance), and $(1+\frac{1}{M})$ is a correction factor that converges to 1 as the number of imputations, M, increases. In this way the pooled standard error $\sigma_{\bar{\theta}}$ incorporates the between-imputation uncertainty with the within-imputation uncertainty that would occur in any estimation method.

As long as the data is MAR, the pooled parameter estimates and standard errors are unbiased. With list-wise deletion, the SEs are larger due to the smaller sample size after discarding data from partial respondents. SEs under single imputation (in which only one imputed dataset is created) are too small because they do not account for the between-imputation uncertainty; MI minimises this bias (Newman, 2014).

Moreover, MI is robust to the violation of the normality assumptions and yields suitable results even with small sample sizes or reasonably high proportions of missing data (Kang, 2013). For missingness of 50% or more in a variable, however, MI risks becoming unstable (Wulff and Ejlskov, 2017).

It is advised to use techniques such as MI when the percentage of missing data is 10% or higher (Newman, 2014). While the amount of total missing data in the MNLD sample is low (4%), a few variables have much more; the variable with the most amount of missing data is mother's ethnicity (30%). MI, therefore, seems appropriate for this analysis. To implement MI, we assume that the LMND data is missing at random.

Multivariate Imputation via Chained Equations (MICE)

Multivariate imputation via chained equations (MICE) is a popular approach to multiple imputation. MICE imputes missing values by taking each variable in turn and predicting values based on regression with the other variables.

Imputation follows an iterative process, sampling from the observed data. Consider a dataset with three variables, X, Y and Z, in which X contains missing values that depend on the other two variables. If Y and Z are complete, then the missing X values can be predicted with regression from Y and Z and imputed. In this case, no iterations are necessary. However, if Z also has missing values that depend on X, a problem arises. The two variables are interdependent; imputing X values from Z and then Z from the now-complete X will produce different results than if the order of imputation was reversed. Therefore, the imputations need to follow an iterative procedure.

In the first round or "iteration", imputations for the variable with the least missing data are estimated using only complete data. Then, the variable with the second least missing values is imputed using the complete data and the previously imputed values. After each variable has been through this cycle (one iteration), the process is repeated using the data from the last iteration (Raghunathan et al., 2001).

In the case of X and Z above, the two variables iterate from each other until they stabilise. The number of iterations must be sufficient such that by the end of the process, the distributions of imputed values stabilise, and the order in which the variables were considered does not matter. This process can be computationally intense when dealing with large datasets containing many variables. In such circumstances, the MICE algorithm can be amended to specify and restrict predictors in a given regression to those that exceed a specified minimum correlation with the dependent variable, thus saving computation time without sacrificing information that could affect the missing values (van Buuren and Groothuis-Oudshoorn, 2011).

Perhaps the greatest benefit of this sophisticated method is its flexibility to handle different variable types by assigning each to a suitable distribution. Linear regression is used to impute incomplete continuous variables, while logistic regression is used for binary data, Poisson regression for count data, and polytomous regression for categorical variables (Raghunathan et al., 2001).

Standard Logistic Regression and Model Selection with Multiply-imputed Data

Before model selection by backwards elimination, univariate logistic regression was performed on each of the twenty predictor variables.

Consider the observed birth outcome y_i as a realisation of a Bernoulli random variable Y_i taking values 0 for live births and 1 for stillbirths, with probability π_i of stillbirth. The probability distribution is given by

$$Pr\{Y_{ij} = y_{ij}\} = \pi_{ij}^{y_{ij}} (1 - \pi_{ij})^{1-y_{ij}}.$$

The probability π_i of stillbirth for individual i can be expressed as a linear function of K observed covariates $\boldsymbol{x}_k$ and parameters $\boldsymbol{\beta}_k$, through the transformation of the logit function as described in Equations 5.1 and 5.2 in the previous chapter.

The Wald chi-squared test. The significance of each variable was calculated with a Wald test. While the likelihood ratio test is popular for non-imputed data, the easier-to-obtain Wald test statistic has been favoured (and found to be more accurate) with imputed data, as it can be calculated from Rubin's aforementioned pooled statistics (Wulff and Ejlskov, 2017; Eekhout et al., 2017).

The Wald test works by testing the null hypothesis that some or all of the parameters in a given model $\boldsymbol{\theta}$ are equal to their "true" values $\boldsymbol{\theta}_0$, which are usually set to zero. In this case it tests whether the variables corresponding to these parameters have an influence on the dependent variable.

Consider the set of k variable coefficient estimates $\hat{\boldsymbol{\theta}} = (\hat{\theta}_1, \ldots, \hat{\theta}_k)^t$, and the variance-covariance matrix, $U = \text{var}\left(\hat{\boldsymbol{\theta}}\right)$ of $\hat{\boldsymbol{\theta}}$. For the null hypothesis $H_0 : \theta_1 = ... = \theta_k = 0$ or in general $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$, the Wald test takes the form

$$W = (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)^t U^{-1} (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0) \sim \chi^2_k$$

(Rubin, 1987).

In the univariate analyses, the significance of each variable was calculated with a Wald test, compared against the null (empty) model. At the preliminary stage, each variable's Wald statistic was compared with a χ^2 distribution with 1 degree of freedom, and any variable with a p-value of less than 0.2 was retained for multivariate analysis. This relatively large p-value was used to prevent potentially important variables from being removed before the multivariate stage (Mickey and Greenland, 1989).

Multivariate variable selection. The iterative backwards selection process began with a full logistic regression model containing all of the remaining significant predictors. Each possible way of removing one variable from the model was considered, and each of these slightly smaller models were compared with the full model through a Wald test before removing the variable that was least significant to drop (i.e. the largest p-value) from the full model. This drop-the-least-significant process was repeated until there were no more variables to omit without weakening the model, i.e. all of the Wald test p-values were below 0.05).

This selection process was possible to manually achieve with multiply-imputed data within Rubin's framework, although it can be computationally infeasible with very large datasets or a large number of imputations. At each stage of model selection, the models were fitted to all imputed datasets, and their estimates pooled wherein Wald tests can be applied to the pooled values (Wood et al., 2008).

6.1.2 Geographic Variation with Random Effects

As with the analysis for England and Wales in the previous chapter (Section 5.1.2), we wished to determine whether there is any additional area-level variation in stillbirth risk across areas of Scotland after accounting for the individual-level covariates. Like the England and Wales analysis, the LMND data contains a variable denoting the Local Authority district of residence for each mother. From this, the larger Health Board Area for each mother could also be derived.

To investigate the existence of such geographic variation, random effects were added to the final model from the backwards selection process in a similar fashion to Equation 5.6 from the previous chapter, remembering that the Bernoulli model in this analysis is a special case of the Binomial model depicted in this equation.

6.1.3 Exploring Causal Pathways with Mediation

Mediation is a method of exploring the process or mechanism by which one variable affects another (MacKinnon et al., 2007). In its simplest form, mediation occurs when the effect of an independent variable X on a dependent variable Y is at least partially transmitted through a third variable M known as the mediator.

Figure 6.1 shows the single-mediator model. Path a represents the relationship between X and mediator M, while b represents the relation of M to Y. Note that b is not simply the effect of M on Y but the effect of M on Y controlling for the variable X; mediation is supported if b remains significant after controlling for X. The product ab describes the *indirect effect*, the pathway from X to Y through M. c' is the *direct effect* of X on Y while controlling for M. If c' and b are statistically significant, this is evidence for *partial mediation* (MacKinnon et al., 2007). If c' is no longer significant when controlling for M, this suggests that the effect of X on Y is *fully mediated* by M. In application, partial mediation is more common (Gunzler et al., 2013). The *total effect* of X is the sum of the indirect and direct effects.

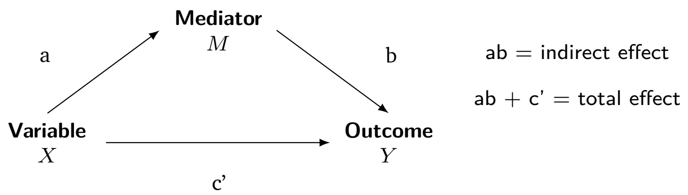


Figure 6.1: Mediation path diagram with single mediator

Figure 6.2 displays a slightly more complex mediation model involving two independent variables (X_1 and X_2) and two mediators (M_1 and M_2), alongside the calculations for the multiple indirect and direct effects present. Such models can form the elements of a more complicated structural model.

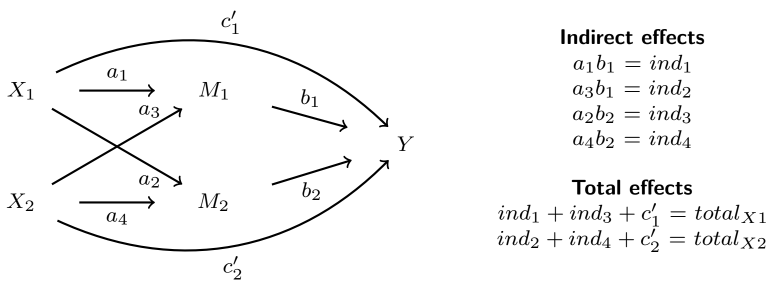


Figure 6.2: Mediation path diagram with two variables and two mediators

6.1.4 Structural Equation Modelling (SEM)

Structural equation modelling (SEM) can provide a flexible framework for mediation analysis, using a system of linked regression-style equations to describe the complex web of relationships between variables. In SEM, mediator variables can act as both independent and dependent variables within a model. It is through this relationship that SEM is able to infer causal relationships (Gunzler et al., 2013). These type of variables are referred to as endogenous variables, while wholly independent variables are called exogenous variables.

Consider the simple mediation model in Figure 6.1. Assuming linear relationships, the SEM equations for the i^{th} subject ($i = 1, \ldots, n$) with exogenous variable x_i, mediator m_i and outcome y_i is

$$y_i = b_0 + b_1 m_i + c' x_i + \epsilon_{y_i} \tag{6.1}$$

$$m_i = a_0 + a_1 x_i + \epsilon_{m_i} \tag{6.2}$$

where the residuals ϵ_y and ϵ_m are assumed normally distributed with means zero and variances σ_y^2 and σ_m^2 respectively.

The model can be reduced by plugging (6.2) into (6.1) to obtain

$$\begin{aligned} y_i &= b_0 + b_1(a_0 + a_1 x_i + \epsilon_{m_i}) + c' x_i + \epsilon_{y_i} \\ &= (b_0 + b_1 a_0) + (b_1 a_1 + c')x_i + (b_1 \epsilon_{m_i} + \epsilon_{y_i}) \end{aligned} \tag{6.3}$$

where $b_1 a_1 + c'$ is the total effect estimate for exogenous variable X (as in Figure 6.1) (Muthén, 2011).

SEM with Non-continuous Outcomes and Mediators

SEM also allows the incorporation of binary or ordinal mediators and outcomes into a model. Muthén (2011) and Muthén and Asparouhov (2014) provide a general overview of mediation analysis with non-continuous mediators and outcomes using SEM.

If the outcome variable Y is binary, Equation 6.1 is replaced with a corresponding probit or logistic regression equation.

The probit link function serves the same purpose as the aforementioned logit link function (Equations 5.1 and 5.2 in the previous chapter) in that it transforms the linear combination of K observed covariates $\boldsymbol{x}_k$ and parameters $\boldsymbol{\beta}_k$ into a probability. The probit link, however, achieves this through the inverse-normal function. For a binary outcome y_i taking the value 0 for live births and 1 for stillbirths, the probability π_i

of stillbirth can be expressed as

$$\Phi^{-1}(\pi_i) = \sum_{k=1}^{K} x_{ik}\beta_k \quad \text{or} \quad \pi_i = \Phi\left(\sum_{k=1}^{K} x_{ik}\beta_k\right).$$

Within SEM analysis with binary endogenous variables, probit models are often used over logit models for mathematical convenience, although meaningful results from the two models are generally indistinguishable (Scott, 1997). Going forward, this study uses probit models for all SEM analysis.

Latent variables. When dealing with a binary or ordinal observed response variable Y, the latent variable Y^* can represent the underlying continuous response behind Y; the observed response is determined by the latent variable falling below or exceeding certain threshold(s) (Skrodal and Rabe-Hesketh, 2004).

Hence the binary birth outcome Y in this study is modelled as representing an underlying latent response Y^* where

$$y_i = \begin{cases} 0 & \text{if } y_i* \leq \tau \\ 1 & \text{if } \tau < y_i* \end{cases}$$

for some threshold τ.

For a model with a binary or ordinal mediator M, the model is similarly measuring an underlying continuous mediator M^*. For an observed mediator with, for example, three levels taking values 0, 1 and 2, the latent variable is incorporated as such:

$$m_i = \begin{cases} 0 & \text{if } m_i^* \leq \tau_1 \\ 1 & \text{if } \tau_1 < m_i^* \leq \tau_2 \\ 2 & \text{if } \tau_2 < m_i^* \end{cases}$$

for some threshold values τ_1 and τ_2. Then for a structural equation model with an exogenous variable X, binary outcome Y and ordinal mediator M, Equations (6.1) and (6.2) are replaced with

$$y_i^* = b_0 + b_1 m_i^* + c' x_i + \epsilon_{y_i} \tag{6.4}$$

$$m_i^* = a_0 + a_1 x_i + \epsilon_{m_i}, \tag{6.5}$$

where the variance of ϵ_{y_i} is fixed at 1 for probit models and the variance of ϵ_{m_i} is denoted σ_m^2. Similar to Equation (6.3), the model can be reduced to a single equation

$$y_i^* = (b_0 + b_1 a_0) + (b_1 a_1 + c') x_i + (b_1 \epsilon_{m_i} + \epsilon_{y_i}) \tag{6.6}$$

where $b_1 a_1 + c'$ is the total effect estimate for exogenous variable X. The variance of the combined error terms is

$$\text{var}\left(b_1 \epsilon_{m_i} + \epsilon_{y_i}\right) = b_1^2 \, \text{var}\left(\epsilon_{m_i}\right) + 1^2 \, \text{var}\left(\epsilon_{y_i}\right) = b_1^2 \sigma_m^2 + 1$$

This model is displayed as a path diagram in Figure 6.3.

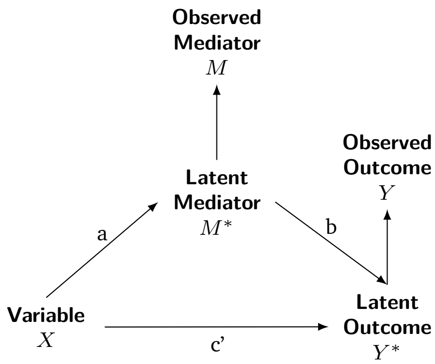


Figure 6.3: Mediation path diagram with a latent mediator and outcome

Standardisation of the effect estimates. We wish to compare total effect estimates across specifications of the independent X variables. This can be achieved with standardisation, in which the total effect for each exogenous variable X is divided by the total standard deviation for the mediation model. The standardised effect β for exogenous variable X in the aforementioned latent model (Equation (6.6)) is

$$\beta = \frac{b_1 a_1 + c'}{\sqrt{\text{var}\left(b_1 \epsilon_{m_i} + \epsilon_{y_i}\right)}} = \frac{b_1 a_1 + c'}{\sqrt{b_1^2 \sigma_m^2 + 1}}.$$

The standardised effects can be directly compared across different predictors within the same sample (Kline, 2011).

Choice of mediators for LMND data. When applying SEM to the MNLD dataset, we chose mediator variables based on their proximity to stillbirth in the conceptual model (see literature review in Section 2.3.1). The fetal and obstetric factors (mode of birth, birth weight, and gestational age), as well variables related to birth history (previous pregnancies and previous stillbirths) were considered as mediators while the remaining socio-economic, demographic, behavioural, and health factors were considered as exogenous variables.

Practicalities of SEM in R

The package `lavaan` in R is capable of running structural equation models for latent variable analysis.

Categorical Variables. The lavaan package does not yet easily accommodate categorical variables, but such information is often possible to include with some tweaking. Among exogenous variables, binary variables needed to be re-coded as nominal dummy (0/1) variables. Similarly, nominal categorical variables with l levels were replaced with a set of $l - 1$ dummies, as was the case for the variables socio-economic status, ethnicity, marital status, age, smoking status, drug mis-use, and diabetes status. Within lavaan, an exogenous ordinal categorical variable can, as long as its coding reflects an order (1, 2, 3,...), be treated as a numeric variable. It was possible to code the maternal age groups in this manner; however, given the evidence in the literature review and previous analysis with England and Wales that the relationship between maternal age and stillbirth is more "U-shaped" than linear, it was decided to treat these age groups as separate nominal categories.

For endogenous categorical variables, however, lavaan can accommodate binary and ordinal but not nominal categorical variables (Rosseel, 2014). Therefore, the nominal variable for mode of birth could not be included as a mediator in the model. Since the mode of birth should appear at the end of a causal chain to stillbirth (as shown in the conceptual model in Section 2.3.1) it did not make sense to include the variable instead as exogenous, and so it was dropped from the structural equation model. The remaining categorical mediator variables – birth weight, parity and previous stillbirth – were treated as ordinal. Note that birth weight is coded as "normal", "low", and "very low" with "normal" representing the baseline, and therefore its ordinal scale is decreasing in birth weight. The other ordinal mediators are coded in an increasing order (See Table 4.3).

Similarly, based on its placement in the conceptual model, it would have been ideal to include the variable diabetes, an indicator of maternal health, as a mediator. As a nominal variable, the lavaan package could not support it as a mediator, but since the literature review suggests a link between maternal diabetes and preterm birth (represented in this model by the mediator gestational age), it was included as an exogenous variable.

Model Estimation. The usual approach to estimating fit coefficient in SEM is the maximum likelihood (ML) approach. The ML estimator assumes that the variables in the model are multivariate normal, i.e. that the joint distribution of the variables is distributed normally. However, models with categorical variables tend to be in violation of this assumption and, thus, the ML estimator is not recommended (Mîndril, 2010).

Instead, diagonally weighted least-squares (DWLS) estimation – a modification of weighted least-squares (WLS) – was used for the estimation of the model parameters. Introduced by Muthén (1984), WLS estimates the underlying continuous latent variable y^* through polychoric correlations, which correct for loss of information when ordinary Pearson correlations are used with the "cruder" categorical observed variable. These polychoric correlations are used to create the asymptotic covariance matrix consisting of the covariances of the observed sample variances and covariances. The WLS estimator is then the inverse of the asymptotic covariance matrix. The DWLS estimator, however, inverts only the diagonal elements of the matrix, making it computationally more practical. The DWLS method is the recommended approach for parameter estimation when dealing with categorical data and for ordinal/mixed mediators in the SEM literature (Nguyen et al., 2016; Rosseel, 2017).

Method of Regression. With a rare binary outcome, the default and preferred regression method would be logistic (Vanderweele), as performed in the standard regression. However, in `lavaan`, this method is not yet possible with weighted least squares estimators and defaults to using probit models for a binary outcome (Yves et al., 2018). The probit link has been shown to be an appropriate method for studies with a binary outcome and continuous or ordinal mediators (Nguyen et al., 2016).

While, unlike logistic models in which parameter estimates are interpretable as logarithms of odds ratios, the estimates in a probit model have no straightforward interpretation. However, multiplying a probit coefficient by approximately 1.6 has been shown to approximate a logistic coefficient (Amemiya, 1981). The standardised probit estimates from the mediation model were multiplied by this factor for comparison with the standard logistic regression.

Standard Errors and Confidence Intervals in SEM

By default in `lavaan`, the indirect and total effects of the mediation model were calculated by the delta method. The ideal method for calculating these defined parameters – non-linear combinations of parameter estimates – is through bootstrapping. However, this method is very computationally intensive and time-consuming. Both methods are described below.

Confidence limits with delta method. The delta method can be used to estimate the variance of a non-linear combination of parameter estimators. Consider a sequence of random vectors $\{\hat{\boldsymbol{\theta}}_n\}$, each of length K, such that its distribution converges to a multivariate normal distribution with mean 0 and covariance matrix V, i.e.

$$\sqrt{n}(\hat{\boldsymbol{\theta}}_n - \boldsymbol{\theta}) \xrightarrow{d} N(0, V).$$

Then, the multivariate delta method states that for a differentiable function $g(\boldsymbol{\theta})$ with partial derivatives $\left(\frac{\boldsymbol{\partial g}}{\boldsymbol{\partial \theta}}\right)^T = \left(\frac{\partial g}{\partial \theta_1}, ..., \frac{\partial}{\partial \theta_K}\right)$,

$$\sqrt{n}(g(\hat{\boldsymbol{\theta}}_n) - g(\boldsymbol{\theta})) \xrightarrow{d} N\left(0, \left(\frac{\boldsymbol{\partial g}}{\boldsymbol{\partial \theta}}\right)^T V \left(\frac{\boldsymbol{\partial g}}{\boldsymbol{\partial \theta}}\right)\right).$$

(Sobel, 1982, 1986) used the multivariate delta method to derive asymptotic standard errors of indirect (and total) effects in mediation. Assuming that the sample is large enough for this normal approximation method to be used, the standard error is

$$\sigma_{\hat{a}\hat{b}} = \sqrt{\hat{b}^2\sigma^2_{\hat{a}} + \hat{a}^2\sigma^2_{\hat{b}}}$$

with parameter estimates $\hat{a}$ and $\hat{b}$, and their estimated variances $\sigma^2_{\hat{a}}$ and $\sigma^2_{\hat{b}}$. This is the most commonly used formula for the standard error of mediation effects.

The variable effect is divided by this standard error and compared to a standard normal distribution to test for significance ($H_0 : ab = 0$). Confidence limits can then be constructed:

$$\hat{a}\hat{b} \pm z_{(1-\alpha)}\sigma_{\hat{a}\hat{b}}.$$

Confidence intervals with bootstrapping. The bootstrap method is a re-sampling procedure that was first used in mediation analysis by (Bollen and Stine, 1990) to create confidence intervals for the indirect and total effects. This non-parametric method makes no assumptions about the distribution of the indirect effect ab. The simplest method of obtaining confidence intervals is the percentile interval, which is based on ordering the bootstrapped replications in ascending order.

The bootstrap procedure uses the original data to mimic a random sampling process from a theoretically infinite population. The following non-parametric procedure was used:

1. Draw samples (with replacement) from the original data D to generate K new datasets of the same size as the original samples, D^*_k: $k = 1, \ldots, K$.
2. For each of these K bootstrapped samples, calculate the estimate of interest $\hat{\theta}^*_k$, in this case for regression coefficient θ.
3. Order the set of these K estimates $\Theta^*_K = \{\theta^*_{(1)}, \theta^*_{(2)}, \ldots, \theta^*_{(K)}\}$ where $\theta^*_{(1)} < \theta^*_{(2)} < \ldots < \theta^*_{(K)}$.
4. The bootstrap $100(1-\alpha)\%$ confidence interval for θ is then $[\hat{\theta}^{*,a/2}; \hat{\theta}^{*,1-a/2}]$ where $\hat{\theta}^{*,a/2}$ represents the $a/2$ percentile of the ordered bootstrapped estimates Θ^*_K.

Comparison. An advantage of the delta method is that each model estimate is only computed once, and is consequently much faster to compute than bootstrapped standard errors and confidence intervals. However, many have suggested that the assumption of the distribution of ab being normal may not hold, especially for small sample sizes, and therefore the bootstrap method for obtaining confidence is preferred (Bollen and Stine, 1990; MacKinnon et al., 2002).

The bootstrap makes no assumption about the distribution of the sample or the variables and can be employed with smaller sample sizes. For non-linear combinations of parameter estimates (like ab or the total effect $c' + ab$), asymmetric confidence intervals based on the bootstrap are recommended, especially for mediated effects in more complicated models, including those dealing with categorical outcomes (MacKinnon et al., 2007).

A disadvantage of the bootstrap procedure is the computational time required to generate model estimates for K datasets if K is high. Therefore in this study, the delta method was adopted for preliminary analysis, and bootstrapping was introduced later for the final model (with $K = 500$ samples) to ensure that the indirect and total effect estimates are appropriate.

6.1.5 Mediation through SEM with Multiply Imputed Data

The estimation of mediation effects with multiple imputation is the same as described in Section 6.1.4. The estimate of indirect effect ab is the average of the estimates for M imputed dataset:

$$\hat{a}\hat{b} = \frac{1}{M}\sum_{m=1}^{M} \hat{a}_m\hat{b}_m.$$

The `lavaan` package in R is able to run structural equations modelling with multiply-imputed data. However, due to the creation of the dummy variables, some tweaking of the imputation process was required, as described below.

Passive Imputation

Passive imputation aims to maintain consistency among transformed, combined or recoded variables within an imputed set (van Buuren and Groothuis-Oudshoorn, 2011). In this study, passive imputation was required to ensure that the values of the dummy indicators for a categorical variable were consistent and did not code more than one dummy as “1” for a given observation. For example, the categorical variable for smoking status can take one of the values “never”, “former” and “current smoker” for each subject. When separated into $0/1$ dummy indicators for each smoking status, it would be possible for the imputation procedure to assign an individual as both “never” and “current smoker”.

To restrict this impossible scenario from occurring, passive imputation was employed. The procedure firstly imputed the categorical variable and then coded the dummies to automatically correspond with this variable.

Bootstrapping with MI

Bootstrapping can be applied to multiply-imputed data to obtain confidence intervals for mediation analysis with missing data (Wang et al., 2014). Extending the bootstrap procedure in Section 6.1.4:

1. For each of the M imputed datasets D_m, draw K samples (with replacement) to generate $M \times K$ new bootstrapped datasets of the same size as the imputed dataset, $D^*_{m,k}; m = 1, \ldots, M; k = 1, \ldots, K$.

2. For each of these $M \times K$ bootstrapped samples, calculate the estimate of interest $\hat{\theta}^*_{m,k}$.

3. The ordered set of these estimates is $\Theta^* = \{\hat{\theta}^*_{m,k}; m = 1, \ldots, M; k = 1, \ldots, K\}$.

4. As before, the bootstrap $100(1-\alpha)\%$ confidence interval for θ is then $[\hat{\theta}^{*,a/2}; \hat{\theta}^{*,1-a/2}]$ where $\hat{\theta}^{*,a/2}$ represents the $a/2$ percentile of the ordered bootstrapped estimates Θ^*

(Schomaker & Heumann, 2018).

For this study, $M = 10$ imputed datasets were generated, with $K = 500$ bootstrapped replication samples for each.

Model Selection for Structural Equation Models

There are a number of popular test statistics to test the fit of a structural equation model to the data. The Chi-square, or χ^2, test, for example, investigates whether the minimum squared distance between the covariance matrix implied by the model and the observed sample covariance matrix is small enough that the it could be reasonably explained as sampling error. Other fit indices derived from the χ^2 statistic and the number of degrees of freedom in the model include the Confirmatory Fit Index (CFI), Tucker-Lewis Index (TLI), and the Root Mean Square Approximation of Error (RMSEA). Each of these measures has a defined cut-off beyond which a model is generally considered to be significant; CFI and TLI > 0.95, RMSEA < 0.06 and for χ^2, a non-significant p-value is ideal (Hooper et al., 2008; Kline, 2011). (Enders and Mansolf, 2016) confirmed that these measures were suitable even when constructed with pooled test statistics from multiply-imputed data.

However, the χ^2 test can be sensitive to sample size. For incorrect models that do not imply covariance matrices similar to the sample matrix, the value of χ^2 tends to increase along with the sample size, and thus may incorrectly suggest that the matrices are not significantly different (Kline, 2011). Moreover, a typical mediation model tends to be saturated, or exactly-identified (i.e. with every possible path between variables considered, there are zero degrees of freedom). This saturation causes these measures to indicate a perfect fit even if the model is not suitable.

Instead, we investigated each path to determine whether a more parsimonious model, i.e. a less complex model with fewer paths, would not significantly weaken the model fit. This was achieved through a series of Wald tests, which are appropriate for testing the significance of WLS estimated parameters (Bergsma et al., 2009; Wulff and Ejlskov, 2017). Unlike the model selection process for the standard logistic regression described above in Section 6.1.1, this selection process was not step-wise; each path (or selection of paths from dummies representing one variable) was considered independently and compared to the full model containing all paths. Paths that were insignificant (at the 5% significance level) were rejected.

6.2 Results for the Analysis of Stillbirth Data in Scotland

6.2.1 Multiple Imputation of the Data

All available variables, including the outcome measure of stillbirth, were used in the MICE imputation procedure. Ten data sets were imputed of the 21 variables, using 15 iterations. A predictor matrix was used to speed up the imputation procedure by specifying variables in the datasets that could be used to predict others, as described in Section 6.1.1. For any given variable being imputed (the target), only variables with an absolute correlation value of at least 0.1 between itself and the target were used to predict the missing values of the target variable.

The geographic variable for Local Authority (LA) could not be used in fixed regression due to quasi-separation in the dataset; some of the smaller LAs recorded only one or no stillbirths. However, LA was included in imputation as an auxiliary variable – a variable that is not part of the model but can explain missingness of variables in the model. As a predictor, it was complete and correlated with some of the variables containing missing values. Therefore it could influence the imputation process considerably.

The resulting datasets were inspected to ensure that the imputed values lay within a reasonable range. For continuous variables, the imputed values lay within the range of the original values, and the mean and median remained the same. For categorical variables, imputed values were approximately split between the levels so that each variable maintained the proportion of values in each level similar to the original data.

6.2.2 Exploratory Univariate Analyses

Table 6.1 shows the results of the univariate logistic regression of each predictor on stillbirth. Odds ratios and 95% confidence intervals compare each categorical level with its baseline. Each variable's significance is measured with a Wald test.

Table 6.1: Univariate association between risk factor and stillbirth for the MNLD, Scotland. Odds ratios (OR) and 95% Confidence Intervals (CIs).
Bold type p-values denotes significant variable at 80%

Risk Factor	**OR**	**95% CI**	**Wald Statistic**	**P-value**
Birth-related factors				
Mode of birth			334	**<0.001**
Normal	1			
Forceps	0.36	(0.25, 0.51)		
Breech	86.48	(68.47, 109.24)		
Elective caesarian	0.19	(0.12, 0.31)		
Emergency caesarian	0.57	(0.44, 0.75)		
Other	20.48	(6.27, 66.95)		
Birth weight			1316	**<0.001**
Normal ($\geq$ 2500g)	1			
Low (1500-2499g)	13.78	(11.24, 16.92)		
Very low (<1500g)	133.94	(111.02, 161.59)		
Gestational Age (continuous)			2756	**<0.001**
Weeks	0.67	(0.66, 0.68)		
Parity			6.374	**<0.001**
0	1			
1	0.62	(0.51, 0.76)		
2	0.88	(0.7, 1.1)		
3	0.86	(0.65, 1.15)		
4 or more	1.11	(0.85, 1.45)		
Previous stillbirth			4.45	**0.035**
No	1			
Yes	2.04	(1.05, 3.94)		
Previous neonatal death			0.59	0.442
No	1			
Yes	1.47	(0.55, 3.95)		
Previous spontaneous abortion			0.18	0.674
No	1			
Yes	0.96	(0.8, 1.16)		
Sex of baby			1.33	0.249
Male	1			
Female	1.10	(0.94, 1.28)		
Socio-economic and demographic factors				
Socio-economic status			5.43	**<0.001**
Managerial or professional	1			
Intermediate	1.09	(0.84, 1.4)		
Smaller employer or self-employed	0.74	(0.48, 1.15)		
Supervisor/ craft related	1.04	(0.74, 1.46)		
Routine occupation	1.14	(0.92, 1.4)		
Long term unemployed	5.62	(2.75, 11.49)		
Student, not stated or not classifiable	1.40	(1.11, 1.77)		
Carstairs deprivation quintile			0.98	0.426
1 – least deprived	1			
2	0.86	(0.98, 1.08)		

Continued on next page

Table 6.1 continued from previous page

Risk Factor	**OR**	**95% CI**	**Wald Statistic**	**P-value**
3	0.79	(0.92, 1)		
4	0.82	(0.64, 1.05)		
5 – most deprived	0.88	(0.7, 1.12)		
Not a resident of Scotland	1.18	(0.29, 4.78)		
Urban and rural areas			1.11	0.330
Urban area	1			
Small town	0.82	(0.63, 1.07)		
Rural area	0.95	(0.76, 1.2)		
Ethnicity			2.64	**0.049**
White	1			
Black	0.95	(0.51, 1.75)		
South Asian	1.44	(0.91, 2.26)		
Other	1.81	(1.14, 2.88)		
UK born			0.29	0.593
Yes	1			
No	1.06	(0.86, 1.31)		
Parents' marital status			4.09	**0.006**
Married – to each other	1			
Joint registration – same address	1.15	(0.96, 1.37)		
Joint registration – different address	1.45	(1.15, 1.83)		
Sole registration	1.44	(1.03, 2.01)		
Maternal age			1.62	**0.151**
18-19 years	1.01	(0.66, 1.53)		
20-24 years	1.04	(0.82, 1.13)		
25-29 years	1			
30-35 years	0.95	(0.77, 1.17)		
35-39 years	1.04	(0.81, 1.32)		
40-45 years	1.58	(1.11, 2.26)		
Health and behavioural factors				
Smoking status			15	**<0.001**
Never	1			
Smoker during pregnancy	1.64	(1.37, 1.96)		
Former smoker	1.08	(0.83, 1.4)		
Drug misuse during pregnancy			2.66	**0.104**
No	1			
Yes	1.50	(0.92, 2.43)		
Alcohol consumption			0.72	0.487
None	1			
1 to 3 units per week	0.72	(0.36, 1.43)		
4 or more per week	0.77	(0.39, 1.53)		
Body Mass Index (continuous)			15	**<0.001**
BMI	1.03	(1.01, 0.04)		
Diabetes			11	**<0.001**
No	1			
Yes – pre-existing	3.49	(2, 6.1)		
Yes – gestational (or unknown)	0.57	(0.26, 1.28)		

Of the birth-related factors, Wald tests showed that mode of birth, birth weight, gestational age, parity and previous stillbirth were significantly associated with stillbirth. Regarding the mode of birth, the odds of stillbirth were monumentally increased for breech births and unknown “other” modes, while the interventions of forceps and caesarean sections, both elective and emergency, had a protective effect. Compared to a “normal” birthweight of 2500 grams or above, the odds of stillbirth were thirteen-fold for low birth weights and a further ten-fold for very low birth weights (less than 1500g). Conversely, the odds of stillbirth decreased by 33% with each increasing week of gestational age. Increased parity was generally associated with a reduced risk of stillbirth until the number of previous births reached four or more when the relationship reversed. The odds of stillbirth were doubled for women who had already experienced a stillbirth. However, the baby’s sex and the mother’s history of neonatal death or spontaneous abortion were not significant.

