Screening heroin smokers attending community drug clinics for change in lung function: A cohort study

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Short title

Lung function decline in inhaled drug users

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Design: RN,KM, TB, SMG, SR, JR, HB
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Abstract

Background: Heroin smokers have high rates of chronic obstructive pulmonary disease (COPD), respiratory morbidity, hospital admission and mortality. We assessed the natural history of symptoms and lung function in this population over time.

Methods: A cohort of heroin smokers with COPD was followed for 18-24 months. At baseline and follow-up, respiratory symptoms were measured by Medical Research Council Dyspnoea Scale (MRC) and COPD Assessment Tool (CAT), and post-bronchodilator spirometry was performed. Frequency of healthcare-seeking episodes was extracted from routine health records. Parametric, non-parametric and linear regression models were used to analyse the change in symptoms and lung function over time.

Results: Of 372 participants originally recruited, 161 were assessed at follow-up (mean age 51.0 [SD 5.3], 74 [46%] female) and 106 participants completed post bronchodilator spirometry. All participants were current or previous heroin smokers and 122 (75.8%) had smoked crack. Symptoms increased over time (MRC score by 0.48/year (p<0.001) and CAT score by 1.60/year (p<0.001). Forced expiratory volume in 1 second (FEV_1) declined annually by 90ml (SD 190, p<0.001). This deterioration was not associated with change in tobacco or heroin smoking status or use of inhaled medications.

Conclusion: Heroin smokers experience a high and increasing burden of chronic respiratory symptoms, and a decline in FEV_1 that exceeds the normal age-related decline observed amongst tobacco smokers with COPD and healthy non-smokers. Targeted COPD diagnostic and treatment services hosted within opiate substitution services could benefit this vulnerable, relatively inaccessible, and underserved group of people

Words 242/250

1 Introduction

Illicit drug use is common, with 8.5% of adults in England and Wales having reported taking an illicit drug in 2016/2017 [1]. Over the last thirty years smoking rather than injecting heroin has become more common [2-6]. In recent years smoking heroin rather than injecting has been used as a possible method of harm reduction[7, 8] .

Although the effects of illicit drug use are well documented, there is limited evidence about the chronic effects of inhaled illicit drug use on the respiratory system. Multiple case reports highlight acute asthma attacks in heroin users, and observational studies report a high prevalence of respiratory disease in heroin users admitted to acute hospitals [9, 10]. Severe early onset emphysema associated with premature mortality has been reported among heroin users [11-13]. However large-scale diagnostic studies in this hard-to-reach population are lacking. Chronic respiratory symptoms are common in those inhaling heroin, yet access to formal diagnosis including lung function measurement is limited [14-16].

We recently reported post bronchodilator spirometry in 703 heroin smokers attending for opiate substitution therapy (OST) at community drug service clinics in Liverpool; 50% of heroin smokers had either COPD or COPD-asthma overlap (ACO) despite a mean age of 47 years [17]. This was associated with extensive respiratory symptoms, which given the known high rates of COPD hospitalisation and a continuing trend towards inhalation as the mode of drug use is likely to put increased burden on health systems [4, 6, 18]. In light of this, screening and treatment programmes for heroin smokers could be a viable method for identifying and treating disease in this relatively inaccessible patient group [19].

We performed a longitudinal cohort study of heroin smokers attending community drug services and who were recruited as an original cohort of 703 heroin smokers described in terms of baseline characteristics in our previous paper [17]. The aim was to ascertain their change in health status, respiratory symptoms and lung function over an 18-24 month period.

Methods

Setting

The study was performed in 31 community drug service clinics in Liverpool, UK. Clinics are run by Addaction, a large independent charity commissioned by the local city council public health department. A keyworker who knew the client and who coordinated their OST worked with the study team in each clinic.

Participants

Participants were invited to take part if they had previously completed spirometry in the baseline screening project that took place between December 2015 and June 2016[17], were over the age of 18 years, and were still fully enrolled in Addaction's service. All participants were current or previous smokers of heroin and were currently or recently treated with methadone or buprenorphine. Participants were given the study information prior to being booked for their regular appointment and were offered a study visit at their usual clinic. Those missing their usual appointment were offered another at a central venue. Written informed consent was obtained from all participants.

Variables and Data Source

Baseline data collection has been previously described [17]. In brief, participants completed a questionnaire detailing demographic data, and self-reported tobacco and illicit drug use. Oxygen saturations were measured, and pre-and post-bronchodilator spirometry was completed.

