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Why Do We Find it so Hard to Calculate the Burden of Neurodevelopmental Disorders?

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Abstract

Context: Neurodevelopmental Disorders (NDDs) comprise a spectrum of prevalent disorders affecting social, communication, activity, attention, motor coordination and literacy and numeracy skills. NDDs are highly heritable, frequently co-occur, predominantly persist throughout life and are commonly associated with adverse psychological and psychosocial outcomes for both the individual and their family. However, these features of NDDs are rarely acknowledged or considered within research (including burden-of-illness studies) or by healthcare and educational professionals.

Review: We summarise up-to-date UK and USA prevalence information and compare the relative co-occurrence rates both among NDDs and between NDDs and other psychiatric and medical conditions. We then catalogue the known psychosocial outcomes for individuals with NDDs, their parents and siblings and their children, including considering the heritability of NDDs. We also discuss population groups where NDDs are currently under-diagnosed and consider cases where NDDs may be mis-diagnosed.

Conclusions & Recommendations: We offer suggestions to advance our knowledge of the burden of NDDs and shape the future research agenda to develop interventions, management plans and policies to address the burden. This is of vital importance to ensure individuals with NDDs and their families receive the best possible care.

Keywords: Neurodevelopmental disorders; Prevalence; Co-occurrence; Psychosocial outcome; Burden-of-illness

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Introduction

Neurodevelopmental Disorders (NDDs) comprise a spectrum of disorders that include Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), Developmental Coordination Disorder (DCD, also called Dyspraxia), Developmental Language Disorder (DLD, also called Dysphasia and previously called Specific Language Impairment), Dyscalculia (also called Mathematical or Arithmetic Disability), Dyslexia (also called Reading Disability), Intellectual Disability (ID, also called cognitive disability, previously called mental retardation) and Tic Disorders (including Tourette Syndrome and chronic tic disorder). Some definitions of NDDs also include Foetal Alcohol Syndrome, although we have not included it.

The prevalence of NDDs varies globally; however, the burden associated with NDDs is considerable, yet arguably underestimated. This paper provides a comprehensive review of the literature on NDDs, including the scale of the effect, and posits that both missing diagnoses and mis-diagnosis as well as the general 'messiness' of NDDs considerably limits our understanding of this spectrum of disorders. We offer three recommendations to advance our knowledge of the burden of NDDs and shape the future research agenda to develop interventions, management plans and policies to address this burden.

Prevalence

The exact prevalence rates of NDDs vary considerably between

countries and are generally higher in the United States of America (USA) than in the United Kingdom (UK) **(Table 1)**. Although it was historically considered that children 'grew out of' most NDDs excepting ASD and ID, there is now good evidence that the impact of NDDs is lifelong for many individuals. In ASD, it has controversially been claimed that 'optimal outcome' (i.e. no or sub-clinical ASD symptoms) may occur in 3-20% of individuals, dependent on symptom severity, age of diagnosis and age of treatment [1]. In any case, most if not all individuals will have persisting challenges to a greater or lesser degree throughout life. The majority of studies indicate ADHD also predominantly persists into late adolescence and adulthood, with persistence occurring in between 50% and 80% of cases [2-7]. However, a few studies indicate much lower persistence of childhood ADHD and an independent cohort of young adult-onset ADHD [8,9]. Approximately 70% of children with DCD continue to exhibit significant motor difficulties through adolescence and into adulthood [10] and around 73% of 5-year-old children with language impairments continue to have these impairments when aged 18-20 years [11]. Dyslexia and Dyscalculia show similarly high rates of persistence. Jacobson found that among Dyslexic children aged 8-9 years, 83% failed to achieve reading standards expected for their age and experience at age 15-16 years despite the majority of these pupils receiving remedial instruction [12]. Additionally, 85% of these children had persisting phonological deficits and 60 % had persisting decoding deficits at age 18-19 years [13]. Mussolin et al. found that adults aged 18-50 years who had been diagnosed with Dyscalculia as children were slower and more error-prone when completing a mathematics battery [14]. The persistence of Tic Disorders depends on the diagnosis: Provisional Tic Disorder (formerly Transient Tic Disorder) represents the bulk of childhood cases and is classified as a tic disorder that resolves within a year [15]; however, Chronic Tic Disorder (by definition) and Tourette Syndrome are more

Table 1 Estimated childhood prevalence of NDDs.

