



# The collective burden of childhood dementia: a scoping review

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Childhood dementia is a devastating and under-recognized group of disorders with a high level of unmet need. Typically monogenic in origin, this collective of individual neurodegenerative conditions are defined by a progressive impairment of neurocognitive function, presenting in childhood and adolescence. This scoping review aims to clarify definitions and conceptual boundaries of childhood dementia and quantify the collective disease burden.

A literature review identified conditions that met the case definition. An expert clinical working group reviewed and ratified inclusion. Epidemiological data were extracted from published literature and collective burden modelled. One hundred and seventy genetic childhood dementia disorders were identified. Of these, 25 were analysed separately as treatable conditions. Collectively, currently untreatable childhood dementia was estimated to have an incidence of 34.5 per 100 000 (1 in 2900 births), median life expectancy of 9 years and prevalence of 5.3 per 100 000 persons. The estimated number of premature deaths per year is similar to childhood cancer (0–14 years) and approximately 70% of those deaths will be prior to adulthood. An additional 49.8 per 100 000 births are attributable to treatable conditions that would cause childhood dementia if not diagnosed early and stringently treated. A relational database of the childhood dementia disorders has been created and will be continually updated as new disorders are identified (<https://knowledgebase.childhooddementia.org/>).

We present the first comprehensive overview of monogenic childhood dementia conditions and their collective epidemiology. Unifying these conditions, with consistent language and definitions, reinforces motivation to advance therapeutic development and health service supports for this significantly disadvantaged group of children and their families.

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## Introduction

Childhood dementia is a unifying taxonomy representing a heterogeneous collective of childhood neurodegenerative disorders. Defined as global neurocognitive decline with multiple developmental skill loss following a period of developmental progress,<sup>1</sup> the hallmark of childhood dementia is enduring and progressive loss of previously acquired developmental skills, in contrast to static or transient intellectual loss.<sup>1,2</sup> Moreover, childhood dementia can be distinguished from conditions such as intellectual disability, which reflect relative loss of developmental trajectory without regression.<sup>1</sup>

In contrast to adult-onset dementia, childhood dementia has received little recognition in the medical literature, nor the lay media; in part reflecting the low prevalence of individual constituent disorders and their typical classification on discrete pathological grounds, rather than under a broader superordinate clinical phenotype, a concept that is widely accepted for adult-onset dementia. Indeed, while the literature reveals a great many individual disorders causing dementia in childhood, ‘childhood dementia’ as a disease classification is unrecognized in the World Health Organisation’s (WHO) International Classification of Diseases (ICD), the Diagnostic and Statistical Manual of Mental Disorders (DSM) or any other diagnostic system worldwide. Furthermore, childhood dementia has not been considered in any dementia policies or strategies globally, for example, the WHO’s ‘Global action plan on the public health response to dementia 2017–2025’.<sup>3</sup>

Further impacting recognition is consensus toward inclusion criteria amongst the childhood dementia disorders and the language used to describe them. These disorders have previously been described as ‘progressive childhood encephalopathy’<sup>4,5</sup> and ‘progressive intellectual and neurological deterioration’ (PIND)<sup>2</sup> as well as childhood dementia,<sup>1</sup> albeit using slight variations in their definition. However, none of the terms are ubiquitously employed as standard throughout the medical literature and this inconsistency of both language and definition is hampering efforts to understand the burden of disease, and to advocate for improved care and treatment of this group of patients.

Several studies have attempted to assess the prevalence and impact of childhood dementia. The Australian Childhood Dementia Study was a surveillance study through the Australian Paediatric Surveillance Unit between May 1993 and June 1995, which also included a brief clinician survey of the psychosocial impact. This study included children under 14 years of age with multiple losses of already attained development skills, duration of illness greater than 3 months, skill loss most likely due to CNS dysfunction, evidence of generalized brain dysfunction, a condition not explicable in terms of acute drug toxicity, prolonged ictal confusion or other causes of delirium and skill loss that is progressive, or almost certainly will be, progressive.<sup>1</sup> A similar definition was used by the British Paediatric Surveillance Unit (BPSU) for their monitoring of neurocognitive decline in relation to variant Creutzfeldt-Jakob disease (vCJD), and in this context, the differential diagnosis of PIND was assessed. The term dementia was not used in the PIND study, which includes both acquired and genetic pathologies giving rise to progressive neurological deterioration with onset under 16 years of age.<sup>2</sup> Other studies have examined incidence rates of ‘progressive

childhood encephalopathy’, focusing on children presenting before 15 years of age with signs of progressive CNS disease associated with impairment of cognitive functioning.<sup>4,5</sup>

This is a large, complex and heterogeneous group of disorders and their rarity means that consistently reported data are not always available. This scoping review aims to firstly clarify working definitions and conceptual boundaries of childhood dementia. Second it synthesizes available published data on the epidemiology of the childhood dementia disorders to quantify the collective burden of childhood dementia and identifies gaps in available data.

