Childhood Dementia in Australia:

quantifying the burden on patients, carers, the healthcare system and our society

childhood dementia INITIATIVE

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KEY POINTS

- Childhood dementia is a recognised, albeit little known group of disorders, comprised of more than 70 individual genetic conditions.
- Childhood dementia disorders are progressive and devastating in nature and pose a significantly complex medical challenge, with patients typically relying on fulltime supportive care and extensive healthcare services in the mid-later stages of the disease.
- This study demonstrates for the first time the burden associated with childhood dementia in Australia, the tremendous negative impact it has on affected children, families and the community, and the resulting economic costs.
- Effective therapeutic intervention remains an unmet clinical need for the vast majority of childhood dementia disorders.
- It is estimated that the collective incidence of disorders that cause childhood dementia is 36 per 100,000 live births. This equates to 129 births in Australia each year.
- In 2021, it is estimated there will be 2273 Australians living with a childhood dementia, 1396 of whom will be under the age of 18.
- Collectively, the life expectancy for childhood dementia in Australia is estimated to be 28 years.
- The Years of Life Lost (YLL) and Years of Life lost due to Disability (YLD) from 2021 to 2030 in Australia is estimated to be 10,962 and 4,513, respectively.
- In an average year, the estimated economic cost is substantial: $40.4 million to the Australian healthcare system, $39.7 million in indirect costs, $233.5 million in costs of life years lost and $75.0 million costs to the National Disability Insurance Scheme (NDIS).
- The total economic cost of childhood dementia in Australia from 2021 to 2030 is estimated to be $3.9 billion, with an annual average of $389 million.
- This analysis identifies the high level of unmet need for new therapies and importantly, highlights opportunities for the development of therapies for childhood dementia.

EXECUTIVE SUMMARY

Introduction

'Childhood dementia' is, by its very name, confronting, complex and heartbreaking; a term often met with incredulity when heard for the first time. Indeed, childhood dementia is a recognised, albeit little known, group of disorders comprised of more than 70 individual genetic conditions. Sharing many striking clinical similarities with adult-onset dementia, childhood dementia is characterised by global progressive neurocognitive decline, multiple loss of already attained developmental skills, and a severely reduced quality of life and life expectancy.

Like all dementias, there are currently no effective therapies for the vast majority of childhood dementia conditions and where available, treatments are often limited; at best, only slowing the rate of disease progression.

Despite the large number of paediatric neurological disorders known to cause childhood dementia, collectively, childhood dementia itself, as a diagnostic group of diseases, has received little recognition or attention in the medical and scientific literature. Instead, the individual disorders are most often considered as discrete conditions rather than as part of the broader superordinate class.

Children with dementia typically suffer significant morbidities associated with their genetic disorder, including seizures, severe physical disability, organ failure, loss of speech, vision and other primary functions. Indeed, this drastically reduces quality of life for the affected individual and confers a tremendous emotional, physical and financial burden on all those involved in their care and support.

The direct healthcare costs and indirect societal costs associated with childhood dementia disorders collectively have not been assessed in Australia nor, to the best of our knowledge, in any healthcare system worldwide. Although each respective disorder is considered rare[1] or ultra-rare[2], collectively childhood dementia is relatively common and likely to have considerable, wide-ranging impacts on the Australian healthcare system including the National Disability Insurance Scheme (NDIS), as well as to families, carers and society at large.

The objectives of this study are to:

1) define and identify the population affected by childhood dementia;

2) quantify the current burden of childhood dementia on the Australian economy; and

3) estimate the projected financial costs of childhood dementia to the Australian healthcare system (considering both direct and non-direct healthcare costs) as well as to individuals, caregivers and to society over the next decade.

[1] The most widely accepted definition of a rare disease is one that affects less than five in 10,000 people.
Source: National Strategic Action Plan for Rare Diseases, February 2020,
https://rva.blob.core.windows.net/assets/uploads/files/NationalStrategicAPRD.pdf

[2] Ultra-rare diseases are defined as having a prevalence of <1 per 50000 persons
Source: National Institute for Clinical Excellence. NICE Citizens Council Report Ultra Orphan Drugs. London, NICE, 2004
https://europepmc.org/article/NBK/NBK401721

Methodology

- The current analysis utilises desktop research to define and identify current and forecasted number of cases and costs associated with childhood dementia in Australia from 2021 to 2030.
- The incidence and life expectancy estimates were derived for each individual condition through extensive literature research. These estimates were used to calculate an incidence and Years of Life Lost (YLL) estimate for each condition in addition to a prevalence and life expectancy estimate for childhood dementia as a whole.
- A Disability Adjusted Life Year (DALY)[3] was assigned to each condition based on an average health state weight (0.312) from the Global Health Estimate study (2015).
- An average annual healthcare cost estimate of $27,900 based on three studies (Wyatt et al., 2012; Imrie et al., 2009; Hendrie et al., 2011) is applied to all individual conditions.
- The annual indirect costs, derived from Imrie et al. (2009), equate to $27,433 and are applied to all conditions.
- An estimate of $213,000 per year for the Value of a Statistical Life Year (VSLY; as recommended by the Australian Government's Office of Best Practice Regulation) is applied to the YLL to measure the opportunity cost of a life year lost due to premature mortality.
- An average annual cost to the NDIS of $97,000 is applied using age-specific costs to estimate the spend over an individual's lifetime, depending on life expectancy for each condition.