Among the socio-economic and demographic factors, socio-economic status, ethnicity, parents’ marital status, and maternal age were significant at a 20% level. In particular, compared to those in managerial or professional occupations, women who were long-term unemployed had five times the odds of stillbirth. Compared to white women, there was not a significant difference in odds for black or South Asian women, but an 80% increased risk for women of “other” ethnicities. The parents being married also had a protective effect against stillbirth, with single mothers and parents registering a birth with separate addresses having 44% and 45% increased odds of stillbirth. Finally, older maternal age (40-45 years) was significantly associated with stillbirth compared to women aged 25-29 years. Deprivation level, urban/rural code and whether the mother was born in the UK does not appear significant at the 20% level.

Although the consumption of drugs and alcohol were not found to be significantly linked to stillbirth, smoking during pregnancy was associated with 64% increased odds compared to never-smokers. Body mass index was also associated with a 3% increase in odds for each unit increase in BMI. Finally, mothers with diabetes were found to have almost 3.5 times the odds of stillbirth than women without diabetes.

All factors significant at the 20% level were included in further multivariate analysis.

6.2.3 Standard Multivariate Regression

For variables which showed an association with stillbirth in the univariate logistic regression analysis (at a 20% level), a multivariate model was created to determine whether the association between the potential risk factors and stillbirth remained after adjusting for confounders. The variables considered were the mode of birth, birth weight, gestational age, parity, previous stillbirth, socio-economic status, ethnicity, parents’ marital status, maternal age, smoking status, drug misuse status, body mass index and diabetes.

Table 6.2 shows the results of the multivariate logistic regression of these predictors. Odds ratios and 95% confidence intervals compares the levels of each categorical variable with their baseline level. In the presence of other confounding variables, many of the predictors, such as previous stillbirth, maternal age, marital status and smoking status appear to lose their effect on stillbirth. This is explored further with model selection.

Table 6.2: Odds ratios (ORs) and 95% confidence intervals (CIs) for multivariate logistic regression of all risk factors for stillbirth significant in univariate analyises from the MNLD, Scotland
Bold type denotes significant category level (from baseline) with p-value < 0.05.

Risk Factor	**OR**	**95% CI**	**P-value**
Birth-related factors			
Mode of birth			
Normal	1		
Forceps	**0.46**	(0.32, 0.67)	<0.001
Breech	**5.80**	(4.17, 8.06)	<0.001
Elective caesarian	**0.17**	(0.1, 0.28)	<0.001
Emergency caesarian	**0.19**	(0.14, 0.26)	<0.001
Other	3.26	(0.67, 15.72)	0.142
Birth weight			
Normal ($\geq$ 2500g)	1		
Low (1500-2499g)	**7.31**	(5.52, 9.67)	<0.001
Very Low (<1500g)	**19.08**	(11.47, 31.72)	<0.001
Gestational Age (continuous)			
Weeks	**0.85**	(0.81, 0.88)	<0.001
Parity			
0	1		
1	**0.70**	(0.56, 0.87)	0.002
2	0.81	(0.63, 1.05)	0.116
3	0.76	(0.55, 1.06)	0.102
4 or more	**0.66**	(0.48, 0.91)	0.012
Previous stillbirth			
No	1		
Yes	0.95	(0.44, 2.06)	0.898
Socio-economic and demographic factors			
Socio-economic status			
Managerial or professional	1		
Intermediate	1.07	(0.8, 1.42)	0.668
Small employer and self-employed	0.64	(0.4, 1.03)	0.066
Supervisors/ craft related	0.83	(0.56, 1.21)	0.322
Routine occupations	0.91	(0.71, 1.16)	0.433
Long term unemployed	**3.01**	(1.19, 7.62)	0.020
Students, not stated or not classified	0.96	(0.7, 1.31)	0.778
Ethnicity			
White	1		
Black	1.01	(0.5, 1.99)	0.990

Continued on next page

Table 6.2 continued from previous page

Risk Factor	**OR**	**95% CI**	**P-value**
South Asian	1.42	(0.86, 2.34)	0.165
Other	**2.02**	(1.19, 3.43)	0.009
Parents' marital status			
Married – to each other	1		
Joint registration – same address	0.98	(0.78, 1.23)	0.839
Joint registration – different address	1.01	(0.75, 1.38)	0.931
Sole registration	0.98	(0.65, 1.47)	0.902
Maternal age			
18-19 years	0.68	(0.42, 1.11)	0.124
20-24 years	0.79	(0.61, 1.04)	0.088
25-29 years	1		
30-34 years	1.07	(0.85, 1.35)	0.560
35-39 years	1.05	(0.8, 1.39)	0.728
40-44 years	1.38	(0.9, 2.1)	0.138
Health and behavioural factors			
Smoking status			
Never	1		
Former smoker	1.03	(0.76, 1.4)	0.845
Smoker during pregnancy	1.16	(0.92, 1.47)	0.205
Drug misuse during pregnancy			
No	1		
Yes	0.70	(0.4, 1.23)	0.212
Body Mass Index (continuous)			
BMI	**1.04**	(1.02, 1.06)	<0.001
Diabetes			
No	1		
Yes – pre-existing	**2.89**	(1.52, 5.51)	0.001
Yes – gestational (or unknown)	0.48	(0.2, 1.15)	0.101

Model Selection with Backwards Elimination

A standard step-wise backwards elimination process was conducted manually, starting with a model containing all of the variables mentioned above. The removal of each variable was considered, one by one, with a Wald test measuring significance at a 5% significance level. The least significant variable was dropped from the analysis. This process was repeated until the removal of a variable resulted in a significant difference to the model. Table 6.3 shows the order of removal of insignificant variables.

Table 6.3: Backwards model selection of potential risk factors for the MNLD, Scotland

Backward Stepwise Selection		**Wald Stat**	**P-value**
Start	All potential risk factors		
Step 1	*Parents' marital status* removed	0.033	0.992
Step 2	*Previous stillbirth* removed	0.029	0.998
Step 3	*Smoking status* removed	0.853	0.443
Step 4	*Drug misuse status* removed	1.165	0.282
Step 5	*Maternal age* removed	1.165	0.142
Step 6	*Parity* removed	2.315	0.055

After adjusting for confounding, the factors marital status, smoking and drug misuse, and maternal age were no longer significant. Birth-related variables such as parity and previous history of stillbirth also lost their significance after confounding.

The resulting "optimal model" therefore, consisted of the variables that remained in the model, significant at a 5% level with a Wald test and includes the mode of birth, birth weight, gestational age, socio-economic status, ethnicity, body mass index and diabetes.

Selected Multivariate Model

Estimates in the form of odds ratios (ORs) for the "optimal" selected logistic model are displayed in Table 6.4 along with their confidence intervals (CIs) and p-values.

Table 6.4: Odds ratios (ORs) and 95% confidence intervals (CIs) of selected risk factors for stillbirth from the MNLD, Scotland. Bold type denotes significant category level (from baseline) with p-value < 0.05.

Risk Factor	OR	95% CI	P-value
Birth-related factors			
Mode of birth			
Normal	1		
Forceps	**0.50**	(0.35, 0.73)	<0.001
Breech	**5.80**	(4.18, 8.05)	<0.001
Elective caesarian	**0.17**	(0.11, 0.28)	<0.001
Emergency caesarian	**0.20**	(0.15, 0.26)	<0.001
Other	2.94	(0.59, 14.63)	0.188
Birth weight			
Normal ($\geq$ 2500g)	1		
Low (1500-2499g)	**7.57**	(5.74, 9.98)	<0.001
Very low (<1500g)	**19.69**	(11.9, 32.58)	<0.001
Gestational age (continuous)			
Weeks	**0.85**	(0.79, 0.91)	<0.001
Socio-economic and demographic factors			
Socio-economic status			
Managerial or professional	1		
Intermediate	1.02	(0.77, 1.35)	0.885
Smaller employer or self-employed	0.61	(0.38, 0.99)	0.044
Supervisor/ craft related	0.80	(0.55, 1.16)	0.238
Routine occupation	0.84	(0.67, 1.05)	0.133
Long term unemployed	**2.68**	(1.1, 6.55)	0.031
Student, not stated or not classifiable	0.81	(0.63, 1.05)	0.118
Ethnicity			
White	1		
Black	1.01	(0.59, 1.73)	0.980
South Asian	1.40	(0.92, 2.14)	0.171
Other	**2.03**	(1.2, 3.43)	0.008
Health and behavioural factors			
Body Mass Index (continuous)			
BMI	**1.04**	(0.96, 1.12)	<0.001
Diabetes			
No	1		
Yes – pre-existing	**2.99**	(1.57, 5.7)	<0.001
Yes – gestational (or unknown)	0.50	(0.21, 1.22)	0.121

Some of the more extreme odds ratio effects in the univariate analysis seem to have decreased in magnitude from triple-figures to more realistic values once adjusted for confounding in the multivariate analysis. Babies born in breech position are almost six times more likely to be stillborn compared to a normal delivery. The interventions of forceps or caesarean births were associated with less than half the odds of stillbirth compared to normal deliveries. Babies with low and very low birth weights were highly associated with 7 and 20 times the odds of stillbirth respectively. An increase in gestational age continued to have a protective effect, with the odds of stillbirth decreasing by 15% (previously 33%) with each increasing week of gestational age.

Compared to managerial or professional occupations, women who were self-employed or employers in a small business had 20% reduced odds of stillbirth, while unemployed women had more than double the odds. This did decrease from the odds ratio of 5.6 in the univariate analysis. The results showed no significant difference in the risk of stillbirth between white women and black or South Asian women, but double the odds for women of “other” ethnicities.

An increase in BMI continued to be associated with an increase of stillbirth risk, while the magnitude of the effect of diabetes was only slightly reduced once confounding was adjusted for, with triple the odds of stillbirth for women with diabetes compared to those without.

Interpreting odds as probabilities and rates As stated in the previous chapter (Section 5.2.5), odds ratios are not a directly interpretable metric for use in policy-relevant discussions. Therefore we shall also consider these results in terms of predictive probabilities and rates.

Consider as a baseline a hypothetical woman whose information corresponds to the reference level for each categorical predictor and the median value for each continuous predictor; i.e., a white woman in NS-SeC level 1 with BMI 26 and no diabetes who had a baby of normal weight via a normal vaginal delivery at 39 weeks gestation. The probability of stillbirth for this woman is 0.00247, or 2.5 stillbirths per 1000 births.

Keeping all other variables the same, the probabilities of stillbirths for caesarean deliveries are lower; 0.04/1000 births for an elective and 0.5/1000 for an emergency induction. Breech births, on the other hand, have a much higher rate of 14.2 stillbirths per 1000 births. Low and very low birthweight babies have rates of 18 and 46 stillbirths per 1000 births. The median gestational age in the sample is 39 weeks, but babies with gestational ages of 35 have a stillbirth rate of 4.8 per 1000 births, while at 30 weeks gestation the rate is 11 per 1000.

Looking at demographic factors such as ethnicity, black mothers in this population have similar probability to white mothers (2.5 per 1000 births). For South Asian women, the rate increases to 3.5 per 1000. Health factors such as the mother’s BMI are also important predictors. A high BMI of 35 increases the probability of stillbirth to 0.00348, or 3.5 per 1000 births. However, a mother’s diabetes condition has the biggest effect of the observed social and health factors, with a probability of 0.00735 or 7.4 per 1000 births, keeping all other variables the same as the baseline.

Random Effects: Introducing Local Authority

The linked database contains a geographic variable for the 33 Local Authorities (LA) in Scotland. To explore any potential geographical variation in stillbirth counts, a random effect was added to the existing model, considered first at a Local Authority level (33 areas) and secondly at a more aggregated level with Health Board Areas (15 areas) which were amalgamated from the LAs.

Table 6.5 shows the results for the random effects model considering a random effect for Local Authority. The odds ratios and p-values in the random effects model remained identical to those in the fixed effects model, and the variance of zero suggests that there is no additional geographic variation in stillbirth counts after accounting for the fixed effects. Considering the larger Health Board Areas as random effects achieved the same results.

We conclude that if there exists any geographic variation in stillbirth rates, it can be fully or virtually-fully explained by the observed fixed variables alone. There is no need to consider an additional area-level random effect to explain all the observed variation.

Findings from the standard multivariate fixed model shall be further discussed in the context of the existing literature in Section 6.3. We note that, when included amongst the numerous birth-related variables, many distal socio-economic, demographic, behavioural or health variables lost their significance in the model. Given their univariate significance, it is possible that some of these variables still have an important relationship with stillbirth that is mediated through the more immediate birth-related variables. This shall be explored in the next section.

Table 6.5: Odds ratios (ORs) and 95% confidence intervals (CIs) of selected risk factors for stillbirth from the MNLD, Scotland, with random effects for Local Authority. Bold type denotes significant category level (from baseline) with p-value < 0.05.

Random Effects	**Variance**	**SD**	**Num Groups**
	0.000	0.000	33
Fixed Effects	**OR**	**95% CI**	**P-value**
Birth-related factors			
Mode of birth			
Normal	1		
Forceps	**0.50**	(0.35, 0.73)	<0.001
Breech	**5.80**	(4.18, 8.05)	<0.001
Elective caesarian	**0.17**	(0.11, 0.28)	<0.001
Emergency caesarian	**0.20**	(0.15, 0.26)	<0.001
Other	2.94	(0.59, 14.63)	0.188
Birth weight			
Normal ($\geq$ 2500g)	1		
Low (1500-2499g)	**7.57**	(5.74, 9.98)	<0.001
Very low (<1500g)	**19.69**	(11.9, 32.58)	<0.001
Gestational age (continuous)			
Weeks	**0.85**	(0.79, 0.91)	<0.001
Socio-economic and demographic factors			
Socio-economic status			
Managerial or professional	1		
Intermediate	1.02	(0.77, 1.35)	0.885
Smaller employer or self-employed	0.61	(0.38, 0.99)	0.044
Supervisor/ craft related	0.80	(0.55, 1.16)	0.238
Routine occupation	0.84	(0.67, 1.05)	0.133
Long term unemployed	**2.68**	(1.1, 6.55)	0.031
Student, not stated or not classifiable	0.81	(0.63, 1.05)	0.118
Ethnicity			
White	1		
Black	1.01	(0.59, 1.73)	0.980
South Asian	1.40	(0.92, 2.14)	0.171
Other	**2.03**	(1.2, 3.43)	0.008
Health and behavioural factors			
Body Mass Index (continuous)			
BMI	**1.04**	(0.96, 1.12)	<0.001
Diabetes			
No	1		
Yes – pre-existing	**2.99**	(1.57, 5.7)	<0.001
Yes – gestational (or unknown)	0.50	(0.21, 1.22)	0.121

6.2.4 Mediation Model with SEM

In a similar fashion to the standard multivariate model, the factors that were significantly associated with stillbirth at the 20% level were initially included in the model selection process for the structural equation model (SEM).

As described in Section 6.1.4, the birth-related variables (birth weight, gestational age, parity and previous stillbirths) were considered as mediators (endogenous variables) while the remaining socio-economic, demographic, behavioural, and health factors were considered as exogenous variables. Levels of the six categorical exogenous variables were represented by (ordinal) 0/1 dummy variables; the baseline levels for each categorical variable were consistent with previous standard regression analysis. The categorical mediator variable for birth weight was treated as ordinal. Recall that birth weight is coded as "normal", "low", and "very low" with "normal" representing the baseline, and therefore its ordinal scale is decreasing in birth weight, while the other ordinal mediators (parity and previous stillbirth) are coded in an increasing order, and gestational age is a continuous variable. Therefore, a positive estimate for gestational age indicates an increased gestational age while a positive estimate for birth weight indicates a lower birth weight (in other words, an increase in the risk of low birth weight). We noted in the aforementioned section why the nominal variable for the mode of birth could not be included in this structural equation model.

Full Model

With the division of categorical exogenous factors into dummy variables, the full saturated model contained 28 variables, or nodes, and 119 paths. It would be unrealistic to create a mediation diagram displaying each individual path and estimate, but the relationships are loosely described in Figure 6.4 with the eight exogenous variables, four mediators and the outcome of stillbirth.

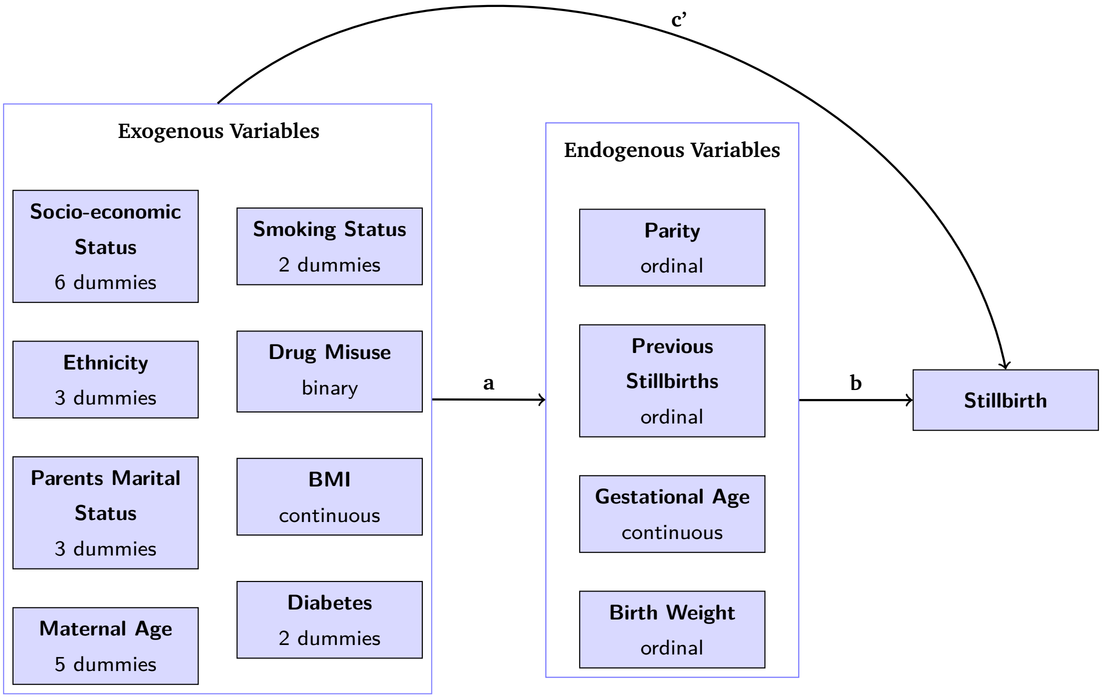


Figure 6.4: Potential mediation pathways to stillbirth for selected variables from the MNLD, Scotland

The full model estimates are displayed in the Appendix. Table B.1 shows the unstandardised direct and intermediate effects from the mediation analysis, while Table B.2 displays the resulting indirect and total effects (including standardised total effects). Confidence intervals were calculated through the asymptotic delta method. As mentioned in Section 6.1.4's discussion of SEM methods, logistic regression was not possible in R and so probit regression was conducted. The probit results are most easily interpreted in relation to an approximate logit result, which can be obtained by multiplying the standardised probit estimates by 1.6 (Amemiya et al., 1981).

Mediating Effects. Almost all of the exogenous variables significantly predict the four mediators. However, when treated as mediators, parity and previous stillbirth did not significantly predict stillbirth. Any indirect effects that included these paths were not significant at the 5% level; therefore these two mediators were removed from the causal pathway in the final model.

The majority of independent variables in this model were associated with a decreased gestational age and an increased risk of low birth weight (compared to their baseline levels, in the case of categorical variables). In many cases, such as for socio-economic status (with the exception of the indicator for unemployment), these opposing indirect effects cancelled each other out, resulting in insignificant total effects overall.

Full and Partial Mediation. Accounting for the indirect effects through gestational age and birth weight and adjusting for confounding from the other factors, some direct effects from independent factors – ethnicity, maternal age and marital status – appeared no longer significant. Thus gestational age and birth weight may *fully mediate* the effects of ethnicity, maternal age and marital status on stillbirth, and *partially mediate* the effects of socio-economic status, smoking status, drug misuse, body mass index and diabetes, which maintained a significant direct effect.

Total Effects. Regarding socio-economic status, due to the *cancelling out* of the two significant indirect effects in many cases, only the unemployed group continued to have an overall increased risk of stillbirth (0.56; 95% CI (0.26-0.86); logit approximation 0.69). Notably, this unemployed group was the only socio-economic group with a significant direct effect on stillbirth.

Adjusting for confounding, Black and South Asian women also pose an increased risk of stillbirth compared to white women with estimates 0.25 (95% CI (0.08-0.42); logit approx. 0.31) and 0.21 (95% CI (0.05-0.37); logit approx. 0.26), respectively. These effects mainly occur though an increased risk of low birth weight, although the significantly lower gestational age for pregnancies of South Asian mothers also increased their stillbirth risk. Of the maternal age groups, only those aged 40-45 maintained a significant increased risk of stillbirth in comparison to the baseline group (age 25-29) (0.19; 95% CI (0.15-0.32); logit approx. 0.23). This was mainly mediated through an increased risk of low birth weight.

Interestingly, once accounting for mediating effects, the direct effects of smoking and drug misuse during pregnancy on stillbirth *reversed* in direction to their initial results observed in the standard analyses without mediation, suggesting a protective direct effect on stillbirth. However, subdued by stronger indirect effects through an increased risk of low gestational age and low birth weight, smoking posed an overall increased risk of stillbirth (total effect 0.16; 95% CI (0.08-0.23); logit approx. 0.19) while drug misuse had no significant overall effect.

Conversely, while an increase in the mother's body mass index had a protective indirect effect on the stillbirth rate through a reduced risk of low birth weight, the more harmful direct effect of higher BMI values on stillbirth resulted in an overall increased risk of stillbirth with each increase in BMI unit (0.01; 95% CI (0-0.01); logit approx. 0.01). The development of gestational diabetes during pregnancy was not significant to the risk of stillbirth.

Finally, those with pre-existing diabetes had increased risk of stillbirth in comparison to those without it (0.43; 95% CI (0.21-0.65); logit approx. 0.53). Despite the significance of the indirect effects, this large overall effect was for the most part due to the impressive direct effect of having pre-existing diabetes on stillbirth.

We return to the logit approximations for these effect estimates for comparison with the standard logistic multivariate regression (without mediation) later in Section 6.2.5.

The model is exactly identified; it contains every possible path between variables. With zero degrees of freedom, it is difficult to obtain a measure for goodness of fit. Therefore Wald tests were employed to examine individual pathways, as described in Section 6.1.4.

Path Selection

As mentioned above, the variables for parity and previous stillbirths were not significant as mediators to stillbirth in the model and were therefore removed from the model.

Each of the paths between the remaining eight exogenous variables, two mediators and the outcome stillbirth were tested for significance with a Wald test to investigate whether the model would significantly change if the path in question was removed (i.e. if its coefficient was zero).

Most of the exogenous factors are categorical and represented by multiple dummy variables. The Wald test allowed for each categorical variable to be tested as a collection of the dummy variables representing it by fixing all of the dummies for that factor to 0; with socio-economic status, for example, the Wald test measured the effect of removing the paths from all six dummies representing socio-economic status to a given mediator from the model.

Unlike the model selection process for the previous standard logistic regression in Section 6.2.3, this selection process was not step-wise; each path (or collection of paths from dummies representing a given categorical variable) was considered independently and compared to the full model containing all paths. Insignificant paths (at the 5% level) were removed.

Results are displayed in Table 6.6, where the majority of paths between exogenous variables, mediators and stillbirth were found to be significant to the model. The only exceptions were the direct pathways from ethnicity, marital status and maternal age to stillbirth; the model did not significantly change when these were removed. The effects of these variables on stillbirth appear to be fully mediated by gestational age and birth weight, and so these direct paths were removed from the final model.

Table 6.6: Mediation path selection from the full SEM mediation model for the MNLD, Scotland Wald test statistics and p-values. Bold type denotes significant effect with p-value $p<0.05$.

Direct Path: exogenous to stillbirth	**Wald Stat**	**P-value**
Socio-economic status → stillbirth	16	**0.013**
Ethnicity → stillbirth	2.01	0.570
Parents marital status → stillbirth	1.07	0.785
Maternal age → stillbirth	1.49	0.914
Smoking status → stillbirth	8.08	**0.018**
Drug misuse → stillbirth	4.28	**0.038**
Body Mass Index → stillbirth	59	**<0.001**
Diabetes → stillbirth	14	**0.001**
Intermediate Path: mediators to stillbirth	**Wald Stat**	**P-value**
Gestational age → stillbirth	883	**<0.001**
Birth weight → stillbirth	3169	**<0.001**
Intermediate Path: exogenous to gestational age	**Wald Stat**	**P-value**
Socio-economic status → gestational age	131	**<0.001**
Ethnicity → gestational age	156	**<0.001**
Parents marital → gestational age	85	**<0.001**
Maternal age → gestational age	165	**<0.001**
Smoking status → gestational age	672	**<0.001**
Drug misuse → gestational age	123	**<0.001**
Body Mass Index → gestational age	95	**<0.001**
Diabetes → gestational age	46	**<0.001**
Intermediate Path: exogenous to birth weight	**Wald Stat**	**P-value**
Socio-economic status → birth weight	344	**<0.001**
Ethnicity → birth weight	87	**<0.001**
Parents marital status → birth weight	89	**<0.001**
Maternal age → birth weight	609	**<0.001**
Smoking status → birth weight	466	**<0.001**
Drug misuse → birth weight	144	**<0.001**
Body Mass Index → birth weight	6.08	**0.014**
Diabetes → birth weight	3006	**<0.001**

Final Model with Insignificant Paths Removed

The final model consisted of eight independent variables, two mediators and the outcome of stillbirth. The mediators were examined in the same model thus adjusting for the covariance between them. Levels of the six categorical independent variables were represented by dummy exogenous variables in the SEM. The mediation model contains 58 paths; for clarity, these paths and their estimates are divided between three diagrams, with Figure 6.6 displaying the effects of socio-economic status and ethnicity, Figure 6.7 displaying marital status and maternal age, and 6.8 the remaining variables relating to behaviour and health (smoking/drug status, body mass index and diabetes status).

Figure 6.5 summarises the whole mediation process in an informal path diagram. Table 6.7 shows the resulting indirect and total effect estimates from these paths, along with standardised total effects and approximated logit estimates.

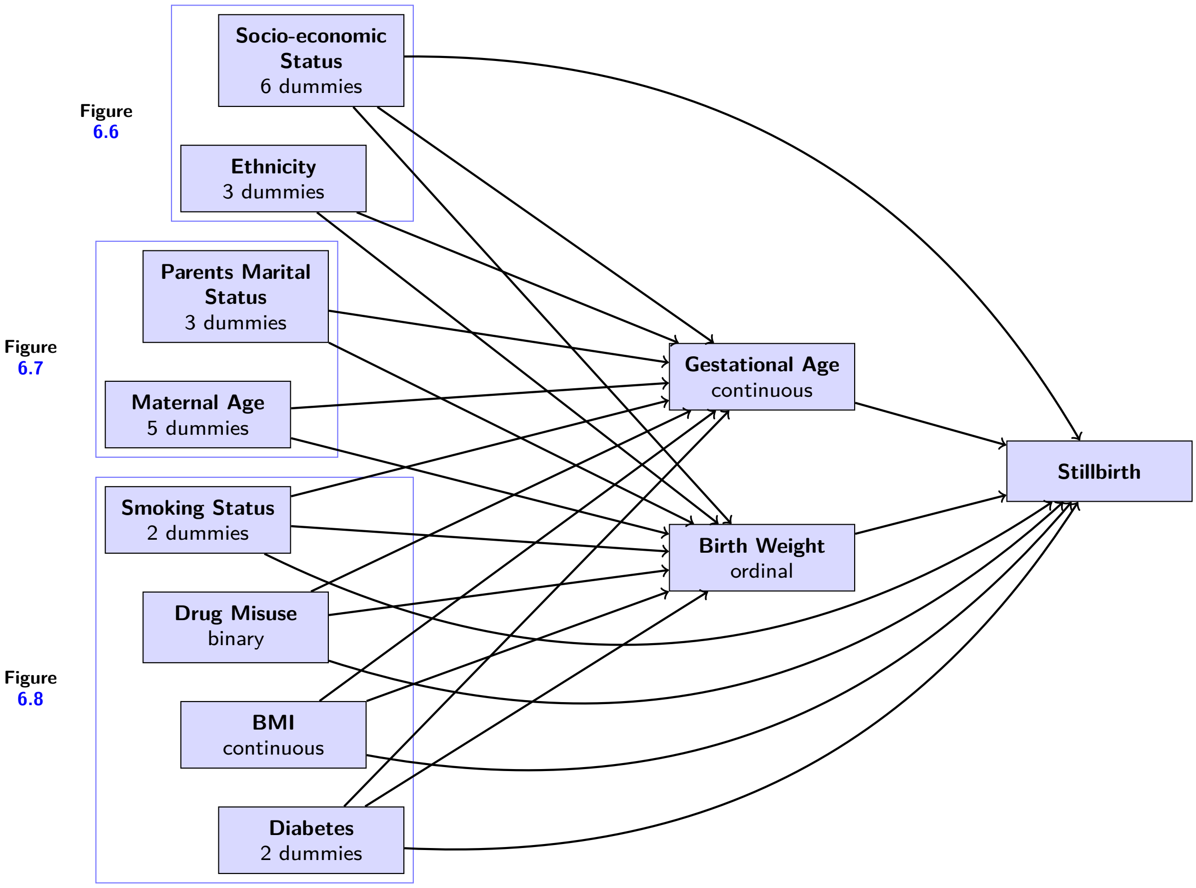


Figure 6.5: Mediation pathways for the significant relationships between stillbirth and model-selected variables from the MNLD, Scotland

Figure 6.5 shows that all of the independent variables significantly predicted the two mediators – gestational age and birthweight. The more detailed sub-figures show that the majority of the exogenous variables in this model were associated with a decreased gestational age and an increased risk of low birth weight (compared to their baseline levels, in the case of categorical variables). Both mediators had significant relationships with stillbirth; accounting for the effect of the exogenous variables on the mediators, a significantly increased risk of stillbirth was seen for babies with higher gestational age and low birth weight. Therefore, in general, the significant indirect effects in Table 6.7 showed an increased risk of stillbirth for those with low birth weight and a decreased risk through an increase in gestational age. In many cases, these opposing indirect effects cancelled each other out, resulting in insignificant total effects overall.

Full and partial mediation. Direct effects were included for five of the eight independent variables: socio-economic status, smoking status, drug misuse, body mass index and diabetes. Four of these variables retained a significant direct effect on stillbirth in the presences of the mediators. The direct relationship between drug misuse and stillbirth was no longer significant at the 5% level as it had been in the full model, despite its significance in the model selection process.

With the presence of a significant direct effect, we conclude that gestational age and birth weight partially mediated the effects of socio-economic status, smoking status, body mass index and diabetes on stillbirth, but fully mediated the effects of ethnicity, marital status, maternal age and drug misuse, after adjusting for the other variables in the model.

Total effects. For the five independent variables that retained their direct effect paths in the model – socio-economic status, smoking status, drug misuse, body mass index and diabetes – all effect estimates were near-identical in the final model to those in the full model, and all of the total effects were identical to 2 decimal places. Of the socio-economic status groups (Figure 6.6), only the long-term unemployed group continued to have an overall increased risk of stillbirth compared to the baseline group of women in managerial and professional occupations (0.56; 95% CI (0.26-0.86); logit approximation 0.69).

As with the full mediation model, an unusually protective direct effect was observed for women who smoked during pregnancy (Figure 6.8), but the stronger indirect effects through an increased risk of low gestational age and low birth weight for smokers resulted in a significantly increased overall risk of stillbirth for those who smoke during pregnancy (0.16; 95% CI 0.08-0.23); logit approx. 0.19). Also echoing the full mediation model, the total effect of drug misuse was still not significant at the 5% level as it had been in the full model, despite the variable's significance in the model selection process. Despite the protective effect of the mother's body mass index on the risk of low birth weight, this indirect effect on stillbirth was overpowered by the more harmful direct effect, resulting in an overall increased risk of stillbirth with increased BMI (0.01; 95% CI 0.00-0.01); logit approx. 0.01). The presence of diabetes before pregnancy also highly increased the overall risk of stillbirth compared to those without it (0.43; 95% CI 0.21-0.65); logit approx. 0.53).

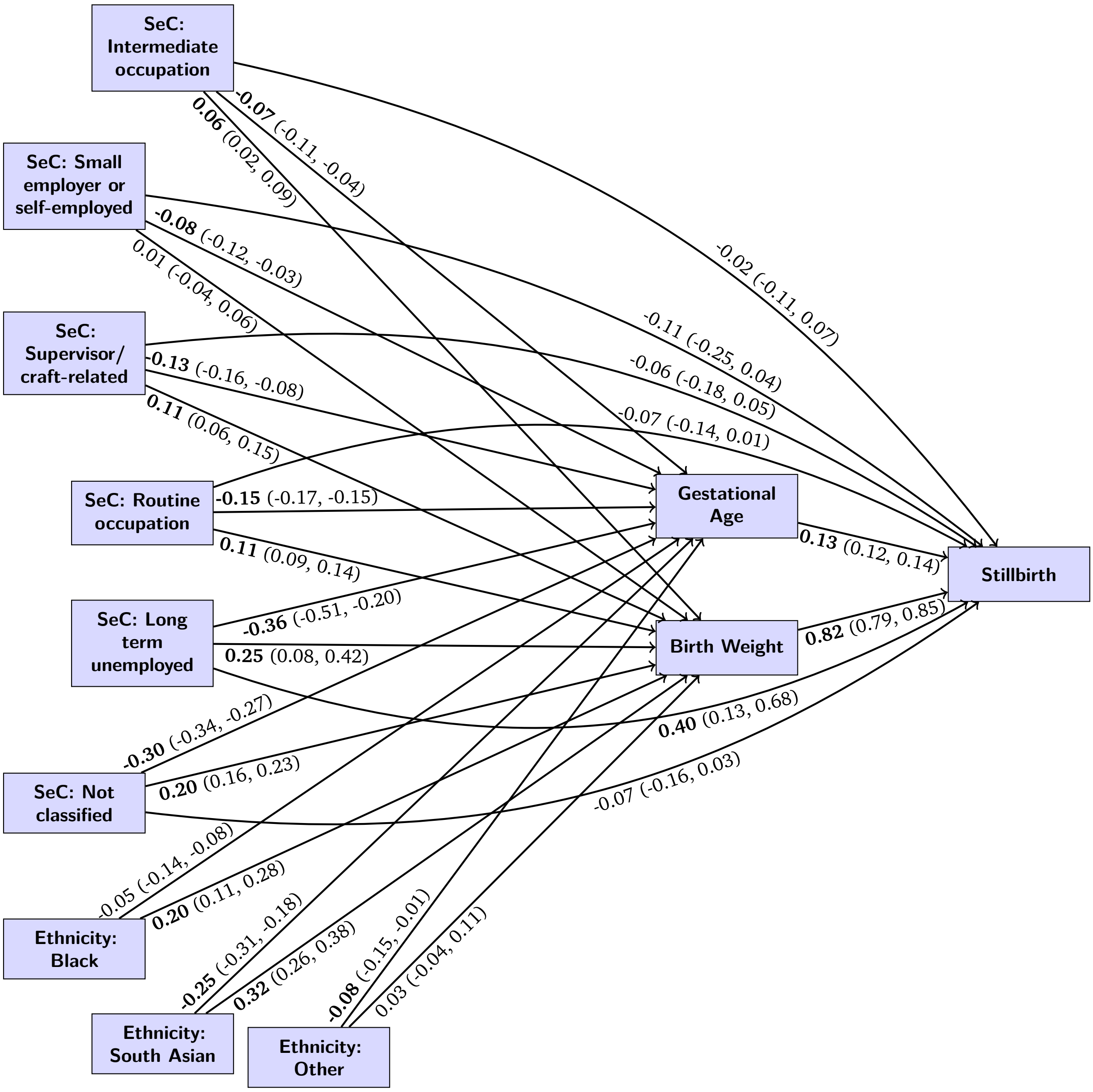


Figure 6.6: Mediation pathways between socio-economic status, ethnicity and stillbirth from the MNLD, Scotland, with probit effect estimates and 95% confidence intervals (CI).
Bold type denotes significant effects with p-value < 0.05.