NDD	UK		USA	
	Est. childhood prevalence (%)	References	Est. childhood prevalence (%)	References
ASD[a]	0.6-3.5	[203-208]	0.5-2.5	[209-216]
ADHD	0.5-2.2	[207,217-220]	2.0-16.1	[56,175,221-246]
DCD	1.8	[247]	<10.1[b]	[248]
DLD	possibly >0.5, <2.2[c]	[249,250]	7.4	[251]
Dyscalculia	3.6	[252]	<5.7-6.4[d]	[253,254]
Dyslexia	2.3-6.2	[252,255,256]	8.3-12.0	[254,257,258]
ID[e]	0.3-0.5 (severe) 2.2-2.5 (mild) 2.7-10.6 (MLD) 0.03 (SLD)	[255,259-261]	1.14-3.6 (all) 0.3-0.4 (severe) 3.7-7.9 (mild)	[259,262-267]
Tic Disorders	6.0 (all) 0.7-3.0 (TS) 1.1 (CTD)	[268-270]	2.7-18.5 (all) 0.3-3.8 (TS)	[239,271-277]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CTD, chronic tic disorder; DCD, developmental coordination disorder; DLD, developmental language disorder; ID, intellectual disability; MLD, moderate learning difficulty; SLD, severe learning difficulty; TS, Tourette's Syndrome; UK, United Kingdom; USA, United States of America.

a. As the prevalence of ASD has increased markedly in the last thirty years, only studies whose data was collected within the last 15 years are included in this estimate.

b. No estimate of the prevalence of DCD using DSM diagnostic criteria has been made for the USA. However, 10.1 % of American children scored <5th centile on the Movement Assessment Battery for Children, a test often used to determine Criterion A of a DSM-IV or -V diagnosis of DCD [248]. In contrast, an estimated 4.2-4.5 of UK children score this [27,247].

c. The prevalence of DLD among UK 3-year-olds is estimated to be 0.5-0.7% but excluded children of normal intelligence [250]. Lindsay and Strand found that 2.2% of all students aged 5-16 in English schools had Speech, Language or Communication Needs at School Action Plus or above, indicating special educational needs requiring external services [249]. This figure includes children with speech, language and/or communication difficulties other than DLD but excludes children who only require within-school support, children whose parents refuse to have them assessed for special educational needs, children who are electively home-educated, etc. Thus, it is hard to tell if this is an over- or underestimate.

d. No estimate of the prevalence of Dyscalculia has been made for the USA. However, Badian (1983) found 6.4% of American children in Grades 1-8 scored <20th centile on the Stanford Achievement Test (SAT) Mathematics Computation Subtest and later [254] found the prevalence of this score was 5.7%. No control was made for IQ, so this figure includes children with general learning disorders as well as those with a specific mathematics learning disorder (i.e. Dyscalculia). Thus, it is an overestimate.

e. Prevalence rate estimates of ID depend greatly on diagnostic criteria. In this table, we list the prevalence of severe (IQ < 50), mild (IQ 50-70) and all ID (IQ ≤ 70). Prevalence rates for all ID are frequently estimated to be lower than would be expected by combining prevalence estimates for severe ID and mild ID as mild ID is frequently under-counted in overall estimates. Within the UK, there are few ID prevalence rate estimates using IQ cut-offs. However, there are prevalence rates for moderate and severe learning difficulties (MLD and SLD) – somewhat vague descriptions used to assess special educational need.

persistent. For example, in between 50% and 90% of individuals with Tourette Syndrome at least some tic symptoms persist into adulthood [16-18].

Co-occurrence

The impact of NDDs on the individual is not only lifelong but also dependent on the degree of co-occurrence. Relatively few individuals exhibit a single 'pure' disorder and many exhibits more than two co-occurring disorders (**Table 2**). Even among those with a 'pure' NDD, subclinical co-occurrence is common, for example autism symptoms in children with ADHD [19] or with DLD [20,21]. Indeed, it has been argued that the term 'comorbidity' is of questionable value in the context of NDDs [22]. This is certainly the case for Tourette Syndrome, where 88 % of individuals have at least one co-occurring condition [23], and ASD, where 70% of individuals have at least one co-occurring NDD or psychiatric disorder [24]. The specific pattern and degree of co-occurrence among NDDs has clinical relevance: for example, co-occurrence has a relationship with severity of symptoms and is, unsurprisingly, associated with poorer outcomes as there are complex cumulative and interactional impacts between NDDs [19,25-27].

