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Title: Mental health problems in children with intellectual disability

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Summary

Intellectual disability ranks in the top ten causes of disease burden globally; and is the top cause among under-fives. About 2-3% of children have an intellectual disability, while about 15% of children experience difficulties consistent with an intellectual disability (global developmental delay, borderline intellectual functioning). The present review discusses the prevalence of mental health problems, interventions to address these, and issues of access. We take a global perspective where possible given the majority of children with intellectual disability live in low and middle-income countries (LMICs). Approximately 40% of children with intellectual disability present with a diagnosable mental health problem, a rate that is at least double that in typically developing children. Most risk factors for poor mental health and barriers to accessing support are not unique to intellectual disability. With proportional universalism as the guiding principle for achieving reduction of mental health suffering at scale, we discuss four directions for addressing the mental health inequalities in intellectual disability.

Key Messages

The rate of mental health problems in children with intellectual disability is at least double that in typically developing children both in high-income countries and in LMICs.

There are substantial gaps in the evidence currently available for effective interventions to address the range of mental health problems in children with an intellectual disability.

Access to treatment and interventions is an issue in high-income countries and in LMICs.

Universal and selective prevention approaches to prevent or reduce mental health problems by reducing exposure to known risk factors should actively include children with intellectual disability.

Intellectual disability could provide an exemplar paradigm in the generation of evidence for interventions that address differential susceptibility to mental health problems in multiply-disadvantaged populations.

A significant first step in increasing access to low-intensity, common psychological therapies is expediting their efficacy and effectiveness testing in intellectual disability.

The exclusion of children with intellectual disability from ongoing intervention testing and a narrow focus on certain groups of children with intellectual disability when not scientifically-justified are research practices that hinder the development of inclusive evidence and evidence that is representative of the complexity in neurodevelopmental disabilities.

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Introduction

Intellectual disability is a term that refers to a heterogeneous group of neurodevelopmental conditions, primarily characterised by significant limitations in cognitive functioning and adaptive behaviour (e.g., daily living skills, social participation, communication skills).[1] Limitations need to be present in the developmental period (typically 0 to 18 years). Cognitive or intellectual functioning has traditionally been measured through IQ tests. An IQ of below 70-75 is recommended for a clinical diagnosis. Currently, clinical diagnosis also requires a score of two or more standard deviations below the population norm on a standardised measure of adaptive skills. The term intellectual disability was formalised circa 2007[2] to replace mental retardation, a term still used in several countries today. Both the term and the classification of the condition have evolved in the past 15 years. The incoming revision of the International Classification of Diseases (ICD-11[3]) renamed 'mental retardation' as disorder of intellectual development, and positions it within neurodevelopmental disorders. ICD-11 recognises that standardised assessments may not be possible in several LMICs, where behavioural indicators could instead identify intellectual disability and describe its severity.[4]

In high-income countries, 2–3% of children have an intellectual disability.[5,6] In LMICs there is some, albeit limited, epidemiological evidence that prevalence might be higher,[7,8,9] largely due to higher incidence resulting from increased exposure to several well-established risk factors for intellectual disability, such as undernutrition, low levels of home stimulation, and infections.[10] In addition to classification by severity level (mild, moderate, severe, profound), cause of intellectual disability often distinguishes cases into genetic (linked to an identified genetic or chromosomal anomaly, e.g., Down Syndrome, Fragile X) and non-genetic (no known genetic cause). Genetic syndromes are more likely in children with severe or profound intellectual disability. Intellectual disability can also be characterised as syndromic and non-syndromic.

Up to the age of 5 years, when standardised assessment is less reliable, children are more likely to be assigned a diagnosis of (global) developmental delay. There are no robust epidemiological data on the prevalence of global developmental delay, though it is considered to affect about 1% to 3% of under-fives in high-income countries.[11] A related condition is Borderline Intellectual Functioning (BIF). People whose cognitive functioning falls one standard deviation below the population mean (i.e., an IQ score of approximately 70 to 85) are at risk of BIF; a condition not included in current diagnostic systems as a separate diagnostic entity but considered a health meta-condition.[12] BIF affects about 11% to 13% of the population in high-income countries.[12] In childhood, these children are mostly thought of as slow learners and BIF is not identified as a separate condition. While BIF is no longer part of intellectual disability diagnostic codes, the profile of mental health needs in this group resembles that of intellectual disability, warranting consideration in the present review.

Comorbid neurodevelopmental disorders in children with intellectual disability

Notwithstanding the difficulties diagnosing additional neurodevelopmental disorders in intellectual disability, especially at the more severe levels, autism and Attention-Deficit Hyperactivity Disorder (ADHD) are highly prevalent in intellectual disability.

Among children with an intellectual disability about 18% are estimated to also have autism, and this is increasing over time due to the increasing identification of autism overall.[13] Autism is significantly more likely in genetic syndromes: 61% in females with Rett syndrome, 54% in Cohen's syndrome, and over 20% in Fragile X, Tuberous Sclerosis, Cornelia de Lange, Angelman's and CHARGE syndromes.[14] Within autism, intellectual disability prevalence is 33%,[15] while BIF is present in 25% of autistic children.[16]

ADHD is present in approximately 39% of children with intellectual disability,[17] while 6·9% of all people with ADHD also have intellectual disability.[18] ADHD is more likely in genetic syndromes associated with intellectual disability (e.g., in over 50% of boys with Fragile X syndrome and 65% of children with Williams syndrome).[19]

The strong genetic links between intellectual disability, ADHD and autism point to shared genetic causes across neurodevelopmental conditions, while the less strong genetic links between these neurodevelopmental disorders and overall mental health problems in intellectual disability suggest that environmental risk accounts for a large part of the variance in mental health problems seen in children with neurodevelopmental conditions.[20]