In high and upper-middle income countries the primary monogenic causes constitute the greatest burden of childhood dementia, with a more predictable incidence than acquired diseases, such as subacute sclerosing panencephalitis (SSPE). Therefore, we hypothesized that although the monogenic childhood dementia disorders are individually rare and ultra-rare in frequency, including an increasing number of novel genetic origin, when considered collectively their incidence is high and associated with an extraordinary, shared burden of disease.

## Literature search and analysis

### Case definition

Here we define the primary monogenic childhood dementia disorders as: progressive neurocognitive decline, presenting before 18 years of age, as characterized by multiple losses of prior attained development skills in the context of generalized (not focally restricted) brain dysfunction, secondary to disease of monogenic aetiology.

Non-progressive causes of intellectual disability (e.g. head injury) and progressive acquired disorders such as uncorrected nutritional deficiencies and infectious encephalitides were excluded from this definition. Additionally, neurocognitive decline as a result of uncontrolled epilepsy (the primary epileptic encephalopathies) were considered distinct from the primary dementias. Conditions for which epilepsy is an adjunct feature, without necessarily impacting the neurodegenerative disease course, were considered appropriate for inclusion. Additionally, while polygenic susceptibility is recognized in relapsing-remitting and primary progressive multiple sclerosis, and other progressive neuroimmune and autoimmune neuroinflammatory conditions (e.g. anti-NMDA receptor encephalitis), these were excluded in the absence of a definitive monogenic aetiology.

Treatable disorders, such as neurometabolic encephalopathies, where episodic crises may result in cumulative cognitive impairment when untreated [e.g. urea cycle disorders and phenylketonuria (PKU)], were included. However, these were subject to independent cohort analysis, recognizing that in most contemporary health settings, early diagnosis and compliance with effective management mitigates progressive decline in such cases.

### Review protocol

A literature review and Human Phenotype Ontology database search was conducted to compile a list of conditions that met the case definition. The searches were conducted between June and October 2021.

The Human Phenotype Ontology (HPO) database ([hpo.jax.org](http://hpo.jax.org)) was used to identify disorders for possible inclusion. Disorders associated with the following HPO terms were compiled: developmental regression, psychomotor deterioration, dementia, progressive psychomotor deterioration, progressive neurologic deterioration, progressive neurodegeneration, mental deterioration, intellectual deterioration, progressive cognitive decline, cognitive decline.

In addition, a PubMed search using the following query was conducted:

[(‘developmental regression’) OR (‘dementia’) OR (‘progressive neurodegeneration’) OR (‘mental deterioration’) OR (‘cognitive decline’)] AND (‘childhood’) AND (‘genetic’). The results were limited to ‘Child: birth-18 years’ and human studies only.

The flow diagram ([Supplementary Fig. 1](#)) describes the process to select childhood dementia disorders for the study. Duplicates were removed and disorders excluded due to onset over the age of 18, non-monogenic aetiology, no or minimal cognitive involvement or non-progressive course, focal brain dysfunction or classified as primary epileptic encephalopathies. Some disorders were excluded because so few cases have been described in the literature that it was not possible to judge whether they complied with the inclusion criteria. For those disorders where inclusion was unclear, an independent expert clinical working group (authors N.J.C.S., M.A.F., J.C. and collaborators R.W., C.E., B.D. and A.I.) was consulted to review and ratify inclusion.

### Burden of disease data extraction

Incidence and life expectancy data were extracted from published literature for the final list of 170 conditions using PubMed and Google Scholar. If more than one source of incidence or life expectancy data was found, preference was given to large cohorts and Australian studies or those with similar ethnic diversity.

Where only a subset of patients with a condition met the eligibility criteria, the proportion of those patients was applied to the identified incidence estimate as detailed in [Supplementary Table 1](#). Where the available information reported a range for either the incidence or life expectancy a simple average was taken.

The characteristics of the childhood dementia disorders were analysed based on accepted pathological classification of disease. Where some conditions fit into the classification of more than one subgroup, allocation was based on the more specific aetiological category. For example, metachromatic leukodystrophy was classified as a ‘lysosomal disorder of lipid metabolism and transport’ instead of the more general category, leukodystrophy, describing conditions that affect the white matter of the brain.

### Data analysis

The incidence data from the literature were used to calculate the collective incidence of childhood dementia per 100 000 births. The numbers of children and persons expected to be living with a childhood dementia condition were estimated from the incidence, life expectancy and birth cohort data. Full methods are available in the [Supplementary material](#).

Life expectancy for all of the childhood dementia disorders collectively was calculated from the life expectancies of each individual condition and weighted by their incidence.

An overall survival curve was derived from the incidence and life expectancy [mean  $\pm$  standard deviation (SD)] of the individual conditions included in the analysis. Where the SD for the life expectancy was not available for a given disorder, it was estimated

to be one-third of the mean (which was approximately the ratio of mean to SD observed in the disorders where both mean and SD were available).