In Sweden, the reality of overlapping symptoms and multiple disorders has been recognised by the terms MBD (Minimal Brain Dysfunction, covering a spectrum of deficits, including attention, learning and/or motor deficits, despite normal intelligence) [28], DAMP (Deficits in Attention, Motor Control and Perception, broadly correlating to ADHD plus DCD) [29] and, more recently, ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, describing symptoms observed in very early childhood that may resolve into ≥ 1 NDDs) [30]. Recognition of the NDD profile has led to clinical pathways and research teams working in a multi-disciplinary manner. Examples of this include a multi-professional, multi-agency referral pathway model in Swansea, UK [31] and the Province of Ontario Neurodevelopmental Disorders (POND) Network in Canada, which has brought together a multi-disciplinary team to research NDDs as a whole [32]. In the United States, similar

Table 2 Estimated co-occurrence of NDDs.

		Proportion with secondary diagnosis of… (%)							
		ASD	ADHD	DCD	DLD	Dyscalculia	Dyslexia	ID[a]	Tic Disorders
Primary diagnosis	ASD		3-78[b]	25-85[c]	21[d]	NE	14[e]	15-51[f]	8-60[g]
	ADHD	6[h]		18-53[i]	24[j]	7-18[k]	18-45[l]	11-24[m]	9-33[n]
	DCD	6[o]	19-53[p]		≥45[q]	31-51[r]	24-56[s]	NA[t]	≤34[u]
	DLD	4-8[v]	18-61[w]	30-71[x]		62[y]	48-87[z]	≤27[aa]	NE
	Dyscalculia	NE	39[ab]	25-44[ac]	NE		26-48[ad]	NE[ae]	NE
	Dyslexia	NE	18-50[af]	16-53[ag]	NE	39-48[ah]		NE[ae]	8[ai]
	ID[a]	10-28[aj]	18-55[ak]	NA[t]	54-79[al]	5[am]	14-17[an]		NE
	Tic Disorders	3-22[ao]	26-82[ap]	13-24[aq]	18[ar]	22-23[as]	22-36[at]	3[au]	

NA, not applicable; NE, no estimates available.

a. Note that most of the available co-occurrence data regarding ID and other NDDs is from individuals with mild ID (IQ 50-70).
b. [24,180,278-287].
c. [288-292].
d. [293].
e. [35].
f. [210-212,214,267,294-297].
g. [35,298,299].
h. [300].
i. [22,181,289,290,301-306].
j. [307].
k. [308-310].
l. [22,302,308,309,311-313].
m. [302,314-316].
n. [302,306,313].
o. [317].
p. [301,318].
q. [319].
r. [320,321].
s. [27,320].
t. Children with an IQ<70 are specifically excluded from being given a diagnosis of DCD [15,151].
u. [26].
v. [20,322].
w. [280,323-325].
x. [185,290,323,326-332].
y. [322].
z. [322,333-335].
aa. [324].
ab. [336].
ac. [290,337].
ad. [336,338-340].
ae. There are no co-occurrence rate estimates for individuals with a primary diagnosis of Dyslexia or Dyscalculia and a secondary diagnosis of ID, likely because when these conditions co-occur the ID is usually diagnosed first and considered the primary diagnosis.
af. [22,311-313].
ag. [22,290,341].
ah. [338-340].
ai. [313].
aj. [267,342,343].
ak. [342-344].
al. [342,344].
am. [342].
an. [342,343].
ao. [23,345-350].
ap. [23,307,313,345,348-354].
aq. [350,353].
ar. [307].
as. [23,349,355].
at. [23,313,349,350,352,355].
au. [23,349].

arguments about co-occurrence have been made regarding psychiatric disorders, resulting in the Research Domain Criteria (RDoC) project [33]. Although this project is creating a research classification system and not considering diagnostic criteria or pathways, it marks a paradigm shift by considering psychiatric disorders in terms of affected neurobiological and behavioural systems rather than traditional categories or diagnostic criteria.