At follow up participants completed a questionnaire which evaluated self-reporting medication prescriptions, health care access, and ongoing tobacco and illicit drug use. The index of multiple deprivation (IMD), which is an official geographic measure of relative deprivation in England was used a proxy of social-economic status [20]. Participants also completed the COPD assessment tool (CAT) [21] and the Medical Research Council (MRC) dyspnoea scale [22], and consented to allow review of 2 years of medical records for respiratory related diagnosis and prescriptions from primary care pharmacy records (EMIS), and hospital records where applicable.

1 Oxygen saturations were measured, and pre-and post-bronchodilator spirometry was

2 performed on all participants who consented and did not have medical contraindications.

3 Spirometry was performed by trained clinical staff and completed according to American

4 Thoracic Society (ATS) guidelines [23]. All traces were double-reviewed for quality and

5 grading by an experienced respiratory physician. As with the baseline survey, participants

6 were asked not to take a short acting bronchodilator within 8 hours of visit or a long-acting

7 bronchodilator within 24 hours. If they had taken a short acting inhaler, only post

8 bronchodilator spirometry was recorded.

9 Subjects were categorised based on original screening. A diagnosis of asthma was given if

10 airflow obstruction (Forced Vital Capacity /Forced Vital Capacity (FEV_1/FVC) ratio <0.7) was

11 fully reversible to inhaled salbutamol i.e. either FEV_1/FVC normalised or FEV_1 increased by ≥

12 400ml, or if spirometry was normal but the participant had a prior physician diagnosis of

13 asthma. Those with non-reversible airflow obstruction were characterised as COPD unless

14 they had a prior physician diagnosis of asthma, in which case their condition was labelled

15 asthma-COPD overlap (ACO). We report the lung function change of those participants who

16 had been diagnosed with COPD or ACO at baseline, those with an asthma diagnosis were

17 excluded [17].

18 All spirometry data was reported using the European Community for Steel and Coal

19 reference ranges for consistency with prior work [24]. Abnormal spirometry was defined

20 using Global Initiative for Chronic Obstructive Lung Disease (GOLD) [25]. Change in lung

21 function was based on post-bronchodilator FEV_1.

22 Sample Size

23 We aimed to follow up as many of the participants with COPD or ACO from baseline as

24 possible.

25 Statistical analysis

26 Univariate analysis was carried out using descriptive statistics to explore the characteristics

27 of the study populations. Paired t-tests and Wilcoxon sign rank tests (with bootstrapping to

28 estimate the confidence interval of the difference) were used to assess change between the

29 two time points. Time was used as a continuous variable to account for variation between

30 follow ups dates and to calculate an annualised change). A linear regression model was used

1   to estimate the effect of potential factors (change in inhaled illicit drug use, change in

2   tobacco smoking, change in inhaler use) on changes in FEV_1 over time. Data were analysed

3   using Stata version 14.2 statistical software and R version 3.4. Statistical significance was

4   tested at the conventional 5% level.

5   Ethics

6   Ethical approval was gained from Health Research Authority (HRA) via the integrated

7   Research Application System (IRAS) number: 235151

8

Results

A total of 372 participants had previous COPD or ACO and were eligible for inclusion. The study follow-up took place between December 2017 to April 2018. Baseline questionnaire and clinical data were collected from 161 participants; 109 were lost to follow up, 49 did not attend the follow up appointment, 26 declined at the appointment, 23 were medically unfit and 4 did not take part for other reasons. 106 completed post-bronchodilator spirometry at both baseline and follow-up to ATS standards. Those remaining (n=55) did not meet ATS standards (22), were medical unfit (3), died (1) or declined post-bronchodilator spirometry (29) (Figure 1). Compression of participants characteristics can be seen in table E1.

The characteristics of the population are given in Table 1. Participants had a mean (SD) age of 51 (5.3) years, and 46 (28.6%) were female. The majority of participants were unemployed with high levels of socioeconomic deprivation (mean IMD score 51.5 is in the lowest quintile for the England). All participants were taking OST with 76 (47.2%) reporting current heroin use.