On the other hand, for the three independent variables – ethnicity, maternal age and marital status – the total effect estimates differed slightly from the previous full model, generally with more significance among the category levels. The effects for all three of these independent variables were entirely mediated through gestational age and birth weight.

Regarding ethnicity, black and South Asian women still had an increased risk of stillbirth compared to white women (0.15 (95% CI 0.09-0.22); logit approx. 0.20) and 0.23 (95% CI 0.18-0.28; logit

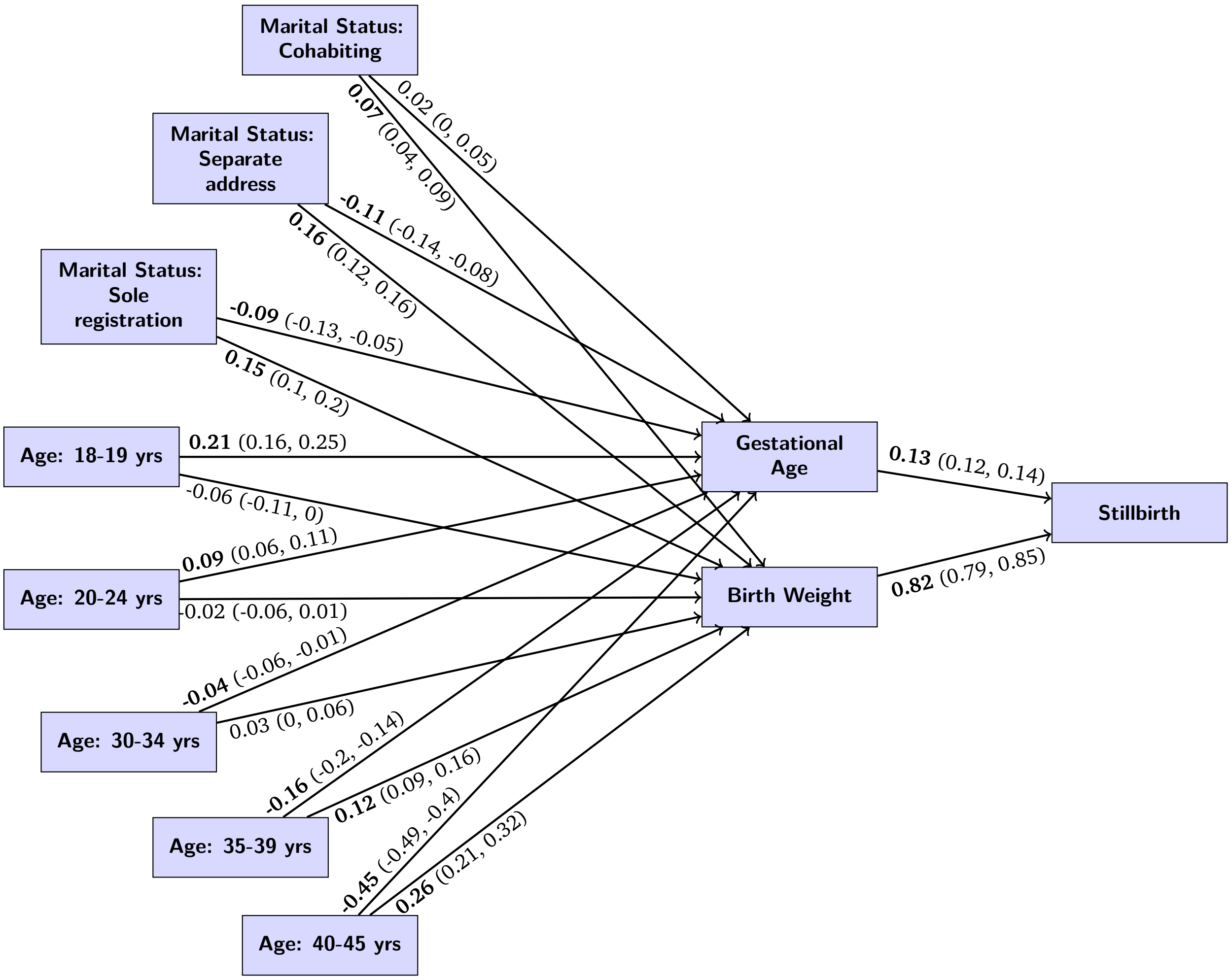


Figure 6.7: Mediation pathways between parents' marital status, maternal age and stillbirth from the MNLD, Scotland, with probit effect estimates and 95% confidence intervals (CI).
Bold type denotes significant effects with p-value < 0.05.

approx. 0.28), respectively). Compared to married parents, unmarried women also had an increased risk regardless of whether they were cohabiting with the father, lived separately from the father or registered as a single mother (0.06 (95% CI 0.0.04-0.08), 0.11 (95% CI 0.08-0.14) and 0.10 (95% CI 0.07-0.14), respectively). In the full model, marital status had not observed any significant overall effect on stillbirth. Primarily mediated through an increased risk of low birth weight, advanced maternal age resulted in an increased risk of stillbirth for women aged 35-39 and 40-45 (0.08 (95% CI 0.05-0.1) and 0.16 (95% CI 0.12-0.2) respectively), compared to those aged 25-29. In the previous model, only the eldest age group had maintained a significant total effect.

Various goodness-of-fit indices depict a very good fit, with a Comparative Fit Index (CFI) of 1.000, Tucker-Lewis Index (TLI) of 1.001, Root Mean Square Error of Approximation (RMSEA) of 0.000, and χ^2 =4.322 (p$\leq$0.959) with 11 degrees of freedom. However, although some paths were removed from the

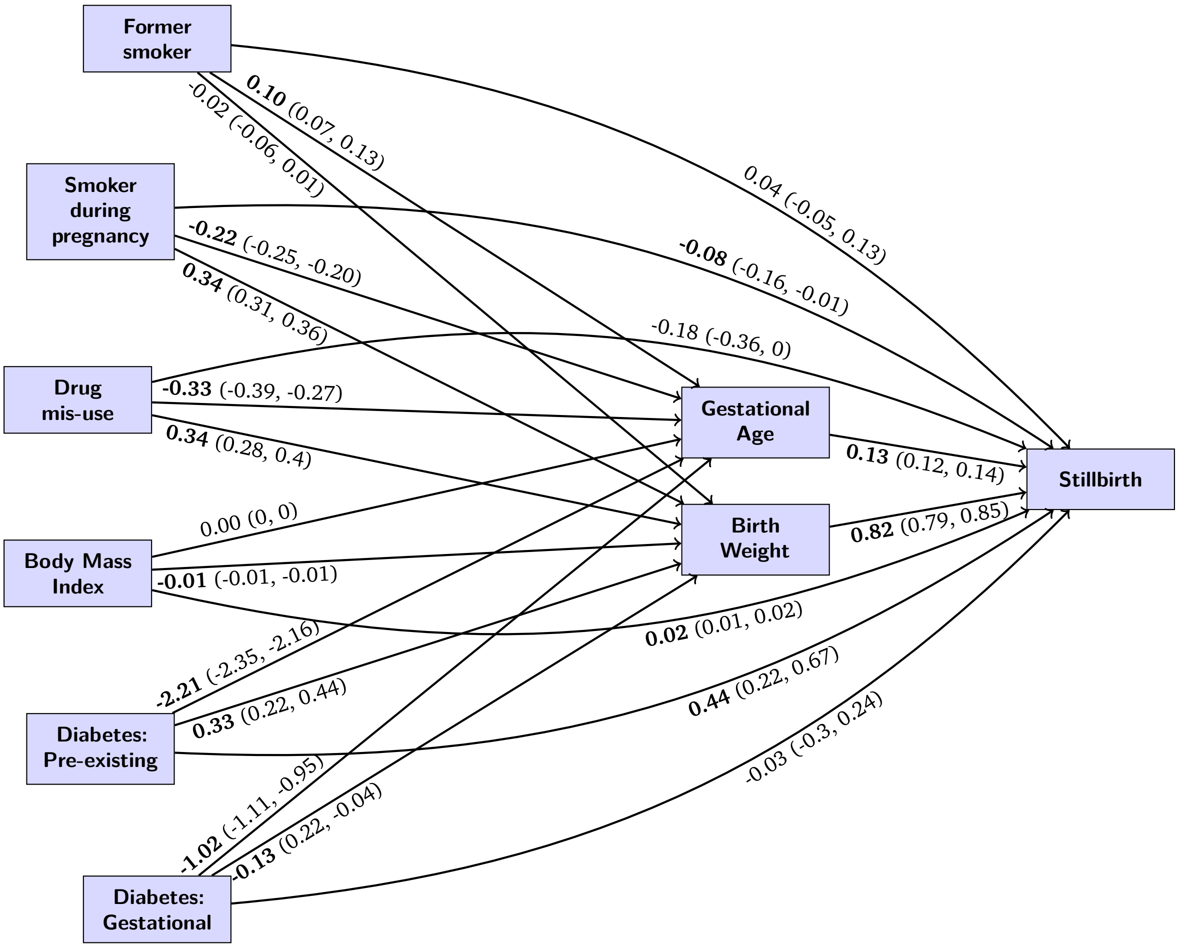


Figure 6.8: Mediation pathways between smoking/drug status body mass index, diabetes and stillbirth from the MNLD, Scotland, with probit effect estimates and 95% confidence intervals (CI).
Bold type denotes significant effects with p-value < 0.05.

full model, the final model is still almost exactly identified and therefore these fit indices may not be appropriate.

Table 6.7: SEM mediation model indirect and total effects for all model-selected pathways for the MNLD, Scotland, with 95% confidence intervals (CI), standardised total effects and logit approximations ($\times 1.6$). Bold type denotes significant effects with p-value < 0.05.

	Unstandardised Indirect Effect				Unstandardised Total Effect		Standardised Total Effect	
	via gestational age		via birth weight					
Exogenous Variable	**Probit Est.**	**95% CI**	**Probit Est.**	**95% CI**	**Probit Est.**	**95% CI**	**Probit Est.**	**Logit Est.**
Socio-economic status								
Intermediate	**-0.01**	(-0.01, -0.01)	**0.05**	(0.02, 0.08)	0.02	(-0.07, 0.11)	0.01	0.02
Small employer and self-employed	**-0.01**	(-0.02, 0)	0.01	(-0.04, 0.05)	-0.11	(-0.25, 0.03)	-0.09	-0.14
Supervisors/craft related	**-0.02**	(-0.02, -0.01)	**0.09**	(0.05, 0.13)	0.01	(-0.1, 0.13)	0.01	0.01
Routine occupations	**-0.02**	(-0.02, -0.02)	**0.09**	(0.07, 0.12)	0.01	(-0.07, 0.08)	0.01	0.01
Unemployed	**-0.04**	(-0.07, -0.03)	**0.20**	(0.06, 0.34)	**0.56**	(0.26, 0.86)	**0.44**	**0.70**
Not classified	**-0.04**	(-0.04, -0.03)	**0.16**	(0.13, 0.19)	0.05	(-0.04, 0.15)	0.04	0.06
Ethnicity								
Black	-0.01	(-0.02, 0.01)	**0.16**	(0.09, 0.23)	**0.15**	(0.09, 0.22)	**0.13**	**0.20**
South Asian	**-0.03**	(-0.04, -0.02)	**0.26**	(0.21, 0.31)	**0.23**	(0.18, 0.28)	**0.18**	**0.28**
Other	**-0.01**	(-0.02, 0)	0.03	(-0.04, 0.09)	0.02	(-0.04, 0.07)	0.01	0.02
Parents marital status								
Cohabiting	0.00	(0, 0.01)	**0.05**	(0.03, 0.08)	**0.06**	(0.04, 0.08)	**0.04**	**0.07**
Separate address	**-0.01**	(-0.02, -0.01)	**0.13**	(0.09, 0.16)	**0.11**	(0.08, 0.14)	**0.09**	**0.14**
Sole registration	**-0.01**	(-0.02, -0.01)	**0.12**	(0.08, 0.16)	**0.10**	(0.07, 0.14)	**0.08**	**0.13**
Maternal age								
18-19 yrs	**0.03**	(0.02, 0.03)	-0.05	(-0.09, 0)	-0.02	(-0.06, 0.02)	-0.02	-0.02
20-24 yrs	**0.01**	(0.01, 0.01)	-0.02	(-0.05, 0.01)	-0.01	(-0.03, 0.01)	-0.01	-0.01
30-34 yrs	**0.00**	(-0.01, 0)	0.03	(0, 0.05)	0.02	(0, 0.04)	0.02	0.03
35-39 yrs	**-0.02**	(-0.03, -0.02)	**0.10**	(0.07, 0.13)	**0.08**	(0.05, 0.1)	**0.06**	**0.10**
40-45 yrs	**-0.06**	(-0.06, -0.05)	**0.22**	(0.17, 0.26)	**0.16**	(0.12, 0.2)	**0.12**	**0.20**
Smoking status								
Former smoker	**0.01**	(0.01, 0.02)	-0.02	(-0.05, 0.01)	0.03	(-0.06, 0.12)	0.03	0.04
Smoked during pregnancy	**-0.03**	(-0.03, -0.02)	**0.27**	(0.25, 0.3)	**0.16**	(0.08, 0.23)	**0.12**	**0.19**
Drug mis-use								
Yes	**-0.04**	(-0.05, -0.03)	**0.27**	(0.22, 0.32)	0.05	(-0.12, 0.23)	0.04	0.07
Body mass index	**0.00**	(0, 0)	**-0.01**	(-0.01, -0.01)	**0.01**	(0, 0.01)	**0.01**	**0.01**
Diabetes								
Pre-existing	**-0.29**	(-0.31, -0.26)	**0.27**	(0.18, 0.36)	**0.43**	(0.21, 0.65)	**0.33**	0.53
Gestational	**-0.13**	(-0.14, -0.12)	**-0.11**	(-0.18, -0.03)	-0.27	(-0.54, 0)	-0.21	-0.33

Bootstrapped Confidence Intervals

Bootstrap percentile confidence intervals for the final mediation model's indirect and total effects were calculated by drawing 500 bootstrap random samples from each of the multiply-imputed datasets.

Table 6.8 displays 95% confidence intervals obtained via bootstrapping compared to the robust 95% confidence intervals previously calculated by the asymptotic delta approach.

Each of the sixty-nine effect estimates falls within both corresponding confidence intervals, and the two sets of confidence intervals are, for the most part, consistent in suggesting significance, with a few exceptions. For the total effects of maternal age, the bootstrap confidence interval for women aged 30-34 years does not contain zero, suggesting that this group have a small but significant positive relationship with stillbirth (estimate = 0.02) compared to the baseline group (women aged 25-29 years). However, the delta approach did not find this estimate to be significant. Similarly, the total effect of having gestational diabetes (compared to those who do not have diabetes) appears to have a significant negative effect according to the bootstrap confidence interval, but this is not the case with the delta approach (estimate = -0.269).

Overall, the bootstrap and delta results for this analysis are consistent, and although the bootstrap method is preferred (Section 6.1.4), the asymptotic method was appropriate as a preliminary method with this large dataset.

Table 6.8: Comparison of two types of confidence intervals (CIs) (at the 5% level) for the indirect and total effects of the final SEM mediation model. Estimates in bold type denote significance with p-value <0.05. CIs in bold type denote significance in that the interval does not contain 0.

Indirect Effect: via gestational age	Estimate	Asymptotic Delta CI	Bootstrap Percentile CI
Socio-economic status			
Intermediate occupation	**-0.009**	**(-0.01, -0.01)**	**(-0.01, -0.01)**
Small employer or self-employed	**-0.010**	**(-0.02, -0.00)**	**(-0.02, -0.01)**
Supervisor/craft related	**-0.016**	**(-0.02, -0.01)**	**(-0.02, -0.01)**
Routine occupation	**-0.019**	**(-0.02, -0.02)**	**(-0.02, -0.02)**
Long term unemployed	**-0.045**	**(-0.07, -0.03)**	**(-0.08, -0.02)**
Not classified	**-0.039**	**(-0.04, -0.03)**	**(-0.04, -0.03)**
Ethnicity			
Black	-0.006	(-0.02, 0.01)	(-0.01, 0.00)
South Asian	**-0.031**	**(-0.04, -0.02)**	**(-0.04, -0.03)**
Other	**-0.010**	**(-0.02, -0.00)**	**(-0.02, -0.00)**
Parents marital status			
Cohabiting	0.003	(0, 0.006)	(0, 0.006)
Separate address	**-0.014**	**(-0.02, -0.01)**	**(-0.02, -0.01)**
Sole registration	**-0.011**	**(-0.02, -0.01)**	**(-0.02, -0.01)**
Maternal age			
18-19 yrs	**0.026**	**(0.02, 0.03)**	**(0.02, 0.03)**
20-24 yrs	**0.011**	**(0.01, 0.01)**	**(0.01, 0.01)**
30-34 yrs	**-0.005**	**(-0.01, -0.00)**	**(-0.01, -0.00)**
35-39 yrs	**-0.021**	**(-0.03, -0.02)**	**(-0.03, -0.02)**
40-45 yrs	**-0.057**	**(-0.06, -0.05)**	**(-0.07, -0.05)**
Smoking status			
Former smoker	**0.013**	**(0.01, 0.02)**	**(0.01, 0.02)**
Smoked during pregnancy	**-0.029**	**(-0.03, -0.03)**	**(-0.03, -0.03)**
Drug misuse			
Yes	**-0.042**	**(-0.05, -0.03)**	**(-0.05, -0.03)**
Body mass index			
BMI	**0.000**	**(0, 0)**	**(0, 0)**
Diabetes			
Gestational	**-0.287**	**(-0.31, -0.26)**	**(-0.32, -0.26)**
Pre-existing	**-0.131**	**(-0.15, -0.12)**	**(-0.15, -0.12)**
Indirect Effect: via birth weight			
Socio-economic status			
Intermediate occupation	**0.048**	**(0.02, 0.08)**	**(0.02, 0.08)**
Small employer or self-employed	0.006	(-0.04, 0.05)	(-0.04, 0.05)
Supervisor/craft related	**0.088**	**(0.05, 0.13)**	**(0.05, 0.12)**
Routine occupation	**0.093**	**(0.07, 0.12)**	**(0.07, 0.12)**
Long term unemployed	**0.204**	**(0.07, 0.34)**	**(0.04, 0.34)**
Not classified	**0.158**	**(0.13, 0.19)**	**(0.13, 0.19)**
Ethnicity			
Black	**0.159**	**(0.09, 0.23)**	**(0.10, 0.21)**
South Asian	**0.260**	**(0.21, 0.31)**	**(0.22, 0.30)**
Other	0.027	(-0.04, 0.09)	(-0.03, 0.08)
Parents marital status			
Cohabiting	**0.053**	**(0.03, 0.08)**	**(0.03, 0.07)**
Separate address	**0.125**	**(0.10, 0.16)**	**(0.010, 0.16)**

Table 6.8 continued from previous page

	Estimate	Delta CI	Bootstrap CI
Sole registration	**0.120**	**(0.08, 0.16)**	**(0.08, 0.16)**
Maternal age			
18-19 yrs	**-0.046**	**(-0.09, -0.00)**	**(-0.09, -0.00)**
20-24 yrs	-0.020	(-0.05, 0.01)	(-0.04, 0.01)
30-34 yrs	**0.025**	**(0.00, 0.05)**	**(0.01, 0.05)**
35-39 yrs	**0.100**	**(0.07, 0.13)**	**(0.08, 0.13)**
40-45 yrs	**0.217**	**(0.17, 0.26)**	**(0.17, 0.26)**
Smoking status			
Former smoker	-0.018	(-0.05, 0.01)	(-0.05, 0.01)
Smoked during pregnancy	**0.271**	**(0.25, 0.30)**	**(0.25, 0.30)**
Drug misuse			
Yes	**0.273**	**(0.22, 0.32)**	**(0.23, 0.31)**
Body mass index			
BMI	-0.007	(-0.01, -0.01)	(-0.01, -0.01)
Diabetes			
Gestational	**0.269**	**(0.18, 0.36)**	**(0.17, 0.36)**
Pre-existing	**-0.105**	**(-0.18, -0.03)**	**(-0.19, -0.04)**
Total Effect: direct+indirect via gest. age+indirect via birth weight			
Socio-economic Status			
Intermediate occupation	0.018	(-0.07, 0.11)	(-0.08, 0.10)
Small employer or self-employed	-0.110	(-0.25, 0.03)	(-0.26, 0.02)
Supervisor/craft related	0.011	(-0.10, 0.13)	(-0.11, 0.11)
Routine occupation	0.008	(-0.07, 0.08)	(-0.07, 0.08)
Long term unemployed	**0.559**	**(0.26, 0.86)**	**(0.17, 0.83)**
Not classified	0.052	(-0.04, 0.15)	(-0.05, 0.14)
Ethnicity			
Black	0.153	(0.09, 0.22)	(1.00, 0.21)
South Asian	0.228	(0.18, 0.28)	(0.19, 0.26)
Other	0.017	(-0.04, 0.07)	(-0.03, 0.06)
Parents marital status			
Cohabiting	**0.056**	**(0.04, 0.08)**	**(0.04, 0.08)**
Separate address	**0.111**	**(0.08, 0.14)**	**(0.09, 0.14)**
Sole registration	**0.108**	**(0.07, 0.15)**	**(0.07, 0.14)**
Maternal age			
18-19 yrs	-0.020	(-0.06, 0.02)	(-0.06, 0.02)
20-24 yrs	-0.009	(-0.03, 0.02)	(-0.03, 0.015)
30-34 yrs	0.020	(-0.00, 0.04)	**(0.00, 0.04)**
35-39 yrs	**0.079**	**(0.05, 0.10)**	**(0.06, 0.10)**
40-45 yrs	**0.160**	**(0.12, 0.2)**	**(0.12, 0.20)**
Smoking status			
Former smoker	0.033	(-0.06, 0.12)	(-0.06, 0.10)
Smoked during pregnancy	**0.156**	**(0.09, 0.23)**	**(0.09, 0.22)**
Drug misuse			
Yes	0.053	(-0.12, 0.23)	(-0.12, 0.20)
Body mass index			
BMI	**0.009**	**(0.01, 0.01)**	**(0.01, 0.01)**
Diabetes			
Pre-existing	**0.427**	**(0.21, 0.67)**	**(0.16, 0.61)**
Gestational	-0.269	(-0.54, 0.00)	**(-0.56, -0.07)**

6.2.5 Comparison of Mediation and Standard Models

We wish to compare the findings from the mediation model with those in the standard logistic multivariate model without mediation in Table 6.2. This multivariate model contained all eight of the independent variables under consideration in the mediation model, as well as the four mediators. Without mediations, each of the eight independent variables was in itself a significant risk factor for stillbirth (at least at a 20% level, with most beyond a 5% level), as observed in the univariate analysis in Section 6.2.2.

The coefficient values for the standard multivariate model and the "full" mediation model are not directly comparable for a number of reasons. First, the standard model uses logistic regression while the mediation model uses probit; variance of the logistic distribution is $\sqrt{3}/\pi$, while the scale of the probit is set to 1. As suggested by (Amemiya, 1981), we scale the probit estimates by 1.6 to get comparable values. Secondly, the birth-related variables are included as nominal categorical variables in the standard model, but as latent ordinal variables in the mediation model, which makes direct comparison difficult. Moreover, the mediation model is missing the crucially significant variable for the mode of birth from its analysis, which may have affected the effects of the remaining variables. These inconsistencies in the models must be kept in mind when attempting to compare them.

Considering the overall importance of the independent variables, it is noteworthy that marital status, maternal age, smoking and drug misuse were did not have a significant association with stillbirth in the standard multivariate model. Regarding ethnicity, this model found that only the amalgamated "other" ethnic group has a significant effect on stillbirth (compared to white women), which was not the case for the mediation model, which observed significant differences in stillbirth risk for black and South Asian women, compared to white women. Only three of the independent variables had significant, comparable effects on stillbirth in both models: socio-economic status, body mass index and diabetes.

Table 6.7 shows the *standardised* total effects for the exogenous variables with approximate estimates for an equivalent logit model. In the mediation model, the total approximate log-odds of long-term unemployment on the risk of stillbirth (compared to the baseline group of those in managerial occupations) was 0.696, which was higher than the log-odds estimate of 0.428 (OR 2.68) in the standard logistic model. Likewise, the total approximate log-odds of maternal diabetes on stillbirth, accounting for mediation, was 0.533, higher than the standard model's log-odds estimate of 0.475 (OR 2.99).

Conversely, the total effect of body mass index on stillbirth was lower in the mediation model; each incremental increase in body mass index resulted in an increase of 0.011 in the approximated log-odds of stillbirth in the mediation model, compared to a 0.017 increase in the standard model's log-odds (or a 4% increase in the odds of stillbirth).

On the whole, the mediation analysis revealed a greater effect of unemployment and of diabetes on stillbirth than in the standard model, and a slightly smaller effect of BMI. The overall effects of ethnicity, marital status, maternal age, smoking status and drug misuse were much more significant in the mediation analysis, whether they were partially or fully mediated by gestational and birth weight.

6.3 Discussion of the Scotland Analysis

In this chapter, we have presented an analysis of individual-level linked birth data in Scotland. We explored a large number of available variables through both standard multivariate analysis and mediation analysis. This section assesses the use of the data in question, summarises the findings of these analyses and attempts to place them in the context of previous literature. It also reviews the strengths and limitations of the methods used.

6.3.1 The Linked Data

Scotland has been praised for its linkage of perinatal health information (Delnord et al., 2016) and numerous studies on adverse birth outcomes have been conducted using the Maternity and Neonatal Linked Database (MNLD) (Norman et al., 2009; Sutan et al., 2010; Wood et al., 2012). Our investigation contributes to this existing knowledge with the analysis of more recent data using mediation analysis, focussing more deeply on the associations between socio-economic position and stillbirth in Scotland with individual level social factors.

Missing Data. Approximately 4% of the data was missing due to either non-response or recording error. The methods used in this study to tackle missing data assume that the data is missing at random (MAR), although in practice, it is difficult to confirm whether data from a variable is missing at random. For the data to be not missing at random (NMAR), missingness would have to depend on the variable itself. One might argue this is true for the behavioural variables of smoking/alcohol/drugs; an American study estimated that only 75% of pregnant smokers disclose their status to health providers. If smoking/drinking women did not provide this information out of fear that their response would be socially unacceptable, then these variables would be not missing at random (Kim et al., 2009). However, in either case, the use of multiple imputation is the best option for reducing bias, especially compared to list-wise deletion.

6.3.2 Summary of Findings

It would not be appropriate to directly compare the magnitude of the estimates between the standard model and mediation (SEM) model. The mediation model estimates, calculated with a probit link function, can be multiplied by 1.6 to better reflect the logistic regression estimates from the standard model, therefore aiding interpretation (Amemiya, 1981). However, a direct comparison was still difficult because the categorical outcome and mediators are treated as nominal in the standard model and ordinal in the mediation model, out of necessity for SEM. Instead, the general direction and significance of the estimates between the two types of models are compared.

Initial Findings

Individually, significant associations with stillbirth were found for the socio-demographic factors socio-economic status (SES), ethnicity, parents' marital status, and maternal age, as well as behavioural and health factors such as smoking status, drug misuse, BMI and presence of diabetes. No relationship was found, on the other hand, between stillbirth and the mother's weekly alcohol intake. Additionally, the mode of birth, birth weight, gestational age, parity and stillbirth history were associated with subsequent stillbirth, but the sex of the foetus, the history of neonatal death or spontaneous abortion was not. No significant relationship was found for area-based factors such as deprivation level, urban/rural code, or whether the mother was born in the UK.

When adjusting for confounders in multivariate analysis, marital status, maternal age, smoking, drug misuse, parity and previous stillbirth lost their significant relationship with stillbirth. Babies born in breech position were almost six times more likely to be stillborn compared to a normal delivery. Medical interventions such as the use of forceps or caesarean births were associated with less than half the odds of stillbirth compared to normal deliveries. Babies with low birth weights had greatly increased odds of stillbirth while an increase in gestational age had a protective effect.

There was no evidence of a random effect for geographic area within Scotland. It is possible that the restriction of the data to Scotland reduces the scope for regional variation, and that a similar analysis of the entire UK would expose more regional differences.

Incorporating Mediation

When mediation was introduced, much of the effects of the more distal socio-economic and health factors were mediated by gestational age and birth weight. Many of the "adverse" social, behavioural and health indicators were associated with a decreased gestational age and/or low birth weight. Parity and stillbirth history did not mediate any of these effects.

The effects of ethnicity, marital status, maternal age and drug misuse were fully mediated by gestational age and birth weight after adjusting for confounding factors. Meanwhile, the effects of socio-economic status, smoking status, BMI and diabetes on stillbirth were partially mediated; some elements continued to pose a direct risk of stillbirth after mediation, including being unemployed, having an increased BMI and having pre-existing diabetes.

Regarding socio-economic status (SES), when adjusting for confounders, the standard multivariate model found that women who were self-employed or small-business employers had reduced odds of stillbirth compared to those in managerial or professional occupations, while unemployed women had more than double the odds. When accounting for mediation, only the unemployed group maintained its increased risk of stillbirth; it must be noted, however, that the number of women in this group is very small, suggesting it may be less reliable than other estimates in the model.

The standard multivariate analysis showed no significant difference in the risk of stillbirth between white women and black or South Asian women. With mediation, however, the total effects of ethnicity suggested that those of of black and South Asian ethnicities were at significantly higher risk of stillbirth compared to white women. Similarly, marital status, maternal age smoking status and drug misuse status had no significant effects on stillbirth in the standard multivariate analysis. However, in the mediation model, unmarried women had a small but significant increased stillbirth risk compared to married women regardless of whether they were cohabiting with the father, lived separately from the father or registered as a single mother. Accounting for other confounding and mediation, older mothers (age 35-45 in the sample) had a higher risk of stillbirth compared to women aged 25-29 years. Similar findings were observed for drug misuse and smoking during pregnancy. Former smokers seem to have no additional risk of stillbirth compared to non-smokers.

Although the total effect of smoking showcased an increased risk of stillbirth, the mediation model contained an unusually protective direct effect of smoking once accounting for mediators. This could be due to a missing moderator effect, which would affect the strength of the relation between smoking status and either (or both) of the mediating fetal characteristics. This is essentially an interaction term, i.e. the effect of gestational age or birth weight on stillbirth may be different for smokers compared to non-smokers. A low birth rate or low gestational age for non-smokers could be more serious as it may indicate latent medical problems.

Increased body mass index was consistently associated with a higher risk of stillbirth. In the multivariate analysis, the odds of stillbirth increase by 4% for each additional unit increase in BMI. This relationship holds in the mediation model, diminished slightly by a small protective indirect effect through gestational age. Likewise, the presence of pre-existing diabetes in the standard multivariate model initially tripled the odds of stillbirth compared to those without diabetes. This relationship remains, and is even higher, with mediation, although the relatively small number of women in this group calls the reliability of this result into question.

Overall, the fact that ethnicity, marital status, maternal age and drug use were fully mediated by gestational age and birthweight could explain their loss of significance in the standard multivariate model, which also accounted for gestational age and birthweight. The mediation model showed that despite not having a direct effect, they are still relevant in the causal pathway to stillbirth due to their strong relationship with gestational age and birthweight.

Suitability of the Mediators

In the standard regression analysis, babies with lower birth weights and lower gestational age had higher odds of stillbirth. However, in many cases it may not be true that these factors lead to stillbirth, but rather they are a product of the stillbirth, i.e. the stillbirth occurs for other reasons, leading to an early or induced labour, leading to a lower gestational age and birth weight. We note that birth weight was coded in decreasing order of weight ("normal", "low", "very low") since, in the standard regression, the category "normal" would be treated as the baseline. In the mediation model, the birth weight is treated as ordinal with a decreasing order. This is contrary to gestation age, whose effect measures the change in stillbirth as gestational age increases. Therefore, care should be taken when interpreting the indirect effects that are based on these variables.

In the model, parity and other details of birth history were treated as mediators alongside the pregnancy-related variables, but might be better suited as exogenous variables. These two factors had significant associations with stillbirth in univariate analyses, but neither was important to the multivariate model once accounting for confounding factors. If considered as exogenous in the mediation analysis, however, they may showcase indirect effects on stillbirth, similar to maternal age and ethnicity.

Comparison with Literature

In general, the variables found to be significant in this study are in keeping with the literature (see Literature Review in Chapter 2). Findings from the standard multivariate model are similar to the UK study by Gardosi et al. (2013a) for which ethnicity, parity, smoking, maternal obesity and pre-existing diabetes were significant risk factors after accounting for confounding. The UK literature reported mixed results when it came to the significance of area-based deprivation scores. This study found no evidence of a relationship between deprivation (measured with the Carstairs score) and stillbirth. Indeed, neither of the other area-based variables – local authority and urban/rural code – had a significant association with stillbirth, which is also in keeping with the literature.

The majority of the significant pathways in the mediation analysis reflected the pathways in the literature review's conceptual model (Figure 2.4). The pathways observed in this analysis are displayed in Figure 6.9.