Results

- This study identified over 70 individual genetic conditions that can be consistently defined as causing childhood dementia, according to a previously published set of disease criteria (Nunn et al., 2002; Verity et al., 2010).
- It is estimated that the collective incidence of disorders that cause childhood dementia is 36 per 100,000 births (or 1 in 2,800 births). This equates to 129 births in Australia in an average year.
- In 2021, it is estimated there will be 2,273 Australians living with a childhood dementia, 1,396 of whom are under the age of 18.
- Collectively, the average life expectancy for childhood dementia in Australia is estimated to be 28 years.
- The YLL and YLD from 2021 to 2030 in Australia is estimated to be 10,962 and 4,513, respectively.
- In an average year, the estimated economic cost is substantial: $40.4 million to the Australian healthcare system, $39.7 million in indirect costs, $233.5 million in costs of life years lost and $75.0 million costs to the NDIS.
- The total economic cost of childhood dementia in Australia from 2021 to 2030 is estimated to be $3.9 billion, with an annual average of $389 million.

[3] The World Health Organisation (WHO) defines DALY as lost year of "healthy life". DALYs for disease are calculated as the sum of the number of Years of Life Lost (YLL) due to premature mortality and years Lost to Disability (YLD) for each condition.

Discussion

This is the first paper to quantify the burden of disease in a range of conditions that cause childhood dementia in any healthcare system worldwide. The analysis undertaken in this study defines and identifies the Australian population affected by childhood dementia and estimates the resultant direct and indirect costs incurred to the Australian economy currently and over the next decade.

We identified more than 70 disorders that cause childhood dementia. This list is not exhaustive and is expected to grow over time. In addition, due to the rarity of the conditions, high quality, contemporary evidence measuring the burden of childhood dementia is limited. Of the 70 identified disorders, 32 were excluded from the analysis due to the fact that incidence and life expectancy data were not available. There is limited robust data on the costs attributed to each condition in this list, therefore, the costs attributed to childhood dementia as a whole are expected to be higher than those provided in this analysis.

The economic cost of childhood dementia in Australia is estimated to be $389 million annually. While this may be considered low in comparison to other childhood conditions, there are two attributing factors that must be considered; childhood dementias confer only a short life expectancy of around 28 years, and given the lack of treatment options across the 70 identified conditions, the burden of care is disproportionately met by the affected families themselves, support services and carers.

This analysis identifies the high level of unmet need for new therapies and importantly, highlights opportunities for research and development of therapies for childhood dementia targeting overlapping disease mechanisms. Importantly, and promisingly, there exist on the horizon for patients with childhood dementia encouraging emergent therapies including gene transfer and editing technologies. These treatments have the potential to significantly improve patient outcomes and reduce the burden of these conditions on patients, their families and carers, society and indeed the Australian economy.

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LIST OF ACRONYMS

ACRONYM	DESCRIPTION
ABS	Australian Bureau of Statistics
ADHD	ADHD Attention Deficit Hyperactivity Disorder
AGU	Aspartylglucosaminuria
ASHE	Annual Survey of Hours and Earnings
AUD	Australian Dollar
CNS	Central Nervous System
DALYs	Disability Adjusted Life Years
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERT	Enzyme Replacement Therapy
GBD	Global Burden of Disease
GHE	Global Health Estimates
GP	General Practitioner (Primary Care Physician)
ICD	International Classification of Disease
LE	Life Expectancy
MPS	Mucopolysaccharidosis
NCL	Neuronal ceroid lipofuscinoses
NDIS	National Disability Insurance Scheme (Australia)
NHS	National Health Service (UK)
NKH	NonKetotic Hyperglycinemia
NPC	Niemann-Pick disease type C
NSRC	National Schedule of Reference Costs (UK)
OBPR	Office of Best Practice Regulation (Australia)
OMIM	Online Mendelian Inheritance in Man
ONS	Office for National Statistics (UK)
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)

LIST OF ACRONYMS cont.