The majority were both prescribed an inhaler and were collecting prescriptions (defined as at least 50% pick up rate), from a pharmacy 131 (81.4%). No inhalers were prescribed or collected for 21 (13.3%), and data were unavailable for 9 (5.5%). Of those where data were available 129 (84.9%), 88 (57.9%) and 78 (51.3%) collected prescriptions for short-acting beta$_2$-agonist (SABA), long acting anti-muscarinic (LAMA) and an inhaled corticosteroid/long acting beta 2 agonist combination, respectively (Figure 2). Three quarters had attended a primary care practitioner for respiratory complaints within the preceding two years, with 18 (11%) requiring admission to hospital, staying for a mean 11.5 days. Those admitted to hospital were universally treated with bronchodilators, antibiotics and steroids, three participants were offered non-invasive ventilation, two were treated in high-dependency areas and none had level 3 care (invasive ventilation) (Table 2).

The mean FEV_1 was 2.05L (SD 0.96) at follow up compared to 2.23 (SD 0.97) at baseline. Of those diagnosed with COPD/ACO at baseline and post-bronchodilator spirometry at both time points, 94 (88.7%) had spirometry indicative of COPD at follow up , with 38 (35.9%) having severe or very severe COPD (using GOLD guidelines) at follow-up compared to 26

1   (24.6%) at baseline. A further 5 (4.7%) had full reversibility (over 400 ml) and therefore were

2   diagnosed with asthma and 7 (6.6%) had normal spirometry at follow up (Table 3).

3   Participants reported a significant annualised increase in respiratory symptoms with the

4   MRC and CAT scores increasing by a median of 0.48 (p<0.001) and 1.60 (p<0.001),

5   respectively. They experienced a significant annualised decline in FEV_1 and median oxygen

6   saturation of 90ml (p<0.001) and 0.92% (p<0.001), respectively (table 4). Change in smoking

7   status and inhalers use were pre-hypothesised possible clinical factors that could influence

8   FEV_1 change. Since baseline, 49 (31.2%) participants reported a decrease in heroin smoking,

9   and 73 (46.5%) reporting an unchanged usage (Figure 3). Change in drug use was not

10   associated with change in FEV_1. The final model showing change in drug and tobacco

11   smoking status and inhaler use is presented in Table 5

Discussion

13   In a population of heroin smokers we found a high burden of lung disease. In the previously

14   published baseline data 50% of heroin users had COPD or ACO, with a mean MRC of 3.1 and

15   CAT score of 22.9 [17]. At follow-up participants' respiratory symptoms had worsened

16   significantly from baseline, with annual increases in both CAT score (1.60) and MRC score

17   (0.46), and mean oxygen saturation dropping from 97% to 95% from baseline to follow up.

18   We found that lung function measured by FEV_1 declined by 90ml annually, which was both

19   statistically and clinically significant. The proportion of subjects classified as having severe or

20   very severe disease with this rising from 25% to 36% over the 2-year follow up period.

21   Neither ongoing illicit drug use nor prescriptions of inhaled medication were associated with

22   change in lung function.

23   The symptoms reported in this study are consistent with those of studies in this population,

24   with increased dyspnoea amongst heroin users being the common symptom [12, 13, 27].

25   The decline in health status measured by a CAT score increase of 1.60 annually, is greater

26   than 1 unit change seen in stable COPD patients[26] . The rate of decline in FEV_1 is

27   considerably higher than both the 30ml/year age-related decline seen in non-smokers and

28   in people with tobacco-related COPD (which is reported at 35-79ml per year, of which all

29   but one paper reported an annual decline of 69ml or less) [27, 28]. To date research on lung

30   function in heroin smokers has focused on cross-sectional studies. The results from this

1 longitudinal cohort study support and enhance previous cross-sectional studies that

2 suggested heroin users are at a high risk of COPD and suggests that their decline is worse

3 than that of tobacco smokers. Walker et al found heroin smokers developed early onset

4 emphysema, with a mean age of diagnosis being 41 years, suggesting likely early

5 progression of disease compared to non-heroin smokers [11]. In Amsterdam, Buster et al

6 reported difference in FEV_1 from predicted values, finding that heroin smokers had a FEV_1 of

7 260ml less than predicted FEV_1 [14].

8 The rapid decline in FEV_1 and the increase in respiratory symptoms in this population

9 suggests heroin smoking is a driver of decline in lung function. Similarly, once established

10 this decline appears to continue even in those who stop smoking drugs.