Social and environment risks and intellectual disability

Social and environmental adversity and factors related to that (e.g., antenatal substance misuse, maternal health and mental health problems, environmental pollution) are well-established causes of (non-genetic) intellectual disability and undoubtedly contribute to many of the inequalities faced by people with intellectual disability in terms of life expectancy and mortality, physical and mental health.[21,22] Similarly to typically developing children, socio-economic adversity in the form of income poverty, material hardship and living in a deprived neighbourhood are risk factors for mental health problems in children with intellectual disability. Maternal mental health problems, harsh/adversarial parenting or inconsistent parenting also contribute to mental health problems in children with intellectual disability.[23,24]

Diagnosing mental health disorders in children with intellectual disability

When considering the prevalence of specific mental health disorders, it is worth bearing in mind that clinical diagnoses in this population represent a challenge compared to typically developing children. Limited communication skills and/or cognitive limitations may render self-report difficult (or perceived to be unreliable). 'Diagnostic over-shadowing' – the attribution of a mental health symptom to the intellectual disability – further hinders the recognition of mental health problems. Co-occurring conditions such as autism may also contribute to diagnostic overshadowing, for example the attribution of social withdrawal to autism rather than underlying depression. Additionally, the phenomenology of mental health symptoms differs in people with more severe intellectual disability, and adapted diagnostic manuals have been developed to assist clinicians (e.g., Diagnostic Manual Intellectual Disability; DM-ID-2[25]). Siegel et al [26] recently published practice guidelines for the assessment of mental health problems in children with intellectual disability.

Prevalence of mental health problems in children with intellectual disability

Approximately 40% of children and adolescents with an intellectual disability present with a mental health problem, either diagnosed or at diagnosable levels. The evidence arising from systematic reviews and meta-analyses in the past 10 years is consistent: 30% to 50% in

Enfield et al.[27] and 38% to 49% in Buckley et al.[17] When compared to typically developing children, levels of mental health problems are always significantly higher in intellectual disability. [27]

The worldwide prevalence of mental health problems in children and adolescents is approximately 13%.[28,29] Recent rates from the US and UK of – *epidemiologically defined* – mental health problems suggested that prevalence might be higher at 16% (i.e., 1 child in every 6). [30] With a prevalence of 40% in intellectual disability, 2 in every 5 children with intellectual disability will present with a mental health problem; the prevalence of mental health problems in children with intellectual disability is ***at least double*** that in the overall child population.

Psychiatric symptoms across neurogenetic syndromes are much higher, ranging between 32% and 74%, with substantial variation seen at syndrome-level (lower rates in Down syndrome, higher rates in Prader Willi).[31] Current meta-analytic evidence reports no association with severity of intellectual disability.[17,27] However, severity is not defined in a consistent manner across studies (some studies used IQ levels, some clinical classifications or other criteria), and emerging evidence suggests there may be a strong association with severity of limitations in adaptive skills (e.g., social skills [31]).

Between 80% and 90% of studies included in systematic reviews of prevalence of mental health problems are from high-income countries. Therefore, the prevalence estimates reported above cannot be generalised to LMICs. In the absence of comparable evidence, the Multiple Cluster Indicators Surveys (MICS) by UNICEF provide a unique opportunity to derive such estimates, including for children at risk of intellectual disability.[8] Figure 1 shows age- and gender-adjusted Prevalence Rate Ratios (APRRs with 95% CI) for emotional problems (parent report of child showing on a daily basis signs of depression or anxiety) in children at risk of intellectual disability across 39 LMICs (286,943 5–17 year-old children). The overall APRR is 3·14 (95% CI: 2·42, 4·08, $p<0.001$), suggesting that emotional problems are two to four times more likely in children with intellectual disability compared to their non-disabled peers.

Therefore, despite the vastly different definitions of intellectual disability and mental health problems between robust meta-analyses from high-income countries and epidemiological estimates from LMICs, there is a convergence in estimates where, again, rates are ***at least double*** compared to children without intellectual disability. However intellectual disability is defined, rates of mental health problems are consistently higher in intellectual disability. Many of the children who will require mental health services will not necessarily be diagnosed as having an intellectual disability, especially in countries where specialist diagnostic services or universal developmental surveillance are not available.

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Emotional disorders

Latest meta-analytic estimates indicate that about 5% of children with intellectual disability present with any anxiety disorder, with rates higher in adolescence (7·9%).[33] For comparison, the worldwide prevalence of any anxiety disorder is 6·5% in childhood. [28] Some reviews in intellectual disability report higher rates (10–17%) of anxiety in intellectual disability, though these tend to include a smaller number of studies. [34] Specific phobias are the most frequent anxiety disorders. In genetic syndromes, anxiety symptoms are higher; half of children with Williams syndrome will present with any anxiety disorder (between 48% and 58%).[31,35] Specific phobias (e.g., noise, blood/injury/injection, animals) and generalised anxiety disorders are the two most prevalent disorders in Williams syndrome with rates of 39% and 10%, respectively.[35] Similarly, 43% of children with 22q11.2 deletion score in the clinical range for anxious/depressed.[31]

Meta-analytic evidence from autism studies suggests that anxiety symptoms tend to be more prevalent among autistic children with an IQ in the BIF range, whereas those with an IQ that places them in the intellectual disability range tend to score significantly lower on anxiety symptoms.[36,37] This is not necessarily the case for specific sub-types of anxiety such as obsessive compulsive disorder or separation anxiety. The question as to whether anxiety is higher or lower among autistic children with and without an intellectual disability is complicated by issues of measurement (i.e., symptoms versus diagnosable disorder), type of anxiety, and method of intellectual disability ascertainment (only IQ scores versus clinical diagnosis).