Average ages of onset and diagnosis were calculated from data from the literature. A weighted average was calculated based on the incidence. Mean or median diagnostic delay was tabulated if available from the literature.

## Results

One hundred and seventy genetic disorders or groups of disorders were identified that meet the inclusion criteria for childhood dementia. These disorders are caused by pathogenic variants in at least 200 individual genes, plus an additional multitude of genetic causes of mitochondrial disease (>200 genes).

From the original group of 170 disorders, 76 could not be included in the analysis due to insufficient incidence or life expectancy data ([Supplementary Table 3](#)). Another 25 disorders were analysed separately as treatable conditions ([Supplementary Table 2](#)).

Of note, estimation of mitochondrial disease incidence presented a unique, disease-specific challenge, given their genetic heterogeneity and pleiotropy. Childhood dementia can be a component of at least 12 clinical categories of mitochondrial disease ([Supplementary Table 1](#)) and can be caused by pathogenic variants in more than half of the over 300 genes known to underlie mitochondrial disease.<sup>6–8</sup> Leigh syndrome alone can be caused by pathogenic variants in one of more than 89 different genes (both in the nuclear and mitochondrial genome).<sup>9</sup> Consequently, published data were supplemented with diagnostic frequency and relevant genotype-phenotype data obtained from the Australian Laboratory that has acted as the major national referral laboratory for paediatric mitochondrial disease for several decades (updated from their previous epidemiological study,<sup>10</sup> David Thorburn, 2020, personal communication).

Of the remaining 69 disorders, individual incidences varied from 0.03 per 100 000, as seen in MPS VII (Sly syndrome) and fucosidosis (type I and II) to 7 per 100 000 for the group of mitochondrial disorders ([Supplementary Table 1](#)). Collectively, the incidence is estimated to be 34.5 per 100 000 (1 in 2900 births) ([Table 1](#)). This equates to 107 births in 2021 in Australia, 240 in the UK and 1262 in the USA.

The mean life expectancy was estimated to be 16.3 years with a range from 1 to 52.4 years. This translates to an expected prevalence of 5.3 per 100 000 persons. In 2021 it is estimated that 1394, 3568 and 17 587 persons were living with childhood dementia in Australia, the UK and the USA, respectively. Around two-thirds are predicted to be under the age of 18: 969, 2367 and 12 162 children in Australia, the UK and the USA in 2021, respectively ([Table 2](#)).

Overall survival over time ([Fig. 1](#)) was estimated from the incidence and life expectancy (mean  $\pm$  SD) of the individual conditions included in the analysis. Median survival was 9 years of age, with approximately one-third (29%) of those born with a childhood dementia condition reaching adulthood (18 years of age) and 10% reaching the age of 50 (compared to 99.5% at 18 years and 96.8% at age 50 in a general population).<sup>11</sup>

Based on the incidence of, and survival curves for childhood dementia presented in [Fig. 1](#), it is estimated that 91 Australians, 204 Britons and 1077 Americans (USA) will have died prematurely due to childhood dementia in 2021. The years of life lost (YLL) due to premature mortality and years lived with disability (YLD) for Australia, the USA and the UK are presented in [Table 2](#).

Data on age of onset and diagnosis were available for 52 and 46 disorders accounting for 78% and 71% of births, respectively ([Supplementary Table 4](#)). The mean (weighted for incidence) age

**Table 1** Collective epidemiology of childhood dementia disorders in high and upper-middle income countries

Epidemiological outcome	Incidence per 100 000 births	Life expectancy average (years) <sup>a</sup>	Prevalence per 100 000 population	Prevalence per 100 000 children
All childhood dementia	84.3	55.7	28.7	58.3
Treatable childhood dementia <sup>b</sup>	49.8	83.0	23.4	41.8
Currently non-treatable childhood dementia	34.5	16.3	5.3	16.5

<sup>a</sup>Mean calculated from the life expectancies of each individual condition (Supplementary Tables 1 and 2) and weighted by their incidence. Note that a median life expectancy of 9 years was also calculated using survival curves for the currently non-treatable childhood dementia conditions.

<sup>b</sup>Life expectancy similar to the general population with treatment, assuming early diagnosis and treatment compliance.

**Table 2** Collective impact of currently non-treatable childhood dementia disorders in 2021 in example countries

Epidemiological outcome 2021	Australia	UK	USA
Births	309 996	694 684	3 659 289
Childhood dementia births	107	240	1262
Children living with childhood dementia (<18 years old)	969	2367	12 162
People living with childhood dementia	1394	3568	17 587
Premature deaths due to childhood dementia	91	204	1077
Premature deaths in children due to childhood dementia (<18 years old)	74	166	873
Years of life lost (YLL)	1191	2669	14 059
Years of life lost to disability (YLD)	284	636	3349

Sources of population data are listed in the Supplementary material. Includes 69 conditions with data available, listed in Supplementary Table 1.

of onset is 2.5 years (range 0 to 13.1 years) and age of diagnosis is 4 years (range 0.15 to 35.5 years). Median or mean time to diagnosis was reported for 19 conditions with more than half of these taking two or more years to reach a diagnosis after onset (range 0.13 to 16 years). In three studies the median time to diagnosis was six or more years.