11 Although COPD hospital admissions vary greatly across the UK, those with COPD tend to

12 have high health care usage, particularly in areas of high deprivation [29, 30]. Previous

13 research has also shown that heroin users with respiratory exacerbations are more likely to

14 be readmitted with exacerbations than current / ex-tobacco smokers (OR: 1.00 versus

15 0.22/0.26) [18]. It is also clear that with high levels of health care access observed in this

16 population, it is likely that ongoing trends towards inhaling heroin will further increase the

17 use of, and burden on, the health system [4, 6].

18 Strengths of our study include that we followed up the participants over a 18-24 month

19 period, in a community clinic setting. We have shown that it is feasible to engage this client

20 group in both baseline and follow up spirometry allowing for a diagnosis to be made. The

21 lost to follow up rate is a major limitation of this study, reducing the power of statistical

22 analysis and makes stratification of our results by age or GOLD stage unfeasible. Given a

23 larger group, this information would potentially be helpful for targeting care, and is an area

24 for future investigation. This population smoke a mix of heroin, crack and tobacco,

25 establishing a causal relationship with therefore difficult. The participants in the study were

26 generally from a poor socio-economic background, and there is potential that their living

27 condition environment could contribute to the rate of decline. Without significant

28 heterogeneity of such potentially confounding factors, we have been unable to address this

29 question further. There is also potential for selection bias, with those who regularly attend

30 methadone clinics and have concerns about their respiratory system more likely to

31 participate in the study.

In summary, our findings show the significant respiratory impairment with which heroin smoking is implicated, and a concerning accelerated rate of decline over time. Future studies with larger cohorts, possibly in the context of a targeted public health intervention, are needed to understand if specific sub-groups are especially vulnerable, and how the personal and healthcare costs associated with chronic respiratory illness could be best averted. The study methodology is in support of it being feasible to co-locate respiratory and drug services to one community location. Future studies may benefit from a parallel group of herion users without spirometric abnormalities at baseline to determine their rate decline compared to those with COPD. These results combined with previous studies support the call for enhanced screening for inhaled drug users [19]. A pilot followed by clinical trial would be needed to assess if screening and treatment services would be clinically and cost effective in this population.

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1 Table 1

	n=161
Sex, n female (%)	46 (28.6)
Age in years, mean (SD**)**	51.0 (5.3)
IMD Score	51.5 (12.7)
Occupation	
Unemployed, n (%)	137 (85.1)
Employment, n (%)	24 (14.9)
Housing	
Own home (including rented), n (%)	124 (77.0)
Homeless, n (%)	6 (3.7)
Other, n (%)	31 (19.3)
Cigarette Smoking Status	
Current, n (%)	133 (82.6)
Ex, n (%)	27 (16.8)
Never, n (%)	1 (0.6)
Cigarettes smoked per day/ SD	11 (7.0)
Heroin Smoking Status	
Current, n (%)	76 (47.2)
Ex, n (%)	85 (52.8)
Bags smoked per week*, n (SD)	4.0 (7.0)
Crack smoking	
Current, n (%)	33 (20.5)
Ex, n (%)	89 (55.3)
Never, n (%)	39 (24.2)
Rocks smoked per week, n (SD)	2.18 (1.4)
Cannabis Smoking Status	
Current, n (%)	38 (23.8)
Ex, n (%)	53 (33.1)

Never, n (%)	69 (43.1)
Cannabis joint per week, n (SD)	12 (17.1)
Ever injected Heroin, n (%)	30 (18.5)
Current Methadone dosage, mean mL/day (SD)	45.7 (21.6)
Current buprenorphine dosage, mean mg/day (SD)	10.4 (8.8)

1

2 Table legend

3 Characteristics of those 161 people with baseline COPD or ACO derived from follow up

4 questionnaire data. * a bag is esimated to equate to 0.1g

5

1   Table 2

	n=161
Taking an inhaler regularly	
Yes, n (%)	131 (81.4)
No, n (%)	21 (13.0)
Not known, n (%)	9 (5.6)
Reported GP visits in last 2 years for respiratory conditions	
Yes, n (%)	121 (75.2)
No, n (%)	25 (15.5)
Not known, n (%)	15 (9.3)
Number Primary care visit (GP or Nurse), mean (SD)	8.6 (7.0)
Emergency hospital visits for respiratory conditions	
Yes, n (%)	17 (10.6)
No, n (%)	114 (70.8)
Not known, n (%)	30 (18.6)
Emergency hospital visits of those who did attend, mean (SD)	2.6 (1.9)
Admitted to hospital in last 2 years for respiratory conditions	
Yes, n (%)	17 (10.5)
No, n (%)	121(74.7)
Not known, n (%)	24 (14.8)
Length of hospital stay, mean days (SD)	11.5 (13.0)

2

3   Table legend

4   Healthcare utilisation from 2 years prior to follow up, amongst those who completed follow

5   up questionnaires. Data was gathered from electronic medical records; participants not

6   appearing on these systems are coded as "Not known", but might engage with extra-

7   regional, informal or private healthcare providers.