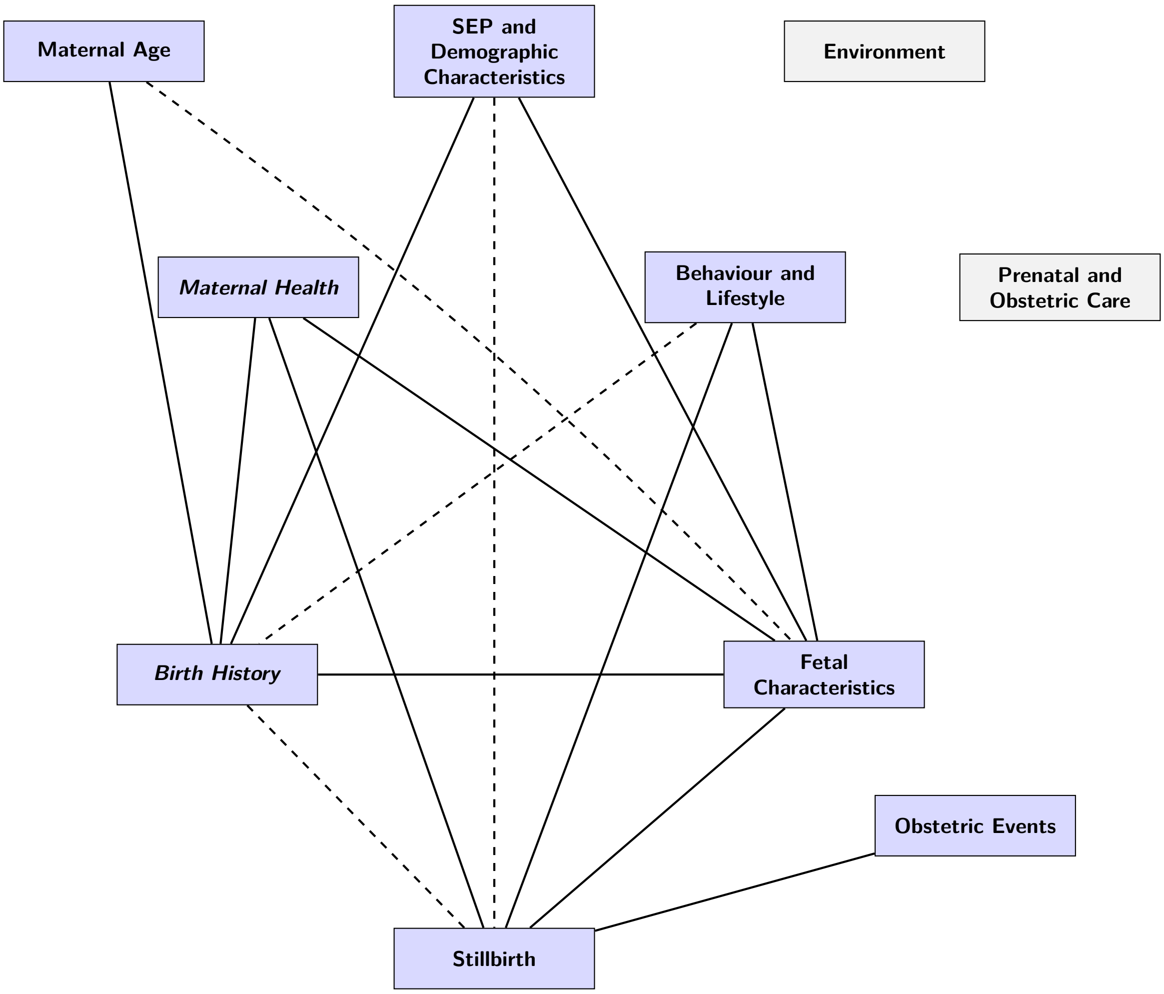


Figure 6.9: Pathways to stillbirth observed from available variables in the MNLD for Scotland. *Grey boxes indicate variable topics not covered in the data. Dashed lines indicate paths that don't appear in the main Conceptual Model (Figure 2.4).*

The conceptual model does not feature a direct pathway from SEP or maternal age to stillbirth. Similarly, many of the more distal factors representing SEP in this study – ethnicity, marital status and maternal age – showed a univariate association with stillbirth, but when accounting for mediating factors, the direct association disappeared.

The occupation-based measure for socio-economic status, the NS-SeC, was the only one of these distal variables to maintain a direct effect after accounting for more immediate variables, as represented by the dashed line in the figure. In particular, unemployed women were more likely to experience stillbirth than those in the highest NS-SeC level; however, this result may be exaggerated due to the small number of unemployed women in the population.

High BMI and smoking during pregnancy were affirmed to be very important preventable risk factors along with the other more intermediate factors relating to behaviour (drugs) and maternal health (diabetes), which maintained a direct association with stillbirth even after adjusting for mediators; this is reflected the literature and the conceptual model.

Note that the variables related to birth history (parity and previous stillbirth) were considered as mediators in this study, while the maternal health variables were not. The maternal health variables would have perhaps also been suited as mediators, as they are further along the causal chain in our conceptual model (note these variables have exchanged places in Figure 6.9). However, it was not possible to consider the nominal categorical variable for diabetes as a mediator with R (see below for the discussion of methods). The obstetric-related variable for the mode of birth was highly significant in the standard multivariate analysis, although we were unable to include it in the mediation model due to software limitations. It is included by itself in the figure.

This study observed some associations between explanatory variables and stillbirth that were found to be not present in the conceptual model, which are denoted by dashed lines in Figure 6.9. These associations likely appear because there are other confounding or mediating variables that are unaccounted for. For example, the significant relation between socio-economic status and stillbirth could be mediated by access to prenatal care, or obstetric events could mediate the relation between parity and stillbirth.

Many of the key factors in this model are modifiable, such as BMI, smoking/drug misuse during pregnancy and, to a certain extent, maternal age. Preventative interventions such as smoking cessation programmes, weight management programs and advice on optimal timing of childbearing have been suggested in the literature (Vais and Kean, 2015).

Contribution to new knowledge. While there have been some studies on perinatal health using the MNLD, some of which are even specific to stillbirth, none to our knowledge have employed mediation in an attempt to disentangle the effects of the many available explanatory variables. To our knowledge, no studies of stillbirth in the UK have implemented as many potential risk factors in a mediation model, structural equation model or otherwise hierarchical analysis.

6.3.3 Discussion of Methods

Model selection of MI data. Model selection of multiply imputed data was possible with Rubin's framework, in which at each stage of model selection, the models were fitted to all imputed datasets, and their estimates pooled wherein Wald tests can be applied to the pooled values. This method was considered the gold standard for variable selection with MI data by Wood et al. (2008) in their study comparing multiple alternative approaches. The merits and drawbacks of variable selection are later discussed in Section 8.7.

Comparing the standard regression and mediation models. A scaling factor of 1.6 was used to approximate logit estimates from the mediation model's probit estimates that would be comparable with the initial standard regression results (without mediators). The literature suggests a scaling factor of anywhere between 1.6 and 1.8, but it generally makes little difference which value within this interval is used (Rassen et al., 2008). However, the magnitudes of the estimates for the two types of models are still not directly comparable; the outcome, among other variables, is treated as a nominal categorical variable in the standard model, but an ordinal representation of a latent variable in the SEM, which may produce slightly different results. To our knowledge, structural equation modelling has not often been applied to multiple nominal categorical variables. It has only recently been possible to include categorical variables in SEM at all within software such as R's `lavaan` package or Mplus. Nominal exogenous variables were transformed into dummy 0/1 indicators for each variable level and treated as ordinal. It was not possible with the current software to treat nominal mediators in the same way. For this reason, the variable for the mode of birth was discarded from the mediation model, and some nominal behaviour/health variables (such as smoking status or diabetes) could not be treated as mediators.

Comparing the asymptotic delta and bootstrapped confidence intervals. Two types of confidence intervals were calculated for the mediation model's indirect and total effects: the asymptotic delta approach and the bootstrap percentile approach. As discussed in Section 6.1, the bootstrapping method is considered be more accurate (Bollen and Stine, 1990; MacKinnon et al., 2002), but computationally intensive, and so the asymptotic delta approach was initially used for preliminary analysis, with bootstrapped asymmetric confidence intervals employed to check the final model. The two sets of confidence intervals for the final model are extremely similar; the vast majority of bootstrapped intervals are identical to their delta counterparts up to two decimal places, with only two cases in which the bootstrap intervals suggest that a predictor's effect on stillbirth is notably more significant than originally implied by the delta method.

Finally, it must be noted that in the final mediation model, although insignificant paths had been removed and the model was no longer saturated, it still had only 11 degrees of freedom, and therefore the fit measures (CFI, TLI, RSMEA) would still essentially indicate that the model gave a near-perfect fit, even if the model was not suitable.

6.3.4 Conclusion and Further Work

A major strength of this study lies in the vast amount of relevant available explanatory variables from the linked data. This study contributes to the literature with, to our knowledge, the first mediation analysis of routine perinatal health data in the UK. The effects on stillbirth of maternal age, ethnicity and marital status were fully mediated by gestational age and birth weight. These results suggest that, in keeping with the literature (see conceptual model Figure 2.4), these variables may not be direct causes of stillbirth, but are still relevant in the causal pathway to stillbirth, due to their strong relationship with gestational age and birthweight. After accounting for the mediating effects of gestational age and birthweight, the study found high BMI and smoking during pregnancy to be very important preventable risk factors, supporting the literature, although additional risk was observed for the unemployed group and for those with diabetes. A limitation of the mediation model is that it was unable to include nominal categorical predictors (i.e. the mode of birth) in the model, as the current software could not accommodate nominal categorical mediators.

Further work. The MNLD has the abundant potential for further research regarding the causal pathways to stillbirth, such as considering moderating effects (i.e. interactions) within mediation. Extending the SEM model to multiple levels of mediation would allow us to replicate the causal pathways in the conceptual model further. It may be possible to construct a mediation model with two or more stages of mediators, for example treating the variables relating to birth history, behaviour and health as the first set of mediators linking the more distal socio-economic factors to the fetal characteristics, and then onto stillbirth. However, until statistical packages such as `lavaan` can accommodate categorical mediators, this may not be possible. With the individual birth-level data linking women to more than one observation (whether that is via multiple births or multiple pregnancies in the time period), there is the potential to perform multilevel modelling with mothers as the "group" level. This study was only able to focus on singleton births, but multi-level mediation models are possible (MacKinnon et al., 2007). This setup of linked data could be utilised further with a detailed exploration of birth spacing, an understudied potential risk factor for stillbirth, looking at individual women and their pregnancies across time.

The next chapter will cover the final analysis, this time investigating stillbirth in Brazil.

Chapter 7

Associations Between Socio-economic Factors and Stillbirth in Brazil

This chapter will examine the relationship between stillbirth and various socio-economic indicators in Brazil at the individual level, using the National Household Sample Survey (PNAD) 2013 described in Chapter 4. As outlined in Section 4.3.3, the outcome variables for stillbirth provided in the PNAD 2013 require novel new methods to analyse the data.

The main challenge, introduced in Section 4.3.3 of the data comparison chapter, is that although the data is at the individual-level for each woman, the birth outcomes are given as counts - the numbers of live births and stillbirths. The following section introduces a non-standard method that converts the observed live birth and stillbirth counts for each woman into lists of possible birth sequences. By deriving the appropriate likelihood function, we are able to perform regression on a new binary outcome for live birth verses stillbirth. We are then able to analyse socio-economic factors in relation to this outcome and, following model selection, to derive an optimal model that contains the most significant factors.

A second challenge presented was that the data contains each woman's age at the time of the survey but is unable to account for her age(s) at the time(s) of delivery. The births in the data could have occurred at any point in the women's reproductive history. This study aims to group women by their age-at-survey and treat them as separate cohorts of 18-24 years, 25-39 years and 40-49 years; it will attempt to interpret the pattern of births over the lifetimes of different generations of women. Along with analysis of the full sample, the data is divided by age cohort and three separate analyses of the optimal model are conducted before comparing their results.

Finally, an informal goodness of fit measure is proposed to assess how well the model reflects the data.

7.1 Methods Used in the Analysis of Stillbirth Data in Brazil

This section lays out the approaches to analysing the birth and stillbirth counts for women in the PNAD sample. Firstly, it presents the derivation of the likelihood function that can analyse the birth counts as binary outcomes. Secondly, it describes the model selection method used, before finally putting forward an informal approach to goodness of fit.

Complete lists of potential sequences of live births and stillbirths for each woman are generated from their observed aggregated counts. Through this, new birth-specific variables are introduced for every possible permutation of birth order; a birth order number (whether a given birth in the sequence is the woman's first, second, third birth, ...) and the number of previous stillbirths had prior to that birth. A likelihood function is constructed that treats each possible birth individually. The analysis is then based not on the total birth count but on each birth; the woman's age at delivery remains unknown, but the pseudo order of births created can account for the stage in the woman's reproductive history of the observed birth.

7.1.1 Transforming the Birth Outcome: The Aggregate Data Likelihood Function

The PNAD dataset contains, for each woman in the sample, the numbers of live births and stillbirths, but not the order in which they occurred. Parity, the number of previous births, is clearly an important determinant of stillbirth, as observed in the literature review and in Table 4.5 of Chapter 4 which shows higher stillbirth rate for women in the sample with higher parity.

We wish to compute the likelihood of stillbirth for the women in this sample, considering their parity and number of previous stillbirths. Therefore, using the observed birth and stillbirth counts, we need to consider every possible sequence of birth order for each woman. The likelihood will then be a product over individual births in each sequence, summed over all the possible sequences for a woman, given their observed number of births and stillbirths (and other parameters).

To do this, we pre-process the data into long-format, transforming the PNAD's birth counts into birth-level data with each row representing an observed birth with a binary outcome (live/stillbirth).

Transforming the Birth Data into Long-format

The number of birth order sequences, m, for a woman with n total births, of which s are stillbirths is

$$m = \binom{n}{s} = \frac{n!}{(n-s)!s!}.$$

For example, a woman with two live births (L) and two stillbirths (S) would have six birth order sequences: $LLSS$, $LSLS$, $LSSL$, $SLLS$, $SLSL$ and $SSLL$. A woman with only one birth will have one sequence. A woman with no stillbirths, regardless of the number of live births, will also have only one sequence. The highest number of possible sequences observed in the data for one woman is 7,315 (22 births including four stillbirths).

The possible birth sequences for each woman, w, can be represented as an $m \times n$ matrix, in which the j^{th} row $\boldsymbol{y}_j$ $(j : 1, \ldots, m)$ represents a birth order sequence of n births. Each element, y_{ij}, represents the i^{th} birth in sequence j $(i : 1, \ldots, n; j : 1, \ldots, m)$ and takes the value

$$y_{ij} = \begin{cases} 0 & \text{if live born} \\ 1 & \text{if stillborn.} \end{cases}$$

In the aforementioned example, a woman with $n = 4$ births including two stillbirths (and therefore $m = 6$ birth order sequences), would be represented as such:

$$\begin{matrix} \boldsymbol{y}_1 \\ \boldsymbol{y}_2 \\ \boldsymbol{y}_3 \\ \boldsymbol{y}_4 \\ \boldsymbol{y}_5 \\ \boldsymbol{y}_6 \end{matrix} \begin{pmatrix} 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 \end{pmatrix}$$

To convert the dataset into long-format where each row represents a possible birth (in a given sequence), we transpose and combine the birth sequence vectors $\boldsymbol{y}_j$ into a column of birth outcomes. From here, a column for birth order i is attached, along with a column for the number of previous stillbirths in the sequence up to the observed birth. The other explanatory variables for each woman (described in Section 4.3) are also attached. The birth order number and the number of previous stillbirths can be treated as explanatory variables.

For analysis of this data, a specialised likelihood function is required, as detailed below.

The Likelihood Function

We view the observed birth y_{ij} as a realisation of a random variable Y_{ij} that takes values 0 if live born and 1 if stillborn. Then the distribution of Y_{ij} is Bernoulli with parameter π_{ij}, the probability of stillbirth. The probability distribution is given by

$$Pr\{Y_{ij} = y_{ij}\} = \pi_{ij}^{y_{ij}} (1 - \pi_{ij})^{1-y_{ij}}.$$

The outcome y_{ij} can be expressed as a linear function of K observed explanatory variables $\boldsymbol{x}_k$, parameters α_1 and α_2 for the birth order and number of previous stillbirths respectively, and $K-2$ parameters β_k for the socio-economic variables specific to each woman:

$$y_{ij} = \log(\frac{\pi_{ij}}{1-\pi_{ij}}) = \alpha_1 x_{ij1} + \alpha_2 x_{ij2} + \sum_{k=3}^{K} \beta_k x_{ijk} \tag{7.1}$$

Through transformation with the logit function, the probability π_{ij} of stillbirth is then a function of the explanatory values and their parameters:

$$\pi_{ij} = \frac{\exp(\alpha_1 x_{ij1} + \alpha_2 x_{ij2} + \sum_{k=3}^{K} \beta_k x_{ijk})}{1+\exp(\alpha_1 x_{ij1} + \alpha_2 x_{ij2} + \sum_{k=3}^{K} \beta_k x_{ijk})}. \tag{7.2}$$

Note that the values of the birth-related variables, x_{ij1} and x_{ij2}, will differ between births in the sequence, whereas the socio-economic variable values, x_{ijk}, will remain constant over each woman.

The likelihood of stillbirth for a given birth order sequence j is then the product of the probabilities within the sequence,

$$\mathcal{L}_j(\pi|y) = \prod_{i=1}^{n} \pi_{ij}^{y_{ij}} (1-\pi_{ij})^{1-y_{ij}},$$

and the likelihood of stillbirth for the w^{th} woman in the sample is the sum of the probabilities for each of her possible birth order sequences,

$$\mathcal{L}_w(\pi|y) = \sum_{j=1}^{m} \mathcal{L}_{jw}(\pi|y) = \sum_{j=1}^{m} \prod_{i=1}^{n} \pi_{ijw}^{y_{ijw}} (1-\pi_{ijw})^{1-y_{ijw}}$$

for birth i $(i : 1, ..., n)$, in sequence j $(j : 1, ..., m)$ for woman w $(w : 1, ..., 61, 748)$ in the dataset.

The logs of these likelihoods are summed to obtain the overall minus log-likelihood. This likelihood contribution can then be optimised to estimate the model's covariate coefficients. Through the `optim()` function in R, an iterative optimisation process was run using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm, a quasi-Newton method (Steenbergen).

Table 7.1 displays the application of the likelihood function on the long-format birth data for two example women. Both women have four births. The first woman has only live births and therefore only one birth order sequence. The probability of stillbirth within this sequence is the product of the probabilities of stillbirth for each birth in the sequence. With one sequence, the probability of stillbirth for the woman is the same as the probability for the sequence.

The second woman has two stillbirths and therefore six sequences (as previously shown). The probabilities for these sequences are summed to produce the probability of stillbirth for the woman.

Table 7.1: An example construction of the aggregate data likelihood function

Mother w	Seq. j	Outcome y_{ij}	Birth order i	Num. prev. stillbirths	
1	1	0 - live	1	0	$\times$ $Pr(\text{stillbirth}\|j=1)$ = $Pr(\text{stillbirth}\|w=1)$
		0 - live	2	0	
		0 - live	3	0	
		0 - live	4	0	
2	1	0 - live	1	0	$\times$ $Pr(\text{stillbirth}\|j=1)$ +
		0 - live	2	0	
		1 - still.	3	0	
		1 - still.	4	1	
	2	0 - live	1	0	$\times$ $Pr(\text{stillbirth}\|j=2)$ +
		1 - still.	2	0	
		0 - live	3	1	
		1 - still.	4	1	
	3	0 - live	1	0	$\times$ $Pr(\text{stillbirth}\|j=3)$ +
		1 - still.	2	0	
		1 - still.	3	1	
		0 - live	4	2	
	4	1 - still.	1	0	$\times$ $Pr(\text{stillbirth}\|j=4)$ +
		0 - live	2	1	
		0 - live	3	1	
		1 - still.	4	1	
	5	1 - still.	1	0	$\times$ $Pr(\text{stillbirth}\|j=5)$ +
		0 - live	2	1	
		1 - still.	3	1	
		0 - live	4	2	
	6	1 - still.	1	0	$\times$ $Pr(\text{stillbirth}\|j=6)$
		1 - still.	2	1	
		0 - live	3	2	
		0 - live	4	2	

$$\sum_{j=1}^{6} Pr(\text{stillbirth}|j) = Pr(\text{stillbirth}|w=2)$$

7.1.2 Model Selection

Consider our baseline model to consist of new birth-related explanatory variables "birth order number" and "number of previous stillbirths". Before multivariate model selection, univariate regression was performed on each of the eighteen socio-economic predictor variables. The significance of each variable was assessed using a likelihood ratio test, compared against both the null model and the baseline model containing the birth-related variables.

As with the analysis of the Scottish data in chapter 6 , backwards model selection was initially considered, i.e. starting with a full model of the (individually significant) socio-economic covariates and reducing to an optimal model. However, such a model would be unsuccessful due to issues of collinearity between variables; some of the employment-related variables have an identical "unemployed" level, leading the likelihood function's optimisation routine to be unable to converge. Instead, it was necessary to build upwards from the baseline model so that the strongest potential predictor of the collinear variables could be selected. A pseudo forward selection was attempted using likelihood ratio tests (LRTs).

The Likelihood Ratio Test

Consider two nested models. The likelihood ratio test measures the improvement in fit that the additional explanatory variable(s) from the larger model (the alternative model) makes compared to the simpler model (the baseline) where these additional variables are not included. It tests the null hypothesis that the baseline model is true (i.e. that the additional parameters are indeed zero) against the alternative hypothesis that these parameters are not zero.

The test uses the Chi-square distribution to test the significance of the likelihood ratio test (LRT) statistic,

$$\text{LRT statistic} = -2(\ell_{base}(\hat{\pi}) - \ell_{alt}(\hat{\pi})),$$

where ℓ_{base} and ℓ_{alt} are the log-likelihood values for the baseline and alternative models respectively (Wilks, 1937). The test statistic is compared with an appropriate chi-squared value (with degrees of freedom equal to the number of parameters added) to produce a p-value. If the p-value is below a given cut-off point (usually 0.05), the test rejects the null hypothesis, suggesting that the alternative model (with additional explanatory variable(s)) is significantly different from the null model, and the additional variables should be included.

Process for Model Selection

Starting with the baseline model (consisting of the two birth-related variables) socio-economic variables are added systematically with the following procedure:

1. Test each of the socio-economic explanatory variables separately against the baseline model, calculating an LRT statistic each time. Only covariates proving significant at the 20% level are considered for multivariate analysis. This relatively large p-value was used to prevent potentially important variables from being removed before the multivariate stage (Mickey and Greenland, 1989).

2. List these variables in ascending order of significance level from these LRTs, starting with the most significant variable.

3. Starting with the most significant, add the variables to the model one at a time. Perform the likelihood ratio test on the nested models at each stage and keep the new variable only if its

addition improves the likelihood of the model at the 5% significance level i.e. if its likelihood ratio test gives a p-value less than 0.05.

4. Obtain parameter estimates and confidence intervals for the final model containing only the significant variables.

Note that this method is *not* standard stepwise forward selection. At each stage, standard stepwise forward selection considers all possible ways of adding one new variable (Effroymson, 1960). However, this would require a far greater number of model fits; with n variables, the r^{th} step would require $n - r$ models to be fitted to decide which variable to take forward. Considering the lengthy computation time of our likelihood function in R for each model, performing the standard method was not practical. Our compromise was to add each variable in order of significance (compared to the baseline), but not reassess the significance of all variables at each step.

Since the variables are added in order of significance, it is expected to see more variables accepted at the beginning of the process, and most of the rejections occurring towards the end of the list. The merits and drawbacks of variable selection in general are later discussed in Section 8.7.

Stratifying by Age Cohort

Once the optimal model was obtained, the model was repeated with the three age cohorts (15-24 years, 25-39 years, and 40-49 years) treated separately. As mentioned in Section 4.3.3, the mother's age at delivery for a given birth was unknown, and so the age at the time of survey was instead used to group the women into cohorts. By stratifying the age cohorts in this way, we investigated whether the effects of these explanatory variables on stillbirth have changed over time.

7.1.3 Sensitivity Analysis with Single Birth Subset

The aggregate data likelihood function allowed the model to account for parity, a key determinant of stillbirth, along with previous stillbirths. Given that the lifetime rates introduced in Section 4.3.5 appear to be influenced by parity, a sensitivity analysis was also conducted to determine whether correlations between parity and the socio-economic predictors affected the predictors' estimates.

The sensitivity analysis used the *single birth* subset of women who had exactly one birth in their lifetime. With this binary outcome, it was possible to run a standard binary logistic regression. Firstly, a model was run containing the selected covariates from the main aggregate likelihood model (with the obvious exception of parity and previous stillbirth) for comparison.

Following this, a standard stepwise forward selection procedure was conducted to obtain an "optimal" model for the single birth subset, to determine whether the choice of important predictors differed for this subset that did not need to account for birth history.

7.1.4 Goodness of Fit

We wish to assess how well the model reflects the data through an informal goodness of fit test, measuring how "close" the observed values are to what would be expected under the fitted model. Since the model makes some strong assumptions, namely that each woman's socio-economic situation was the same at the time of pregnancy as at the time of survey in 2013, we wish to confirm that the premise of the model is reasonable.

Goodness of fit often is determined with a Pearson's Chi-Square goodness of fit test (Pearson, 1990) which compares the observed sample distribution with the expected probability distribution by dividing the sample data into intervals, or categories. Observed counts in each category are compared with the corresponding expected counts. The chi-squared procedure tests the null hypothesis that there is no difference between the observed and the expected values against the alternative hypothesis that there is a significant difference between these values. The Chi-Square goodness of fit test statistic is

$$\chi^2 = \sum_C \frac{(O_C - E_C)^2}{E_C}$$

for counts of observed values O_C and expected values E_C in category C. The test with c categories is conducted with $c - 1$ degrees of freedom. To test the null hypothesis, the test statistic is compared with the χ^2 table value with the corresponding number of degrees of freedom. If the test statistic is greater than the table value, the null hypothesis is rejected, and we conclude that there is a significant difference between the observed and the expected values. A p-value can also be constructed to show the extent of this significance; a p-value higher than 0.05 does not reject the null hypothesis, suggesting that there is no significant difference between the observed and expected values, and that the model adequately fits the data.

Meeting the assumptions of the Chi-square Goodness of Fit test. In the context of this data, the test assumes that the probability of the outcome is the same for each observation in the category. However, this is not the case for our model as the probability of stillbirth is dependent on numerous socio-economic covariates, and is consequently different for each woman. Additionally, we are not taking into account that the expected values have been fitted from the observed data itself. Therefore, we may conduct the chi-square goodness of fit test but use the resulting p-values only as a rough guideline as to which categories might have the biggest problem with the model fit.

Alternative Informal Approach to Goodness of Fit

As an alternative to the chi-square test, for which not all of the assumptions are met, we use an informal approach to goodness of fit with a similar premise, categorising the data and comparing empirical values with our model-based estimates.

Categorising the observed counts. We start by dividing the observed data into categories C_b of women with b births $(b : 1, ..., 4)$. Although there are women in the observed data with more than four births, they make up only 8% of the sample, and the counts in each category are too small, and so they are ignored. Assuming that the number of stillbirths for everyone in category C_b is binomial, $Y_{C_b} \sim Binomial(W_b, p_b)$ where b is the number of births $(b : 1, ..., 4)$, W_b is the number of women in the category and p_b is the overall probability of stillbirth for those in the category (i.e. given that they have had b births). The observed probability $\hat{p}_b$ is therefore the sum of total observed stillbirths over the total births in C_b

$$\hat{p}_b = \sum \frac{Y_{C_b}}{bW_b}$$

with variance

$$var(\hat{p}_b) = \frac{\hat{p}_b(1-\hat{p}_b)}{nW_b}.$$

We also wish to present the confidence intervals for the observed values. A standard confidence interval (CI), however, would not account for the stillbirth probability being strictly non-negative and may take values less than zero. We account for this by constructing a confidence interval for $log(\hat{p}_b)$ which, once back-transformed to $\hat{p}_b$, will only take non-negative values. This adjusted confidence interval was calculated using the Delta method which estimates the variance of a function of a random variable, approximated by:

$$var(f(X)) \approx var(X) \times (f'(E(X)))^2.$$

Therefore

$$\begin{aligned} var(log(\hat{p}_b)) &\approx var(\hat{p}_b) \times f'(log(\hat{p}_b))^2 \\ &= \frac{\hat{p}_b(1-\hat{p}_b)}{nW_b} \times \frac{1}{\hat{p}_b^2}. \end{aligned}$$

The 95% interval for $\hat{p}_b$ is then

$$\begin{aligned} CI &\approx exp\left((log(\hat{p}_b) \pm 1.96\sqrt{\frac{\hat{p}_b(1-\hat{p}_b)}{nW_b}\frac{1}{\hat{p}_b^2}}\right) \\ &= \hat{p}_n \times exp\left(\pm 1.96\sqrt{\frac{\hat{p}_b(1-\hat{p}_b)}{nW_n\hat{p}_b^2}}\right) \end{aligned}$$

Calculating the expected counts. Divide the data into further subcategories C_{bs} of women with b births and s stillbirths for $n : 1, ..., 4$ and $s : 0, ..., 4$. Having calculated the stillbirth likelihood for each woman, $\mathcal{L}_w(\hat{\pi})$, in Section 7.1.1, we sum the probabilities for the women in each subcategory C_{bs} to obtain the E_{bs} expected number of women with b births and s stillbirths:

$$E_{bs} = \sum_{w \in C_{bs}} \mathcal{L}_w(\hat{\pi}).$$

The expected number of births and stillbirths are $b \times E_{bs}$ and $s \times E_{bs}$ respectively, and the expected stillbirth rate for women in category C_b, women with b births, is then

$$\text{expected rate} = \frac{\sum_{s=1}^{b} sE_{bs}}{\sum_{s=1}^{b} bE_{bs}} \times 1,000$$

Comparing the observed and expected rates. The observed and expected probabilities and their CIs are multiplied by 1,000 to obtain the stillbirth rates. These are plotted against the expected stillbirth rates from the model to compare how well the model predicts the observed data. Once more, this procedure is repeated with categories C_b further stratified by the three age cohorts to determine the goodness of fit of the three separate models.

Concluding Remarks

This complex method using count data was used as an approximate solution to the lack of individual-level birth information available in the PNAD data. If a woman's risk of stillbirth was independent of her birth history, then a standard binomial regression analysis on the total number of births and stillbirths would likely suffice. Section 7.2.1 of the upcoming results section, investigating the effect of parity and previous stillbirth on subsequent stillbirth odds, shows this not to be the case, and justifies the need for such an elaborate model set up.

7.2 Results for the Analysis of Stillbirth Data in Brazil

This section contains the preliminary regression coefficient estimates obtained from the aggregate data likelihood function, starting with the “baseline” model containing the two new birth-related variables - “birth order number” and “number of previous stillbirths” - that were derived when converting the count data to individual-level birth data. The eighteen socio-economic variables were then investigated, both in univariate analysis and adjusting for these important birth-specific variables.

Fourteen moderately significant variables (at the 20% level) were carried forward into the model selection process. Starting with the baseline model, the socio-economic variables were added systematically until an optimal model was reached. Analysis of the optimal model was further stratified by the age cohort.

7.2.1 Exploratory Analysis of the New Birth-related Variables

Binary regression was performed on the two birth-related variables that were derived when converting the birth counts into sequences; “birth order”, which denotes the order number of the observed birth, and “number of previous stillbirth”, which informs of any stillbirths prior to the observed birth. These variables were treated as categorical, initially with ten levels each (i.e. first birth, second birth,... ten or more births). In exploratory analysis, there appeared to be a clear cut-off point beyond which the effects of later births were no longer significant: four births for the birth order and two births for previous stillbirth. The categorical variables’ levels were collapsed to those in the regression results in Table 7.2.

Table 7.2: Association between stillbirth and generated birth characteristics from the PNAD, Brazil. Odds ratios (OR), 95% Confidence Intervals (CI) and p-values. Bold type estimates denote significance (from the baseline) at the 5% level.

Risk Factor	OR	95% CI	P-value
Birth order			
First	1		
Second	1.28	(0.952, 1.732)	0.102
Third	**4.78**	(3.971, 5.753)	<0.001
Fourth or later	**2.98**	(2.455, 3.616)	<0.001
Previous stillbirths			
None	1		
One	**4.98**	(4.298, 5.771)	<0.001
Two or more	**12.86**	(9.382, 17.615)	<0.001

Here, the effects of these variables appear non-linear. The odds of stillbirth for a woman’s second birth are 28% higher than for the first. For a third birth, the odds jump to 4.78 times that of a first birth. For women having their fourth (or later) birth, the odds decrease slightly compared to the third, although still remain triple that of a first birth. Compared to a woman with no previous stillbirths, the odds of the observed birth being stillborn increase almost 5-fold if there has been one previous stillbirth and more-than-double again if there have been two or more previous stillbirths.

These birth-specific factors will form the baseline model upon which the model selection process for the socio-economic factors will be built in Section 7.2.3.

7.2.2 Univariate Analysis of Socio-economic Risk Factors

Table 7.3 shows the univariate analyses of the risk factors' association with stillbirth. Odds ratios and 95% confidence intervals compare each categorical level with its baseline. Each variable's significance is measured with a likelihood ratio test (LRT). The first column of results shows the univariate models with each of the eighteen factors compared to a null model. The second column tests the inclusion of each risk factor to a baseline model containing the two birth-related variables (birth order number and previous stillbirths).

Table 7.3: Univariate association between stillbirth and risk factors from the PNAD, Brazil. Odds ratios (OR) and 95% confidence intervals (CIs) for estimates. Second likelihood ratio test (LRT) adjusts for birth order and previous stillbirths. Bold type LRT p-values denote significant variables at the 20% level.