PIND	Progressive Intellectual and Neurological Deterioration
PKAN	Pantothenate Kinase-Associated Neurodegeneration
SD	Standard Deviation
SRT	Substrate Reduction Therapy
TGA	Therapeutic Goods Administration (Australia)
VSLY	Value of a Statistical Life Year
WHO	World Health Organisation
YLD	Years Lost due to Disability
YLL	Years of Life Lost

1 INTRODUCTION AND OBJECTIVES

1.1 Background

Childhood dementia is defined as global neurocognitive decline with multiple developmental skill loss after a period of normal development (Nunn et al., 2002). One of the hallmark characteristics of childhood dementia is enduring and progressive loss of previously acquired developmental skills, in contrast to static or transient loss, for example in the case of head injury, encephalitis or near drowning (Nunn et al., 2002; Verity et al., 2010). Furthermore, childhood dementia may be distinguished from conditions such as intellectual disability or developmental delay, which are characterised by relative loss of trajectory compared with normal development (Nunn et al., 2002; Haugen et al., 2019).

To date, childhood dementia has received little recognition or attention in the medical and scientific literature, owing largely to the fact that the individual conditions constituting the childhood dementia group are most often considered as discrete conditions rather than as constituents of the broader superordinate disease-state. Indeed, the literature reveals that the childhood dementia group is comprised of a great many individual disorders, with one study identifying 147 known paediatric neurodegenerative conditions with progressive intellectual and neurological deterioration (Verity et al., 2010).

It is of interest to note, that despite this considerable number of conditions described as forms of dementia in childhood, 'childhood dementia' itself remains unrecognized as a class of disease in the World Health Organisation's International Classification of Diseases (ICD), the Diagnostic and Statistical Manual of Mental Disorders (DSM) or any other diagnostic system worldwide.

Although individually each of these conditions is considered rare or ultra-rare, childhood dementia collectively is relatively common. Given the severe, devastating and wide-reaching impact on affected children, their families and carers, childhood dementia therefore undeniably represents an important health issue in Australia.

1.1.1 Causes of childhood dementia

The aetiology and pathogenesis of childhood dementia is wide-ranging and, in some individual cases, remains undefined. This study focuses upon those identified childhood dementia disorders of genetic origin, a large proportion of which are attributable to inborn errors of metabolism, also known as inherited metabolic disorders. Most inherited metabolic disorders result from an enzyme defect in biochemical and metabolic pathways that affect the essential metabolism of cellular proteins, fats or carbohydrates, or impaired organelle function. Other rare genetic neurodegenerative conditions such Rett syndrome and Juvenile Huntington's disease make up the remainder of the childhood dementia group.

The focus on disorders of genetic origin excludes acquired disorders, such as encephalopathies arising from infectious, viral or toxic aetiologies, those related to nutritional deficiencies and those associated with autoimmune or endocrine disorders. However, the hereditary dementias constitute the substantive burden of childhood dementia in Australia and other developed nations.

The major broad classifications of childhood dementia include:

- Lysosomal diseases; including mucopolysaccharidoses, disorders of lipid metabolism and transport, glycoproteinosis and neuronal ceroid lipofuscinoses
- Other disorders of lipid metabolism and transport
- Disorders of amino acid and other organic acid metabolism
- Vitamin-responsive inborn errors of metabolism
- Disorders of mineral absorption and transport
- Peroxisomal diseases
- Mitochondrial disorders
- Leukodystrophies
- Neurodegeneration with brain iron accumulation
- Other rare neurodegenerative diseases

1.1.2 Diagnosis, morbidity and mortality

The pathway to diagnosis of these many conditions varies between diseases, and typically involves a combination of early clinical symptom assessment, brain imaging, detection of biochemical markers in urine and blood, and genetic testing. Given the non-specificity of initial presenting symptoms, the rarity of the individual diseases and general lack of awareness in the medical community, the diagnosis of childhood dementia disorders are often delayed, sometimes for years after the first symptoms are noticed. Commonly, children are misdiagnosed with autism, developmental or intellectual delay, attention deficit hyperactivity disorder (ADHD) and others, before reaching a definitive diagnosis.

Newborn screening for these conditions is limited, justified in part by a lack of therapeutic intervention for the vast majority of these disorders (section 3.2)

The symptomatology of childhood dementia disorders is highly variable with considerable clinical and phenotypic heterogeneity. Childhood dementia does however share many similarities with the hallmark features of adult-onset dementias, including:

- Decline in cognitive ability
- Problems with attention and concentration
- Memory loss and learning difficulties
- Problems with thinking and reasoning
- Confusion and disorientation
- Uncooperative and disruptive behaviour
- Wandering and restlessness
- Emotional disturbance (anxiety, fear, panic attacks, etc)
- Personality and behavioural changes (aggression, irritability, hyperactivity, etc)
- Sleep disturbance (often severe)
- Deterioration of social skills, and socially appropriate behaviour
- Psychotic symptoms and hallucinations
- Loss of speech
- Incontinence

In contrast to most adult-onset dementias however, and in addition to these cognitive, neuropsychological and behavioural manifestations, childhood dementia disorders are commonly associated with seizures, sensory decline (vision and hearing), movement disorders including ataxia, spasticity, dyskinesia, dystonia, gait disturbances, muscle weakness and abnormal muscle tone, and progressive neuromotor decline.