8

1   Table 3

	Baseline	Follow up
FEV_1, mean L (SD)	2.23 (0.97)	2.05 (0.95)
FEV_1, % predicted (SD)	69.1 (2.6)	64.6 (2.7)
FVC, mean L (SD)	4.07 (1.2)	3.69 (1.1)
FVC, % predicted (SD)	102.7 (23.7)	95.5(23.4)
FEV_1/FVC, ratio (SD)	0.54 (0.13)	0.53 (0.14)
Diagnosis (GOLD)		
ACO, n (%)	4 (3.8)	-
Asthma, n (%)	-	5 (4.7)
Normal, n (%)	-	7 (6.6)
Severity (GOLD)		
Mild, n (%)	37 (34.9)	23 (21.7)
Moderate, n (%)	39 (36.8)	33 (31.1)
Severe, n (%), n (%)	15 (14.2)	24 (22.7)
Very Severe, n (%)	11 (10.4)	14 (13.2)

2

3   Table legend

4   Diagnosis and post-bronchodilator spirometry at baseline and 2-year follow-up of the 106

5   participants diagnosed with COPD or ACO at baseline who completed follow-up

6

1   Table 4

Variable	Baseline	Follow up	Change per year	Bootstrapping /CI	p value
FEV_1 L, mean (SD)	2.23 (97.12)	2.05 (95.60)	-0.09 (0.19)	-0.05- -0.13	<0.001
MRC Score, median (P25-,P75)	3 (2-4)	4 (3-5)	0.46 (0.0-1.0)	0.52 (0.36-0.67)	<0.001
CAT Score, median (P25-P75)	25 (17-31)	29 (23-33)	1.60 (-0.48-4.32)	0.46 (0.29-0.60)	<0.001
SpO_2 (%), median (P25-P75)	97 (96-98)	95 (93-96)	-0.92 (-1.63-0.0)	0.53 (0.38-0.66)	<0.001

2

3   Table legend

4   Annualised change in spirometry and symptoms in the 106 participants diagnosed with

5   COPD or ACO at baseline who completed follow-up . *FEV_1 Force vital capacity in 1 second,*

6   *MRC Medical Research Council Dyspnoea score, CAT COPD Assessment Test, SPO2 Peripheral*