Disorders that were identified as treatable were analysed separately. Treatable disorders are defined as those that are typically diagnosed early enough for successful treatment and average life expectancy does not usually differ from that of the general population in high and upper-middle income countries. This included some large groups of disorders—urea cycle disorders, organic acidurias and amino acidopathies and some individual disorders—biotinidase deficiency, cobalamin c disease, holocarboxylase synthetase deficiency, Wilson disease and chronic infantile neurological cutaneous and articular (CINCA) syndrome. An additional 49.8 per 100 000 births are attributable to these conditions that would cause childhood dementia if not diagnosed early and stringently treated (Supplementary Table 2).

The 69 currently untreatable childhood dementia disorders with incidence data available (Supplementary Table 1) were grouped by aetiopathological classifications and incident data used to calculate the proportion of births in each category (Table 3). The largest group of conditions was those designated ‘diseases not otherwise categorized’, which accounts for 27% of births and includes disparate disorders such as Rett syndrome and juvenile Huntington disease. This was followed by the lysosomal disease and mitochondrial disorder categories, accounting for 22% and 20% of births, respectively.

## Discussion

This paper reconceptualizes the classification of childhood dementia disorders. This group of disorders is notoriously complex with simultaneous neurodegenerative and neurodevelopmental processes at play and considerable variability both within and between

disorders in terms of aetiology, onset and rate of progression. However, these disorders have in common devastating and progressive neurocognitive decline and a severely shortened life expectancy. This scoping review has refined the definition of genetic childhood dementia and lists the major disorders and groups of disorders. In addition, the collective characteristics of childhood dementia are reported in terms of incidence, prevalence, age of onset and diagnosis and life expectancy.

## Definition and classification of the childhood dementia disorders

This review identified 170 disorders caused by pathogenic variants in at least 200 individual genes (plus an additional multitude of genetic causes of mitochondrial disease) as fitting the case definition. Other studies have identified between 28 and 220 disorders causing progressive cognitive decline in childhood, although there are differences in definition and grouping of disorders.<sup>1,2,4,12</sup>

Delineating the boundaries of the childhood dementia disorders was challenging and relied on an experienced panel of clinicians to ratify their inclusion or exclusion. One such challenge was that some of the disorders have a highly variable phenotype and only a subset develop dementia in childhood, for example, cerebrotendinous xanthomatosis, mitochondrial disorders and congenital disorders of glycosylation. For these disorders, the clinicians erred towards inclusion if a significant proportion of the diagnoses would experience childhood dementia, they were marked as variable, and this variability was considered in the data analysis. In addition, some disorders such as Zellweger syndrome are so severe, and have a large impact on neurodevelopment that the neurocognitive decline begins from a low baseline of development. Similarly, these disorders were highlighted as such.

For other disorders, neurocognitive decline is overshadowed by more prominent features, for example the ataxia and immune dysfunction typical of ataxia-telangiectasia. However, recognition of