Accumulation of Adversity

There is increasing evidence that many individuals with NDDs accumulate problems over time in a cascading and cumulative manner. Cairney et al. proposed the 'Environmental Stress Hypothesis' to explain the developmental cascade from childhood DCD to childhood internalising problems to adult clinical depression and anxiety [34]. Other NDDs also show very high rates of co-occurring and/or secondary health problems, particularly psychiatric conditions **(Table 3)**. For example, Hofvander et al. found that 80% of adults with Asperger's disorder and 100% of adults with autism or PDD-NOS had at least one co-occurring DSM-IV Axis I diagnosis [35]. Kirby et al. found that 20% of employed and 33% of unemployed adults with DCD had clinical depression and 79% of employed and 73% of unemployed adults with DCD had borderline or abnormal levels of anxiety [36]. The long-term impact is not always psychological. DCD, for example, has been shown to have an impact on physical health: children who scored ≤ 5th percentile on the Bruininks-Oseretsky Test of Motor Proficiency, and thus had possible DCD, were at greater risk of being overweight or obese [37] and had lower cardiorespiratory fitness [38] than their typically developing peers.

As well as being associated with an accumulation of medical problems over time, NDDs have also been shown to be associated with adverse psychosocial outcomes. ASD is associated with: lower quality of life [39]; poor social and romantic functioning [21,40]; school bullying [41]; physical and sexual abuse [42,43]; inappropriate sexual behaviours [44]; risky driving behaviour [45]; unemployment [21,46-48]; and, among the employed, low earnings [47]. ADHD has been found to be the most powerful predictor of violent offending among imprisoned male offenders [49]. It has also been associated with: lower quality of life [50,51]; poor academic achievement [52,53]; not being in education, employment or training (NEET) [54]; unemployment [55,56]; problem gambling [57,58]; risky sexual behaviour [59,60]; teenage pregnancy [61]; marriage breakdown and divorce [56,62-64]; multiple marriages [64]; violent and non-violent offending [65]; accident and injury [66,67]; suicide [68]; and all-cause mortality [69]. DLD has also been associated with similar difficulties: lower self-esteem [70-72], shyness [72], poor educational achievement [73-76], early parenthood [76], low socio-economic status (SES) of occupation [75,76] and being NEET [74]. DCD has been associated with lower quality of life [77], poorer self-concept [78], social isolation [79], poor academic achievement [80],

Table 3 Other mental and physical health conditions commonly co-occurring with NDDs.

NDD	Other commonly co-occurring condition(s)	
	Mental	Physical
ASD	Anxiety disorders, eating disorders, gender dysphoria, mood disorders, obsessive-compulsive disorder, personality disorders, schizophrenia, substance use disorders [35,281,283,286,356-360]	Allergies, ear infections, epilepsy or seizures, gastrointestinal disorders, hearing impairment, immune disorders, generalised joint hypermobility, metabolic disorders, neurotransmitter disorders, overweight and obesity, sleep disorders [267,361-372]
ADHD	Anxiety disorders, gender dysphoria, mood disorders, obsessive-compulsive disorder, personality disorders, schizophrenia, substance use disorders [302,314,360,373-376]	Allergies, asthma, epilepsy or seizures, gastrointestinal disorders, headaches or migraine, hearing impairment, generalised joint hypermobility, overweight and obesity, vision impairment, sleep disorders [300,362,365,373,377,378]
DCD	Anxiety disorders, mood disorders, personality disorders, substance use disorders [26,36,81,379]	Epilepsy or seizures, generalised joint hypermobility, overweight and obesity, sleep disorders [82,195,362,364,380-383]
DLD	Anxiety disorders, mood disorders, obsessive-compulsive disorder, personality disorders, schizophrenia [384-386]	Epilepsy or seizures [387]
Dyscalculia	Mood disorders, schizophrenia [388-390]	Epilepsy or seizures [196,391]
Dyslexia	Anxiety disorders, mood disorders, schizophrenia [388-390,392,393]	Epilepsy or seizures [196,198]
ID	Anxiety disorders, eating disorders, mood disorders, personality disorders, schizophrenia, substance use disorders [394-402]	Various, depending on aetiology of ID
Tic Disorders	Anxiety disorders, mood disorders, obsessive-compulsive disorder, personality disorders [23,271,307,348-350,403-405]	Allergies, epilepsy or seizures, sleep disorders [23,349,406,407]