Depressive disorder (any) is present in approximately 2·8% of children and adolescents with intellectual disability, with dysthymic disorder and major depressive disorder present in 2·8% and 3·4% of children, respectively. [33] For comparison, the worldwide prevalence of depressive disorder is estimated at 2·6% but major depressive disorder is seen in 1·3% of children. [28] There is no robust evidence yet of prevalence increases in adolescents with intellectual disability, but an earlier diagnosis of affective disorder (before puberty) increases the risk for rapid cycling bipolar disorder.[38] Diagnosing depression in this population can be challenging, in particular when communication difficulties and more severe cognitive impairment are present. However, for unipolar depression at least, there is a suggestion that it presents at similar rates in severe intellectual disability (compared to milder levels),[39] with anhedonia and depressed mood the most reliable behavioural indicators of depression in severe intellectual disability.[40] Anxious/depressed symptoms are highly prevalent in Williams syndrome, 22q11.2 deletion, and Prader Willi (41%, 58% and 71%, respectively).[31] Similar to anxiety, there is some, albeit limited, evidence that rates of depressive disorders are lower in autism combined with intellectual disability (or low IQ) compared to autism alone.[41]

Meta-analytic evidence on the prevalence of all other disorders, i.e., other than emotional, is more limited, mostly because primary studies in these areas are very few. Below we review any evidence available from systematic reviews and/or population studies.

Behavioural disorders

Here, we consider both disruptive disorders and challenging behaviours: the latter term refers to behaviours that pose a significant risk to the individual or others. As a term, it is not a diagnostic code, though services do use the term to describe need and plan interventions. Oppositional Defiant Disorder (ODD) is present in approximately 12% of children with intellectual disability [34] (3·6% is the worldwide prevalence for comparison [28]). Symptoms used in the evaluation of ODD in typical development (e.g., often angry and resentful, refuses to comply with requests) are valid on the whole in intellectual disability.[42] Conduct disorder rates (3·6% worldwide prevalence [31]) are present in 5% of children with intellectual disability. [34] When considering diagnosable symptoms rather than disorders, epidemiological evidence from Australia and UK has shown that between a quarter to half of all children with intellectual disability present conduct problems at clinically ‘abnormal’ or ‘borderline and abnormal’ levels.[43,44] Conduct problems are present at similar levels for children with BIF, [43,45] but tend to be much higher (between 58% and 65%) when children with intellectual disability also present with autism.[44]

Self-injurious behaviour, aggression and destructive behaviours occur frequently in intellectual disability. In a study across nine European countries and the US of people with intellectual disability aged 2 to 91 years old, 1122 out of 1335 presented at least one behaviour deemed to be challenging, with head hitting, hitting, pushing, pulling or grabbing others, destroying things and yelling and screaming present in over 30% of cases. [46] Systematic reviews in specific syndromes suggest that aggression is present in 36% of people with Fragile X, self-injury is present in 49% of people with Fragile X syndrome and between 25% and 62% of people with Cornelia de Lange. [47,48] Self-injurious behaviour is likely present at similar levels between children with autism only (42%) compared to both autism and intellectual disability, though hair pulling and self-scratching are more frequent when the child also has an intellectual disability.[49]

Behavioural disorders increase the burden of care for parents and families and are usually the main reason for contact with health care services. Challenging behaviours tend to have a communicative function, i.e, they may substitute for the poorer communication skills in intellectual disability, although their causes are many and varied. They are associated with mental health problems (e.g., depression [40]) though should not be misrepresented as an atypical mental health presentation but their presence should alert to the need for a more detailed mental health investigation. Similarly, challenging behaviours are associated with physical health problems or chronic health conditions (reflux, pain, visual impairment, incontinence [50]), and again, where present, challenging behaviours signal the need for a detailed physical investigation.

Eating Disorders

Meta-analytic data on eating disorders in intellectual disability are not readily available, with a single epidemiological study in the UK indicating a prevalence of 0·2%. [21]

Trauma Disorders

Post-Traumatic Stress Disorder is thought to present in 0·2–2·5% of children with intellectual disability, and symptoms include disruptive/agitated behaviour indicative of fear while repetitive play may indicate re-experiencing or re-enactment. [21,51] The prevalence of developmental trauma or Complex Post-Traumatic Stress Disorder [3] among children with intellectual disability is not known, though adverse childhood experiences are more likely in children with intellectual disability compared to typical development, [21] including physical, sexual and emotional abuse [52] which in turn have been linked to post-traumatic stress in intellectual disability.[53,54]

Psychosis

In a total population study of about half a million children, the prevalence of psychotic disorder in intellectual disability was 4·2% (compared to 1·1% in children without intellectual disability), while among children whose mother had schizophrenia 24·4% of children with intellectual disability also developed psychotic disorder (compared to 6·5% of children without intellectual disability).[55] Among children with early-onset schizophrenia, a large proportion are thought to have neurodevelopmental disabilities, and there is substantial comorbidity between intellectual disability and schizophrenia (across the lifespan[56]), especially with 22q11.2 deletion syndrome where about 30% of those affected will present with schizophrenia.[57] Shared genetic pathways between intellectual disability (and other neurodevelopmental disorders) and schizophrenia[58] support the need to consider intellectual disability in adolescents or children presenting with psychotic symptoms.