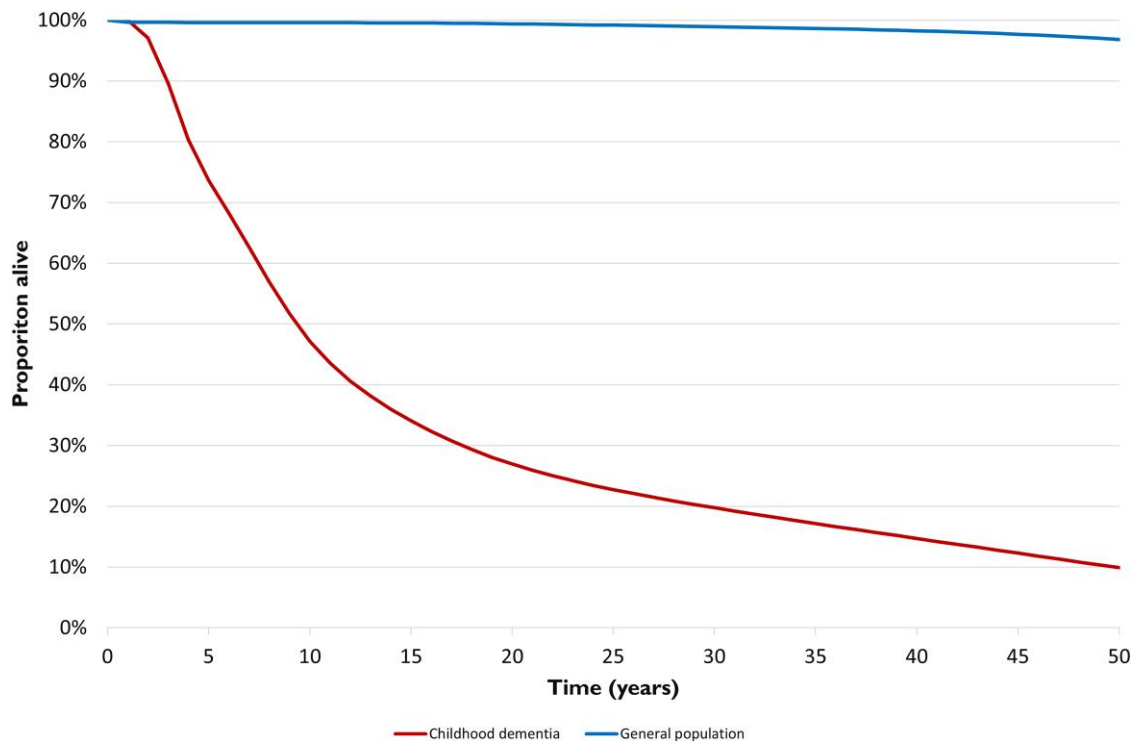


Figure 1 Overall survival of the cohort born with currently untreatable childhood dementia.

Table 3 Functional classifications of currently non-treatable childhood dementia conditions

Aetiopathological classification	% of childhood dementia births
Inborn errors of metabolism (65.6% of births)	
Lysosomal disorders (22.4% of births)	
Lysosomal disorders of lipid metabolism and transport	10.1
Mucopolysaccharidoses	7.3
Glycoproteinosis	1.4
Other lysosomal diseases	3.6
Other disorders of lipid metabolism and transport	0.7
Disorders of amino acid and other organic acid metabolism	6.7
Vitamin-responsive inborn errors of metabolism	4.8
Disorders of mineral absorption and transport	1.0
Peroxisomal disease	9.5
Mitochondrial disorders	20.3
Other inborn errors of metabolism	0.1
Leukodystrophies not otherwise categorized	6.6
Neurodegeneration with brain iron accumulation	0.6
Diseases not otherwise categorised	27.3

Includes 69 conditions with data available, listed in [Supplementary Table 1](#).

the cognitive decline, even if less striking than other childhood dementia disorders, has a significant impact for some children and may enable interventions to improve quality of life.<sup>13</sup> Conversely it is important to recognize that children with dementia have a range of comorbidities depending on the subtype (e.g. bone, joint, gastrointestinal, cardiac, respiratory) that have significant impacts on quality of life, and must not be overlooked. Likewise,

degeneration of neural networks in adult-onset dementia may mediate diverse phenotypes not isolated to neurocognitive decline, including weakness, spasticity, bulbar issues and movement disorders. A continuum has been described with amyotrophic lateral sclerosis and frontotemporal dementia<sup>14</sup> and Parkinson's disease and Lewy body dementia.<sup>15</sup>

The inclusion of Rett syndrome was also controversial as this is largely considered a progressive neurodevelopmental disorder, and not neurodegenerative. It is characterized by rapid developmental regression in girls aged 1 to 4 years followed by a pseudostationary phase into adulthood where the cognitive decline appears to stabilize.<sup>16</sup> Affected adults experience progressive neurological decline, particularly in the motor domain<sup>17</sup> but assessment of cognitive ability is challenging due to profound physical disabilities.<sup>18</sup> Rett syndrome was included in the PIND study<sup>2</sup> and the Australian Childhood Dementia Study<sup>1</sup> but was excluded in studies of progressive childhood encephalopathy in Norway<sup>4</sup> and Sweden.<sup>5</sup>

More disorders will be identified as fitting the criteria for childhood dementia as new evidence emerges. A salient example is infantile-onset Pompe disease (IOPD), a neuromuscular disorder, which if left untreated, causes death in the first year of life due to heart failure. Early treatment with enzyme replacement therapy (ERT) in countries with newborn screening programmes are significantly improving patient survival. However, the ERT is unable to cross the blood-brain barrier and there is increasing evidence of CNS involvement and cognitive decline in these children.<sup>19</sup>

The aetiopathological classification of the disorders allows the identification of overlap of disease pathophysiology, with the possibility that common pathways may be affected, which suggests that in some circumstances single therapeutics could treat multiple clinical conditions. The majority are classified as inborn errors of metabolism (IEMs) (66% of births) with the largest subcategories within this group being lysosomal disorders and mitochondrial

disorders. This is in line with other studies that reported 62.5–75.0% of all PIND cases are caused by IEMs.<sup>12</sup>

This study focused on the primary monogenic causes as they constitute the greatest burden of childhood dementia in high and upper-middle income countries and for the purposes of modelling, they have a more predictable incidence than acquired diseases such as SSPE. It is important to acknowledge that SSPE, caused by the persistence of the measles virus in the CNS, is a significant cause of childhood dementia in countries where immunization rates are low, such as sub-Saharan Africa and Southeast Asia.<sup>20</sup> In high and upper-middle income countries, SSPE is very rare<sup>21</sup>; however, immunization rates are declining leading to an increase in SSPE incidence.<sup>22</sup>