	Univariate models			Adjusted for birth order and previous stillbirth		
Risk Factor	**OR**	**95% CI**	**LRT P-value**	**OR**	**95% CI**	**LRT P-value**
Age cohort			**<0.001**			**0.001**
15-24 years	0.95	(0.81, 1.11)		1.36	(1.15, 1.601)	
25-39 years	1					
40-49 years	1.28	(1.19, 1.39)		1.07	(0.99, 1.16)	
Ethnicity			**<0.001**			**0.050**
White	1					
Black	1.40	(1.23, 1.59)		1.19	(1.04, 1.36)	
Brown/mixed	1.20	(1.11, 1.31)		1.04	(0.95, 1.13)	
Other	1.02	(0.69, 1.51)		0.83	(0.56, 1.24)	
Marital status			**0.012**			0.682
Married	1					
Single	0.94	(0.80, 1.10)		1.05	(0.89, 1.23)	
Separated/divorced/widowed	0.96	(0.80, 1.16)		1.03	(0.85, 1.25)	
Not disclosed	0.83	(0.71, 0.98)		1	(0.84, 1.17)	
Socio-economic status			**<0.001**			**<0.001**
1: Managerial, administrative, professional	1					
2: Intermediate	1.24	(11, 1.54)		1.32	(1.06, 1.64)	
3: Small employers, self employed	1.40	(1.157, 1.684)		1.09	(0.90, 1.32)	

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Table 7.3 continued from previous page

Risk Factor	Univariate models OR	95% CI	LRT P-value	Adjusted for birth order and previous stillbirth OR	95% CI	LRT P-value
4: Supervisory, technical	1.09	(0.84, 1.41)		1.04	(0.80, 1.35)	
5: Routine, semi-routine, agricultural	1.23	(1.040, 1.448)		0.93	(0.78, 1.10)	
Long term unemployed - seeking work	1.63	(1.32, 2.03)		1.32	(1.06, 1.65)	
Economically inactive	1.15	(0.97, 1.36)		0.87	(0.73, 1.03)	
Highest education level			**<0.001**			**<0.001**
Primary and below	1.09	(11, 1.18)		0.83	(0.76, 0.91)	
Secondary	1					
Tertiary and above	0.89	(0.77, 1.03)		0.97	(0.84, 1.12)	
Work history			0.268			**0.021**
Has worked	1					
Never worked	0.95	(0.86, 1.04)		0.89	(0.81, 0.98)	
Age began working			**0.011**			0.331
<9 yrs	1.19	(1.07, 1.32)		1.01	(0.91, 1.13)	
10-14 yrs	1.03	(0.91, 1.16)		1.03	(0.91, 1.17)	
15-19 yrs	1					
Not employed	1.06	(0.96, 1.18)		0.94	(0.85, 1.05)	
Location of work	1		**<0.001**			0.597
Fixed establishment						
Outdoors, home, employers home	1.20	(1.08, 1.33)		0.98	(0.88, 1.09)	
Not disclosed	1.16	(1.06, 1.27)		0.95	(0.87, 1.05)	
Hours per week working			**0.002**			**0.100**
$\leq$ 14 hrs	1.28	(1.08, 1.52)		1.04	(0.88, 1.24)	
15-39 hrs	1.17	(1.03,1.32)		1.02	(0.91,1.16)	
40-44 hrs	1					
45+ hrs	1.29	(1.13, 1.47)		1.21	(1.06, 1.39)	
Unemployed/unknown	1.18	(1.07, 1.31)		1.03	(0.93, 1.14)	
Household income range (per capita)			0.652			**<0.001**
No wage or $\leq$ 1/2 min wage	0.98	(0.85, 1.10)		0.72	(0.65, 0.81)	
$>$ 1/2 to 1 min wage	1.02	(0.91, 1.14)		0.90	(0.80, 1.011)	
$>$ 1 to 3 times min wage	1					
$>$ 3 to 5 times min wage	1.09	(0.94, 1.27)		1.20	(1.03, 1.41)	
Not disclosed	1.05	(0.86, 1.28)		0.93	(0.76, 1.14)	
Household construction			0.332			0.454
Adequate	1					
Inadequate	1.13	(0.88, 1.44)		0.91	(0.71, 1.17)	
Household services			0.781			**<0.001**
Adequate	1					

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Table 7.3 continued from previous page

Risk Factor	Univariate models			Adjusted for birth order and previous stillbirth		
	OR	95% CI	LRT P-value	OR	95% CI	LRT P-value
Semi-adequate	1.01	(0.91, 1.12)		0.85	(0.77, 0.94)	
Inadequate	0.93	(0.74, 1.16)		0.69	(0.55, 0.86)	
Household density			**0.011**			**<0.001**
Adequate	1					
Inadequate	0.88	(0.80, 0.97)		0.76	(0.69, 0.84)	
Household basic goods			**0.055**			0.308
Adequate	1					
Inadequate	1.17	(11, 1.36)		0.92	(0.79, 1.08)	
Household status goods			**0.008**			**0.017**
Adequate	1					
Semi-adequate	1.08	(0.96 , 1.21)		0.97	(0.86, 1.09)	
Inadequate	1.17	(1.05 , 1.31)		0.87	(0.79, 0.98)	
Food security			**<0.001**			**0.162**
Secure	1					
Light food insecurity	1.11	(1.01, 1.21)		0.96	(0.88, 1.06)	
Moderate food insecurity	1.45	(1.27, 1.66)		1.12	(0.98, 1.29)	
Severe food insecurity	1.30	(1.11, 1.51)		0.92	(0.78, 1.08)	
Urban/rural code			**0.011**			**<0.001**
Urban	1					
Rural	0.88	(0.78, 0.97)		0.75	(0.67, 0.83)	
Region			**0.016**			**0.002**
North East	1.11	(0.10, 1.28)		0.94	(0.81, 1.08)	
North	1.25	(1.102, 1.420)		1.12	(0.982, 1.273)	
Central West	1.21	(1.02, 1.43)		1.16	(0.98, 1.38)	
South East	1.18	(1.04, 1.35)		1.18	(0.88, 1.35)	
South	1					
Federal District	1.17	(0.79, 0.97)		1.17	(0.88, 1.54)	

Likelihood ratio tests of the univariate models showed that most of the factors relating to the individual - maternal age, ethnicity, marital status, socio-economic status (SeS), education level, the age a woman began working, location of work, and the hours spent per week working - were significantly associated at the 20% significance level with stillbirth. Comparatively fewer household- and geography-related variables were significantly associated with stillbirth: household density, basic goods, status goods, food security, region and urban/rural code.

However, the significance of many factors differed when adjusting for birth order and previous stillbirth. Marital status, the age at which a woman began working, location of work and household basic goods became no longer statistically significant at the 20% significance level, whereas previously insignificant factors such as work history, income range and household services became very significant when accounting for the birth-related variables.

After adjusting for birth order and previous stillbirth, the odds of stillbirth for the youngest cohort (women aged 15-24) were 36% higher than that of the baseline group of women aged 25-39. Black women had 19% higher odds of having a stillbirth than white women.

Compared to the baseline group of those in managerial and professional employment, women in intermediate occupations had 32% higher odds of stillbirth, while the odds for women who were unemployed were 63% higher. Unusually, a lower (up to primary) level education had a protective effect against stillbirth (17% lower odds) compared to those with secondary qualifications, as did having never worked compared to those who had (11% lower odds). Compared to women who worked 40-45 hours per week, those who worked 45 or more hours per week had 21% increased odds.

Women in households with no income or income worth less than half of the minimum wage had 28% lower odds of stillbirth, while women in wealthier households earning 3-5 times the minimum wage had 20% higher odds than those on 1-3 times the minimum wage.

Of the variables related to household, significant results include those living in smaller spaces (an apartment or simply a room) had 19% higher odds than those living in houses.

Those in households with semi-adequate and inadequate services (water source, waste disposal, etc.) had lower odds of stillbirth. Similarly, women in overcrowded households and women with inadequate status goods had reduced odds. Women in rural areas had 25% lower odds of stillbirth than those in urban areas.

In the unadjusted univariate model, significant regional differences in stillbirth odds exist, with the North, Central West and South East regions displaying significantly higher odds than the baseline South region. However, the significance of these estimates diminishes after adjusting for the birth-specific variables.

When adjusting for birth order and previous stillbirth, the direction of some of the variable estimates change significantly, sometimes in directions that at first appear counter-intuitive, for example in the case of the variables for education, income, household services and household status goods. These estimates are likely compensating for the dramatically increased odds observed in Section 7.2.1 for births of high parity. The lower stillbirth odds for women from low-income households, for example, may be slightly counter-balancing the fact that low-income families tend to have more children. This shall be explored further in the discussion (Section 7.3).

The thirteen variables that were significantly associated with stillbirth at the 20% level ($p \leq 0.2$) when accounting for the birth-related variables were carried forward in the model selection process.

7.2.3 Multivariate Analysis

This section first presents the model selection process, building up from the baseline model, before displaying the final model. The final model is stratified by the three age cohorts; women in the sample aged 15-24, 25-39, and 40-49.

Model Selection with Simplified Forward Selection

A pseudo forward selection procedure was conducted as described in 7.1.2. The moderately significant factors from the univariate analysis (at the 20% level) were listed in descending order of significance (i.e. ascending p-values) and considered in the model one at a time, as shown in Table 7.4. Likelihood ratio tests were used to decide whether to keep the factor in the final model, this time using a stricter p-value cut-off of 0.05.

Table 7.4: Forward Selection of Risk Factors from the PNAD, Brazil
Likelihood Ratio Test (LRT) statistics with corresponding degrees of freedom and subsequent p-values. Bold type LRT p-values denotes significant variable at the 5% level.

Forward Stepwise Selection		**LRT Stat.**	**df**	**P-value**	**keep/ drop**
Start	*stillbirth* ∼ *birth number* + *previous stillbirths*				
Step 1	*stillbirth* ∼ ... + *previous stillbirths* + ***income range***	65.06	4	**<0.001**	Keep
Step 2	*stillbirth* ∼ ... + *income range* + ***urban/rural***	15.76	1	**<0.001**	Keep
Step 3	*stillbirth* ∼ ... + *income range* + *urban/rural* + ***density***	15.00	1	**<0.001**	Keep
Step 4	*stillbirth* ∼ ... + *density* + ***socio-economic status***	36.66	6	**<0.001**	Keep
Step 5	*stillbirth* ∼ ... + *status* + ***household services***	0.92	2	0.630	Drop
Step 6	*stillbirth* ∼ ... + *socio-economic status* + ***education***	4.28	2	0.118	Drop
Step 7	*stillbirth* ∼ ... + *socio-economic status* + ***age***	23.16	2	**<0.001**	Keep
Step 8	*stillbirth* ∼ ... + *socio-economic status* + *age* + ***region***	21.26	5	**<0.001**	Keep
Step 9	*stillbirth* ∼ ... + *region* + *work hours* + ***status goods***	5.42	2	0.067	Drop
Step 10	*stillbirth* ∼ ... + *region* + *work hours* + ***work history***	0.21	1	0.602	Drop
Step 11	*stillbirth* ∼ ... + *region* + *work hours* + ***ethnicity***	10.95	3	**0.012**	Keep
Step 12	*stillbirth* ∼ ... + *age* + *region* + ***work hours***	16.97	5	**0.002**	Keep
Step 13	*stillbirth* ∼ ... + *ethnicity* + ***food security***	9.78	3	**0.021**	Keep

Many of the remaining household variables (household services, status goods) were no longer significant when other variables were included. Similarly, level of education and work history lost their significance.

The "optimal" final model, therefore, includes the birth order number, number of previous stillbirths, age, ethnicity, socio-economic status, hours spent working per week, household income range, household density, food security, urban/rural code, and region.

Selected Multivariate Model

Estimates for the “optimal” selected model containing eleven explanatory variables, the two birth-specific factors and nine socio-economic factors, are displayed in Table 7.5 along with their corresponding confidence intervals. Results for the same model performed separately on the three age cohorts are also presented.

For the overall sample of women, the birth-related factors continue to have the biggest impact, with the odds of stillbirth more than quadrupling for the third and later births compared to a first birth, while having had two or more stillbirths multiplies the odds of another by more than 11 compared to those with no prior history of stillbirth.

The odds of stillbirth were 52% higher for the youngest age cohort compared to the baseline middle group (age 25-39 years), which is an increase from 36% when accounting only for the birth-specific variables.

Women of black and brown/mixed ethnicity had 23% and 10% odds, respectively, compared to white women; the odds for the brown/mixed group were not significant in the previous univariate analyses.

Compared to those with managerial and administrative positions (the highest socio-economic status bracket) women in intermediate occupation had 42% higher odds, an increase from 32% when accounting only for the birth-specific variables. The group of unemployed women, which previously had a 32% increased odds of stillbirth compared to the baseline status bracket, no longer had a significantly different effect.

Household income range, according to the likelihood ratio tests, was the most significant socio-economic indicator of stillbirth accounting for birth-specific variables. Its effects were maintained when adjusting for other socio-economic confounders; women from households earning less than the minimum wage had reduced odds of stillbirth compared to households earning 1-3 times the minimum wage, while wealthier households had increased odds.

Similarly, the odds for women from overcrowded households were 22% lower than those who were not, which is a small reduction from the 26% lower odds before adjusting for other socio-economic factors.

The effect size of the urban/rural code lessened from 25% lower odds for rural households to 19% lower when accounting for confounding socio-economic variables. Finally, while regional differences were not present in the previous adjusted model when socio-economic confounders were introduced, a 20% and 19% increase in odds was observed for the North East and South East regions, respectively, compared to the baseline South region.

Table 7.5: Optimal multivariate models, stratified by age cohort, for the association between stillbirth and risk factors from the PNAD, Brazil Odds ratios (OR) and 95% Confidence Intervals (CIs) for estimates. Bold type estimates denotes significance (from the baseline) at the 5% level.

Risk Factor	**All women** 61748 women		**Aged 18-24 years** 7338 women		**Aged 25-39 years** 32257 women		**Aged 40-49 years** 22153 women	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Birth order								
First	1							
Second	**1.53**	(1.15, 2.03)	**2.18**	(1.22, 3.91)	**1.95**	(1.35, 2.82)	0.82	(0.42, 1.59)
Third	**5.80**	(4.79, 7.03)	**6.55**	(3.56, 12.06)	**6.33**	(4.8, 8.33)	**4.94**	(3.57, 6.85)
Fourth or later	**4.62**	(3.75, 5.68)	**4.42**	(1.66, 11.77)	**4.68**	(3.43, 6.38)	**3.75**	(2.69, 5.23)
Number previous stillbirth								
None	1							
One	**4.80**	(4.14, 5.57)	**5.02**	(2.17, 11.62)	**4.42**	(3.48, 5.6)	**5.03**	(4.13, 6.13)
Two or more	**11.78**	(8.51, 16.33)	6.58	(1, 43.31)	**11.49**	(6.17, 21.42)	**11.67**	(7.87, 17.3)
Age cohort								
15-24 years	**1.52**	(1.28, 1.8)						
25-39 years	1							
40-49 years	0.98	(0.9, 1.06)						
Ethnicity								
White	1							
Black	**1.23**	(1.08, 1.42)	0.85	(0.45, 1.62)	**1.26**	(1.03, 1.54)	**1.26**	(1.04, 1.54)
Brown/mixed	**1.10**	(1, 1.21)	1.10	(0.76, 1.59)	1.10	(0.96, 1.26)	1.10	(0.96, 1.26)
Other	0.93	(0.62, 1.4)	1.19	(0.34, 4.17)	0.97	(0.52, 1.79)	0.87	(0.48, 1.58)
Socio-economic status								
1: Managerial, administrative, professional	1							
2: Intermediate	**1.43**	(1.14, 1.78)	1.13	(0.31, 4.19)	**1.51**	(1.09, 2.08)	**1.40**	(1, 1.96)
3: Small employers, self employed	1.19	(0.98, 1.45)	0.98	(0.24, 3.9)	1.25	(0.92, 1.7)	1.12	(0.86, 1.47)
4: Supervisory, technical	1.12	(0.86, 1.47)	0.99	(0.21, 4.69)	1.26	(0.86, 1.84)	0.99	(0.67, 1.46)
5: Routine, semi-routine, agricultural	1.07	(0.89, 1.29)	1.10	(0.32, 3.82)	1.23	(0.93, 1.62)	0.92	(0.72, 1.19)
Unemployed - seeking work	1.29	(0.98, 1.69)	1.34	(0.34, 5.32)	1.44	(0.97, 2.13)	1.11	(0.73, 1.7)
Economically inactive	0.85	(0.67, 1.07)	0.86	(0.23, 3.25)	0.93	(0.65, 1.31)	0.74	(0.53, 1.05)

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Risk Factor	All women		Aged 18-24 years		Aged 25-39 years		Aged 40-49 years	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Hours per week working								
$\leq$ 14 hrs	1.08	(0.9, 1.29)	**0.13**	(0.02, 1)	1.17	(0.91, 1.51)	1.10	(0.86, 1.42)
15-39 hrs	0.90	(0.79, 1.03)	0.77	(0.41, 1.43)	0.95	(0.79, 1.15)	0.86	(0.72, 1.03)
40-44 hrs	1							
45+ hrs	1.09	(0.95, 1.25)	1.33	(0.71, 2.49)	0.97	(0.78, 1.19)	1.17	(0.97, 1.43)
Unknown/unemployed	**1.23**	(1.04, 1.47)	1.01	(0.53, 1.93)	1.20	(0.93, 1.54)	**1.33**	(1.02, 1.73)
Household income range (per capita)								
No wage or $\leq$ 1/2 min wage	**0.68**	(0.6, 0.78)	**0.53**	(0.3, 0.93)	**0.61**	(0.5, 0.75)	**0.76**	(0.63, 0.91)
> 1/2 to 1 min wage	**0.86**	(0.77, 0.97)	0.67	(0.4, 1.15)	**0.78**	(0.65, 0.94)	0.94	(0.8, 1.1)
> 1 to 3 times min wage	1							
> 3 to 5 times min wage	**1.26**	(1.07, 1.48)	**2.50**	(1.19, 5.24)	**1.36**	(1.05, 1.75)	1.15	(0.92, 1.42)
Not disclosed	0.91	(0.74, 1.12)	0.99	(0.42, 2.33)	0.84	(0.61, 1.15)	0.93	(0.7, 1.24)
Household density								
Adequate	1							
Inadequate	**0.78**	(0.7, 0.87)	**0.65**	(0.46, 0.93)	0.88	(0.76, 1.02)	**0.73**	(0.61, 0.88)
Food security								
Secure	1							
Light food insecurity	1.05	(0.95, 1.16)	1.28	(0.87, 1.88)	0.98	(0.85, 1.14)	1.08	(0.93, 1.25)
Moderate food insecurity	**1.26**	(1.09, 1.46)	1.62	(0.93, 2.8)	**1.26**	(1.02, 1.57)	1.21	(0.98, 1.5)
Severe food insecurity	1.05	(0.89, 1.24)	1.75	(1, 3.08)	0.81	(0.61, 1.07)	1.17	(0.93, 1.47)
Urban/rural code								
Urban	1							
Rural	**0.81**	(0.73, 0.91)	0.68	(0.42, 1.09)	**0.82**	(0.69, 0.97)	**0.82**	(0.7, 0.97)
Region								
North East	1.01	(0.87, 1.17)	0.93	(0.53, 1.64)	0.99	(0.79, 1.25)	1.02	(0.82, 1.27)
North	**1.20**	(1.05, 1.38)	1.03	(0.60, 1.78)	**1.29**	(1.04, 1.59)	1.14	(0.93, 1.39)
Central West	1.13	(0.95, 1.35)	0.75	(0.35, 1.60)	1.20	(0.93, 1.56)	1.12	(0.87, 1.45)
South East	**1.19**	(1.04, 1.36)	0.99	(0.57, 1.73)	1.23	(1.00, 1.51)	1.17	(0.97, 1.42)
South	1							
Federal District	1.10	(0.83, 1.46)	0.78	(0.17, 3.48)	1.34	(0.90, 1.98)	0.94	(0.62, 1.43)

Comparison of age cohorts

For the most part, estimates for the models of the three age cohorts reflect the estimates from the main model in size and direction, with a few notable differences.

Differences in stillbirth odds between different ethnic groups and socio-economic classifications appeared to be no longer significant from their baseline values for the youngest cohort group. Young people with low work-hours had lower odds of stillbirth than those with full-time work hours, while the opposite effect was true (although not as significant) for the older cohorts.

As in the main model, those in the smallest household income range bracket had lower odds of stillbirth across all age cohorts compared to those earning 1-3 times the minimum wage, ranging from a 47% reduction in odds for the youngest group to a 24% reduction for the oldest group. For the middle group of women aged 25-39, the next smallest income bracket (1/2 to 1 minimum wage) also had 22% lower odds than those earning above the minimum wage. The estimate in the main model that households with moderate food insecurity had 26% higher odds of stillbirth was maintained in the middle age cohort, while these findings were less significant for the younger and older age cohort.

Women aged 25-49 living in rural areas had 18% lower odds of stillbirth compared to their urban counterparts, but there was no significant difference for the younger cohort. Finally, the overall observation that women in the North East region had higher odds of stillbirth was maintained only in the middle age cohort with a 29% increase compared to the South region, while the aforementioned regional differences were no longer significant in the younger and older age cohort.

7.2.4 Sensitivity Analysis with Single Birth Subset

A sensitivity analysis using the *single birth* subset of women who had exactly one birth in their lifetime was conducted via a standard binary logistic regression.

Firstly, a model was run containing the selected covariates from the main aggregate likelihood model (with the obvious exception of parity and previous stillbirth) for comparison. Following this, a standard stepwise forward selection procedure was conducted to obtain an "optimal" model for the single birth subset.

Comparison with the Final Model for the Whole Sample

Table 7.6 shows the estimates and corresponding confidence intervals for the final "optimal" selected model from the previous section, for both the whole sample of mothers and the single birth subset.

Table 7.6: Sensitivity analysis (comparison): overall optimal multivariate model for subset of women with one birth from the PNAD, Brazil
Odds ratios (OR) and 95% Confidence Intervals (CIs) for estimates. Bold type estimates denotes significance (from the baseline) at the 5% level.

	Main Analysis (All Women)			Women with One Birth		
Risk Factor	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Birth order number						
First	1					
Second	**1.53**	(1.15, 2.03)	0.004			
Third	**5.80**	(4.79, 7.03)	<0.001			
Fourth or later	**4.62**	(3.75, 5.68)	<0.001			
Number previous stillbirth						
None	1					
One	**4.80**	(4.14, 5.57)	<0.001			
Two or more	**11.78**	(8.51, 16.33)	<0.001			
Age group						
15-24 years	**1.52**	(1.28, 1.8)	<0.001	**1.49**	(1.02, 2.16)	0.036
25-39 years	1			1		
40-49 years	0.98	(0.9, 1.06)	0.576	1.22	(0.83, 1.76)	0.311
Ethnicity						
White	1			1		
Black	1.23	(1.08, 1.42)	0.003	1.39	(0.79, 2.34)	0.233
Brown/mixed	1.10	(1, 1.21)	0.041	1.56	(0.25, 5.1)	0.544
Other	0.93	(0.62, 1.4)	0.742	1.21	(0.86, 1.71)	0.282
Socio-economic status						
1: Managerial, administrative, professional	1			1		
2: Intermediate	**1.42**	(1.14, 1.78)	0.002	**3.08**	(1.51, 6.78)	0.003
3: Small employers, self employed	1.19	(0.98, 1.45)	0.086	**3.05**	(1.43, 6.95)	0.005
4: Supervisory, technical	1.12	(0.86, 1.47)	0.390	**3.12**	(1.36, 7.4)	0.008
5: Routine, semi-routine, agricultural	1.07	(0.89, 1.29)	0.464	**2.87**	(1.46, 6.21)	0.004
Long term unemployed - seeking work	1.29	(0.98, 1.69)	0.072	2.55	(0.96, 7.07)	0.064
Economically inactive	0.85	(0.67, 1.07)	0.163	1.59	(0.68, 4.04)	0.310
Hours per week working						
<=14 hrs	1.08	(0.9, 1.29)	0.394	0.90	(0.34, 2)	0.817
15-39 hrs	0.90	(0.79, 1.03)	0.118	0.99	(0.6, 1.59)	0.967
40-44 hrs	1			1		
45+ hrs	1.09	(0.95, 1.25)	0.222	1.14	(0.71, 1.79)	0.584
Unknown/ unemployed	**1.23**	(1.04, 1.47)	0.018	1.53	(0.82, 2.7)	0.160
Household income range (p.c.)						
No wage or <=1/2 min wage	**0.68**	(0.6, 0.78)	<0.001	**0.46**	(0.27, 0.78)	0.004
More than 1/2 to 1 min wage	**0.86**	(0.77, 0.97)	0.016	**0.66**	(0.44, 1)	0.048
More than 1 to 3 times min wage	1			1		
More than 3 times min wage	**1.26**	(1.07, 1.48)	0.005	**1.77**	(1.14, 2.74)	0.011
Not disclosed	0.91	(0.74, 1.12)	0.370	0.53	(0.18, 1.22)	0.182
Household density						

Continued on next page

Table 7.6 – continued from previous page

Risk Factor	Main Analysis (All Women)			Women with One Birth		
	OR	95% CI	P-value	OR	95% CI	P-value
Adequate	1			1		
Inadequate	**0.78**	(0.7, 0.87)	<0.001	**0.44**	(0.25, 0.73)	0.002
Food security						
Secure	1			1		
Light food insecurity	1.05	(0.95, 1.16)	0.347	1.00	(0.64, 1.53)	0.985
Moderate food insecurity	**1.26**	(1.09, 1.46)	0.001	**2.75**	(1.48, 4.77)	0.001
Severe food insecurity	1.05	(0.89, 1.24)	0.583	1.72	(0.59, 3.94)	0.254
Urban/rural code						
Urban	1			1		
Rural	**0.81**	(0.73, 0.91)	<0.001	1.08	(0.63, 1.76)	0.771
Region						
North East	1.01	(0.87, 1.17)	0.919	1.72	(0.94, 3.19)	0.081
North	**1.20**	(1.05, 1.38)	0.010	**1.81**	(1.07, 3.17)	0.032
Central West	1.13	(0.95, 1.35)	0.166	**2.00**	(1.03, 3.82)	0.036
South East	**1.19**	(1.04, 1.36)	0.013	1.34	(0.8, 2.3)	0.278
South	1			1		
Federal District	1.10	(0.83, 1.46)	0.516	1.09	(0.32, 2.93)	0.871

In general, higher magnitudes of socio-economic effects were observed for the single birth subset compared to the full sample (accounting for birth history), particularly for socio-economic status (SeS) and food security. Compared to mothers in professional occupations, women in all other forms of employment had 2.8-3.1 times the odds of stillbirth, twice the magnitude of their effects in the model for the full sample, although these numbers may be unreliable due to the small count of ten stillbirths in the reference group. Similarly, women (with one birth) from households with moderate food insecurity had 2.75 times the odds of stillbirth, more than double the odds than for the full sample of women (accounting for birth history). The same pattern is evident in the regional effect estimates; the odds of stillbirth are 80% and 72% higher for the North and North East regions, respectively, in comparison to the South region.

Conversely, the effects of ethnicity, the hours worked per week, and urban/rural code seemed to disappear for women with only one birth, whilst income range and household density continue to give counter-intuitive estimates.

Model Selection for Single Birth Subset

Table 7.7 displays the estimates and corresponding confidence intervals for single birth subset's own "optimal" model from a standard stepwise forward selection procedure.

Table 7.7: Sensitivity analysis: selected multivariate model for subset of women with one birth from the PNAD, Brazil
Odds ratios (OR) and 95% Confidence Intervals (CIs) for estimates. Bold type estimates denotes significance (from the baseline) at the 5% level.

Risk Factor	**OR**	**95% CI**	**P-value**
Marital status			
Married	1		
Single	1.30	(0.65, 3.09)	0.509
Separated/divorced/widowed	0.95	(0.39, 2.56)	0.918
Not disclosed	0.79	(0.37, 1.93)	0.560
Socio-economic status			
1: Managerial, administrative, professional	1		
2: Intermediate	**2.84**	(1.37, 6.36)	0.007
3: Small employers, self employed	**2.50**	(1.14, 5.83)	0.026
4: Supervisory, technical	**2.90**	(1.23, 7.03)	0.015
5: Routine, semi-routine, agricultural	2.11	(1.03, 4.72)	0.054
Long term unemployed - seeking work	**3.19**	(1.29, 8.02)	0.012
Economically inactive	1.87	(0.88, 4.28)	0.120
Highest education level			
Primary and below	**1.82**	(1.31, 2.54)	0.000
Secondary	1		
Tertiary and above	0.96	(0.55, 1.62)	0.877
Household income range (p.c.)			
No wage or <=1/2 min wage	**0.37**	(0.22, 0.63)	0.000
More than 1/2 to 1 min wage	**0.59**	(0.39, 0.89)	0.012
More than 1 to 3 times min wage	1		
More than 3 to 5 times min wage	**2.11**	(1.33, 3.33)	0.001
Not disclosed	0.51	(0.18, 1.17)	0.155
Household services			
Adequate	1		
Semi-adequate	0.66	(0.36, 1.12)	0.149
Inadequate	0.18	(0.01, 0.9)	0.101
Household density			
Adequate	1		
Inadequate	0.43	(0.24, 0.71)	0.002
Household basic goods			
Adequate	1		
Inadequate	**3.55**	(1.9, 6.24)	0.000
Household status goods			
Adequate	1		
Semi-adequate	1.39	(0.89, 2.2)	0.151
Inadequate	**2.28**	(1.37, 3.82)	0.002
Food security			
Secure	1		
Light food insecurity	0.98	(0.62, 1.49)	0.935
Moderate food insecurity	**2.26**	(1.22, 3.95)	0.006
Severe food insecurity	1.22	(0.42, 2.85)	0.674

The resulting model looks quite different in its choice of variables from the model with the full sample. Factors that were significant to the main model such as age cohort, hours worked per week, urban/rural code and region were no longer included. Instead, indicators for education, marital status, and household goods and services appeared to have an effect on stillbirth. Women with one birth who had only a primary level of education (or lower) were 82% more likely to have a stillbirth. Women in households with inadequate basic goods had 3.5 times the odds of stillbirth, whilst a lack of status goods were also associated with 2.3 times the odds.

Interpreting odds as probabilities and rates As discussed in Section 5.2.5 of the results for England and Wales, odds ratios are not directly interpretable. Therefore we shall also consider these results in terms of probabilities and rates, which are preferred policy-relevant discussions. The probabilities are calculated with a transformation described in Section 5.1.1 (Equations 5.1 and Equation 5.2). These predicted probabilities are based on the covariate odds ratios in Table 7.7.

Consider as a baseline a hypothetical woman whose information corresponds to the reference level for each predictor; i.e., a married woman of the highest socio-economic level with a secondary education, whose household income range equals between 1 and 3 times the minimum wage, has adequate household goods and services, and food security. The probability of stillbirth for this woman is 0.00259, or 2.6 stillbirths per 1000 births.

Keeping all other variables the same, the probability of stillbirth for women with tertiary education is not too different from this baseline, with a rate of 2.5 per 1000 births. However, women with only primary education (or less) have an increased rate of 4.7 per 1000 births. Similarly, those in routine occupations have a stillbirth rate of 5.4 per 1000, double that of the baseline, and those who are unemployed have an even greater rate of 8.2 per 1000 births.

Women from households in the lowest income bracket (per person) have lower stillbirth rates (1.0 per 1000 births) than households in the highest bracket (5.5 per 1000). These counter-intuitive results will be discussed in Section 7.3.2. Households with inadequate status goods have a high stillbirth rate of 5.9 per 1000 births, and those with inadequate basic household goods have an even higher stillbirth rate of 9.1 per 1000 births. Meanwhile, households with moderate food insecurity have a stillbirth rate of 5.8 per 1000.

The results of these sensitivity analyses will be further discussed and compared with the aggregate likelihood model in Section 7.3.

Table 7.8: Observed and expected number of women by births and stillbirth counts in the PNAD, Brazil. Bold type estimates denotes a significant difference between the observed and expected distribution at the 5% level.

Women with 1 Birth			
Number of Stillbirths	0	1	Total
Observed num. women	19748	178	19926
Expected num. women	19745	181	19926
χ^2 test statistic			*0.051*
P-value			*0.821*

Women with 2 Births				
Number of Stillbirths	0	1	2	Total
Observed num. women	20438	416	13	20867
Expected num. women	20439	417	10	20867
χ^2 test statistic				*0.636*
P-value				*0.728*

Women with 3 Births					
Number of Stillbirths	0	1	2	3	Total
Observed num. women	10261	623	25	5	10914
Expected num. women	10248	624	41	2	10914
χ^2 test statistic					*12*
P-value					***0.007***

Women with 4 Births						
Number of Stillbirths	0	1	2	3	4	Total
Observed num. women	4694	387	54	4	2	5141
Expected num. women	4692	391	52	6	0	5141
χ^2 test statistic						*14*
P-value						***0.007***

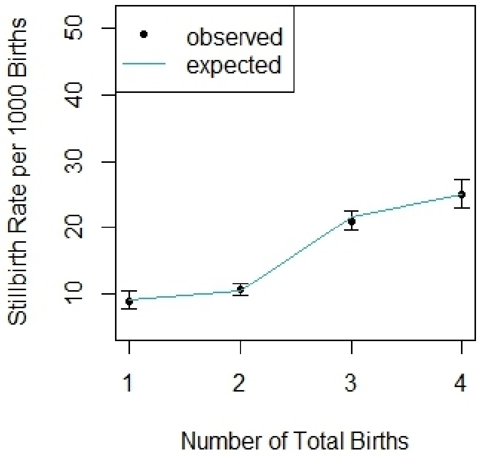
7.2.5 Goodness of Fit

Table 7.8 presents a comparison of the observed and expected numbers of women in the PNAD sample by the number of births and stillbirths, along with a Pearson chi-square statistic for goodness of fit. The high p-values for women with one and two births suggest that there is no significant difference between the observed and expected values, while the model estimates appear less successful at predicting the number of stillbirths for women with three or four births.

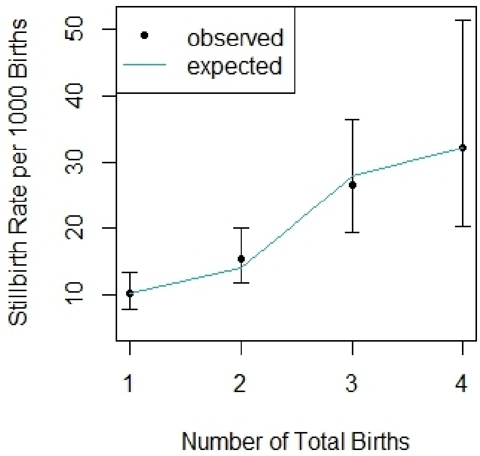
A further breakdown of the four birth tables by each of the three age cohorts can be found in Table B.4 in the Appendix. The majority of the chi-square tests for the twelve groups do not suggest a significant difference between their observed and expected values. Only three groups – women 15-24 with two births, women 40-49 with three births and women aged 40-49 with four births – appear to have a significant difference. These findings suggest that the separate models by age cohort provide a better fit to the data.

Given that many assumptions of the chi-square test for goodness of fit are not met, as described in Section 7.1.4, these chi-square statistics were intended to provide only an informal idea of where the model struggles to reflect the data. An alternative approach to assessing goodness of fit is portrayed in Figure 7.1a, which compares the observed and expected stillbirth rates by the total number of births for an individual woman. Subsequent Figures 7.1b, 7.1c and 7.1d stratify these rates further by age cohort.