7   *Capillary Oxygen Saturation*

8

1 Table 5

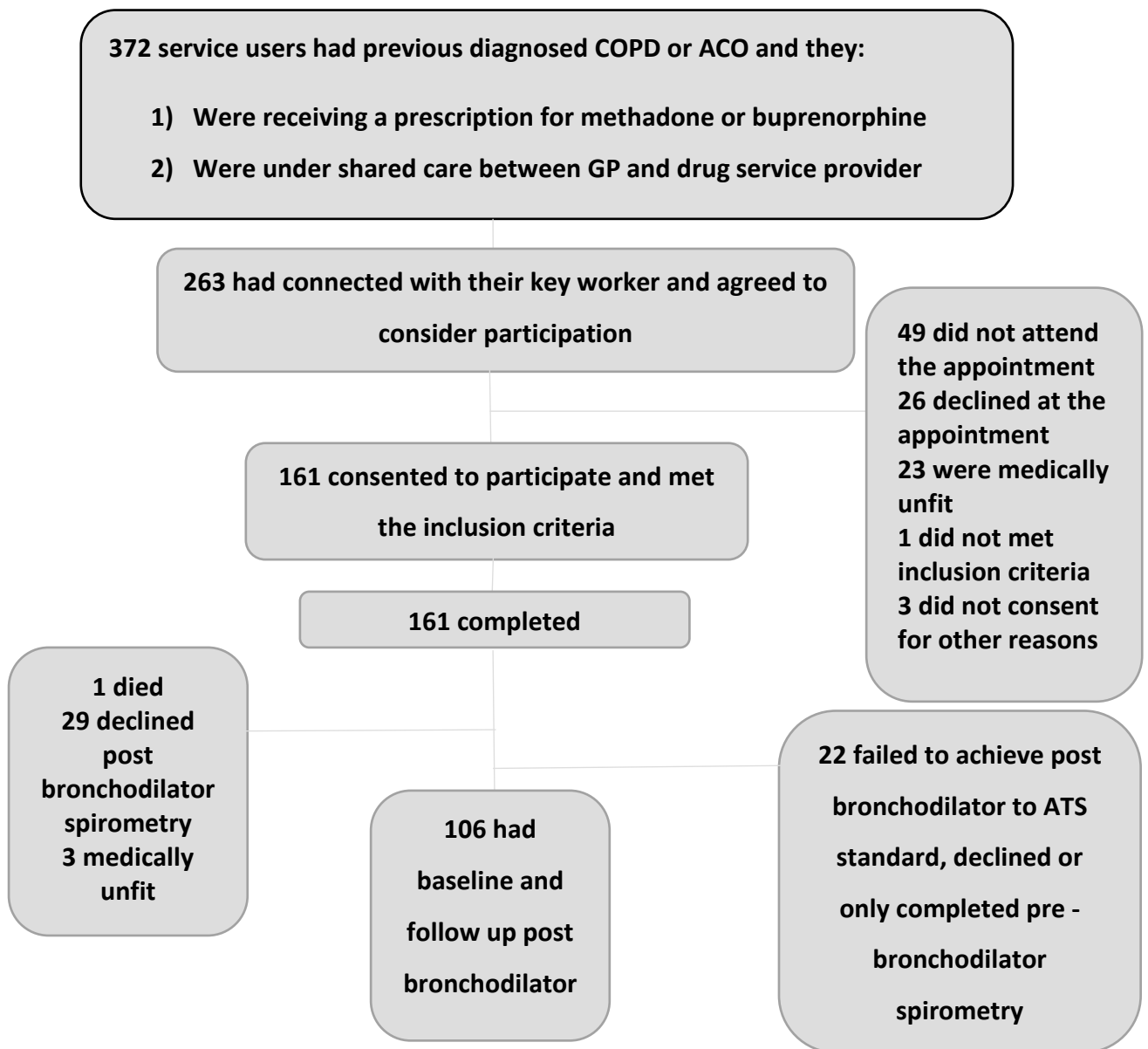|	Coefficient (95% CI) for FEV_1 decrease (ml/year)	p-value (CI)
Change in reported heroin consumption		
No change	Ref	
Increase*	5.92	0.36 (-3.46-15.31)
Decrease†	5.35	0.21 (-6.31-17.03)
Change in reported crack consumption		
No change	Ref	
Increase*	0.18	0.96 (-9.00-7.68)
Decrease†	2.69	0.69 (-10.55-15.94)
Change in tobacco consumption		
No change	Ref	
Increase*	7.81	0.80 (-9.91-7.68)
Decrease†	-1.11	0.34 (-8.51-24.14)
Change in inhaler use		
No change		
Increase*	-3.20	0.48 (-12.12-5.72)
Decrease†	1.79	0.79 (-11.61-15.20)

2

3 Table legend

4 **Linear Regression Model of post bronchodilator FEV_1 change (n=106).** *A positive change is

5 an increase in use since baseline, † A negative change is a decrease in usage since baseline.

6

1   Figure 1

372 service users had previous diagnosed COPD or ACO and they:

1) **Were receiving a prescription for methadone or buprenorphine**

2) **Were under shared care between GP and drug service provider**

263 had connected with their key worker and agreed to consider participation

**49 did not attend the appointment
26 declined at the appointment
23 were medically unfit
1 did not met inclusion criteria
3 did not consent for other reasons**