lower physical activity levels [81-83], difficulties with learning to drive [84,85], falls [86,87] and potentially accidents, particularly those associated with crossing roads [88]. Little research has been carried out into the psychosocial outcomes of Dyscalculia. However, Dyslexia has been associated with a reduced quality of life [89] and lower self-esteem [90,91] as well as with poor self-concept when co-occurring with attention or speech problems [92]. ID has been associated with: lower quality of life [93]; stigmatisation [94]; school bullying [95]; physical and sexual abuse and neglect [96,97]; risky sexual behaviour [98]; violent and sexual victimisation and offending [99]; and all-cause mortality [100]. Tic Disorders have been associated with poor psychosocial outcome: lower quality of life [101]; stigmatisation [102]; poorer self-concept [103]; social difficulties [104]; school bullying [105,106]; reduced competence at school [107]; poor academic achievement [108,109]; suicide [110]; and premature mortality [111].

Familial Impact

The effects of an NDD 'ripple out', reaching beyond the affected individual. Most research into these 'ripple effects' has been focused on the families and, particularly, the parents of individuals with NDDs. Parents of children with NDDs have high levels of parenting stress [112]. In particular, ASD is associated with lower family and maternal quality of life [113], increased parental depression and anxiety [114] and affiliate stigma [115]. ADHD is associated with similar issues: lower parental quality of life [116], poorer family functioning [117] and higher levels of parental depressive disorders and depressive personality disorders [118]. Even Dyslexia, which is generally considered a comparatively mild NDD, can have 'ripple effects'. Mothers of children with Dyslexia have higher levels of stress and both anxious and depressive symptoms [112,119,120] although family functioning is not impaired by the presence of Dyslexia and being a parent of a child with Dyslexia is not a significant risk factor for a mental health disorder [121]. ID is generally associated with a good family quality of life [122,123] but is associated with affiliate stigma [115] and higher rates of maternal psychiatric disorder [124,125] and maternal poor health [126]. Tic Disorders are associated with lower parental health-related quality of life (particularly for mothers), increased maternal depression and increased paternal anxiety [127].

Although some of the associations between child NDD and parental psychiatric difficulties may be attributable to shared genetics, at least some are likely to be causal. This is suggested by various studies showing dose-responses, for example between child DCD symptom severity and parenting stress [128], or changes in parental symptoms following child treatment, for example improvement in parental quality of life and depressive mood following methylphenidate treatment of children with ADHD [129]. Although the majority of research has focused on the parents of children with NDDs, it is possible that siblings and other relatives are also affected. Evidence from ASD suggests that effects on siblings are positive as well as negative, may be complex and are dependent on and/or modulated by other risk factors such as gender, birth order, family size and parental mental health [130].

The impact of NDDs is likely to extend not only to parents and siblings but also to the affected individual's children. In part, this is because NDDs are highly heritable **(Table 4)**. The little research regarding the children of individuals with NDDs has predominantly focused on ADHD. Independent of parental psychopathology or offspring ADHD, parental ADHD is associated with high levels of family conflict and low levels of family cohesion [131] whilst maternal ADHD is associated with less positive parenting and consistent discipline by mothers, poorer maternal problem solving and less maternal monitoring of children's activities [132]. Over-reactive and inconsistent discipline has also been reported for mothers and fathers with ADHD both in clinical [133-135] and community samples [136,137]. Overall, the literature suggests that although ADHD is highly heritable, its severity and persistence and the prevalence of co-occurring conditions may be moderated by the quality of parenting and the ability of parents to obtain and consistently deliver treatment to their offspring, which themselves may be affected by parental ADHD and co-occurring conditions [138-143]. It is likely that the effects of other NDDs also extend to the individuals' children, given the known associations between NDDs and psychiatric illness **(Table 3)** and between parental psychiatric illness and offspring mental health [144].

Issues with Estimating the Burden of Disease

Having considered the scale of the effect NDDs have on affected individuals, their families, their communities and society as a whole, one can begin to calculate the burden of illness that NDDs represent. However, the literature is affected by several major issues which produce biases whose effects are difficult to predict. Thus, anyone attempting to compare the burden of NDDs, either between disorders, between countries and/or over time quickly ends up comparing not only apples to oranges but to a whole fruit bowl of inconsistency and inaccuracy.

Table 4 Heritability of neurodevelopmental disorders, as determined using twin studies[a].