Suicide and self-harm

Suicidality is present in approximately 20% of children with intellectual disability[59,60] and the idea that intellectual disability somehow protects from suicidality is being challenged.[59] In a large study of young people with Prader Willi syndrome, suicidal ideation was seen in 7·7% of children while suicide attempts were present in 2·9% of young people (over the age of 13) with Prader Willi.[61] Suicidal talk is present in 20% of autistic children and adolescents with an IQ below 70 and 15% in those with BIF.[62]

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Treatments and interventions for mental health problems in children with intellectual disability

Two treatment approaches for behavioural disorders have an established evidence-base: (1) personalised interventions based on applied behaviour analysis (ABA) and (2) parent training (group parenting programmes based on behaviour analytic and social learning theory principles). The first approach typically involves assessing the reason a specific behaviour is presented (e.g., head banging may serve the function of avoiding or escaping from aversive interactions with carers) and then developing a plan to reduce this behaviour through a combination of options that target changes in what happens in the person's environment before and after the behaviour, with parallel skills development to enable the person to communicate their needs. As an overall approach, these personalised ABA treatments lead to large reductions in overall challenging behaviour and also specific behaviours, such as self-injury or phobias.[65-68] Some of their individual components are also highly effective: using alternative communication,[69] reinforcement and alternative reinforcement,[68,70] and giving people choice[71]. Choice can reduce challenging behaviour by one standard deviation, robustly across settings, tasks, type of choice exercised, age of the person and type of disability.[71]

Group parent training for parents of children with developmental disabilities (including intellectual disability) reduces behaviour problems by about one third of a standard deviation[74] with specific manualised and/or disability-adapted parenting training programmes (e.g., Incredible Years, Stepping Stones Triple P) producing larger reductions in behaviour problems (about half a standard deviation).[72-74] These treatments also lead to changes in parenting skills and parental confidence to manage their children's behavioural disorders.

Psychological therapies, i.e., therapies that may incorporate behavioural components but also extend beyond them or totally based on other components (e.g., cognitive, social, systemic, psychodynamic) have some –albeit limited– evidence that they can be effective with children and young people with intellectual disability, especially when therapy is provided individually.[75] Currently, the evidence extends to Cognitive Behaviour Therapy (CBT) for anger/aggression, and possibly depression although the evidence is drawn mostly from adults with intellectual disability.[75] Some other psychological therapies are feasible and have attracted research interest, but they are not yet evidence-based practice (e.g., Eye Movement Desensitization and Reprocessing for trauma, CBT for trauma; mindfulness for aggression/anger; psychodynamic psychotherapy; animal-assisted therapy).[75-79] The very limited evidence base for psychological therapies for mental health problems with children with intellectual disability (especially those with more severe disabilities [80]) is mostly due to lack of research in this area.

Physical exercise and occupational therapy have received some attention as mental health treatments. Occupational therapy approaches, including multisensory environments, have a very poor evidence base and the evidence is inconclusive. [81,82] Physical activity may bring about some changes in behavioural disorders,[83] but change in specific mental health symptoms (anxiety/depression) does not appear to be significant,[84] unless mental health is defined more broadly as psychosocial health.[85]

For pharmacological treatments, the two most evidence-based areas are (1) methylphenidate for ADHD symptoms [86,87] and (2) atypical antipsychotics or more accurately dopamine antagonists like risperidone and aripiprazole for behavioural disorders.[88-90] Methylphenidate has been associated with large effect sizes for both hyperactivity and inattention across the spectrum of intellectual disability severity, at least in the short-term.[86,87] For behavioural disorders, both risperidone and aripiprazole produce moderate effect sizes compared to placebo, at least in the short-term.[88-90] Both are generally well tolerated though side effects are significant (in particular weight gain and somnolence), and likely more significant in this population than in typically developing children. Aripiprazole may be preferred because it appears to cause less weight gain compared to risperidone.[91] Risperidone and amphetamines have also been studied as treatments for ADHD in intellectual disability and, on the basis of the current lack of robust evidence, are not recommended.[92,93] Other pharmacological treatments (olanzapine; beta-blockers for behavioural disorders; anti-depressants for depression; benzodiazepines for any outcome) have no evidence or are not recommended.[91,94-96] Some agents may even cause paradoxical effects (e.g. benzodiazepines causing disinhibition).

Current effort in evidence building does not appear to prioritise the mental health of children with an intellectual disability: as an illustration, among 197 active studies in intellectual disability registered in clinicaltrials.org, just 14 have mental health or behavioural disorders as their primary outcome (see Table 1). Of these, just 10 are randomised controlled trials (RCTs), including nine pharmacological treatments, and one parent training programme. There are no RCTs of psychological therapies. Single syndromes appear to be favoured currently rather than cross-syndrome or overall intellectual disability research (Table 1).

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The contribution of LMICs in the generation of evidence for intervention is in the minority,. [98,99] Parent training and parent psychoeducation are feasible in LMICs and likely effective for reducing behavioural disorders in children with intellectual disability.[98] Most interventions tested in LMICs are adapted from high-income countries and cultural adaptations are critical to treatment effectiveness, in particular language, cultural specificity of materials and parents' beliefs prior to the therapy.[99] Other types of treatments such as personalised ABA treatments have not been tested in LMICs at all. [98] Most evidence-based approaches reviewed above require significant resources (specialist staff, universal screening systems, specialist diagnostic services, early intervention services) that are not available in several LMICs.[29] In recognition of these competing factors, the World Health Organisation is currently testing an early intervention model appropriate for low resource settings (WHO Caregiver Skills Training for Developmental Disorders or Delays),[100] with initial data indicating acceptability and positive effects on child development, albeit no evidence is yet available for child challenging behaviours (which represent only a small component of the intervention's core content). [101]

Access to treatments and therapies for children with intellectual disabilities and mental health problems.

Access to therapies and treatments is not a problem just for LMICs, it is a problem for most high-income countries as well. Despite the fact many high-income countries have resources and services that align well with the evidence base, there is a large gap between population need and service access. For example, in the UK, the National Health Institute for Excellence (NICE) guidelines for mental health problems and challenging behaviour in intellectual disability advocate for specialist mental health services to address the complex needs of children with intellectual disability and mental health problems; for parent training as the main prevention tool for children at risk of mental health problems; for personalised behavioural treatments as the first line intervention followed by antipsychotic medication if needed. These guidelines align with the evidence currently available. However, UK population representative data have shown that only 1 in 3 children with an intellectual disability and a mental health problem actually access specialist mental health services.[102] This is the case for other high-income countries (e.g., the U.S.[103]), suggesting that the mental health needs of children with intellectual disabilities are not being met even in countries with evidence-based service guidelines. With 0.1 psychiatrists per 100,000 children in LMICs,[29] the level of unmet need will be far higher.