161 consented to participate and met the inclusion criteria

161 completed

**1 died
29 declined post bronchodilator spirometry
3 medically unfit**

106 had baseline and follow up post bronchodilator

22 failed to achieve post bronchodilator to ATS standard, declined or only completed pre - bronchodilator spirometry
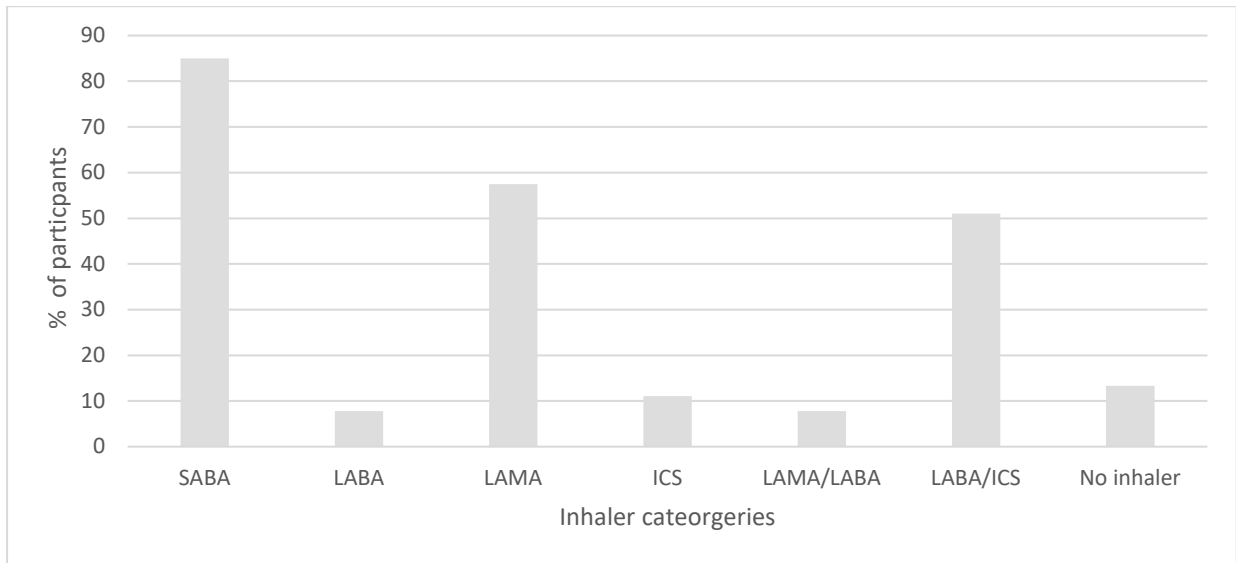
2

3   Figure legend

4   Flow of participants through the study

5

1 Figure 2

2

3 Figure legend

4 Participants prescribed and picking up their inhalers (at least 50% of what was expected as

5 recorded by the pharmacy team) as recorded on the primary care electronic prescribing

6 system. Inhalers reviewed were Short Acting Beta2 Agonist (SABA), Long Acting Beta2

7 Agonist (LABA), Long Acting Anti-Muscarinic (LAMA) and Inhaled Corticosteroid (ICS).

8

1   Figure 3

Participants smoking habits change from baseline
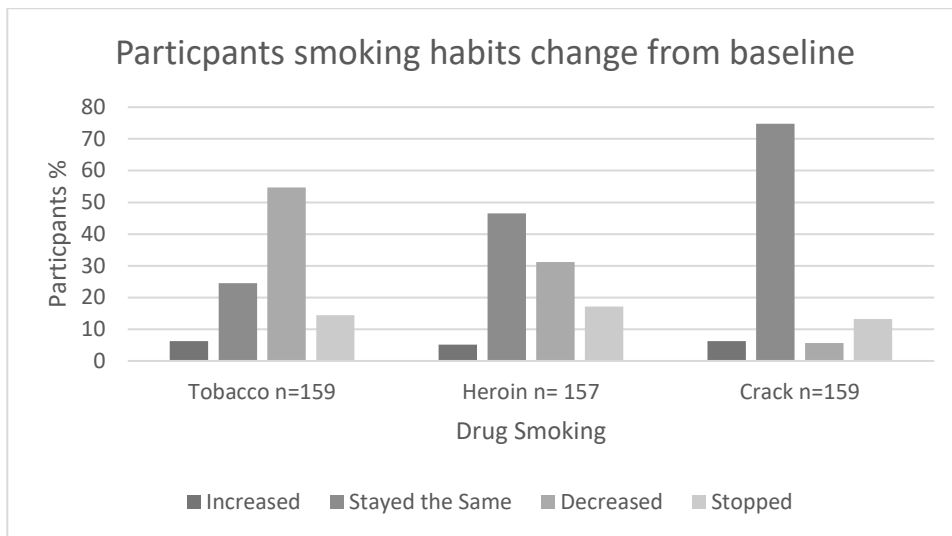
2

3   Figure legend

4   Change in daily consumption of tobacco, heroin and crack in 161 subjects over 2 years. If

5   they have never smoked their smoking status was recorded as "stayed the same".

6