NDD	Heritability estimate (%)	References
ASD	64-91	[408]
ADHD	70-80	[409]
DCD	approx. 70	[410]
DLD	>50	[411]
Dyscalculia	38-43	[412,413]
Dyslexia	40-75	[413-417]
ID	Various (dependent on aetiology)	NA
Tic disorders	25-37	[418]

NA, not applicable.

a. Although imperfect, twin studies provide a useful estimate of heritability [419].

Inconsistency in terminology

One of the primary issues which dog the field of NDD research, and thus impede the calculation of the burden of NDDs, is inconsistency of language. This is perhaps best illustrated by DCD, which has been known by a huge variety of other monikers – developmental apraxia, 'clumsy child syndrome', motor learning difficulty, perceptuo-motor dysfunction, developmental dyspraxia, sensory integration disorder and DCD [145]. The terms MBD [28], DAMP [29] and ESSENCE [30] also include motor difficulties. Similar issues with terminology have been documented for DLD [146]. As well as inconsistency of language, there are inconsistencies in definition. Again, using DCD as an example – do you exclude individuals diagnosed with ASD [147] or include them [15]? Should you use the Motor Assessment Battery for Children-2 [148]; the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition [149], which measures slightly different constructs; the DCD Questionnaire [150]; or another screening or assessment method? And for these tests do you use a cut-off of ≤ 5th percentile or ≤ 15th percentile [151]? Many studies have used different tools and different cut-offs. Such tools and definitions continue to evolve as we gain greater biological insight into NDDs. However, until standardised definitions, exclusions, diagnostic tools and cut-off points are chosen, validated and consistently used, it will remain exceedingly difficult to compare research findings, particularly across countries and over time.

Transferability

Another major issue affecting our ability to calculate the burden of NDDs is geography. This is a limitation of all health economics studies: they are specific to a given country and its characteristics (income/development level, demographics, structure and funding of healthcare, etc.). However, geography has a particularly strong effect on NDD burden-of-illness studies. Partly, this is due to the marked differences noted in diagnosed prevalence between countries **(Table 1)**, which may themselves be driven by geographic differences in service provision and benefits of a diagnosis (see below). However, NDDs are expensive diseases to manage which have an economic impact on a wide variety of public sectors including education, supported housing and employment, criminal justice and loss of tax revenue due to un- or underemployment. Thus, direct medical costs for NDDs may be lower in countries with a healthcare system based primarily on private healthcare and thus less incentive to pay for early medical interventions to offset long-term costs to the public purse. The USA provides an example of this: its private healthcare system has a history of denying timely, effective treatment to individuals with ASD, resulting in the introduction of state-mandated waiver programmes to enforce private insurance coverage [152]. Subsequently, measurable differences in service use and direct medical costs have been observed between mandate-eligible and ineligible children with ASD [153]. Similar differences in healthcare expenditure are likely to exist between countries with primarily public healthcare, such as the UK, and primarily private healthcare, such as the USA.

Missed diagnoses and mis-diagnoses

To ensure calculations of NDD burden are accurate, robust national estimates of prevalence are required. This requires not only consistent naming of a disorder and use of diagnostic criteria, but also that all individuals requiring support are diagnosed in an accurate and timely manner. However, NDDs are frequently under-diagnosed and this differentially affects various demographic groups. There is increasing recognition that ASD may be under-diagnosed in girls [154,155], in part because the female social landscape may camouflage their ASD [156]. However, ASD diagnoses are also missed or delayed in ethnic minorities [157,158], including Gypsy/Romani and Irish Traveller children [159]; individuals living below the poverty line [157]; and those with co-occurring ADHD [157] and/or with psychiatric conditions [160]. Conversely, co-occurring NDDs are under-diagnosed among individuals with ASD [161]. Under-diagnosis of ADHD occurs in girls [162], children looked after by the state or adopted [163] and the prison population [164] whereas DLD is under-diagnosed in D/deaf individuals [165].

Mis-diagnosis is also an issue. ASD may be incorrectly diagnosed as DLD [166] or as a psychiatric condition, particularly among adolescents and adults [167]. Traumatic brain injury may be mis-diagnosed as ADHD [168]. There is concern that individuals may occasionally feign NDDs, notably Dyslexia [169] and ADHD [170], where there is financial or other gain to be made. It is also suspected that doctors sometimes exaggerate or invent symptoms (so-called 'upcoding') in order to gain support for their patients, for example if an individual has significant impairment and meets some criteria of several NDDs but does not pass the diagnostic thresholds for any individual NDD [171]. The introduction of ASD-specific state-mandated healthcare insurance waivers in the USA and other analogous initiatives elsewhere is likely to only exacerbate this by ensuring that those with ASD, but not necessarily those with other, similarly or more severely disabling conditions, receive support [172]. However, notably when considering burden-of-illness studies, under-diagnosis and mis-diagnosis mean that both the prevalence estimates and service use inventories for NDDs may be inaccurate.