Frequent barriers to service access are the lack or adequacy of specialist services, stigma and perceived stigma, poverty and social exclusion (e.g., low education).[104-106] These barriers are not unique to intellectual disability or LMICs; they are repeated across conditions and countries though in LMICs barriers are likely more pronounced. LMICs experience additional gaps in diagnosis and identification of intellectual disability. Where proposed solutions have as their starting point improvement in diagnosis and identification systems, [e.g.,105] LMICs will always fall behind because of reduced resources. At the same time, a growth in specialist mental health provision is unlikely to resolve the problem because: (a) this approach is simply not possible in many LMICs that do not have the resources, (b) the level of need across the population is such that even high-income countries will struggle with rising costs, [107] and (c) this approach will always stumble on stigma– a major barrier in all countries– and poverty, as many countries do not have universal health insurance systems. The further development of evidence-based interventions for children with an intellectual disability and metal health problems is much needed, but at the moment this effort has stalled even in high-income countries, [cf.80] with evidence of a selection bias that results in excluding those with intellectual disabilities from ongoing research.[108] Even if specialist interventions were available, unless they can reach a big part of the population, they are unlikely to create a sizeable reduction in mental health suffering in this group of children.

Future Directions

The wide difference in levels of mental health problems in children with intellectual disability is unjust and at least partly preventable. Children with intellectual disability and mental health problems are first and foremost children. They will come into contact with primary care and community healthcare providers before any specialist input. The majority of risk factors in this group of children are risk factors for mental health problems in all children. Proportionate universalism [109] (Marmot) should be a guiding principle in the effort to achieve reduction of mental health problems at scale in this population, as well as evidence of mechanisms that sustain the large mental health inequalities seen in intellectual disability (primarily differential exposure to risk, differential susceptibility to that risk and differential access to effective healthcare when ill [110]). [111]

Universal and selective prevention models that do not exclude children with an intellectual disability can address mental health inequalities by equalising exposure to well known risk factors.[111] Evidence across the population has shown that universal and selective prevention models produce small but significant reduction in distress, anxiety symptoms, affective symptoms, conduct problems and externalising problems.[112] Where such approaches are inclusive (or at least they do not actively exclude children with an intellectual disability), there is evidence of equal benefit: for example, we found comparable effect sizes from selective prevention (evidence-based parenting programmes not adapted for disability) on child emotional and behaviour problems in families where the child has a disability compared to others, [113] albeit reduced effectiveness at longer-term follow-up highlights the need for more intense input for this group (i.e., proportionate universalism [109]).

Universal and selective prevention is also effective for enhancing social skills in children with intellectual (and other) disabilities [114] as an additional, and crucial, step in preventing mental health problems. Universal and selective prevention is implementable and feasible in LMICs, avoids reliance on the availability of diagnostic and specialist mental health services, and could reduce the impact of stigma on help-seeking behaviours, by not requiring children to be diagnosed with an intellectual disability before receiving support. [100,101,115]

We need to increase our understanding of differential susceptibility to mental health problems in intellectual disability,[110] and this understanding may also be facilitated by research in other disadvantaged groups, as disability currently appears not to be a priority in research on equitable mental health. [106] On the other hand, the generation of evidence on what works to address differential susceptibility would benefit from a paradigm shift; identifying interventions that effectively enhance the capabilities of children with an intellectual disability – as an exemplar of multiply disadvantaged children – to address the negative effect of risk factors and applying this knowledge to other vulnerable groups of children as well.

Specialist policies, specialist services and specialist training of practitioners might intend to meet the needs of those most in need, but evidence has repeatedly demonstrated that they create access barriers for the majority. Specialist services are still vital of course and should be reserved for the most complex cases.[111] At this level, there are two areas of significant need.

The first is addressing the inequality of establishing the effectiveness of common psychological therapies for common psychological problems such as anxiety or depression.

The dearth of evidence in intellectual disability (see above and Table 1) contrasts with the expanding evidence base in autism research and the established evidence in childhood anxiety research.[116,117] The exclusion of children with intellectual disability from the development of the evidence-base for common psychological therapies is unhelpful and discriminatory. Adaptations needed for making CBT more accessible are known.[118] Efficacy testing needs to be expedited, so that children with intellectual disability can benefit from efforts to increase access to common psychological therapies similarly to other children. Low-intensity therapy provided by non-specialist staff is effective in intellectual disability, and holds promise for LMICs.[98]