Three broad groups of disorders (urea cycle disorders, organic acidurias and amino acidopathies; at least 21 disorders) and four individual disorders were analysed as an independent cohort (Supplementary Table 2) as they were considered treatable with a life expectancy similar to the general population assuming early diagnosis and enduring treatment compliance.<sup>23–29</sup> As such, in high and upper-middle income countries, these children would generally not have a childhood dementia phenotype. Most of these disorders are included in newborn screening programmes so are detected presymptomatically and can be treated with relatively simple interventions such as dietary restrictions, supplements and widely available medications. However, despite this, there inevitably will be a small proportion of children (<10%) who will die either in the newborn period or later because of an acute metabolic crisis.<sup>30,31</sup> In addition, within this group of treated individuals, response to treatment is variable, and individuals can have a number of symptoms and disease-associated morbidity. These disorders, even phenylketonuria, which has been screened in newborns since the 1960s, can also remain undiagnosed and untreated, including in high and upper-middle income countries due to immigration from countries without newborn screening.<sup>32</sup>

## Incidence and prevalence

Whilst individually rare, the collective incidence of the monogenic causes of childhood dementia included in this study equates to 34.5 per 100 000 (1 in 2900 births). This is higher than the incidence of cystic fibrosis in Australia (1 in 3139 births)<sup>33</sup> and more than three times higher than spinal muscular atrophy (1 in 11 000 births).<sup>34</sup> Surveillance studies with a similar case definition to ours have reported incidence rates between 10 and 60 per 100 000 births.<sup>2,4,5</sup> The incidence of PINDs in the UK was estimated to be ~10 per 100 000 live births and incidence rates of progressive childhood encephalopathy in Norway<sup>4</sup> and Sweden<sup>5</sup> estimated an incidence of 60 and 58 per 100 000 live births, respectively. The Australian Childhood Dementia Study did not report a birth incidence but the cumulative 2-year prevalence of childhood dementia for children under 15 years was 5.6 per 100 000.<sup>1</sup> The disparity in part reflects case definition and methodology of the respective studies.

It is reasonable to assume that the incidence of childhood dementia is comparable in high and upper-middle income countries with similar consanguinity rates,<sup>5</sup> and this paper uses incidence data from a wide range of such countries including Australia, UK, USA and western Europe. However, some ethnic groups have higher incidence of these disorders. The Ashkenazi Jewish population, for example, has a very high carrier rate of Canavan disease, Tay Sachs disease, Niemann-Pick disease type A and mucopolidosis type IV,<sup>35</sup> which gives parents with Ashkenazi Jewish ancestry an ~2-fold higher risk of having a baby born with a childhood dementia

disorder. Preconception carrier screening programmes in Jewish communities in Australia, Canada, USA and Israel, have resulted in markedly reduced incidence of these disorders.<sup>36,37</sup> A UK study found higher rates of PIND in people of South Asian descent<sup>38</sup> and an Australian study found a higher prevalence of mitochondrial disorders in people of Lebanese descent.<sup>10</sup> As shown by the success of the carrier screening in the Ashkenazi Jewish population and emerging evidence from the Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission), this could significantly reduce the incidence of childhood dementia in the future.

The incidence and prevalence values calculated here are likely to be an under-estimation due to the lack of available data for these rare and ultra-rare diseases. Incidence and life expectancy data were only available for just over half of the 170 identified disorders (55%) and this is an ever-expanding group with an increasing number of ultra-rare and novel single patient disorders discovered. There is also likely to be a sizeable undiagnosed population. In the PIND study, 531 children of 2255 (23.5%) had been investigated without a diagnosis being made or were still under investigation<sup>2</sup> and in the Australian Childhood Dementia Study, 17 of 80 (21%) were undiagnosed or had an uncertain diagnosis.<sup>1</sup>

In countries without newborn screening programmes for treatable conditions, such as PKU and limited access to specialist health-care, it is expected that there would be a substantial increase in childhood dementia burden. We estimated an additional incidence of 49.8 per 100 000 births (Supplementary Table 2) to give a total incidence of 84.3 per 100 000 (1 in 1190) births. In these countries, where access to interventions to manage the disease manifestations is also typically limited, the life expectancy would be expected to be lower for all of the childhood dementia disorders, but few publications are available on the epidemiology of childhood dementia in low and lower-middle income countries. Further research is needed to understand the impact of childhood dementia globally.

## Age of onset and diagnosis

Our data show a mean age of onset of 2.5 years when weighted for incidence (range birth to 13 years). This is in line with other studies—in the PIND study 81% presented before 5 years of age<sup>2</sup> and in Norway 71.4% of the cases presented during the first year of life.<sup>4</sup>

Making generalizations about age of diagnosis is more difficult as this can be greatly influenced by the year of diagnosis and the expertise of the local clinicians. Of concern is the often-lengthy delay to diagnosis after the onset of symptoms—more than half of 19 studies reported two or more years to reach a diagnosis after onset and in three studies, diagnosis took six or more years from onset on average. This delay is partly due to the non-specific nature of presenting symptoms that could indicate more common conditions such as autism, but it is likely that a lack of awareness of this group of conditions and clear diagnostic and referral pathways are contributing factors. With new technology, such as whole genome sequencing, it is hoped that the delays are decreasing but data are not yet available on emerging trends, and even in many advanced countries, there is not widespread, equitable and timely access to this technology.