Health professionals' NDD literacy

A final notable issue affecting prevalence estimates of NDDs and thus burden-of-illness calculations is the low level of awareness among healthcare and education professionals and the general public. Without sufficient awareness, many diagnoses will be missed and thus prevalence estimates will be inaccurate. The rising global prevalence of ASD has been attributed in part to rising awareness [173,174]. A similar pattern has been observed for ADHD [175,176]. However, this does not necessarily extend to other NDDs. For example, only 29 % of Canadian, UK and USA family/general physicians and 23 % of teachers are familiar with DCD (Wilson, Neil, Kamps, & Babcock, 2013) whereas even within academic research Dyscalculia plays the poor relation of Dyslexia, which is far more widely recognised [178]. Awareness of NDDs both among professionals and the public is essential to ensure that people with NDDs get the help they need at the time when they need it.

A particular issue is a lack of awareness that NDDs often co-occur. This is true even within academic circles. Certain combinations of NDD are sometimes considered in research, such as ADHD and ASD [179,180] or ADHD and DCD [181,182]. However, studies in general and economic studies in particular rarely consider the co-occurrence of NDDs as a whole and nearly never consider cases where three or more NDDs are present. There is also a disconnect between the literature regarding social, attention and motor difficulties (ASD, ADHD, DCD) and the literature regarding learning difficulties (Dyscalculia, Dyslexia, ID) with very few studies investigating combinations of disorders spanning this divide. ASD research suffers especially in this respect as it has been the habit of researchers to consider associated symptoms such as motor, attention or learning deficits as just 'part of the syndrome' [161] or even a diagnostic feature [183,184] rather than as co-occurring condition(s), an issue potentially driven by the historic exclusion of ADHD and/or DCD diagnoses in the case of ASD using DSM-IV criteria [147]. Within NDD research as a whole, there is often an obsession with identifying cohorts of 'pure' NDDs or restricting cohorts in other respects such as excluding those with low IQ or co-occurring psychiatric conditions. This occurs despite the fact that all evidence points to 'pure' disorders being in the minority **(Table 2)**. For example, a study of Canadian children with ADHD, DCD, Dyslexia, Conduct Disorder, Oppositional Defiant Disorder, anxiety and/or depression found that 52% of these children had two or more disorders and among those with ADHD this figure was 80% [22]. The artificial siloing of NDD research helps no one and means results are not representative of most individuals with NDDs.

Recognising the 'messiness' of NDDs

Ignoring the messy reality of NDDs means cohorts are often exceedingly unrepresentative of the population, rendering research at best limited and at worst flawed and potentially meaningless. Additionally, by failing to recognise the prevalence of co-occurrence ourselves, we make it even less likely that healthcare professionals, education professionals, governments and funding bodies will also recognise this. This has knock-on effects, both for patients and for economic analyses. If family/general practitioners and teachers are unaware of the rates of co-occurrence, they are more likely to consider the patient with multiple NDDs as a hypochondriac or 'difficult'. However, the reality is that NDDs are associated with a dose-response of cumulative adversity: individuals with multiple co-occurring NDDs are in most need of support. Moreover, some combinations of NDDs and/or psychiatric conditions are associated with worse outcomes than others. For example: presence of a co-occurring psychiatric condition is associated with persistence of ADHD and greater functional impairment [2,6]; co-occurrence of DCD and DLD is associated with lower quality of life than DLD alone [185]; and presence of multiple NDDs is associated with increasingly impaired language and academic skills in a dose-responsive manner [186]. By ignoring the issue of co-occurrence in NDDs and ignoring the fact that not all co-occurring combinations of NDDs are equal, we risk leaving the most vulnerable inadequately supported and trapped in an endless cycle of cumulative adversity. This represents not only an ethical problem but also a financial one as individuals accumulate psychiatric conditions, and/or poorer outcomes such as entering the criminal justice system or becoming or remaining unemployed or homeless [26]. A better understanding of the prevalence, service usage and outcome of various combinations of co-occurring NDDs is sorely needed in order to accurately account for the effects of co-occurrence on the cost of illness.