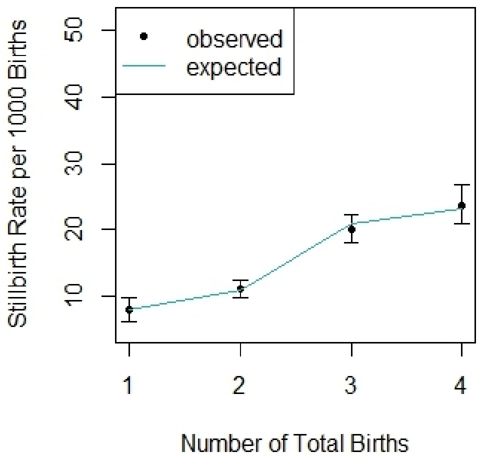
As described in Table 4.5 in the Data Comparison chapter, the stillbirth rates increased with parity, and rates for the youngest and oldest cohort were generally higher than for the middle group. Each of the expected model-based estimates for stillbirth rate fell within the corresponding confidence interval for the observed stillbirth rates, suggesting a reasonable fit. The confidence intervals are wider for the separate age cohorts due to their smaller sample sizes. This is particularly apparent in the youngest cohort, for which the sample contained only 528 births.



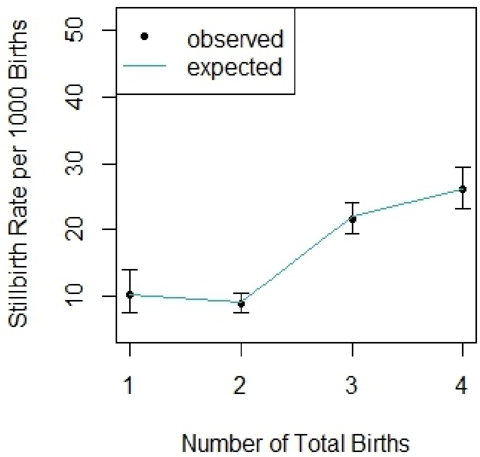
(a) Total sample of women



(b) Age cohort 15-24 years



(c) Age cohort 25-39 years



(d) Age cohort 40-49 years

Figure 7.1: Observed and expected stillbirth rates for each age cohort by number of births in the PNAD, Brazil, with adjusted confidence interval (CI) brackets

7.3 Discussion of the Brazil Analysis

This section summarises the findings of this study and attempts to place them in the context of previous literature. It also reviews the strengths and limitations of the methods used. Beforehand, however, we discuss the suitability of the dataset itself, which shall inform how the results can be interpreted.

7.3.1 Working with the Data

Current Predictors, Past Outcomes and Retroactive Analysis

As described in Section 4.3.3 of the data comparison chapter, an issue stemming from the birth count outcomes was that the data reflected the individual's socio-economic position (SEP) at the time of survey completion, which was not necessarily the same as the (unknown) time(s) of birth. SEP measures, such as education or income, generally improve with age and so the recorded socio-economic information may depict a more advantaged SEP than at the time(s) of pregnancy. Some factors could even have changed *between* pregnancies.

However, the model must assume that for the most part, the women's SEP has not meaningfully changed since (or between) the time(s) of pregnancy, and uses the *current* information to retroactively predict potentially *past* events. If this assumption does not hold, the analysis would underestimate the risk of stillbirth for lower levels of SEP, because they were not recorded, and dilute the protective effects of higher SEP; it could even incorrectly assign an increased risk of stillbirth to higher levels of SEP. To reduce this bias, this study confined the sample to ages 15-49 to concentrate only on women of current potential childbearing age. The majority of births in this sample will have occurred within the decade before the survey (as explained in Section 4.3.3). Stratifying further by age cohort meant that one analysis, of the youngest cohort (age 15-24), was restricted to a sample of more recent births (at most from the last decade) for which the mother's SEP will likely have stayed the same.

Still, as long as the SEP has not changed drastically for too many women in the sample, the model results should indicate the relationship between SEP and stillbirth, with some acknowledged attenuation bias.

Age Cohorts

Like the rest of the data, the variable "age" refers to the age at the time of survey as opposed to age at the time(s) of birth (maternal age). With no measure for it, the model must assume that maternal age is independent of the birth outcome. The literature review and conceptual model (Section 2.3.1 showed that maternal age itself was not directly important in predicting stillbirth when accounting for variables further down the causal chain, such as health and birth history. This result has been observed in hierarchical models conducted with Brazilian data (Oliveira et al., 2010; Fonseca and Coutinho, 2010). Therefore, thanks to the derived variables relating to birth history (birth order and previous stillbirth), the absence of maternal age in the model may not be a great loss.

Instead, we treated age as a cohort effect, partitioning the data by ages 15-24, 25-39 and 40-49 years at the time of the survey. The cohorts of women would have been born in the periods 1989-1998, 1974-1988 and 1964-1973 respectively. Previous editions of the PNAD have been used to analyse fertility rates in age cohorts. Madalozzo (2012), for example, used PNAD 2009 data with women partitioned into two cohorts 18-45yrs (reproductive period) and 45-64 (post-reproductive period).

We assume the women within each cohort share the same baseline risk of stillbirth. With regards to birth history (parity and previous stillbirths), since the cohorts are (at time of survey) at different stages of their reproductive history, we cannot really compare between cohorts, but we can compare within cohorts. Fertility patterns have shifted over time, with women today generally postponing their first births and having fewer births overall than the previous generations (Goldani et al.; Castanheira and Kohler, 2015). Therefore, estimates for our cohort of 15-24-year-olds are not likely to reflect the birth history/SEP situation for the older cohorts when those women were in their teens and early twenties, nor will the estimates for the older cohorts truly predict how risk factors will change for the youngest cohort when they reach their forties.

Appropriateness of the Data Sample

The PNAD is a household survey that provides a representative sample of the national population. However, in order to analyse household-related variables, this study was limited to individuals in permanent private housing and excluded 163 mothers whose living situation did not fit this criterion, whether they were living in improvised housing or collective housing (for example student boarding, hospitals, or care homes). It could be argued that these individuals were disproportionately disadvantaged and that their absence could bias the study. However, the distribution of measures for socio-economic position such as household income, education and employment for these individuals were not significantly different from those in permanent housing, nor were their distributions of geographic variables (region and urban/rural code). Moreover, this population contained only three stillbirths, and it is unlikely that the exclusion of these individuals would affect the model results.

Another issue to note is that just under 10% of women in the data lived in households containing another woman from the data. As well as likely being related, the women within these households share the same household variable information, meaning that observations from these individuals are not strictly independent. However, the majority of these women are likely mothers and daughters and so are in different age cohorts. When the data is divided for separate analyses of the age cohorts, less than 2% of women in the analyses share a household with another in that sub-sample. Although treating related observations as independent would slightly underestimate the standard errors of coefficient estimates, there are not enough of these cases to affect our findings.

7.3.2 Summary of Findings

In this analysis of stillbirth using data from the PNAD, twenty-one potential risk factors were considered, capturing demographics, education, occupation, income, and household characteristics such as quality, services, and location.

Derived Variables for Birth History

The literature (and previous analysis of Scotland's MNLD) showed that parity and previous stillbirths are predictors of subsequent stillbirth, which is confirmed in this analysis, where the birth order represents a woman's parity at each given birth. The estimates for these variables are particularly large in this study; the odds of stillbirth more than quadruple for two or more previous births, or for one or more previous stillbirths, compared to a first birth. We would expect factors relating to birth history to have a stronger effect than the factors relating to SEP because they are closer to stillbirth in the causal chain (see the Conceptual Model in Section 2.3.1), and that is the case here. In fact, the odds ratios for birth order and previous stillbirth are notably more extreme in this analysis than in previous literature for Brazil (Oliveira et al., 2010). An additional reason for their magnitude could be that they are the only variables to reflect the individual's situation at the time of birth, whereas the other variables reflect her SEP in 2013 (as discussed above). The birth-related factors, therefore, are not as prone to noise or bias. As well as having a strong effect in its own right, birth order could also be acting as a proxy for age at birth (maternal age). Without maternal age in the data, any additional indirect effect of maternal age on stillbirth that is unaccounted for by other variables could be present here.

Wider Geography

Significant regional differences in stillbirth rates were present in the model even after adjusting for confounders, with higher odds for stillbirth observed in the North and South East regions compared to the South region. After accounting for the effects of its much higher overall parity, the North East region did not exhibit a significant difference compared to the South.

We note that these *lifetime* stillbirth rates for the regions (calculated with each woman's total births and stillbirths) do not reflect annual regional rates such as those in Figure 2.1 where, in a given year, a higher proportion of births in the North and North East regions will be stillbirths than in the southern states. Conversely, the overall lifetime stillbirth rate in this study for the North East was lower than

Table 7.9: Lifetime stillbirth rates (per 1,000 total births) by region, urban/rural code and parity calculated from the PNAD, Brazil.
**based on stillbirth count less than 10. **based on stillbirth count less than 5*

		Total parity			
	Overall	**1**	**2**	**3**	**4+**
Total	19	8.9	11	21	29
Region					
North East	18	10	11	17	24
North	20	10	11	22	30
Central West	20	12*	9	21	33
South East	19	8	11	23	32
South	16	6	10	20	26
Federal District	19	7**	7*	26	35
Urban/rural code					
Urban	19	9.0	11	22	31
Rural	17	8.4	9	16	22

for the South East, and this gap was exaggerated as parity increased, as shown in Table 7.9. Generally, women in the North East region have more births overall than the southern states, and this inflated the denominator in the lifetime stillbirth rate, making it lower. In the sensitivity analysis of the single birth subset (women with only one birth at the survey date), the rates for both the North and North Eastern regions were higher than for the southern regions.

The same reasoning applies to the urban/rural code. The models counter-intuitively suggested that women in rural areas were less likely to have stillbirths, before and after accounting for birth order and other potential confounders. While more rural women in the sample had at least one stillbirth compared to urban women (4.3% vs 3.9%: calculated from Table 4.9 of the data chapter), rural women also had more births generally, causing their stillbirth rate to be lower.

The effects of these geographic variables were strongly correlated with parity. In model selection for the single birth subset, neither geographic factor was significant to stillbirth when accounting for more individual-level variables.

Socio-economic Measures: Correlation, Causation and Confounding

In the presence of the birth-related variables, some risk factors that initially had a significant relationship with stillbirth no longer did, including marital status, the location of work, the age that the individual began working, and the presence of basic household goods. Conversely, some previously insignificant factors exhibited a strong relationship with stillbirth such as work history, income range, and the adequacy of household services. The direction of the effect estimates changed for many factors too,

Table 7.10: Lifetime stillbirth rates (per 1,000 total births) by education level, household income range and parity calculated from the PNAD, Brazil.
**based on stillbirth count less than 10. **based on stillbirth count less than 5*

		Total parity			
	Overall	**1**	**2**	**3**	**4+**
Total	19	9	11	21	29
Education level					
None/primary	20	12	10	18	27
Secondary	18	7	11	23	36
Tertiary	16	7	11	30	27
Income range (per capita)					
No wage or $\leq$ 1/2 min. wage	19	7	9	18	25
More than 1/2 to 1 min. wage	19	8	11	19	33
More than 1 to 2 times min. wage	19	10	11	25	33
More than 2 times min. wage	21	14	11	29	47

resulting in some counter-intuitive findings, most of which were due to a strong correlation between that variable and parity, as with the geographic variables above.

The association between education and stillbirth changed after adjusting for birth history. By itself, women with primary (or no) level of education had higher odds of stillbirth. However, when accounting for parity (and stillbirth history), the odds for the low/no education group were *lower* than for the more-educated groups. While higher education had a protective effect for first-time mothers in the sensitivity analysis for the single birth subset, for multiparous women with three or more births, the stillbirth rate began to increase with education, as seen in Table 7.10. It is likely that the higher rates for multiparous educated women reflect their age. Educated women tend to postpone childbirth for various reasons (see Section 2.3) and so the higher rates observed could be attributed to the additional risk that comes with (unobserved) advanced maternal age.

Household income range (per capita), too, provides some counter-intuitive results. Initially, the variable was not significantly related to stillbirth in the univariate analysis. However, when adjusted for birth-related variables, low-income households presented significantly lower odds of stillbirth. Table 7.10 displays higher stillbirth rates for wealthier households, with the inequality increasing with parity. Factors that measure a household's resources, such as household services and status goods, may be acting as proxies for income or deprivation and so behaved similarly to the income variable after adjusting for parity.

Model selection and full model. In the variable selection process, education level was dropped after adjusting for socio-economic status, as were most of the variables relating to employment. Many of the factors relating to goods, services and conditions within the household, acting as proxies for poverty or deprivation, ultimately did not maintain a significant relationship with stillbirth when the model already accounted for household income.

The final multivariate model accounted for age cohort, ethnicity, socio-economic status, hours per week spent working, household income range, household density, food security, urban/rural code and region. Women of black and brown/mixed ethnicity were statistically more at-risk of stillbirth than white women. Compared to those in managerial and administrative occupations (the highest socio-economic status bracket), women in intermediate occupations had higher odds of stillbirth. However, there was not a significant difference between the highest and lowest status bracket, or for unemployed women.

Household income (per capita) maintained its strong relationship with stillbirth when adjusting for parity and history of stillbirth, and the other socio-economic confounders; women from very low-income households had reduced odds of stillbirth compared to households earning 1-2 times the minimum wage, while wealthier households had increased odds.

Households with moderate food insecurity were found to have 26% higher odds of stillbirth compared to households with sufficient food, even after accounting for income and the number of people in the house (density).

Sensitivity analysis with the single birth subset. For the subset of women with one birth at the survey date (and therefore no influence from birth history), the magnitudes of many estimates for socio-economic factors were doubled in comparison with the main analysis. A likely explanation for this is that in the main analysis of all women in the sample, the stronger effects of parity and previous stillbirth dampen the effects of these more distal socio-economic and geographic factors.

When model selection was conducted for the subset, factors that were significant to the main (full sample) model such as age cohort, hours worked per week, urban/rural code and region were no longer included. These factors clearly have a strong relationship with parity, and their presence in the main model could perhaps be further explained with interaction effects between them and the number of previous births (or stillbirths).

Instead, important factors in model selection for the single birth subset included education level, household goods (basic and status) and household services. For each of these variables, in the main model, the direction of the effect estimates had reversed after accounting for birth-related variables.

In the sensitivity analysis, women with primary (or no) level of education had 82% higher odds of stillbirth than those who completed secondary education. Compared to households with adequate household goods, women from households with a lack of household status goods (e.g. a freezer, car, computer or internet access) were more than twice as likely to have a stillbirth, while those without *basic* goods (a cooker, fridge, television and phone) where three times as likely. Oddly, a lack of adequate household services (e.g. piped water, a sanitation system) exhibited a protective effect on the odds of stillbirth. This counter-intuitive result is likely affected by extremely small counts; in the single birth subset, there are less than five women living in a households with inadequate household services.

Along with household density, a measure for overcrowding within the household, income range was one of the only variables for which the counter-intuitive results were not explained in some way by the sensitivity analysis for the single birth subset. An alternative reason for these results could be that these two predictors are actually influenced by the outcome happening in the past, i.e. having a stillbirth means *not* having another person in the household later on, and therefore, in general, a lower household density and a higher income range per person. Unfortunately, having the outcome *predict* these predictors certainly breaks the model's assumption that the SEP factors do not meaningfully change over time. Usually, in social studies, household income and density are appropriate measures of SEP (Galobardes et al., 2006). However, given their backwards causal relationship with the outcome in this study, any further work should remove these variables from the model.

Age Cohorts

Findings from the three separate models for the age cohorts are in reasonably close agreement (Table 7.5). The variable effects varied slightly in size, but their directions and significance were largely consistent across the generations, with just a few notable differences which may suggest an evolution in socio-economic position over generations or may simply reflect the different stages of life that the age cohorts are experiencing. Alternatively, the stillbirth counts in some cases were likely too small to observe significant changes for that cohort.

For example, differences in stillbirth odds between ethnic groups appeared to be no longer significant from their baseline values for the youngest cohort group. This change could suggest a reduction in racial disparities for the current generation of mothers with regards to stillbirth, or that racial disparities only come into play for older mothers. The lack of significant difference between socio-economic classifications for the young cohort, however, is most likely due to there being only 1% of young women in the baseline managerial group.

Young people with low work-hours had lower odds of stillbirth than those with full-time work hours, while the opposite effect was true for the older cohort. A likely explanation for this is that younger people are more likely to be supported by parents or in full-time education and therefore don't need to work as much.

Comparison with the Literature

It is difficult to directly compare our main findings with the literature due to the lifetime birth and stillbirth counts in the PNAD not reflecting the binary outcomes used in other studies. Instead, estimates for the sensitivity analysis with the single birth subset more closely resemble the previous literature. The retroactive analysis of past outcomes and the issue of interpreting age within our study (along with the assumption that maternal age is independent of stillbirth) have already been discussed.

Regarding the variables relating to socio-economic position, there is some evidence in the Brazilian literature that work stability had a protective effect against fetal death (Fonseca and Coutinho, 2010). However, no other studies utilised such detailed employment-related variables such as those available in the PNAD regarding hours worked per week, the location of work, the age an individual began working or (as shall be discussed later) the type of employment.

Education is the most common measure of SEP in stillbirth studies in Brazil, potentially due to the easily-available presence of a variable for years-of-schooling among the vital statistics available from DATASUS. The systematic review by Barbeiro et al. (2015) of Brazilian literature on stillbirth found maternal education to be a key determinant, even after adjusting for confounders and birth-related factors. Generally, though, education is considered to have only an indirect effect on stillbirth, mediated by birth history and other factors on the pathway to stillbirth (see the conceptual model). This was the case in our study, where the level of education was significant in univariate analyses (and in the single birth sensitivity analysis) but was lost to the full sample's model selection process after accounting for birth history and other indicators of SEP.

Ethnicity plays a significant role in these findings, yet in general, the Brazilian literature finds ethnicity to have only an indirect effect on stillbirth mediated by socio-economic status and access to prenatal care, if any effect at all (Nyarko et al., 2015; de Almeida et al., 2007; Fonseca and Coutinho, 2010; Oliveira et al., 2010). Perhaps its effect is stronger in this analysis because it is one of the only variables that does not change over time and therefore will be less subject to noise from the "retroactive" data.

Women from rural areas in Brazil were shown by Carvalho et al. (2017) to have higher odds of stillbirth than women in urban areas, but unlike our study, this relationship lost its significance once region, deprivation, parity and various SEP factors were considered alongside it. Regional differences, however, persisted after accounting for these factors, with significantly higher risk in the North and North East.

Notable variables that were not included in the full sample's final model were marital status and household services. There is precedent in the Brazilian literature for a stable marital or (cohabiting) status having a protective association with stillbirth in multilevel studies in Brazil (de Almeida et al., 2007; Fonseca and Coutinho, 2010), but no such observation was found to be significant in this study.

The derived measure for household services (combining indicators regarding clean water, source of fuel, waste management and sewage) comes close to describing environmental conditions in the household but is ultimately not significantly related to stillbirth. There is little literature researching environmental risk factors for stillbirth, and evidence is mixed, but this under-researched element was worthy of exploration.

Available Variables. The variables considered in this study relate only to demographics, socio-economic position, environment (through household services) and birth history, and thus only cover the higher determinants of the conceptual model (see Figure 2.4); the study is unable to account for intermediate variables on the causal pathway to stillbirth.

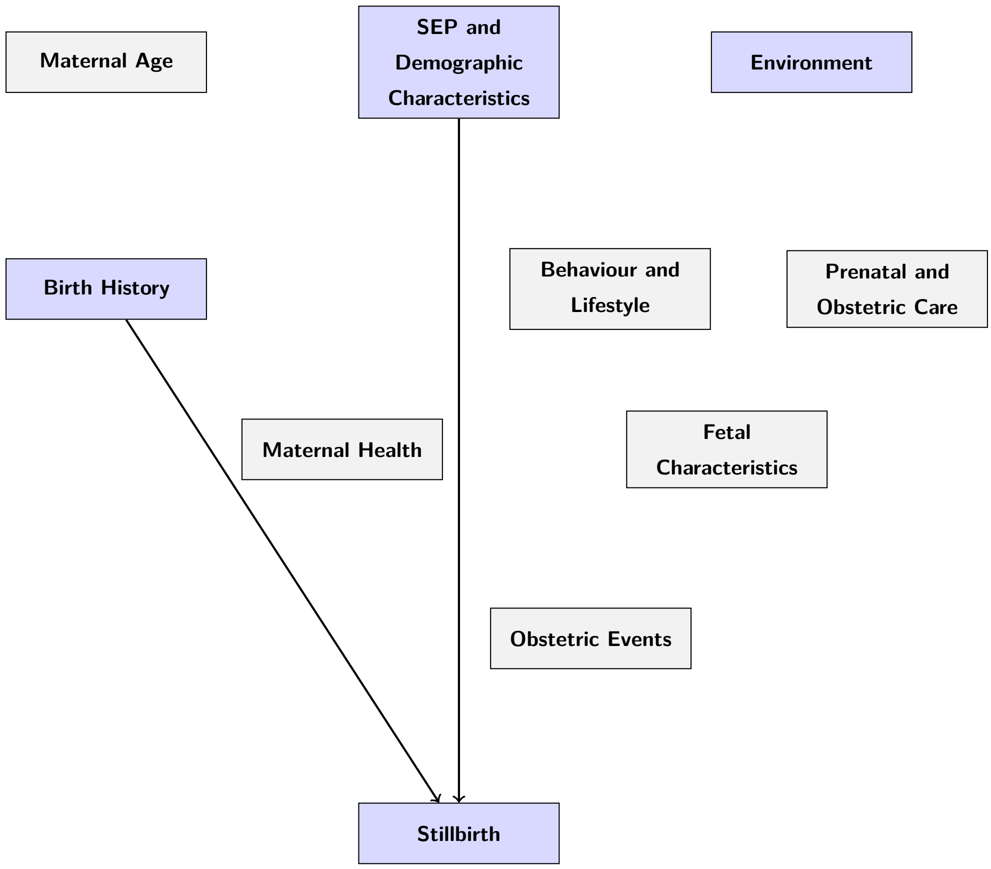


Figure 7.2: Pathways to stillbirth observed from available variables in the PNAD, Brazil. *Grey boxes indicate variable topics not covered in the data.*

Topics not covered in this study that are linked to stillbirth include the use of prenatal care, behavioural factors (such as smoking status), maternal health and morbidity, and essentially anything modifiable. Prenatal care and maternal morbidity are particularly important factors associated with stillbirth in Brazil, according to the aforementioned systematic review (Barbeiro et al., 2015). Information concerning maternal morbidity may also have accounted for more of the indirect effect of maternal age. Knowledge of obstetric events such as the use of caesarean section could confirm our theory regarding the increased odds of stillbirth for high-income households.

Success of the Derived measure for Brazil's socio-economic status (SeS)

For this study, we derived a measure for socio-economic status using PNAD employment-related variables that resembled the UK's NS-SeC measure (described in Section 4.3.4). In univariate analyses, this measure was more significantly associated with stillbirth than other common measures of SEP, such as education, income, and other employment-related variables including the simplified employed/unemployed status. After adjusting for birth variables, SeS was not as significantly associated with stillbirth as household income, but its estimates did seem to be less vulnerable to a correlation with parity. A disadvantage of this measure is that it is difficult to compare socio-economic inequalities for the 27% of mothers in the sample who were not economically active (students, homemakers, retired, etc.) who may have very different socio-economic positions. In future work, the SeS measure of the father or other members of the household could be calculated and incorporated to replace this missing information, as is common with birth registrations. Overall, the derived SeS has the potential to be a significant tool for measuring socio-economic inequality in Brazil, particularly for international comparison with the UK.

Also worthy of mention is the variable for food insecurity as a measure of deprivation; a relatively recent inclusion to the PNAD (and only as part of a one-off supplement), it is perhaps a more accurate measure of deprivation than employment or even income. Two households with the same income can experience different levels of deprivation, depending on family size and the cost of living in their area. Food security, on the other hand, addresses the fundamental question of "is this person struggling to survive?" regardless of any other factors. However, it is not widely collected and not as straightforwardly quantifiable as income, which makes it more difficult to implement in practice.

7.3.3 Methods

Contribution to new knowledge. To our knowledge, this method in which a count outcome is analysed by expanding the data into possible sequences of individual events has not previously been done. Others studies have investigated overall fertility rates with a similar division of age cohorts, but these involved live births only and none were concerned with the order of birth events (including stillbirths) (Kozuki et al., 2013). Through a specially derived likelihood function, we were able to account for the unknown ordering of binary events (live births and stillbirths) using only the overall counts of each potential outcome for each woman. While issues with the data brought about some counter-intuitive results, we emphasise that the statistical methods used for performing binary logistic regression on count data was appropriate and successful. This method could be applied to any aggregated binary count data for which the order of successes and failures is believed to be important.

Model selection. The standard stepwise forward model selection procedure requires, at each step, consideration of all possible ways of adding one new variable. Unfortunately, due to time constraints and the complexity of the aggregate likelihood function, this was not possible for our analysis. Thus a computational short-cut was taken, in which the variables were added in order of significance in univariate analyses. An advantage of the standard stepwise forward selection procedure which was unfortunately lost in the use of this short-cut method is that at each step of the procedure, it re-evaluated which was the most significant variable to add to the current model. If this had been possible for our analysis, the variables might have been added in a different order, possibly resulting in slightly different variables being added to/dropped from the final model.

Goodness of fit. The chi-square results can only be treated as informal guidelines, due to the various assumptions for the goodness of fit measure that have not been met. Firstly, the probabilities of stillbirth for each woman in a given group are not the same owing to their individual covariate information incorporated in the model, i.e. the data is not strictly identically distributed. Secondly, we are not taking into account that the expected values have been fitted from the data itself, which we would expect to lead to statistics smaller in magnitude than if they were based on an independent data set. Finally, for categorical variables with more than two levels, Cochran, W.G. (1952) specifies that ideally no more than 20% of the expected frequencies should be less than 5, and no expected frequency should be less than 1. While the former part of this assumption was met for the whole sample's categories in Table 7.8, neither were met for the age-specific cohort results in Table B.4, where as many as 40% of the expected frequencies for a subgroup were less than 5.

Determining the goodness of fit for the model may instead come down to how well the three age cohort models agree with each other. The variable estimates for each of the age cohorts are very consistent in direction and significance, and for each of the age cohorts, the confidence intervals of observed stillbirth rates (stratified by parity) include the corresponding expected stillbirth rate (Figure 7.1).

7.3.4 Conclusion and Further Work

A strength of this study lies in the number of available variables related to socio-economic position in the data. As described in Section 2.2.2 of the literature review, SEP is a multifaceted concept, and it was valuable to explore different aspects of SEP and their relationship with stillbirth. For the covariate effects to avoid bias, this analysis required a big assumption - that the demographics and SEP of a woman do not change over time after (or between) giving birth. In practice this is unlikely, and care must be taken to eliminate variables that change over time *as a result* of the birth outcome. However, in general, we argue that as long as the SEP has not changed drastically for too many women in the sample, these findings give an indication of the relationship between SEP and stillbirth, with some acknowledged attenuation bias.

The data provided an interesting methodological problem with regards to analysing individual binary events when observations are aggregated into a count outcome. However, care must be taken when putting these results, based on a woman's lifetime number of births, into context. These lifetime stillbirth rates will differ from population stillbirth rates for a given point in time; thus, findings from this study are not entirely comparable with most other studies of stillbirth, which generally investigate a cross-section of births (one per woman) within a given period. Indeed, many of the findings were counter-intuitive, although some were exacerbated by the many resulting correlations between variables, which is a downside of incorporating so many potential variables for SEP. While this data would be beneficial for investigating fertility rates generally, it was not ideally fit for the purpose of investigating the association between SEP and stillbirth. Even without these issues with the outcome variables, the PNAD is a cross-sectional study, which makes it near-impossible to establish a causal relationship between variables.

Further work: The difference between the results of the main model and the sensitivity analysis strongly suggest that parity has an effect on the relationship between socio-economic factors and stillbirth. An investigation of possible interactions between socio-economic covariates and the number of previous births (or stillbirths).

A difficulty with comparing age cohorts in this study arises due to the three cohorts, all evaluated at the same year (2013), being at different points in their reproductive years. Instead, the same analysis, using the aggregated likelihood function, could be applied to multiple PNAD data samples. Looking at cross-sections of Brazil over time, different generations can be evaluated at the same point of their reproductive years (for example all women in their forties). It may also be interesting to make use of the hierarchical structure of the PNAD with multilevel modelling by household or municipality. However, this method may be complicated to implement with this likelihood function.

Finally, Brazil's upcoming PNS (National Health Survey) 2018 will contain suitable health and social data that is arguably better equipped to answer the questions posed in this study. Comparing our results with future analysis of the PNS (when it is made available in 2020) may shed more light on the reliability of our findings.

Overall, this study shows that higher proportions of mothers from disadvantaged backgrounds experience stillbirth in their lifetimes, compared with more advantaged women, but that due to higher parity in these groups, overall lifetime rates (and estimates of stillbirth risk) appear significantly lower. After adjusting for parity, particularly strong risk factors for stillbirth include ethnicity, socio-economic status (based on employment), household income, food security and region. Due to numerous data and methodological differences, the results from this study are not directly comparable with the UK studies in this thesis. A broad comparison of all findings shall be carefully approached in the following chapter.

Chapter 8

Discussion

Stillbirths, as we have seen, are still under-researched in comparison to other child health outcomes. They rarely appear in key international or national health targets or commitments, despite being an immense global burden with 2.6 million cases estimated in 2015 alone (Lawn et al., 2016).

In this thesis we have compared the UK and Brazil as a high-income and middle-income country, respectively. From a public health perspective, we have highlighted a chronological progression of stages for tackling stillbirth in the two countries. As a BRICS nation - one of the five major emerging national economies - Brazil's rapid development over the last thirty years has resulted in immense health inequalities between regions and between urban and rural areas. The UK is comparatively further along in its journey to eradicating preventable stillbirths, but its stillbirth rate still ranks highly among peer high-income countries.

This chapter returns to the research questions outlined at the beginning of the thesis, and brings together our findings to answer them. Firstly, the general role of SEP in stillbirth risk was considered with a literature review and the creation of a conceptual model. The second question explored the tackling of stillbirth in Brazil and the UK through a chronological review of health and social policy in these two countries. In addressing the third question, we evaluated available national routine data suitable for investigating stillbirth in the two countries. We reviewed various data sources, and provided a detailed description of the three datasets used for further study. Finally, the fourth question was concerned with the extent to which inequalities in social and geographic factors affected stillbirth rates in Brazil and the UK; this was addressed via a combination of the literature review in Chapter 2 and the three studies conducted.

This thesis concludes after describing its contribution to new knowledge, study limitations, and implications for policy and practice, including suggested further work.

8.1 The Role of Socio-economic Position (SEP) in the Likelihood of Stillbirth

The first research question asked: *What is the role of socio-economic risk factors in the likelihood of stillbirth, and how are they mediated through more proximate birth-related factors?* We addressed this question in Chapter 2 through a literature review and the subsequent creation of a conceptual model (Figure 2.4) that linked demographic and socio-economic factors to stillbirth via various mediating factors: maternal age, environmental factors, birth history, behavioural factors, maternal health, fetal health/characteristics and obstetric events. While other conceptual models for stillbirth have been proposed, most are dependent only on the factors available in a given study; this all-encompassing model adds to the literature in its detailed exploration of the interplay between a vast number of factors.

The complexity of the conceptual model demonstrated that it is likely there is no single pathway or mechanism to explain stillbirth. Most research has identified multiple risk factors with adjusted odds of high magnitude, suggesting that there exists an intricate web of additive or interactive effects between these risk factors resulting in stillbirth. Different risk factors are prominent in the literature for high-income and middle-income countries. For middle-income countries, the most important factors that contribute to stillbirth are education (Zeitlin et al., 2016), environmental exposure (Yakoob et al., 2009), maternal health (Aminu et al., 2014) and the availability and quality of prenatal and obstetric care (Mcclure et al., 2015). In high-income countries, while education and maternal health are also very significant (Savard et al., 2013), there is more emphasis on behavioural and lifestyle factors such as smoking (Vais and Kean, 2015), obesity (Aune et al., 2014), and advanced maternal age (Flenady et al., 2011a).

Findings from the literature review suggest that SEP itself has little to no direct effect on stillbirth, but it does greatly affect the intermediate factors. At the top of the causal chain, demographic and socio-economic factors may be distant but nevertheless vital for effectively reducing stillbirth. Just as there appear to be differing prominent pathways between SEP and stillbirth for high-income and middle-income countries, there is evidence that inequalities in socio-economic position play more of a role in antepartum stillbirths, as opposed to intrapartum deaths (Wood et al., 2012; Seaton et al., 2012).

Given that some risk factors, such as previous stillbirths, are also linked with adverse outcomes in subsequent pregnancies, the benefits of preventing stillbirth are multiplicative (Lawn et al., 2009). Unfortunately, research into etiologic mechanisms leading to stillbirth can be hindered by the lack of standardised definitions and reporting (Gravett et al., 2010). The importance of consistent definitions and reporting shall be explored further in the following section.

8.2 Policies to Reduce Stillbirth in Brazil and the UK

The second research question asked: *In relation to health and social policy, what are the current practices in monitoring stillbirth rates in Brazil and the UK, and how do these compare with past government initiatives?* We tackled this question in Chapter 3 by gathering and reviewing relevant health and social policies from Brazil and the UK in chronological order, creating a timeline of initiatives for each country up to the present day. To our knowledge, such reviews of policies relating to perinatal health had not yet been conducted in either the UK or Brazil. The timeline of Brazil's policies started from the creation of their national health service - the SUS - in the late 1980s and followed through their commitment to the Millenium Development Goals (MDGs), while the review of UK initiatives relating to stillbirth started from the redefinition of stillbirth in 1992.

A Public Health Perspective

By listing the relevant initiatives chronologically, a pattern emerged. The timelines show a progression of stages for tackling stillbirth from a public health perspective, from the recognition of an official national definition for stillbirth to the implementation of actions to prevent it. Motivated by the conceptual frameworks for public health surveillance and response by McNabb et al. (2002) and Nsubuga et al. (2006), we can loosely group the initiatives into the stages displayed in Figure 8.1: Definition, Registration, Analysis and Response.

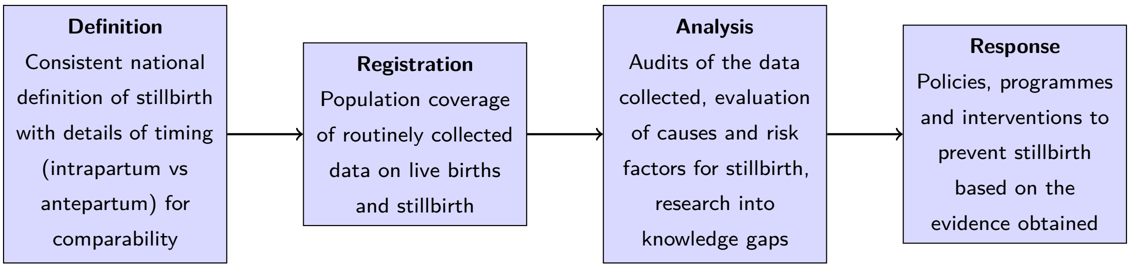


Figure 8.1: Conceptual framework for public health surveillance of stillbirth

While for the sake of international comparison, WHO *defines* stillbirth by gestational age with a threshold of 28 weeks or more, the International Classification of Diseases 10th revision (ICD 10) also defines stillbirth by birth weight (>1,000g) or even by the length of the foetus (>35cm) (Frøen et al., 2009). At a local level, the choice of primary measure and/or cut-off points can vary between (and sometimes within) countries. In countries with advanced neonatal intensive care, the viable gestational age at which a baby can survive is lower than 28 weeks, and so the threshold for defining stillbirths in some areas are as low as 20 weeks (Lawn et al., 2009).