The second area of need is integrating complexity in the generation of evidence for specialist interventions and treatments. A significant number of children with intellectual disability will present with more than one neurodevelopmental condition. An increasing number of children are identified with syndromic intellectual disability and have additional physical health problems and high levels of mental health needs. A significant minority presents with severe or profound limitations and complex physical health issues. These children are not able to have their mental health needs met through the existing evidence,[80] leaving specialist services to make decisions on very poor quality evidence or evidence of unknown relevance to this population. Two major stumbling blocks in developing an evidence base for specialist interventions for these children are (1) the application of many exclusion criteria in the generation of evidence and (2) a narrow focus on a very specific sub-population (e.g., one genetic syndrome - see Table 1 for example). A crucial question is whether the decision to exclude children with intellectual disability from general child mental health trials or the decision to test a mental health intervention with only one group of children with intellectual disability and not others are practices justified by the science or are being driven by other factors (e.g., funding preference, publication bias towards high effect sizes). While, in some cases, the exclusion of children with intellectual disability may have a strong scientific basis (for example, evaluating a talking therapy that requires higher-order cognitive functions), there is a question on whether reasonable adjustments could support their inclusion. Likewise, a narrow focus on one genetic neurodevelopmental syndrome may be justified to understand the genotype-phenotype correlation and develop specific molecular targeted treatments. Mental health treatments for specific neurodevelopmental conditions, however, may have broader utility given converging pathways across conditions. Hence, evaluating condition-specific therapies should not preclude studies that test broader utility early on in intervention programmes. At the level of evidence-base development for specialist mental health interventions, funders need to query more closely the study recruitment criteria and be satisfied that exclusion criteria are as scientifically sound as inclusion criteria. There is a drive for more pragmatic trials to generate evidence relevant to multi-morbidity, and also a drive to move away from specific disorders to neurodevelopmental disorder as an overall group (for example, the recent change in Scottish Government guidelines for a neurodevelopmental service). Both these shifts have the potential for a level change in meeting the mental health needs of children with an intellectual disability. There might be scepticism regarding the application of these approaches, but what is clear at the moment is that prevalence of mental health problems in intellectual disability is very high, the available evidence on what works is limited, and it is questionable whether needs are being met.

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Conclusions

Approximately 40% of children with an intellectual disability have a diagnosable mental health problem. The rate of mental health problems in children with intellectual disability is at least double that in typical development and this is the case in both high-income countries and LMICs. Evidence-based treatments are available for ADHD and behavioural disorders. The evidence for interventions for other types of mental health problems and for the effectiveness of common psychological therapies is limited. The level of unmet need in the population is high and likely higher in LMICs. Current efforts to generate evidence are unlikely to meet the mental health needs of these children. It is time to advocate for a paradigm shift, involving a tiered approach where public health services do not exclude children with intellectual disability while the generation of evidence for universal and secondary prevention champions this group as an exemplar for evidence generation for *all* children; low intensity psychological and behavioural therapies become more accessible; and barriers to developing robust evidence for specialist mental health supports are reduced.

Text Panel 1: Search Strategy and Selection Criteria

We searched electronic databases (Medline, PsychInfo, Embase, Web of Science and Cochrane Library) using terms related to the relevant **Population** (learning disab* OR learning difficult* OR learning impair* OR intellectual* disab* OR intellectual* impair* OR borderline intellectual* OR development* disab* OR development* disorder* OR developmental delay OR development* impair* OR intellectual developmental disorder OR mental* deficien* OR mental* retard* OR mental* handicap* OR mental* disab* OR mental* impair* OR mental* challenged OR subaverage intelligence OR subnormal OR cognitive delay OR autis* or ASD or Asperg* or Autism Spectrum Disorders or Down* Syndrome or trisomy 21 or Smith-Magenis or Rett or Lesch-Nyhan or Prader-Willi or Angelman or fragile X or Cri-du-chat or Cornelia de Lange or de Lange or Rubinstein-Taybi) and **Outcome** (mental health or mental disorder or depress* or mood disorder or affective disorder or low affect or flat affect or dysthym* or emotional disord* or anxiety disorder or anx* or phobi* or feeding disorder or post-traumatic or conduct disorder OR challenging behavi* or maladaptive behavi* or aberrant behavi* or aggress* or SIB or stereotyp* or self-injur* or ruminat*), restricting the search to systematic reviews and meta-analyses (as identified in the title), children and young people. Terms were combined using AND, and in Medline MeSH terms were also used. No time restriction was imposed, but we only searched papers published in the English language. The search resulted in 11,627 papers. When duplicates were removed, 10,410 papers were retained for screening. Searches were supplemented by hand searching the reference lists of relevant publications identified by the electronic searches. We prioritised evidence from meta-analyses that included systematic reviews that had applied robust criteria on study selection (population-based studies, clinical diagnosis) where available. Where no evidence from systematic reviews was available, we drew on evidence from population-based studies (for questions regarding prevalence) or randomised controlled trials (for questions regarding intervention effectiveness). We considered any papers relevant to children with an intellectual disability (with or without co-presenting neurodevelopmental conditions [e.g., autism, ADHD]), borderline intellectual functioning or (global) developmental delay. Papers presenting evidence on children with autism or ADHD without intellectual disability or children with broadly-defined developmental disabilities were not considered.

Text Panel 2: Strengths and limitations of the evidence on prevalence of mental health problems in children with intellectual disability

Systematic reviews and meta-analyses considered tended to include primary studies reporting on both clinical diagnoses and standardised measures of mental health symptoms. The relative diversity in the operationalisation of mental health problems in systematic reviews in intellectual disability reflects the well-known difficulties in establishing valid clinical diagnoses in intellectual disability. While clinical diagnoses rates would be more conservative than symptom rates, two points are worth highlighting: (a) clinical diagnoses in primary studies are not always based on intellectual disability-adapted diagnostic criteria, [c.f. 33] and (b) variation in prevalence can be seen at symptom-level too depending on whether the measure was developed specifically for this population or not.[17,63] The evidence on prevalence of overall mental health problems in children with intellectual disability from two separate systematic reviews that screened primary studies on sample representativeness and size is consistent between reviews from separate teams.[27,17] These findings are also in agreement with another recent systematic review that included individuals with intellectual disability aged 12 years and older.[64] The consistency in findings across different teams and inclusion criteria in these reviews lends confidence that notwithstanding variation in primary study quality this is our best current estimate of overall rates of mental health problems in intellectual disability. Two reviews provide meta-analysed overall prevalence estimates.[17,64] Meta-analysed prevalence data are even less available for specific mental health disorders, such as eating disorders, PTSD, CPTSD, psychosis, either because not enough primary studies are available,[e.g., 51] or no systematic review data are available for children with intellectual disability, and this is also the case for behavioural disorders or challenging behaviours in childhood. Available systematic reviews either include primary studies published over 10 years ago [34] or identify significant heterogeneity, questionable external and internal validity as well as sampling biases in primary prevalence studies. [33] Reviews of genetic syndromes tend to operationalise mental health at the level of symptomatology and either focus on one syndrome,[35] one mental health problem[35] or any mental health symptom across syndromes depending on the availability of primary data.[31] Reviews of mental health problem prevalence in autism are more numerous but, within those, intellectual disability, when considered, is defined by IQ level [36,37] while the issues with the validity of measurement are still present. [63] Between 80% and 90% of studies in reviews of mental health problem prevalence in intellectual disability are from Europe and the US, while LMIC participation is very limited. Limitations in the existing evidence on prevalence call for more primary research focused in childhood, including robust population studies on specific mental health disorders and symptoms, validity of diagnostic approaches and standardised measures for children with intellectual disability.