Early diagnosis is not only critical for the delivery of equitable and quality care, but it also plays a key role in the development of much needed therapeutic interventions for children with dementia. Early diagnosis and intervention before the onset of irreversible neuropathology gives the best chance of successful treatment.<sup>39</sup> For example, although the vast majority of Hurler syndrome (MPS I) patients (83.6%) display symptoms by 1 month of age, diagnosis

was not until a median of 9.3 months<sup>40</sup> and it has been demonstrated that haematopoietic stem cell transplantation (HSCT) during the first 9 months of life is associated with typical cognitive development, while those that are transplanted later show long-term deficits.<sup>41</sup> In addition, currently many childhood dementia clinical trials are limited to pre- or early symptomatic children—those that are most likely to respond to treatment. For example, recruitment for gene therapy clinical trials for Sanfilippo syndrome type A (MPS IIIA) was limited to those under 2 years of age (NCT02716246, NCT04201405), but the average age of diagnosis is 4 years.<sup>42</sup> Therefore, clinical trial recruitment relies on younger siblings being identified, which is slow and heartbreaking for the older sibling. It increases the cost of trials, discourages pharmaceutical industry investment, and delays wider access to treatments. Expanding and improving newborn screening programmes and rapid and reliable diagnostic pathways for childhood dementia disorders would help to break this dichotomy and restore reproductive confidence for families.

## Mortality

The mean life expectancy for currently untreatable childhood dementia was calculated to be 16.3 years and survival analysis predicted the median to be ~9 years. Some children die in infancy, for example Gaucher disease type 2, whereas for some disorders survival into the fifth and sixth decade is not uncommon, for example Rett syndrome.

It is estimated that 91 Australians, 204 Britons and 1077 Americans (USA) died in 2021 due to childhood dementia, respectively. For comparison 92 children aged 0–14 years die annually in Australia from childhood cancer,<sup>43</sup> 260 in Britain<sup>44</sup> and 1050 in the USA.<sup>45</sup>

These statistics not only highlight the need for greater investment in therapeutics but are useful for the planning of improvements to current palliative care services.

## Treatments

Besides the disorders identified as treatable (listed in [Supplementary Table 2](#)), for the remaining 145 disorders, at present, there is a scarcity of effective and available treatments. Most management is hence directed at symptom management, such as anti-epileptic and behaviour-modifying medications. Interventions for optimizing mobility, nutrition and communication are available via physiotherapy, occupational therapy and speech therapy.

Some disorders in this list such as cerebrotendinous xanthomatosis<sup>46</sup> and X-linked adrenoleukodystrophy (X-ALD)<sup>47</sup> could be considered treatable if they were diagnosed prior to the onset of symptoms, or at least very early in the disease course, but in most high and upper-middle income countries this is not usually the case. Newborn screening for X-ALD has been implemented in some regions,<sup>48</sup> which may improve outcomes for these patients.

Childhood dementia conditions in the lysosomal disorder category have some specific treatment strategies. Five ERT medications are currently approved for use; however, four of these therapies are only given intravenously and are unable to cross the blood–brain barrier. This renders them largely ineffective for CNS disease processes and does not address the dementia aspects of these conditions.<sup>49–52</sup> The fifth product, Brineura® (cerliponase alfa), delivered intraventricularly, targets a type of Batten's disease (CLN2). It has been shown to slow progression of motor and language deficits<sup>53</sup> although no long-term studies have been performed to date. HSCT is a treatment option in some cases for a select number of disorders including metachromatic

leukodystrophy,<sup>54</sup> Krabbe disease,<sup>55</sup> MPS I (Hurler syndrome)<sup>56</sup> and MPS II (Hunter syndromes)<sup>57</sup> and X-ALD,<sup>58</sup> but has proved ineffective in multiple other disorders.<sup>59,60</sup> HSCT is most effective if performed pre-symptomatically and risks versus benefits must be weighed up on an individual case basis, as the procedure is associated with significant morbidity and mortality.<sup>61</sup>

Multiple gene therapy technologies are showing promise, and at least 28 clinical trials of gene therapies for childhood dementia disorders are currently active (as of June 2021, [clinicaltrials.gov](https://clinicaltrials.gov)). Two gene therapies have received regulatory authorization—Skysona (Bluebird Bio) for cerebral X-ALD (approved in the USA and EU) and Libmeldy (Orchard Therapeutics) for metachromatic leukodystrophy (approved in the EU). However, reimbursement and access to these expensive therapies remains a challenge.