These measures do not necessarily give equivalent figures, and a single metric can even be measured differently; some countries/organisations/studies calculate gestational age via ultrasound while others approximate it based on the mother's last menstrual period (Lawn et al., 2016). A consistent, suitable definition must be agreed upon before commencing research at a national level.

Once defined, the inclusion of stillbirth in routine vital *registration* systems is crucial, but not yet universal. Many low- and middle-income countries do not yet record stillbirths in civil registration data (Bhutta, 2017). Moreover, collecting socio-economic and health information alongside stillbirths (or linking this information to individuals) is essential for identifying causal factors, gaps in care, and levels of inequality across areas in subsequent *analysis*.

Finally, *response* initiatives in the form of new legislation, targets and interventions are introduced based on the evidence obtained.

Where Do Brazil and the UK Stand?

It is evident that Brazil and the UK are at different stages of their journey to eradicating preventable stillbirths. Brazil is focussed on achieving universal coverage of birth and stillbirth registration; reporting has increased in the last two decades thanks to legislation making the registration of death certificates for stillbirths mandatory, although coverage is not yet universal and the quality of the data recorded is still lacking (Barbeiro et al., 2015). In contrast, the UK has multiple organisations such as MBRRACE-UK and RCOG dedicated to auditing stillbirth cases and researching how to prevent future incidents, although individual-level data is not easily accessible to other researchers, especially in England and Wales.

In terms of intervention, Brazilian health policies are successfully working towards providing universal prenatal and intrapartum care; the Family Health Programme and Community Health Agents, implemented in the 1990s, have been fundamental to the early identification and monitoring of pregnant women, as well as the carrying out of consultations, examinations, and health interventions (Campanha Saúde para as Crianças Primiero, 2011). A study of three birth cohorts in the south-eastern city of Pelotas between 1982 and 2004 observed decreases in both income and education-related inequalities over the time period; this was attributed to the substantial expansion of healthcare to women from low-income backgrounds since the introduction of Brazil's national health service (SUS) (Matijasevich et al., 2012). However, while all of this progress will be indirectly beneficial to stillbirth rates, Brazil is not yet at the stage of setting targets or designing interventions explicitly for the reduction of stillbirth.

The UK, on the other hand, is targeting stillbirth more specifically through fetal growth monitoring and particular interventions such as the GAP programme that will make the biggest impact, according to their prior research. These interventions have been rolled out with the recent Saving Babies Lives "Care Bundle", and its coverage across NHS trusts throughout the country is increasing (NHS England, 2016).

The Department of Health committed to an explicit target - to reduce the rate of stillbirths, neonatal and maternal deaths in England by 50% by 2030. In 2017, on track to meet this goal and with further funding and support promised, the government were actually confident that they would meet the target ahead of schedule, to the point of bringing forward the target deadline to 2025 (DHSC, 2017).

Still, the UK seems not to be addressing significant social inequalities in stillbirth rates, and health outcomes in general, as much as it could be. While national outcomes are improving, there is a widening gap between the health outcomes of the most and least deprived communities (Royal College of Nursing, 2012). There is much to be done before the UK reaches the low rates of other European countries such as Norway, Denmark, Finland, Germany and the Netherlands, who have demonstrated that such reduction is achievable (Flenady et al., 2016).

Using the WHO definition for international comparison, Brazil's stillbirth rates are more than double that of the UK. In some ways, Brazil could be considered a few years behind the UK in its progress toward preventing stillbirths; it is still at the *registration* stage of the policy framework while the UK is at the *response* stage. However, considering that Brazil's commitment to public health launched in the creation of its national health service (SUS) in 1988, thirty years after the UK's NHS, Brazil has come a long way in a short time. Policy makers have even recommended that the UK could learn from Brazil's Community Health Agents programme regarding the expansion of healthcare to remote rural locations in Wales (Johnson et al., 2013). Brazil's low proportion of intrapartum stillbirths rival that of "more developed" countries including the UK (Blencowe et al., 2016), and since 2000, both countries are progressing in overall stillbirth rate reductions at a similar rate with a 15-16% reduction between 2000 and 2015, according to their own national definitions.

The Impact of the MDGs on Stillbirth Rates in Brazil

The research question was also concerned with whether *Brazil's commitment to the UN's Millennium Development Goals (MDGs) 4 and 5, relating to child and maternal mortality, had resulted in policy change that could affect stillbirth rates.*

In terms of new policies, the National Pact to Reduce Maternal and Neonatal Mortality (2004) set out to reduce maternal and neonatal mortality rates by 5% annually to meet the targets for the Millennium Development Goals (BRASIL. Ministério da Saúde, 2007). Other resulting initiatives such as the Stork Network (2011) aimed to reduce infant and maternal mortality by targeting improvements in prenatal and delivery care, and will have inevitably affected stillbirth risk (and other birth outcomes) positively (Barros et al., 2010).

Brazil did meet its MDG4 goal of reducing under-five mortality by two-thirds in 2015, and made notable progress towards its MDG5 goal, achieving near-universal access to basic reproductive healthcare and reducing its maternal mortality ratio (although not quite meeting the targeted 75% reduction). Consequently, other birth outcomes improved. National rates for infant and neonatal mortality (which are subcategories/subsections of child mortality) fell by 66% and 57% respectively between 1990 and 2010 (UNICEF et al., 2011).

However, the decline in the stillbirth rate - 28.9% - was not as remarkable (Blencowe et al., 2016), which was likely due to the aforementioned lack of target-setting and prioritisation for stillbirth reduction. As demonstrated by the efforts to meet the MDGs, governments are more likely to invest in policies and monitoring of outcomes for which they are publicly accountable (Qureshi et al., 2015). In this sense, stillbirths have been neglected by health services and policy in Brazil; although the Ministry of Health has collected information on fetal deaths for more than 25 years, it has not been regularly evaluated (Lima et al., 2006). Routinely auditing data and setting explicit national targets would encourage government action to reduce national stillbirth rates in Brazil and other countries where stillbirths are under-studied. Sadly, while child and maternal mortality continue to be monitored in the new Sustainable Development Goals (SDGs) (with the addition of neonatal mortality), stillbirth remains absent (Murray, 2015). Targets for stillbirth reduction, however, do appear in the international Every Newborn Action Plan, launched by WHO and UNICEF in 2014 (WHO, 2014), in which Brazil is one of 33 countries prioritised as needing attention (WHO, c).

8.3 Collection and Availability of Birth Data with Socio-economic Factors

Research question three asked: *What national, routinely collected datasets are available for the purpose of investigating the relationships between socio-economic factors and stillbirth in Brazil and the UK?* This question was addressed in Chapter 4, in which we evaluated the available routine individual level stillbirth information in Brazil and UK, and its possible linkage to socio-economic information.

Importance of Analysing Routine Data

As noted in Figure 8.1 of the previous section, collection and subsequent analysis of national routine birth and stillbirth registrations are essential for reducing stillbirth on a national scale.

Like other secondary data sources, national routine data is relatively quick and inexpensive to analyse, compared to conducting primary data collection, but such databases provide many additional advantages for researchers and health policy makers, as outlined in the data comparison chapter. Routine datasets are likely to be more up-to-date than other one-off data sources. Their comprehensiveness not only facilitates the generalisability of the findings to reflect a real-world situation (Morrato et al., 2007), but such large samples are particularly beneficial for investigating rare events such as stillbirth. There is an opportunity for analysis of trends across years of collection, and comparisons with other datasets that contain similar standard measures (Kane et al., 2000). On the other hand, like other secondary data sources, the choice of measures for analysis is restricted by the dataset available. Missing data and inaccuracies can also be a common challenge for analysing routine data.

Population-based routine data can be helpful for developing new health policies, interventions and targets through assessing the magnitude of a health problem and which populations are most vulnerable (Morrato et al., 2007). However, routinely collected data can be insufficient for evaluating the subsequent *effectiveness* of an intervention due to lack of specificity or perhaps a misplaced inference of causality. To overcome this, primary studies containing specific measures for evaluating an intervention would need to be in place before enacting new health legislation (Kypri and Davie, 2009).

National Routine Data on Stillbirth in Brazil and the UK

Both the UK and Brazil have routine stillbirth registration, through the Mortality Information System (SIM) for Brazil and separate systems for the UK nations: ONS (England and Wales), National Records Scotland, and Northern Ireland Statistics and Research Agency. By themselves, these data sources do not contain much information on socio-economic position or other mediating risk factors relating to stillbirth, and so other routine data sources were explored.

National Records Scotland is the most efficient system compared to the rest of the UK as it reports stillbirth counts with both the UK definition (at least 24 weeks gestation) and the international definition (28 weeks) in their annual summary of stillbirth data. Stillbirth count tabulations for Brazil, available from DATASUS, can be compiled using their national definition (22 weeks) or the international one. Output for England and Wales from the ONS, however, is restricted to 24 weeks.

The UK. MBRRACE-UK (formerly CMACE) analyses stillbirth cases with some socio-economic and behavioural factors such as deprivation and smoking status, but their available data did not include equivalent information for comparison with live births. The ONS Longitudinal Study (LS) linked birth events with vast amounts of potentially relevant socio-economic information for England from the census, but the sample was too small to analyse the relatively rare event of stillbirth. The NHS Hospital Episode Statistics (HES) for England contains many of the key birth-related and socio-demographic factors as the MNLD, but is tremendously underused for stillbirth (or any) research, likely due to its restricted access.

Ultimately, it was necessary to split the UK analysis; one for England and Wales and another for Scotland, omitting the small amount of data from Northern Ireland (3% of total births in the UK annually).

The analysis for England and Wales used aggregated live births and stillbirth counts by Local Authority and 5-year age group from the ONS. As explained in Section 4.5, we were unable to meet the lengthy approval process for access to the equivalent individual-level data within the time-frame of the thesis. The study suffered from the usual limitations of aggregate data analysis discussed at length in Section 5.3. However, in the absence of time or access to analyse individual-level data, cautious use of aggregate birth data tabulated by a key risk factor offers the best available evidence to inform the development of strategies to reduce stillbirth in England and Wales (Zylbersztejn et al., 2017).

For Scotland, we acquired selected variables from the Maternity and Neonatal Linked Database (MNLD), the most suitable data of the three used for the thesis. The linked database provided comprehensive, individual-level birth information with numerous socio-economic, behavioural, and health indicators. Though, like much of linked data in general, such quality came at a high cost. The benefits and obstacles of linked data shall be elaborated upon later in the section.

While it was possible to analyse them separately, access to comparable data at a UK-wide level would have been helpful to compare the distribution of SEP factors *between* nations of the UK, as Scotland's population has been found to be generally more deprived than that of England (Dundas et al., 2014).

Brazil. Brazil's routinely collected stillbirth and live birth data – collected through the Mortality Information System (SIM) and Live Birth Information System (SINASC), respectively, contain basic information on the birth (gestational age, birthweight, delivery type, pregnancy type (i.e. single/multiple), and cause of death) as well as the socio-demographic factors ethnicity, mother's education and area of residence. Aggregate tabulations, graphs and maps using this data can be easily and freely generated online through the platform DATASUS. Access to the individual-level data itself is very restricted, similar to the UK data.

When routine registration data is not accessible, routine national sample survey data may be an appropriate alternative. Impressively, the Brazilian Institute of Geography and Statistics (IBGE) regularly publishes full anonymised data from their surveys for free and open use. The new National Health Survey (PNS), covering many topics including recent birth events at a detailed individual-level, would be an ideal dataset for this study. However, due to teething issues at the collection stage, IBGE was unable to publish data relating to stillbirths in th 2013 edition. Thus, this study instead used data from the National Household Sample Survey (PNAD).

While the PNAD boasts a wealth of socio-economic information and does include variables on the number of live and stillbirths for women in the sample, these birth variables ultimately do not produce stillbirth rates that reflect the rates across Brazil (tabulated by age, area, or various SEP measures). They produce individuals' lifetime stillbirth rates, which are heavily skewed by parity. While the literature shows that women of lower SEP are generally at a higher risk of a given birth being stillborn than women of higher

SEP, they also have disproportionately more births overall and therefore their lifetime stillbirth rates are lower. This is discussed in detail in Section 7.3. Subsequent analyses of these variables (Section 7.2) are not directly comparable with the findings of the other studies in this thesis, or with other Brazilian literature on risk factors for stillbirth. In the future, Brazil's new National Health Survey (PNS) should provide suitable health and social data that is arguably better equipped to determine the effects of social, environmental, behavioural and healthcare-related risk factors on stillbirth in Brazil.

Incorporating Socio-economic Information through Data Linkage

Birth certificate data in most countries, including the UK and Brazil, provides basic information such as the maternal age, residence and marital status. The usefulness of the data is greatly increased when it includes the gestational age, birthweight and associated maternal disorders (Lawn et al., 2016). However, the key to effectively examining the connection between socio-economic position and stillbirth is through the linkage of routine data systems. Hospital data can be linked with socio-economic information from other data sources, such as census data or registers on education, occupation and income. This valuable research tool allows understanding of the inequalities in health outcomes across socio-economic groups (Delnord et al., 2016).

A major hindrance to the research of linked data is the very high cost of acquiring it, which is prohibitive to the average researcher. The acquisition of linked data can also be extremely time-consuming; firstly due to the lengthy approval process before allowing access for the researcher, and then the expensive time-intensive procedure of linking two or more large datasets.

The UK as a whole has no national linking of perinatal or maternal health data; although Scotland's MNLD has impressive coverage, completeness, and quality, England and Wales have very little routine linkage and Northern Ireland has none (Delnord et al., 2016). Only very recently has data linkage in England begun to catch up to Scotland. In 2016, Harron et al. established the linking of HES mothers records to babies records in a similar fashion to the MNLD. Since then, Harper (2018) established the linking of HES maternity records to ONS registration and notification data for births in 2005-2014. However, no further research or use of this linked data has been announced thus far.

Within Europe, Scotland's diverse perinatal health surveillance is perhaps surpassed only by the Nordic countries (Denmark, Sweden, Norway and Finland), in which every citizen has a universal identification number that is available in all of their routine databases. All medical birth registers contain the personal identification numbers of the mother, father and the neonate, and so are capable of linkage with almost any other routine data relating to the family, such as health (including medical notes), education, social or financial data (Langhoff-roos et al., 2014). Study-specific permission is required for linkages from national authorities in theses countries, which is obtainable, yet extremely expensive.

A Brazilian study by Paixão et al. (2017) demonstrated that a high standard of linkage of large routine databases was also achievable for a middle-income country. Stillbirth data from SIM was linked with information on dengue fever in pregnancy. Since there was no unique identifier, probabilistic linkage was based on maternal name, age and municipality.

Conclusion. This thesis compared the availability and use of routine national data regarding stillbirth between a high income and middle-income country. Individual-level linked routine data is considered the gold-standard, although routine surveys can be useful alternatives if administrative data is not available. Routine birth and stillbirth registrations, containing basic socio-economic information, are collected in both the UK and Brazil, although their data are not accessible to most researchers without extensive time and funding. Scotland's linked perinatal health surveillance allows for the examination of many other health and social indicators, while the rest of the UK is more limited in how stillbirth and social factors can be studies together at a national level. This data is needed if the government is to evidence that stillbirth reduction targets have been met by 2025.

Remarkably, Brazil's IBGE grants free and open access to full anonymised datasets from their national sample surveys, containing vast amounts of social and health information. While limited analysis of stillbirth data is possible using the PNAD household survey, the next edition of their National Health Survey (PNS – due for released in 2020) will include a plethora of information relevant to the study of the relationship between SEP factors and stillbirths.

8.4 Socio-economic Inequalities in Stillbirth Risk across Brazil and the UK

The final research question asked: *To what extent do inequalities in stillbirth rates exist across areas in Brazil and the UK? What are the social factors associated with stillbirth in both Brazil and the UK? How does the impact of these factors differ between the two countries?* These topics were covered in the literature review, and then explored further with the available routine datasets in Chapters 5-7. Due to multiple data and methodological differences, the magnitudes of these results are not directly comparable; a broad comparison of all findings shall be carefully approached.

Geographic Inequalities across Brazil and the UK

Brazil is a large and diverse country with considerable regional variations in stillbirth rates. The 2016 rate for the North Eastern region (11.8 per 1,000 births) is almost 60% larger than for the Southern region (7.4 per 1,000) (DATASUS, 2018). Deprivation, urban/rural classification and various SEP factors did not explain this variation (Carvalho et al., 2017), but access to (and use of) prenatal care might.

In accordance with the literature, results in Chapter 7's Table 7.9 show that for all women with only one birth, the rates for the northern regions were higher than for the southern regions. Analysis of this single birth subset showed that after accounting for confounders such as urban/rural code, women from the North region still had significantly higher odds of stillbirth compared to the affluent South region. This presents the case for researching the effect of SEP on stillbirth risk since the Northern regions are less developed compared to the larger conurbations of the South.

In the UK, Figure 2.2 in Chapter 2 shows that the stillbirth rates for Scotland and Northern Ireland, though more sporadic than for England and Wales (due to smaller birth counts), have been consistently lower than England and Wales since 2010, despite, as we learned in the previous section, Scotland's population being generally more deprived than England (Dundas et al., 2014). This might be attributed to the more advance perinatal surveillance in Scotland, leading to more informed policy-making decisions.

In the Scottish MNLD study in Chapter 6, no significant relationship with stillbirth was found for area-based factors such as deprivation level and urban/rural code. Both UK studies considered random effects for area variation, but they yielded little to no evidence of a significant geographic effect. No geographic random effect was seen for Scotland, while a small amount of variation across counties in England and Wales was detected, at the aggregate level, that was unaccounted for in the observed variables. Perhaps this variation was observed for England and Wales, and not Scotland because analysis for the latter incorporated detail at an individual level and with more variables. Since studies with aggregate data are less able than individual-level studies to correct for confounders, we would expect more heterogeneity and perhaps a higher magnitude of significance from the group-level random effects for England and Wales.

There is a 25% difference in stillbirth rates between regions of the UK (NHS England, 2016), while the difference in Brazil is more than 60%). The existence of significant regional variation is more prevalent in the Brazilian literature than the UK. Brazil is a much bigger country with communities that are harder to reach and to provide healthcare for. Different regions will have different healthcare needs within its more diverse landscape (Vieira et al., 2016), yet limited supplies and low availability of national healthcare (SUS) services are barriers to adequate healthcare in the North and Northeast (Andrade et al., 2009).

Social Inequalities within Brazil and the UK

The literature cites maternal education and the quantity, quality and accessibility of prenatal care as the key social determinants of stillbirth in Brazil. The PNAD did not contain variables relating to prenatal care, but analysis of the single birth subset showed significantly increased odds of stillbirth for less-educated women, in keeping with the literature. This analysis also showed that high socio-economic status, adequate household goods and food security had strong protective effects against stillbirth after adjusting confounding. However, these variables are not widely used in the research of perinatal health (socio-economic status was derived especially for this study), and so there is little literature with which to compare these variables.

The most important social factors in the analysis of the full sample in this study, after adjusting for confounding, were socio-economic status, ethnicity, household income and food security. However, we do not consider these results to be comparable with the literature due to the "lifetime" stillbirth rates produced by the PNAD data being different from population stillbirth rates for a given point in time. This limitation of the data was discussed in more detail in Section 7.3.

Also of note is the phenomenon of caesarean sections in Brazil, particularly among users of private healthcare where caesarean deliveries seem to be perceived as a social trend rather than medical need (Victora et al., 2011b). Brazil had the second highest percentage of caesarean deliveries in 1990-2014, with 55.6% of all deliveries (second only to the Dominican Republic's 56%) compared to the global percentage of 18.6% and the UK's 26.2% (Betrán et al., 2016). Given their high prevalence in Brazil over the last thirty years and the increased risk of subsequent stillbirth following caesarean delivery (see Section 2.3), it is possible that these deliveries will have affected the lifetime rates observed in the PNAD study for Brazil. The increased lifetime stillbirth rates observed in the PNAD among multiparous women in higher-income households may be partially attributable to the popular trend of in elective caesarean sections among wealthier women with private healthcare (Hopkins et al., 2014). Matijasevich et al. (2008) found that in a 2004 cohort of births in Pelotas, caesarean sections were conducted in 5 out of 6 births for the group of women from households earning more than three times the minimum wage. This compound risk from previous caesarian deliveries could have exacerbated the increased odds exhibited for the highest-income households in the PNAD study. On the other hand, Matijasevich et al. attributed the increased use of caesareans between the 1993 and 2004 cohorts to decreased perinatal deaths that year. The effect of Brazil's caesarian epidemic on subsequent birth outcomes warrants further study.

The UK, like many high-income countries, faces advanced maternal age, obesity and smoking as major preventable risk factors (Flenady et al., 2011a). In addition, the UK has one of the highest teenage pregnancy rates among these countries which also presents an increased risk of stillbirth. Babies of Asian/Asian British and Black/Black British ethnicity have significantly higher risk of stillbirth compared to white babies (MBRRACE-UK Collaboration, 2017).

Findings from the analysis of England and Wales in Chapter 5 suggest that, of the limited available variables, advanced maternal age and the baby's ethnicity and had the biggest influence on the odds of stillbirth; the odds of stillbirth generally increased as the percentage of non-white infants in the local authority/age stratum increased. After accounting for the mediating effects of gestational age and birthweight, the study of Scotland data in Chapter 6 affirmed high BMI and smoking during pregnancy to be very important preventable risk factors, although the biggest total risks were for the unemployed group and those with diabetes. This study also contributes to the literature with new findings from a mediation analysis of stillbirth data in the UK. The effects on stillbirth of maternal age, ethnicity and marital status were fully mediated by gestational age and birth weight. The mediation model showed that although these socio-demographic variables were not considered significant in the standard model, they are still relevant in the causal pathway to stillbirth, due to their strong relationship with gestational age and birthweight.

While inequalities in access to prenatal/obstetric care are a major risk factor for Brazil, the UK has comparatively universal access to at least a basic amount of prenatal/obstetric care throughout pregnancy. The UK has moved on to tackling other social risk factors for stillbirth brought on by the circumstances of a high-income country such as an ageing population and women postponing childbirth.

8.5 Measuring Socio-economic Position

Section 2.2.2 of Chapter 2 described how the theoretical construct of Socio-economic Position (SEP) is hard to measure, with no universally agreed-upon standard metric. Prevalent individual-level measures include metrics based upon education, income or employment, while aggregate-level area deprivation scores are also common such as the Carstairs, Townsend and Index of Multiple Deprivation scores in the UK (DETR, 2000; Porta, 2016). These deprivation scores are derived from combining some of the aforementioned topics, possibly along with health, living environment, crime and even car ownership, for small areas.

Deriving the Brazil SeS to Replicating the UK NS-SeC

A commonly used individual-level measure of SEP in the UK's administrative data is the flexible National Statistics Socio-economic Classification (NS-SeC), based on the individual's occupation and hierarchy within the workplace. Brazil has no such standard measure of SEP (V. Guerra, personal communication, April 17, 2017). However the PNAD contained some version of most of the employment-related indicators that make up the NS-SeC (5 levels). In this thesis, we created a new measure, the Brazil Socio-economic Status (SeS), that approximately replicated the NS-SeC (Section 4.3.4).

Comparing the SeS with the equivalent NS-SeC measure in Scotland's MNLD data (also with 5 levels), the distribution of women in each category seemed to reflect the variation in the types of industries and employment common in either country.

The percentage of women in managerial and professional occupations (level 1) was 31% in Scotland and 9% in Brazil, while the percentages in routine occupations (level 5) were 25% and 35% respectively. Perhaps most notable is that the percentage of women who are not economically active in Brazil (28%) is almost double that of Scotland (15%).

Are the SeS/NS-SeC measure appropriate for studying stillbirth? The SeS and its UK counterpart appeared as a main significant risk factor for stillbirth in all three studies conducted for this thesis, even after model selection and accounting for confounding factors. In both the Scotland and Brazil final models, a simplified "employed/unemployed" indicator was trialled in place of the 5-level measure, but was found to be less significant, suggesting that the *type* of employment and not just being employed in itself has an impact on stillbirth. However, given that over a quarter of women in the sample were not economically active, and that the socio-economic conditions within this large group could be very diverse, incorporating the SeS measure for the father or other employed members of the household into the analysis might portray a more complete picture of the mothers' socio-economic situation.

Despite this, although further examination is required, the derived variable has the potential to be a significant tool for measuring socio-economic inequality in Brazil, particularly for international comparison with the UK and consequently much of the EU, which has a comparable measure (Rose and Harrison, 2010).

Availability of Other SEP Measures

The best choice of SEP measure very much depends on the study's context and the question being asked. For early-life outcomes, the parents' education, income and occupation are considered appropriate measures of SEP (Galobardes et al., 2006). But often the choice of measure depends on the variables available. Maternal education is on the Brazilian birth certificate and unsurprisingly appears as one of the most used SEP measure in birth studies. In this thesis, education and income were available in the PNAD for Brazil but not for the UK studies; while these studies could not account for it, perhaps education is also an important factor on the causal pathway to stillbirth in the UK. The literature review suggested that education played an important role even in some high-income countries (Luo et al., 2006; Luque-Fernández et al., 2012; Savard et al., 2013). Perhaps future reviews of birth outcomes in the UK would benefit from the recording of maternal education on birth registrations akin to Brazil.

Area versus individual level measures of SEP The 2012 meta-analysis by Weightman et al. of birth outcomes in the UK stated that the association for outcomes with area deprivation was quite similar to that with social class. Area deprivation indicators are certainly easier to obtain than individual-level SEP measures – the Carstairs and Townsend scores are freely available from the UK Data Service (at electoral ward level for researchers from UK higher education institutions). Weightman et al. lamented that since few studies incorporate both individual and area measures into a single analysis, it is difficult to determine their relative importance for health outcomes. Our analysis of Scotland's MNLD achieved this for stillbirth, finding that in univariate analyses, the individual NS-SeC measure was highly associated with stillbirth while the area-based Carstairs deprivation quintiles had no apparent relationship. Many other UK studies of stillbirth use area-level deprivation quintiles with mixed results (Section 2.3.2). Our findings suggest that focus should instead be placed on individual-level measures of SEP. The NS-SeC is not widely used in UK studies of stillbirth but is often recorded alongside administrative birth and stillbirth data, and so it should be relatively straightforward to implement in the analysis, once a researcher can access the individual-level data. On the other hand, as noted in the previous section, the employment-based NS-SeC measure cannot account for mothers who are not economically active (15% of the MNLD sample), and generally does not take into account the socio-economic resources of her partner or household in general. An alternative individual-level SEP measure may be even more appropriate, but none are as prevalent in current UK administrative data as the NS-SeC.

Availability of Potential Mediating Variables

In a perfect study, one would be able to account for all of the factors on the causal pathway to stillbirth presented in the conceptual model (Figure 2.4); of course, this is not possible in practice. In the three datasets studied, relevant healthcare-related indicators were the most lacking (e.g. access to a hospital, prenatal care received, etc.), particularly in the study of Brazil, for which prenatal care is a key factor for stillbirth in the literature.

Other missing environmental, behavioural and social risk factors included, to varying degrees, nutrition, psychological stress and environmental exposure to harmful substances. These factors remain understudied in the literature. A better understanding of these mechanisms would be instrumental in the devising of new interventions to prevent stillbirths (Yakoob et al., 2009).

8.6 Contribution to New Knowledge

This thesis contributes to new knowledge on a number of levels, firstly through proposing a new conceptual model of the causal pathways to stillbirth. While some studies have previously proposed such conceptual models based on available study variables, very few have attempted to construct an all-encompassing model irrespective of a given dataset and none with this level of detail (a corresponding path-by-path literature review). Vandresse's (2006) model for feto-infant mortality was a notable influence, although this review found that the causal pathways differed even between fetal and infant mortality, and so a separate model for stillbirth is a worthwhile addition to the literature.

Secondly, to our knowledge, there has not yet been a comprehensive review of policies relating to perinatal health in either the UK or Brazil, representing a high-income and middle-income country, respectively. We showed how Brazil is following in the footsteps of the UK from a public health perspective in its evolution as a major emerging economy. This review contextualises the successes and challenges of reducing stillbirth in both countries and should aid policymakers in future decision-making.

Thirdly, a small but noteworthy addition to the world of social science is the creation of a SEP measure for Brazil that is comparable with the UK National Statistic for Socio-economic Classification (NS-SeC); its potential implications have been discussed in the previous section.

Fourthly, while there have been a number of perinatal health studies using the Scottish MNLD, some of which are even specific to stillbirth, none to our knowledge have employed mediation in an attempt to disentangle the effects of the many available explanatory variables. In fact, the use of mediation, or any kind of pathway analysis, seems to be new to the study of perinatal health in the UK or Brazil. Furthermore, no studies of stillbirth in middle-income or high-income countries have investigated as many potential risk factors in a mediation model or other path analysis for stillbirth. We have gained a richer understanding of the inter-relationships between these factors (with new findings previously described in Section 8.4).

Finally, as well as the substantive contributions, we have also introduced two new methodological approaches not specific to stillbirth. Firstly, the handling of data with small count suppression, applied in Chapter 5, does not appear to have been done before. Our approach of calculating the exact likelihood of the unknown suppressed values alongside the known values appropriately accounts for the variability of the missing data and is relatively simple to implement in situations when the missing data can take only a limited number of values (in this case 0, 1 or 2).

Secondly and finally, the most novel method employed in this thesis may be the analysis of an aggregated count outcome as a sequence of individual binary events via the consideration all of its possible sequences. Through a specially derived likelihood function, we were able to account for the unknown ordering of binary events (live births and stillbirths) using only the overall counts of each potential outcome for each woman (see Section 7.1). This method could be applied to any aggregated binary count data for which the order of successes and failures is believed to be important.

8.7 Study Limitations

Methodological and data-related limitations specific to each study are presented in their respective chapters. The scope and interpretations of the analysis for England and Wales were extremely limited by the aggregate nature of the data and the small number of available variables. In the Scotland analysis, while the potential for mediation was a great benefit, it was unable to include the very important nominal variable mode of birth in the model as a mediator, as the current software cannot accommodate nominal categorical mediators.

For Brazil, the stillbirth rates calculated using count data in the PNAD produced "lifetime" stillbirth rates that did not reflect population stillbirth rates for a given point in time, which certainly limited interpretation and comparability with the other studies of stillbirth. The "retroactive" analysis for Brazil, i.e. modelling birth outcomes in the *past* using *current* SEP information, also required an assumption that the demographics and SEP of a woman do not change over time after (or between) giving birth. This assumption was broken by two predictors that turned out to have a reverse causal relationship with stillbirth in that the birth outcomes (happening in the past) influenced the current socio-economic predictor.

When the three studies are considered as a whole, other limitations hindered a comparative discussion of the data and their findings. Firstly, each study had differing available variables. The UK datasets, for example, could not account for food security and Brazil's PNAD did not account for smoking. Either of these variables might have a large impact on stillbirth in the other country, but if that information is not collected, then it can not be tested. Even factors that did appear in more than one of the studies were not accounting for the same confounders, and so it is difficult to compare their magnitudes directly.

The varying definitions for stillbirth have hindered making valid international comparisons. The PNAD defines stillbirth as a cut-off of seven months gestation, approximately 28 weeks by WHO's definition for international comparison. However, both of the UK studies include births from 24 weeks of gestation, following the UK definition.

Section 5.3 discussed the limitations of aggregate data for the analysis of England and Wales data. It is much easier to perform meaningful work with individual-level data, but access to this type of administrative data is outside the financial and time restraints of the average researcher. The difference in the quality of findings between the two UK studies in this thesis showcases how much more can be achieved with Scotland's level of data collection and release.

Model selection strategies Two of the studies – Scotland and Brazil – relied upon some form of stepwise variable selection. The choice of which model selection technique depended on the needs and limitations of data. The standard binary regression models for the Scotland study employed backwards iterative stepwise selection, comparing the nested models with Wald tests (described in Section 6.1). While the likelihood ratio test (Section 7.1.2) is popular for non-imputed data, the easier-to-obtain Wald test statistic has been favoured (and found to be more accurate) with imputed data (Wulff and Ejlskov, 2017; Eekhout et al., 2017).

The SEM model did not use stepwise selection; any paths that were not significant in the full model were simply removed straight away. Brazil used a simplified version of forward selection, comparing the nested models with likelihood ratio tests. Backwards model selection was initially considered, as with the analysis of the Scottish data. However, that model's likelihood function's optimisation routine was unable to converge, due to issues of collinearity. Instead, a pseudo forward selection was used, described in section 7.1.2.

Stepwise selection procedures are advantageous when there are numerous potential predictors. The procedures are relatively quick and simple to perform with easily available statistical software. However, many statisticians criticise the use of stepwise regression for variable selection. Problems with stepwise methods have been summarised by Frank Harrell's book Regression Modeling Strategies (2001). An essential problem is that methods intended for one test are applied to many tests. Statistics such as the Wald and Likelihood ratio tests are based on a single hypothesis being tested. Standard errors of the parameter estimates are biased toward zero, and subsequently the confidence intervals around the parameter estimates are too narrow. P-values are also biased toward zero due to multiple comparisons, while the parameter estimates themselves are biased away from zero, and are likely to be too high in absolute value. There are no reasonable ways of correcting these problems. Models identified by stepwise methods also have a magnified risk of capitalising on chance features in the data. When a large number of predictor variables are under examination, there is an inflated probability that significance may be observed for "noise" variables, due to correlation.

To avoid this bias, one could instead rely on full models constructed with pre-chosen predictors, but the resulting models may be large and complicated. In practice, more parsimonious models might be preferred. For "reasonable" sample sizes and "strong" covariate effects, or a large proportion of irrelevant variables, standard variable selection can work well (Wood et al., 2008). Ambler et al. (2002) identified, through simulation studies with backward elimination, simplified models performed as well as, and occasionally better than, full models.

In the cases of our studies for Scotland and Brazil, however, there were simply too many candidate variables (21 in each study) to include in the final analysis, given their methodological complexity, and so model selection was required as a compromise. For Brazil in particular, the full model was not able to run and so we started with a small selection of predictors and built upwards.

Generally, when selecting variables, one should always consider issues such as clinical importance, model stability, collinearity and confounding, alongside statistical significance.