Text Panel 3: Future Directions – Summary recommendations

Universal and selective prevention

The *reduction of mental health problems at scale* among children with intellectual disability requires a shift in focus towards public health approaches.

Universal models for mental health problem prevention should be inclusive of children with intellectual disability: most social risk factors for poor mental health are not unique to intellectual disability.

Selective prevention that targets social skill development among all children with or at risk of disability can have direct and indirect benefits for children with intellectual disability.

To address mental health inequalities in intellectual disability, epidemiological research is needed to *describe mechanisms of differential susceptibility*: evidence from other disabled groups where available could be transferrable to intellectual disability; but to test the effectiveness of selective prevention on vulnerable population groups, intellectual disability should be studied as the exemplar multiply-disadvantaged population.

Universal and selective prevention is *implementable and feasible in LMICs*, and avoids many known barriers to accessing support.

Specialist treatment and interventions

Investment in specialist services and interventions needs to acknowledge *access* will not be easy for most children, either in LMICs or high-income countries.

Common psychological therapies for common mental health problems need to be tested with children with intellectual disability, as they are for other groups of children.

We need to incorporate *complexity in the building of evidence for specialist mental health interventions*. This requires both a narrow focus on describing phenotype in specific sub-groups (e.g., one genetic syndrome) and a more inclusive stance during mental health intervention testing.

Contributors

VT: Conceptualisation, Methodology, Formal Analysis, Writing-original draft, writing-review and editing

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Declaration of Interests

AL received personal speaking and travel honoraria from Flynn Pharma, Takeda and Livanova. All honoraria were not related to the present review. The other authors declared no conflicts of interest.

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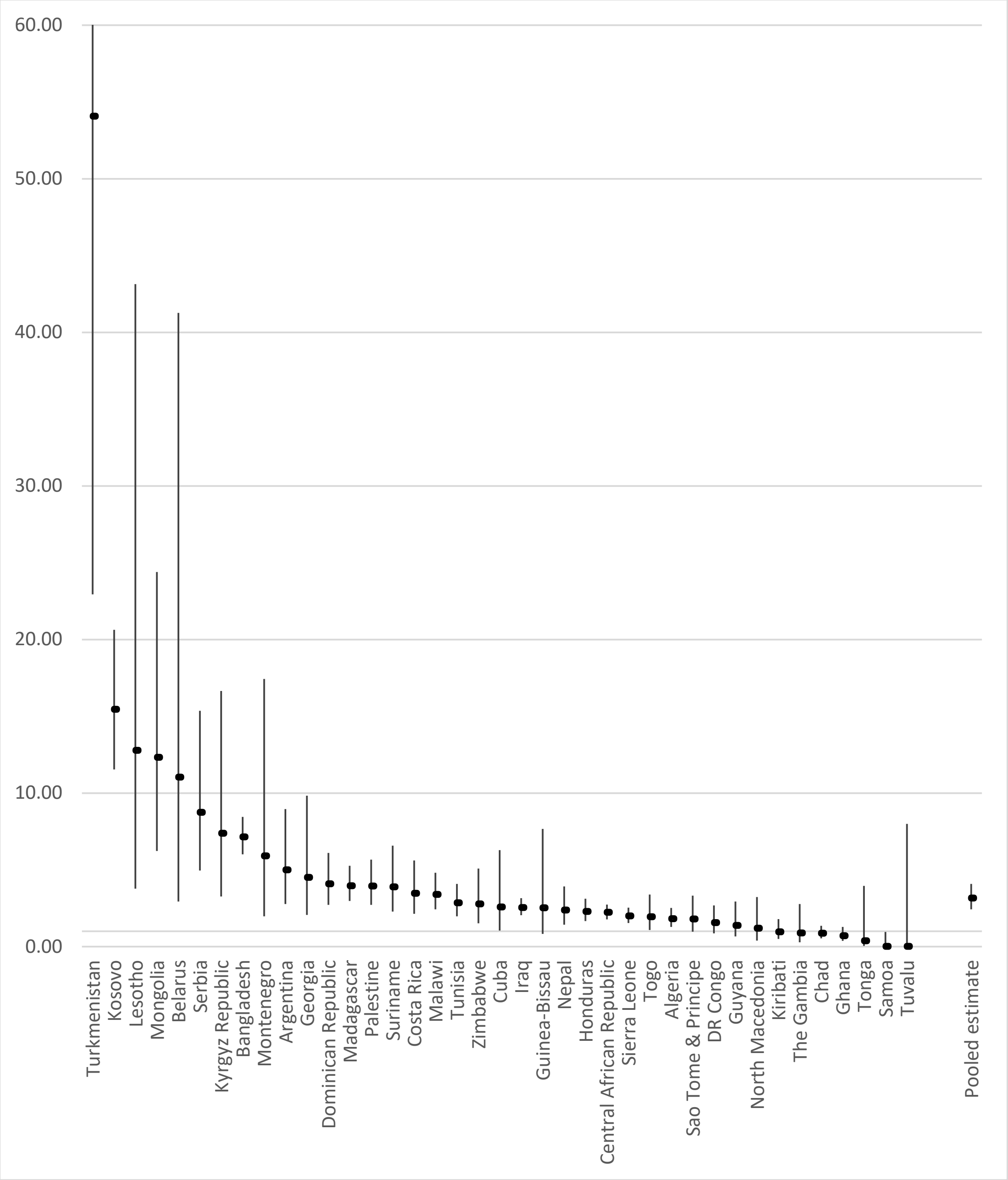