Other therapeutic approaches being researched for the childhood dementia disorders target neurodegenerative mechanisms such as neuroinflammation, mitochondrial dysfunction, lipid accumulation, lysosomal dysfunction and neuroprotective pathways with small molecule drugs. Despite research that suggests overlapping disease mechanisms among the various childhood dementia disorders,<sup>62,63</sup> drug development and clinical trials to date have focussed on one disorder in isolation. Drawing attention to the childhood dementia disorders and their common attributes will lead to concurrent research of multiple disorders and therefore enhanced efficiencies and greater benefit for children with dementia.

## Limitations

Limitations of this scoping review can be attributed to the nature of the childhood dementia disorders. Given the rarity of individual diseases and the paucity of epidemiological data, a combination of mean, median and estimated incidence and life expectancy data from multiple populations was used. For variable disorders with multiple phenotypes, assumptions were made as outlined in [Supplementary Table 1](#). However, data acquisition was restricted to peer reviewed and population verified data as best possible to give an estimate of the scale of the childhood dementia population in high and upper-middle income countries. High quality, up to date studies collecting data on the incidence, natural history, life expectancy and costs of childhood dementia are required to provide a more comprehensive analysis of the burden of childhood dementia.

Several studies have attempted to quantify the economic and societal burden of childhood dementia, either collectively<sup>64</sup> or individually,<sup>65–67</sup> however the evidence is scarce. There is no health state directly applicable to childhood dementia in the WHO Global Health Estimates to allow accurate estimation of disability-adjusted life years (DALYs), nor comprehensive measurement of healthcare expenditure and indirect costs for this group of diseases. Investment in data capture from health systems is warranted, in most jurisdictions this will require improvements in how these disorders are coded, data linkage infrastructure and increased consistency in the use of phenotyping terms (HPO/SNOMED).

## Conclusions and future prospects

This scoping review highlights the importance of grouping these conditions as a phenotypic syndrome, rather than individually rare diseases, in keeping with the approach to adult dementia. By unifying these conditions, we have highlighted the many unmet needs of this significantly disadvantaged group of children and young people

and the data presented here will enable advocacy for systemic change in treatment, care and support for them and their families.

To improve recognition of childhood dementia and outcomes for patients, consistent language and definitions are needed for this group of disorders. The term ‘childhood dementia’ has not been widely adopted despite being described in medical literature since the mid-20th century<sup>68</sup> and the term being increasingly associated with individual conditions, especially Batten disease,<sup>69</sup> Sanfilippo syndrome,<sup>70</sup> Lafora disease,<sup>71</sup> Hurler syndrome<sup>72</sup> and Alexander disease.<sup>73</sup> Patient organizations are adopting the term and individual families are using it to raise awareness and understanding of their child’s condition on social media and in the community. Dementia support organizations are beginning to recognize childhood dementia and include affected families in their service provision.<sup>74,75</sup> More research is needed to understand attitudes and any barriers associated with the term, but it appears there is a groundswell of support for bringing these conditions together under the childhood dementia umbrella to improve outcomes for these children and their families.

Childhood dementia is a chronic, life-limiting condition that requires increasingly complex care, often over many years, and in some cases decades. Children with dementia lack defined care pathways when compared to other childhood diseases, ultimately impacting on their quality of care and long-term health outcomes. In one study, clinicians judged the impact of childhood dementia upon day-to-day family functioning was ‘marked’ or ‘extreme’ in the majority of families.<sup>1</sup> Additionally, emerging research shows that the impacts on mental health and overall quality of life for carers of children with dementia are severe and health and social systems are not effectively meeting the needs of families.<sup>76,77</sup> This highlights the need for the collection of real-world health system data globally and further research into the psychosocial impacts of childhood dementia on families and their experiences of health and social care systems. This will provide the evidence needed to address care and support needs.

Given the significant incidence, prevalence, mortality and lack of effective treatments, more attention and resources need to be channelled towards childhood dementia to develop new treatments, and improve patient management, service planning and provision.

A database of the key characteristics of the childhood dementia disorders listed in this paper is available at [www.childhooddementia.org/knowledgebase](http://www.childhooddementia.org/knowledgebase).

## Data availability

The authors confirm that the data supporting the findings of this study are available within the article, its [Supplementary material](#) and deposited in the Childhood Dementia Knowledgebase: <https://knowledgebase.childhooddementia.org/>.

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## Competing interests

K.L.E., M.M. and G.H. are current employees of Childhood Dementia Initiative. N.J.C.S., M.A.F. and J.C. are non-pecuniary members of the Scientific and Medical Advisory Committee for the Childhood Dementia Initiative.

## Supplementary material

[Supplementary material](#) is available at [Brain](#) online.

## Appendix 1

The members of the Childhood Dementia Working Group who contributed to the authorship of this paper are: David R. Thorburn, Gail Hilton, Ellie Van Velsen, Danielle Cini, Briana Davis, Richard Webster, Carolyn J. Ellaway and Anita Inwood.

Further details are provided in the [Supplementary material](#).

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