What Must We do to Capture the True Burden of NDDs?

We have catalogued the major issues preventing us from capturing and comparing the true burden of NDDs. Rectifying these represents a significant challenge. However, three key recommendations can be made.

Firstly, the issue of co-occurrence needs to be confronted in order that services be targeted appropriately and the cost of these be accurately assessed. One model for this is ESSENCE [30], which proposes that children aged less than three years presenting with any issues in general development, communication and language, social inter-relatedness, motor coordination, attention, activity, behaviour, mood and/or sleep not be compartmentalised off to 'ASD only', 'ADHD only', etc. centres. Instead, they should initially be assessed in a holistic manner for all ESSENCE symptoms in order to consider the overall impairment of the child and thus provide all necessary services in a timely manner. Subsequently, specialist/targeted (e.g. ASD-specific, ADHD-specific) support can be provided on the basis of need. A similar model is advocated by the POND Network [32]. Given the prevalence of co-occurrence among NDDs **(Table 2)** and the demonstrated importance of early treatment for example for ASD [187] or ADHD [188], these seem eminently sensible suggestions. Indeed, we would take it further and suggest that the ESSENCE/POND model should be followed irrespective of age at initial diagnosis and that, particularly among individuals whose diagnosis was delayed until adulthood, assessment for psychiatric conditions should also be automatically considered.

Secondly, we need to address the issue of under-diagnosis of NDDs in certain sociodemographic groups. This is necessary to generate accurate prevalence estimates on which to base burden-of-illness calculations but also in order to improve equity in service delivery. We do not endorse the wholesale screening of all children. However, there is an argument for the targeted use of routine screening following the ESSENCE/POND model within at-risk populations. These populations include those known to be more likely to have NDDs such as looked-after and adopted children [189], children excluded from school [190] and prison populations [49,191]. It may also be beneficial to target populations with certain medical conditions based on their known co-occurrence with NDDs **(Table 4)**. An example is Rolandic epilepsy (also known as Benign Childhood Epilepsy with Centrotemporal Spikes (BECCTS)), which frequently co-occurs with ADHD [192,193], DLD [194], DCD [195], Dyscalculia [196,197] and Dyslexia [198]. In addition, given the heritable nature of NDDs, screening should be considered where there is a strong family history of NDDs.

However, routine screening and increased professional awareness is only part of the process. We as a society need to ensure that diagnosis is a worthwhile process that results in benefits that outweigh the downsides such as stigma [199] or the fear that a 'label' may become a self-fulfilling prophecy [200]. Unless this is done, individuals and/or their families may opt out of gaining a diagnosis [200] as they fear over-diagnosis, i.e. correct diagnosis that nonetheless does not benefit the individual as it comes with stigma and/or little or no medical or educational assistance [201]. This is a valid fear. For example, among American adolescents and young adults with Asperger's Syndrome, symptom severity is *inversely* associated with risk of victimization [202].

Thirdly, we need to base burden-of-illness studies on all aspects of NDDs not just the direct medical costs paid by public or private healthcare insurance. This is a particular issue with NDDs as many of the costs are borne by other public services such as education, supported housing, training and employment. Other costs of NDDs are also hidden, for example under the costs of co-occurring, potentially secondary, psychiatric conditions **(Table 3)** or the costs of unemployment, homelessness or being in the criminal justice system. There is a clear need for society to invest in early diagnosis and timely provision of appropriate medical and educational services for individuals with NDDs in order to minimise the economic and psychosocial burden of these hidden costs. Until robust burden-of-illness calculations are carried out for NDDs that consider all aspects of economic impact, we cannot conduct comprehensive economic evaluations that accurately reflect the population. Without these, we will be unable to ensure that individuals with NDDs receive the best care possible in a timely manner.

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Conflicts of Interest

MAMC declares she has no potential conflicts of interest to disclose. AK is the parent of an adult with NDDs, the chair of Movement Matters UK, patron of the Dyspraxia Association of New Zealand, Advisor to the Dyspraxia Association in the Republic of Ireland, Medical Advisor to the Dyspraxia Foundation in the UK and is on the Hidden Impairment National Group for the Department for Work and Pensions, UK.

Compliance with Ethical Standards

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