Figure 1 Age and Gender Adjusted Prevalence Rate Ratios (with 95% CI) of emotional problems in children with intellectual disability across 39 low- and middle-income countries. Intellectual disability status and emotional problems were determined by responses to the Washington Group for Disability Statistics' module on functional difficulties.[32] All analyses are weighted using UNICEF calculated sample weights to estimate national prevalence rates with standard errors adjusted to take account of the clustered sampling strategies used. The overall APRR was derived from mixed effects multilevel modelling with random-effects specified to allow both the intercept and slope of the association between intellectual disability and emotional difficulties to vary between countries. Thirty of 39 APRRS were significantly larger than 1. Associations between country wealth (per capita Gross National Income [Atlas Method] and prevalence or APRR were not significant. Data Source: UNICEF MICS Round 6 surveys, 2017-2020, 39 surveys, N=286,943 children aged 5-17

Table 1 Current clinical trials on intellectual disability (data from clinicaltrials.gov search 16.11.2021) with a main focus on child mental health[*]

Trial number	**Study Title**	**Target population**	**Target N**	**Study is RCT**	**Primary outcome**	**Country**
NCT02914951	Cognitive-Behavioral Therapy for Irritability in Children With Autism Spectrum Disorder and Intellectual Disability	ASD+IQ 55-85 (8-16 yrs) and ABC-I[**]≥15	6	No	aggression, irritability	USA
NCT04821856	Evaluation of the Effectiveness of Cannabidiol in Treating Severe Behavioural Problems in Children and Adolescents With Intellectual Disability	Intellectual disability (6-18 yrs) and ABC-I ≥18	140	Yes	irritability	Australia
NCT04529226	Study to Compare Clozapine vs Treatment as Usual in People With Intellectual Disability & Treatment-resistant Psychosis	Intellectual disability (16-40 yrs) and treatment resistant psychosis	114	Yes	schizophrenia	Spain
NCT03086876	Evaluation of Parent Intervention for Challenging Behaviour in Children With Intellectual Disabilities (EPICC-ID)	Moderate-Severe intellectual disability (30 -59 months)	258	Yes	challenging behaviour total score	UK
NCT03862950	A Double-Blind, Placebo-Controlled Trial of Metformin in Individuals With Fragile X Syndrome (FXS)	Fragile X (6-35 yrs) and age equivalent higher than 13 or IQ higher than 85 on the Leiter-III)	120	Yes	challenging behaviour total score	Canada

NCT05120505	Metformin in Children With Fragile X Syndrome	Fragile X (2-16 yrs)	20	Yes	challenging behaviour total score	China
NCT04977986	A Randomized, Double-Blind, Placebo-Controlled Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents With Fragile X Syndrome - RECONNECT	Fragile X (3-18 yrs)	204	Yes	irritability	USA, Australia, Ireland, UK
NCT04526379	Communication in Prader-Willi Syndrome: Study of Emotional Control Related to Behavioral Disorders, Their Daily Repercussions and Examination of an Innovative Therapy: Transcutaneous Electrical Nerve Stimulation of the Vagus Nerve - PRACOM1	Prader Willi (9-12 yrs)	60 (but intervention n:12)	No	emotional control	France
NCT03802799	An Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of ZYN002 Administered as a Transdermal Gel to Children and Adolescents With Fragile X Syndrome - CONNECT-FX Open Label Extension (OLE)	Fragile X (3-18 yrs)	300	No	tolerability, irritability, lethargy	USA Australia New Zealand

NCT04219280	Evaluating Assessment and Medication Treatment of ADHD in Children With Down Syndrome	Down syndrome (6-17 yrs) and ADHD	30	Yes	ADHD symptomatology	USA
NCT03848481	Cannabidivarin (CBDV) vs. Placebo in Children and Adults up to Age 30 With Prader-Willi Syndrome (PWS)	Prader-Willi (5-30 yrs) and ABC-I ≥18	26	Yes	irritability	USA
NCT03649477	Phase 3, Randomized, Double-Blind, Placebo-Controlled, 8-week Clinical Study to Assess the Efficacy, Safety, and Tolerability, of Intranasal Carbetocin (LV-101) in Prader-Willi Syndrome (PWS) With Long Term Follow-Up (CARE-PWS)	Prader-Willi (7-18 yrs)	130	Yes	hyperphagia, obsessive compulsive behaviours	USA Canada
NCT04381897	Use of N-Acetylcysteine (NAC) in the Treatment of Repetitive Behaviors (RB) and Self-Injurious Behaviors (SIB) in Cornelia de Lange Syndrome: A Randomized Double-Blind Placebo-Controlled Pilot Study	Cornelia de Lange (13-35 yrs)	10	Yes	obsessive compulsive symptoms, irritability	USA

[*] *Current* was defined as: not yet recruiting, recruiting, enrolling by invitation, active but not recruiting; The study's primary outcome was mental health or behavioural disorders/symptoms. [**] Aberrant Behavior Checklist-Irritability subscale.[97]