Overall, regarding the initial standard analyses attempted in each study, the Scottish MNLD was the simplest to investigate meaningfully and provided informative results. While the other two studies provided interesting methodological challenges to overcome, their findings regarding stillbirth are not nearly as helpful as those for Scotland.

8.8 Implications for Further Work, Policy and Practice

One of the overall goals of this thesis was to devise recommendations for policy and practice to reduce stillbirth rates in both Brazil and the UK.

Brazil. The most recent policies relating to maternal and perinatal health to have come out of Brazil have focussed on universal registration of stillbirth and infant death (Law n^o 72), universal standardised prenatal healthcare (Law n^o 1459) and the reduction of caesarean rates (Resolution n^o 2144). After universal registration and data collection has been achieved, the next stage in our conceptual framework for public health surveillance and response (Figure 8.1) is the auditing of the data and researching the possible causes of stillbirth. Similar to the work of MBRRACE-UK and RCOG in the UK, this will help to acquire a better understanding of the causes of these stillbirths. Particular focus should be dedicated to determining the link between stillbirth and maternal education, since education is one of the main risk factors for stillbirth in Brazil from the literature, alongside the quality and quantity of prenatal care (which is already being addressed by the Stork Network (Law 1459)).

Brazil's situation regarding unnecessary caesarian sections is quite unusual, and its direct link to complications in subsequent pregnancies should be further monitored and researched. Recent legislation attempts to reduce the number of caesarian births; Resolution n^o 2144 states that a woman can still choose a caesarian delivery, provided she receives sufficient unbiased information on the benefits and risks of both vaginal and caesarian delivery, to make an informed choice. For the safety of the foetus, the resolution restricts caesarian sections to 39 or more weeks gestation. The Adequate Childbirth Project is carefully monitoring effect of their interventions on the caesareans rate, but we recommend that it should build in close monitoring of subsequent pregnancies to assess how this change contributes to any changes in adverse birth outcomes.

Regarding further research, Brazil's upcoming National Health Survey (PNS) 2018 will contain a section dedicated to fertility and the use of prenatal care for female respondents that is better equipped to answer the questions posed in this thesis. It collects information on individual births for any women in the sample who have given birth in the previous two years; therefore, it won't suffer from the same limitations as the birth-related outcome variables in the PNAD. The PNS also contains suitable health and social data, including the same household indicators and many of the same socio-economic factors as the PNAD. The PNS includes general health indicators such as health services utilisation and the quantity/regularity of visits from Family Health Strategy agents, which will help to investigate the success of specific interventions. Assuming that the data collection issues that impeded the release of stillbirth-related data in PNS 2013 have been addressed, we recommend future stillbirth-focused analysis of the PNS when it is made available in 2020.

Outside of the world of stillbirth, the newly derived Brazil Socio-economic Status (SeS) should be further examined in other contexts and datasets to determine its general suitability as a SEP measure, especially regarding its international comparability with measures such as the NS-SeC.

The UK. Regarding current policy in the UK, the new Care Bundle has specific strategies for stillbirth reduction focused on smoking, a major risk factor for the UK in the literature, and more biological causes such as intrauterine growth restriction (NHS England, 2016). However, no current policy really addresses the issue of socio-economic inequalities in stillbirth, which were present in both UK studies in this thesis, even after adjusting for confounding behavioural and health factors further down the causal chain (in the of case Scotland). Previous UK research concerning social inequalities in stillbirth is mostly based on area deprivation scores, yet the literature and the Scottish MNLD study suggest that individual-level measures of socio-economic position are more appropriate for investigating health outcomes. Therefore, we recommend the use of the NS-SeC or other individual SEP measure over the use of deprivation scores in future analysis of stillbirth. To address the population of mothers that aren't economically active and therefore don't easily fit into an NS-SeC category, it may be fitting, where possible, to include this measure for the father instead, as his occupation will also appear in most administrative birth data.

It is also clear that the rest of the UK would benefit from considering robust surveillance and linkage of routine birth data similar to the example set in Scotland. It may already be in the process, thanks to the work of Harron et al. (2016) and Harper (2018) in establishing the methodology for linkage of the routine hospital episode statistics (HES) to vital registrations in England.

The MNLD has the abundant potential for further research regarding stillbirth, such as considering moderating effects (i.e. interactions) within the causal pathway or even extending the SEM model to multiple levels of mediation in order to further resemble the conceptual model. Since mothers can be linked to more than one observation (whether via multiple births or multiple pregnancies in the time period), there is potential for multilevel modelling with each woman as a level. This setup of linked data could be utilised further with a detailed exploration of birth spacing, an understudied potential risk factor for stillbirth, looking at individual women and their pregnancies across time. These proposals are described in more detail in the Scotland-specific discussion in Section 6.3.

8.9 Concluding Remarks

This thesis contributes to new knowledge on a number of levels, notably through its comprehensive reviews of the scientific literature concerning the link from social factors to stillbirth and on the policies employed by a high-income and middle-income country to reduce stillbirths nationally, as well as its reasonably novel applications to routine stillbirth data.

More research into the causal mechanisms leading to stillbirth is required. Understanding the convoluted relationships between risk factors is crucial to creating effective interventions that will reduce inequality in stillbirth rates. In particular, considering separate conceptual frameworks for pathways to antepartum and intrapartum stillbirth could be a valuable start on the road to unravelling this web of contributing factors.

Ultimately, this thesis has shown the possibilities and limitations of different types of data, from aggregate-level, individual-level and beyond to the gold standard of data linkage. Each study in this thesis utilised routine data of the highest possible quality that was available and affordable to the general research community. For the UK and Brazil, the hindrance to new knowledge lies not necessarily in the lack of useful routine birth data being collected, but in its subsequent availability to the research community. The protection of potentially identifiable data is paramount, but reducing the barriers to these valuable resources (both the high costs and lengthy data access procedures) could allow researchers to test a wide range of hypotheses. This would provide the best possible use of these resources and expand the potential to improve national health.

Data and methodologies were too different to compare the magnitudes of variable effects between studies. In keeping with the Brazilian literature, less-educated women were at a higher risk of stillbirth. Analysis of "lifetime" stillbirth rates revealed some counter-intuitive relationships between geographic and social factors and stillbirth, which were distorted by high parity among disadvantaged women.

Through investigating the possible causal pathways for stillbirth using Scotland's linked perinatal surveillance database, this research has gone beyond what has been previously done with such high-quality data. While socio-demographic factors such as maternal age, ethnicity and marital status had no direct effect on stillbirth risk, their mediating influence on gestational age and birth weight still played a role in the cause of stillbirth.

These combined findings serve to put forward a case for a more robust collection of stillbirth data, with an emphasis on data linkage. Along with the aforementioned reviews, they may be of value to policy makers as well as funders of research in this area.

It is imperative that governments continue to address the seemingly distant social determinants of stillbirth, as they will consequently affect the impact of all subsequent behavioural and health determinants down the causal chain.

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Appendix A

Literature Review

A.1 Systematic Search String for Literature Review

1. stillbirth
2. fetal
3. foetal
4. death
5. mortalit*
6. **1 OR ((2 OR 3) AND (4 OR 5))**
7. social
8. socioeconomic
9. socio-economic
10. demographic
11. country of origin
12. country of birth
13. ethnic
14. ethnicity
15. marital status
16. education
17. occupation
18. employ*
19. **7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18**
20. maternal age
21. environment*

22. pollut*
23. sanitation
24. contaminat*
25. rural*
26. urban*
27. 21 OR 22 OR 23 OR 24 OR 25 OR 26
28. birth history*
29. parity
30. previous adverse birth
31. previous stillbirth
32. previous caesarian
33. 28 OR 29 OR 30 OR 31 OR 32
34. prenatal care
35. antenatal care
36. 34 OR 35
37. maternal health
38. maternal infection
39. maternal disorder
40. maternal morbidity
41. obesity
42. hypertension
43. malnutrition
44. stress
45. 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44
46. birth weight
47. gestational age
48. preterm
49. growth retrict*
50. multiple birth
51. congenital abnormalit*
52. congenital malform*
53. fetal infection
54. asphyxia
55. 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54
56. obstetric
57. birth trauma
58. breech
59. caesarian

60. 56 OR 57 OR 58 OR 59

61. 6 AND 19
62. 6 AND 20
63. 6 AND 27
64. 6 AND 33
65. 6 AND 36
66. 6 AND 45
67. 6 AND 55
68. 6 AND 60

Appendix B

Additional Tables

B.1 Scotland MNLD Analysis

Table B.1 shows the unstandardised direct and intermediate effects from the full mediation model, while Table B.2 displays the resulting indirect and total effects (including standardised total effects).

Table B.1: Unstandardised direct and mediator effect estimates from the full SEM mediation model, with 95% confidence intervals (CI). Bold type denotes significant effect with p-value <0.05

Variable	Direct Effect		Intermediate Effect							
	→ stillbirth		→ gestational age		→ birth weight		→ parity		→ prev. stillbirths	
	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
Gestational age	**0.13**	(0.12, 0.14)								
Birth weight	**0.82**	(0.79, 0.85)								
Parity	0.02	(-0.02, 0.07)								
Previous stillbirth	-0.05	(-0.15, 0.06)								
Socio-economic status										
Intermediate occupation	-0.02	(-0.11, 0.07)	**-0.07**	(-0.11, -0.04)	**0.06**	(0.02, 0.09)	**0.09**	(0.07, 0.11)	0.05	(-0.03, 0.13)
Small employer or self-employed	-0.11	(-0.25, 0.03)	**-0.08**	(-0.12, -0.03)	0.01	(-0.04, 0.06)	**0.29**	(0.26, 0.31)	0.07	(-0.03, 0.17)
Supervisor/craft related	-0.06	(-0.18, 0.05)	**-0.12**	(-0.16, -0.08)	**0.11**	(0.06, 0.15)	**0.14**	(0.12, 0.17)	0.04	(-0.06, 0.13)
Routine occupation	-0.07	(-0.14, 0.01)	**-0.15**	(-0.17, -0.12)	**0.12**	(0.09, 0.14)	**0.31**	(0.3, 0.33)	**0.15**	(0.09, 0.21)
Long term unemployed	**0.40**	(0.12, 0.67)	**-0.36**	(-0.51, -0.2)	**0.25**	(0.08, 0.42)	**0.75**	(0.65, 0.86)	**0.36**	(0, 0.73)
Not classified	-0.07	(-0.17, 0.02)	**-0.30**	(-0.34, -0.27)	**0.20**	(0.16, 0.23)	**0.71**	(0.69, 0.73)	**0.31**	(0.24, 0.39)
Ethnicity										
Black	0.12	(-0.05, 0.29)	-0.05	(-0.14, 0.04)	**0.18**	(0.09, 0.27)	0.00	(-0.05, 0.04)	**0.18**	(0.04, 0.33)
South Asian	-0.02	(-0.18, 0.15)	**-0.25**	(-0.31, -0.18)	**0.32**	(0.26, 0.39)	**0.09**	(0.05, 0.13)	**0.28**	(0.17, 0.39)
Other	0.03	(-0.18, 0.24)	**-0.08**	(-0.15, -0.01)	0.03	(-0.05, 0.11)	**-0.15**	(-0.19, -0.11)	0.03	(-0.13, 0.19)
Parents marital status										
Cohabiting	-0.03	(-0.1, 0.04)	0.02	(0, 0.05)	**0.07**	(0.04, 0.1)	**-0.07**	(-0.08, -0.05)	0.02	(-0.04, 0.08)
Separate address	-0.02	(-0.12, 0.07)	**-0.11**	(-0.14, -0.08)	**0.16**	(0.12, 0.19)	**-0.05**	(-0.07, -0.03)	0.00	(-0.08, 0.08)
Sole registration	-0.05	(-0.18, 0.07)	**-0.09**	(-0.13, -0.04)	**0.15**	(0.11, 0.2)	**-0.12**	(-0.14, -0.09)	0.00	(-0.11, 0.1)
Maternal age										
18-19 yrs	-0.05	(-0.21, 0.1)	**0.20**	(0.16, 0.25)	-0.05	(-0.1, 0)	**-1.15**	(-1.18, -1.11)	**-0.60**	(-0.8, -0.41)
20-24 yrs	-0.02	(-0.1, 0.06)	**0.08**	(0.06, 0.11)	-0.02	(-0.05, 0.01)	**-0.40**	(-0.42, -0.38)	**-0.16**	(-0.23, -0.09)
30-34 yrs	-0.01	(-0.08, 0.06)	**-0.04**	(-0.06, -0.01)	**0.03**	(0, 0.06)	**0.26**	(0.24, 0.27)	**0.06**	(0, 0.12)
35-39 yrs	-0.04	(-0.12, 0.05)	**-0.17**	(-0.2, -0.14)	**0.13**	(0.09, 0.16)	**0.56**	(0.55, 0.58)	**0.16**	(0.09, 0.22)
40-45 yrs	0.02	(-0.11, 0.15)	**-0.44**	(-0.49, -0.4)	**0.26**	(0.21, 0.32)	**0.81**	(0.78, 0.84)	**0.31**	(0.22, 0.41)
Smoking status										
Former smoker	0.04	(-0.05, 0.13)	**0.10**	(0.07, 0.13)	-0.02	(-0.06, 0.01)	**0.08**	(0.06, 0.09)	0.04	(-0.03, 0.12)
Smoked during pregnancy	**-0.09**	(-0.16, -0.02)	**-0.23**	(-0.25, -0.2)	**0.33**	(0.31, 0.36)	**0.33**	(0.31, 0.34)	**0.18**	(0.12, 0.24)
Drug misuse										
Yes	**-0.18**	(-0.36, 0)	**-0.33**	(-0.39, -0.27)	**0.34**	(0.28, 0.4)	**0.22**	(0.18, 0.26)	0.09	(-0.05, 0.22)
Body mass index	**0.02**	(0.01, 0.02)	0.00	(0, 0)	**-0.01**	(-0.01, -0.01)	**0.01**	(0.01, 0.01)	**0.01**	(0.01, 0.02)
Diabetes										
Pre-existing	**0.46**	(0.23, 0.68)	**-2.25**	(-2.35, -2.16)	**0.33**	(0.22, 0.44)	-0.03	(-0.09, 0.04)	**0.32**	(0.12, 0.51)
Gestational	-0.02	(-0.3, 0.25)	**-1.03**	(-1.11, -0.95)	**-0.13**	(-0.22, -0.04)	0.04	(0, 0.08)	**0.20**	(0.08, 0.32)

Table B.2: Indirect and total effect estimates from the full SEM mediation model, with standardised total effects and subsequent logit approximations. 95% confidence intervals (CI) and bold type denotes significant (unstandardised) effect with p-value <0.05

	Indirect Effect								**Unstandardised Total Effect**		**Standardised Total Effects**	
	Via gestational age		Via birth weight		Via parity		Via prev. stillbirths					
Variable	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI	Probit.	Logit.
Socio-economic status												
Intermediate occupation	**-0.01**	(-0.01, -0.01)	**0.05**	(0.02, 0.08)	0.00	(0, 0.01)	0.00	(-0.01, 0)	0.02	(-0.07, 0.11)	0.01	0.02
Small employer or self-employed	**-0.01**	(-0.02, 0)	0.01	(-0.04, 0.05)	0.01	(-0.01, 0.02)	0.00	(-0.01, 0.01)	-0.11	(-0.25, 0.03)	-0.09	-0.14
Supervisor or craft related	**-0.02**	(-0.02, -0.01)	**0.09**	(0.05, 0.13)	0.00	(0, 0.01)	0.00	(-0.01, 0)	0.01	(-0.1, 0.13)	0.01	0.01
Routine occupation	**-0.02**	(-0.02, -0.02)	**0.09**	(0.07, 0.12)	0.01	(-0.01, 0.02)	-0.01	(-0.02, 0.01)	0.01	(-0.07, 0.08)	0.01	0.01
Long term unemployed	**-0.05**	(-0.06, -0.03)	**0.21**	(0.07, 0.35)	0.02	(-0.02, 0.05)	-0.02	(-0.06, 0.02)	**0.56**	(0.26, 0.86)	**0.43**	**0.69**
Not classified	**-0.04**	(-0.04, -0.03)	**0.16**	(0.13, 0.19)	0.02	(-0.02, 0.05)	-0.01	(-0.05, 0.02)	0.05	(-0.04, 0.15)	0.04	0.06
Ethnicity												
Black	-0.01	(-0.02, 0)	**0.15**	(0.08, 0.22)	0.00	(0, 0)	-0.01	(-0.03, 0.01)	**0.25**	(0.08, 0.42)	**0.19**	**0.31**
South Asian	**-0.03**	(-0.04, -0.02)	**0.26**	(0.21, 0.32)	0.00	(0, 0.01)	-0.01	(-0.04, 0.02)	**0.21**	(0.05, 0.37)	**0.16**	**0.26**
Other	**-0.01**	(-0.02, 0)	0.03	(-0.04, 0.09)	0.00	(-0.01, 0)	0.00	(-0.01, 0.01)	0.04	(-0.17, 0.24)	0.03	0.05
Parents marital status												
Cohabiting	0.00	(0, 0.01)	**0.06**	(0.03, 0.08)	0.00	(0, 0)	0.00	(0, 0)	0.03	(-0.04, 0.1)	0.02	0.04
Separate address	**-0.01**	(-0.02, -0.01)	**0.13**	(0.1, 0.16)	0.00	(0, 0)	0.00	(0, 0)	0.09	(-0.01, 0.19)	0.07	0.11
Sole registration	**-0.01**	(-0.02, -0.01)	**0.13**	(0.09, 0.17)	0.00	(-0.01, 0)	0.00	(0, 0.01)	0.06	(-0.07, 0.19)	0.04	0.07
Maternal age												
18-19 yrs	**0.03**	(0.02, 0.03)	-0.04	(-0.09, 0)	-0.03	(-0.08, 0.02)	0.03	(-0.04, 0.09)	-0.07	(-0.22, 0.08)	-0.05	-0.09
20-24 yrs	**0.01**	(0.01, 0.01)	-0.02	(-0.04, 0.01)	-0.01	(-0.03, 0.01)	0.01	(-0.01, 0.02)	-0.03	(-0.11, 0.05)	-0.02	-0.04
30-34 yrs	**0.00**	(-0.01, 0)	**0.03**	(0, 0.05)	0.01	(-0.01, 0.02)	0.00	(-0.01, 0)	0.02	(-0.06, 0.09)	0.01	0.02
35-39 yrs	**-0.02**	(-0.03, -0.02)	**0.10**	(0.08, 0.13)	0.01	(-0.01, 0.04)	-0.01	(-0.02, 0.01)	0.05	(-0.03, 0.14)	0.04	0.06
40-45 yrs	**-0.06**	(-0.06, -0.05)	**0.22**	(0.17, 0.26)	0.02	(-0.02, 0.06)	-0.01	(-0.05, 0.02)	**0.19**	(0.06, 0.32)	**0.15**	**0.23**
Smoking status												
Former smoker	**0.01**	(0.01, 0.02)	-0.02	(-0.05, 0.01)	0.00	(0, 0.01)	0.00	(-0.01, 0)	0.03	(-0.06, 0.12)	0.03	0.04
Smoked during pregnancy	**-0.03**	(-0.03, -0.02)	**0.27**	(0.25, 0.3)	0.01	(-0.01, 0.02)	-0.01	(-0.03, 0.01)	**0.16**	(0.08, 0.23)	**0.12**	**0.19**
Drug misuse												
Yes	**-0.04**	(-0.05, -0.03)	**0.28**	(0.23, 0.33)	0.01	(0, 0.02)	0.00	(-0.02, 0.01)	0.05	(-0.12, 0.23)	0.04	0.07
Body mass index	0.00	(0, 0)	**-0.01**	(-0.01, -0.01)	0.00	(0, 0)	0.00	(0, 0)	**0.01**	(0, 0.01)	**0.01**	**0.01**
Diabetes												
Pre-existing	**-0.29**	(-0.31, -0.26)	**0.27**	(0.18, 0.36)	0.00	(0, 0)	-0.01	(-0.05, 0.02)	**0.43**	(0.21, 0.65)	**0.33**	**0.53**
Gestational	**-0.13**	(-0.14, -0.12)	**-0.11**	(-0.18, -0.03)	0.00	(0, 0)	-0.01	(-0.03, 0.01)	-0.27	(-0.54, 0)	-0.21	-0.33

B.2 Brazil PNAD Analysis

Variable breakdowns of the PNAD sample by age cohort are displayed in B.3.

An extension of the Goodness of Fit Chi-square tables, broken down by each of the three age cohorts, can be found in Table B.4.

Table B.3: Risk factors for stillbirth in the PNAD 2013, Brazil, by age cohort

	Aged 15-24 years 7338 observations **History of stillbirth**		**Aged 25-39 years** 32257 observations **History of stillbirth**		**Aged 40-49 years** 22153 observations **History of stillbirth**	
Characteristic	**No** (7179)	**Yes** (159)	**No** (31137)	**Yes** (1120)	**No** (21016)	**Yes** (1137)
Ethnicity						
White	2258 (31%)	48 (30%)	12382 (40%)	357 (32%)	9457 (45%)	380 (33%)
Black	638 (9%)	11 (7%)	2829 (9%)	137 (12%)	1737 (8%)	123 (11%)
Brown/mixed	4193 (58%)	98 (62%)	15663 (50%)	615 (55%)	9649 (46%)	627 (55%)
Other	90 (1%)	2 (1%)	263 (1%)	11 (1%)	173 (1%)	7 (1%)
Marital status						
Married	309 (4%)	7 (4%)	1573 (5%)	59 (5%)	1176 (6%)	83 (7%)
Single	5612 (78%)	130 (82%)	15526 (50%)	616 (55%)	6511 (31%)	429 (38%)
Separated, divorced, widowed	129 (2%)	4 (3%)	2177 (7%)	80 (7%)	3328 (16%)	169 (15%)
Not disclosed	1129 (16%)	18 (11%)	11861 (38%)	365 (33%)	1,0001 (48%)	456 (40%)
Socio-economic status						
1: Managerial, administrative, professional	101 (1%)	3 (2%)	2893 (9%)	66 (6%)	2374 (11%)	75 (7%)
2: Intermediate occupations	678 (9%)	15 (9%)	2985 (10%)	85 (8%)	1322 (6%)	53 (5%)
3: Small employers, self employed	401 (6%)	9 (6%)	3152 (10%)	117 (10%)	2617 (12%)	159 (14%)
4: Supervisory, technical	163 (2%)	4 (3%)	1520 (5%)	43 (4%)	927 (4%)	31 (3%)
5: Routine, semi-routine, agricultural	2245 (31%)	54 (34%)	11067 (36%)	455 (41%)	7427 (35%)	428 (38%)
Long term unemployed - seeking work	636 (9%)	18 (11%)	1625 (5%)	75 (7%)	642 (3%)	50 (4%)
Economically inactive	2955 (41%)	56 (35%)	7895 (25%)	279 (25%)	5707 (27%)	341 (30%)
Highest education level						
Primary and below	3795 (53%)	100 (63%)	13776 (44%)	625 (56%)	10791 (51%)	697 (61%)
Secondary	3218 (45%)	51 (32%)	13260 (43%)	390 (35%)	6793 (32%)	327 (29%)
Tertiary and above	166 (2%)	8 (5%)	4101 (13%)	105 (9%)	3432 (16%)	113 (10%)
Work history						
Has worked	4676 (65%)	104 (65%)	26124 (84%)	939 (84%)	17881 (85%)	943 (83%)
Never worked	2503 (35%)	55 (35%)	5013 (16%)	181 (16%)	3135 (15%)	194 (17%)
Age began working						

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Characteristic	Aged 15-24 years History of stillbirth		Aged 25-39 years History of stillbirth		Aged 40-49 years History of stillbirth	
	No (7179)	**Yes** (159)	**No** (31137)	**Yes** (1120)	**No** (21016)	**Yes** (1137)
<9 yrs	921 (13%)	23 (14%)	6629 (21%)	269 (24%)	5053 (24%)	327 (29%)
10-14 yrs	1256 (17%)	32 (20%)	6383 (20%)	214 (19%)	3885 (18%)	169 (15%)
15-19	1411 (20%)	30 (19%)	8605 (28%)	283 (25%)	5729 (27%)	250 (22%)
Not employed	3591 (50%)	74 (47%)	9520 (31%)	354 (32%)	6349 (30%)	391 (34%)
Location of work						
Fixed establishment	1800 (25%)	46 (29%)	12648 (41%)	365 (33%)	8167 (39%)	316 (28%)
Outdoors, home, employer's home	847 (12%)	19 (12%)	6155 (20%)	254 (23%)	5058 (24%)	309 (27%)
Not disclosed	4532 (63%)	94 (59%)	12334 (40%)	501 (45%)	7791 (37%)	512 (45%)
Hours per week working						
$\leq$ 14 hrs	303 (4%)	1 (1%)	1619 (5%)	82 (7%)	1061 (5%)	76 (7%)
15-39 hrs	1143 (16%)	23 (14%)	8483 (27%)	253 (23%)	5924 (28%)	225 (20%)
40-44 hrs	761 (11%)	20 (13%)	5334 (17%)	196 (18%)	3863 (18%)	216 (19%)
45+ hrs	617 (9%)	22 (14%)	4198 (13%)	143 (13%)	3013 (14%)	163 (14%)
Unemployed/unknown	764 (11%)	19 (12%)	1983 (6%)	92 (8%)	806 (4%)	66 (6%)
Household income range (per capita)						
No wage or $\leq$ 1/2 min. wage	3506 (49%)	77 (48%)	10961 (35%)	486 (43%)	5048 (24%)	376 (33%)
> 1/2 to 1 min. wage	2276 (32%)	44 (28%)	9659 (31%)	309 (28%)	5931 (28%)	348 (31%)
> 1 to 2 times min. wage	933 (13%)	21 (13%)	6103 (20%)	182 (16%)	5565 (26%)	236 (21%)
> 2 to 5 times min. wage	206 (3%)	10 (6%)	3079 (10%)	94 (8%)	3396 (16%)	123 (11%)
Not disclosed	258 (4%)	7 (4%)	1335 (4%)	49 (4%)	1076 (5%)	54 (5%)
Household construction						
Adequate	6971 (97%)	152 (96%)	30695 (99%)	1089 (97%)	20782 (99%)	1118 (98%)
Inadequate	208 (3%)	7 (4%)	442 (1%)	31 (3%)	234 (1%)	19 (2%)
Household services						
Adequate	5636 (79%)	129 (81%)	26342 (85%)	923 (82%)	18214 (87%)	913 (80%)
Semi-adequate	1260 (18%)	26 (16%)	4189 (13%)	165 (15%)	2498 (12%)	192 (17%)
Inadequate	283 (4%)	4 (3%)	606 (2%)	32 (3%)	304 (1%)	32 (3%)

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Table B.3 continued from previous page

	Aged 15-24 years History of stillbirth		Aged 25-39 years History of stillbirth		Aged 40-49 years History of stillbirth	
Characteristic	**No** (7179)	**Yes** (159)	**No** (31137)	**Yes** (1120)	**No** (21016)	**Yes** (1137)
Household density						
Adequate	4574 (64%)	113 (71%)	25430 (82%)	865 (77%)	19169 (91%)	1006 (88%)
Inadequate	2605 (36%)	46 (29%)	5707 (18%)	255 (23%)	1847 (9%)	131 (12%)
Household basic goods						
Adequate	6574 (92%)	138 (87%)	29980 (96%)	1057 (94%)	20380 (97%)	1071 (94%)
Inadequate	605 (8%)	21 (13%)	1157 (4%)	63 (6%)	636 (3%)	66 (6%)
Household status goods						
Adequate	567 (8%)	14 (9%)	6256 (20%)	182 (16%)	5391 (26%)	192 (17%)
Semi-adequate	2225 (31%)	42 (26%)	11749 (38%)	365 (33%)	8319 (40%)	412 (36%)
Inadequate	4387 (61%)	103 (65%)	13132 (42%)	573 (51%)	7306 (35%)	533 (47%)
Food security						
Secure	4364 (61%)	83 (52%)	22015 (71%)	699 (62%)	15797 (75%)	718 (63%)
Light food insecurity	1848 (26%)	46 (29%)	6530 (21%)	262 (23%)	3460 (16%)	231 (20%)
Moderate food insecurity	562 (8%)	16 (10%)	1541 (5%)	105 (9%)	1033 (5%)	109 (10%)
Severe food insecurity	405 (6%)	14 (9%)	1051 (3%)	54 (5%)	726 (3%)	79 (7%)
Urban/rural code						
Urban	5893 (82%)	139 (87%)	26745 (86%)	952 (85%)	18340 (87%)	952 (84%)
Rural	1286 (18%)	20 (13%)	4392 (14%)	168 (15%)	2676 (13%)	185 (16%)
Region						
North East	1677 (23%)	41 (26%)	5335 (17%)	199 (18%)	2925 (14%)	206 (18%)
North	2270 (32%)	50 (31%)	9372 (30%)	358 (32%)	5896 (28%)	382 (34%)
Central West	593 (8%)	10 (6%)	2614 (8%)	104 (9%)	1687 (8%)	84 (7%)
South East	1645 (23%)	34 (21%)	8520 (27%)	296 (26%)	6298 (30%)	307 (27%)
South	871 (12%)	22 (14%)	4422 (14%)	127 (11%)	3592 (17%)	135 (12%)
Federal District	123 (2%)	2 (1%)	874 (3%)	36 (3%)	618 (0%)	23 (2%)

Table B.4: Observed and expected number of women by births and stillbirth counts in the PNAD, Brazil, stratified by age cohort

Women Aged 15-24 Years

Women with 1 Birth

Number of stillbirths	0	1	Total
Observed women	4869	50	4919
Expected women	4868	51	4919
χ^2 test statistic			0.01
P-value			*0.920*

Women with 2 Births

Number of stillbirths	0	1	2	Total
Observed women	1708	48	3	1759
Expected women	1710	48	1	1759
χ^2 test statistic				9.2
P-value				***0.010***

Women with 3 Births

Number of stillbirths	0	1	2	3	Total
Observed women	439	36	1	0	476
Expected women	440	33	3	0	476
χ^2 test statistic					2.1
P-value					*0.548*

Women with 4 Births

Number of stillbirths	0	1	2	3	4	Total
Observed women	119	10	2	1	0	132
Expected women	118	11	2	0	0	132
χ^2 test statistic						1.6
P-value						*0.802*

Women Aged 25-39 Years

Women with 1 Birth

Number of stillbirths	0	1	Total
Observed women	10848	86	10934
Expected women	10846	88	10934
χ^2 test statistic			0.03
P-value			*0.862*

Women with 2 Births

Number of stillbirths	0	1	2	Total
Observed women	10958	233	7	11198
Expected women	10960	233	5	11198
χ^2 test statistic				0.57
P-value				*0.752*

Women with 3 Births

Number of stillbirths	0	1	2	3	Total
Observed women	5207	302	12	2	5523
Expected women	5196	307	19	1	5523
χ^2 test statistic					4.6
P-value					*0.206*

Women with 4 Births

Number of stillbirths	0	1	2	3	4	Total
Observed women	2352	180	30	1	0	2563
Expected women	2352	186	22	2	0	2563
χ^2 test statistic						3.9
P-value						*0.420*

Women Aged 40-49 Years

Women with 1 Birth

Number of stillbirths	0	1	Total
Observed women	4031	42	4073
Expected women	4032	41	4073
χ^2 test statistic			0.01
P-value			*0.919*

Women with 2 Births

Number of stillbirths	0	1	2	Total
Observed women	7772	135	3	7910
Expected women	7768	139	3	7910
χ^2 test statistic				0.14
P-value				*0.932*

Women with 3 Births

Number of stillbirths	0	1	2	3	Total
Observed women	4615	285	12	3	4915
Expected women	4608	288	18	1	4915
χ^2 test statistic					9.0
P-value					***0.029***

Women with 4 Births

Number of stillbirths	0	1	2	3	4	Total
Observed women	2223	197	22	2	2	2446
Expected women	2223	193	27	3	0	2446
χ^2 test statistic						35
P-value						***0.000***

Appendix C

Sample Code

A sample of the R code used to create the aggregate data likelihood function for analysis of the Brazilian PNAD is shown below, along with commentary explaining the syntax (which follows the # symbol). After reading in the data and pre-processing the aggregate-level outcome into long format data as shown in Table 7.1 (named `PNAD_long` in this example), the function runs as follows:

```
#VARIABLE SET-UP
id<-PNAD_long$id              # mother ID
scen<-PNAD_long$scen          # sequence number
outcome<-PNAD_long$outcome # binary outcome: live/stillborn
num<-PNAD_long$num            # birth order number
prev<-PNAD_long$prev          # number of previous stillbirths

# Dummy variables for categorising num: birth order number
PNAD_long$num2 <-1*(PNAD_long$num==2)
PNAD_long$num3 <-1*(PNAD_long$num==3)
PNAD_long$num4plus <-1*(PNAD_long$num>=4)
# Dummy variables for categorising prev: number of previous stillbirths
PNAD_long$prev1 <-1*(PNAD_long$prev==1)
PNAD_long$prev2plus <-1*(PNAD_long$prev%in%c(2,3,4,5,6))

#number of birth order sequences for each woman
totscen <- tapply(PNAD_long$scen,PNAD_long$id,max)
#first and last row ID numbers for each woman.
ind_min <- tapply(1:dim(PNAD_long)[1],PNAD_long$id,min)
ind_max <- tapply(1:dim(PNAD_long)[1],PNAD_long$id,max)
```

```
#LIKELIHOOD FUNCTION
likelihood<-function(x,data,totscen,ind_min,ind_max){
#model specification
alpha<-x[1]  #intercept
alpha1<-x[2] #num2
alpha2<-x[3] #num3
alpha3<-x[4] #num4plus
alpha4<-x[5] #prev1
alpha5<-x[6] #prev2plus
linpred<-alpha+alpha1*data$num2+alpha2*data$num3+alpha3*data$num4plus+
alpha4*data$prev1+alpha5*data$prev2plus

#general formula
p <- exp(linpred)/(1+exp(linpred)) # stillbirth probility, given
# the predictor values
obslik <- (p^data$outcome)*(1-p)^(1-data$outcome) #likelihood of outcome
scenlik <- sapply(1:length(totscen), function(u) tapply(
obslik[ind_min[u]:ind_max[u]], data$scen[ind_min[u]:ind_max[u]], prod)
) #likelihood of sequence
indlik <- sapply(scenlik,sum) #likelihood for mother
lik  <- -sum(log(indlik)) #overall log-liklihood
return(lik)
}
#Optimise likelihood with given set of parameters
fit<-optim(par=c(0,0,0,0,0,0),likelihood,method="BFGS",
control=list(REPORT=1,  trace=1,  fnscale=1000, maxit=100),
data=PNAD_long_CombF, totscen=totscen, ind_min=ind_min,
ind_max=ind_max,hessian=TRUE)
```