Some childhood dementia disorders also involve other organs and physiological systems in addition to the central nervous system, including, peripheral nerve disease, visceromegaly (enlargement of abdominal organs), liver disease, growth retardation, gastrointestinal disease, bone and joint anomalies, and cardiac involvement.

The timeline of disease onset and progression varies among the childhood dementia disorders, with some presenting in infancy, progressing rapidly and leading to death in the first year of life. For other disorders, initial symptoms may not present until later in childhood and progress slowly, with survival typically into the teens or early adulthood. The cause of death in childhood dementia disorders is usually attributed to respiratory complications of end-stage disease (such as pneumonia), neurological complications (for example, intractable epilepsy), or cardiac events.

1.1.3 Burden of Childhood Dementia

As a result of their unique and highly complex health needs, individuals with childhood dementia disorders typically rely heavily on healthcare and support services, in addition to the extensive care provided by family members and other unpaid carers. The severity of symptoms and progressive nature of the disorders mean that for many individuals full time multidisciplinary care is required throughout the lifespan, or at least toward the end stages of the disease. The costs of professional care required for individuals with disabilities have been quantified as considerably higher than that of the general population (Vu et al., 2020; Hendrie et al., 2011). Furthermore, a large proportion of this care is provided unpaid and informally by family members (Access Economics 2015) who are required to leave the paid workforce in order to take on these vital support roles.

Individuals with childhood dementia in Australia will qualify for funding under the NDIS. The NDIS provides financial support to eligible people with intellectual, physical, sensory, cognitive, and psychosocial disability, based on their individual needs. The types of support and services funded by the NDIS may include assistance with daily personal activities, transport, workplace help, therapeutic supports, help with household tasks, home modification, mobility equipment and vehicle modifications. The NDIS is a nationally based scheme with funding and governance shared amongst the Commonwealth and state and territory governments. Within the next five years, the NDIS is expected to provide more than $22 billion in funding per year to an estimated 500,000 Australians who have permanent and significant disability.

The economic and societal costs associated with childhood dementia disorders collectively have not been assessed in Australia nor, to the best of our knowledge, in any healthcare system worldwide. Although each respective disorder is considered rare, collectively childhood dementia is relatively common and given the severe nature of the disorders, therefore likely to have considerable, wide-ranging impact on the Australian healthcare system and NDIS, as well as to families, carers and society at large.

1.2 Objectives

The objectives of this study were to:

(1) define the population affected by the genetic childhood dementias according to a previously published defined set of disease criteria (Nunn et al., 2002; Verity et al. 2010);

(2) quantify the current burden of childhood dementia on the Australian economy; and

(3) estimate the projected financial costs of childhood dementia to the Australian healthcare system (considering both direct and non-direct healthcare costs) as well as to individuals, caregivers and to society over the next decade.

In considering the burden of disease of childhood dementia, this analysis examines and quantifies:

- The size of the affected population in Australia
- Direct health care costs of treating and/or management of disease
- Indirect costs of care including productivity loss associated with high caregiver need
- Costs accrued by the NDIS
- The number of years lost to disability (YLD) and premature mortality
- The opportunity costs of these years of life lost to disability (YLD) and premature mortality based on the statistical value of a life year (VSLY)

2 METHODOLOGY

2.1 Analysis structure

The analysis forecasts the number of new cases and costs incurred by or on behalf of individuals with childhood dementia from 2021 to 2030.

The analysis aggregates the following costs and outcomes associated with childhood dementia:

- Total births
- Prevalence
- Years of life lost (YLL)
- Years of life lost to disability (YLD)
- Costs to the healthcare system, the NDIS, indirect costs due to productivity losses, costs associated with premature mortality
- Costs and outcomes are accumulated by the cohort of individuals with childhood dementia over the period of 2021 to 2030. An annual average of each outcome using the aggregated data is calculated as well as an average life expectancy.

2.1.1 Defining the population

The definition for childhood dementia is based on the disease criteria described by Nunn and colleagues (2002) and adopted (albeit slightly modified) by the British Paediatric Surveillance Unit's study of progressive intellectual and neurological deterioration (PIND) (Verity et al., 2010). To the best of our knowledge, these are the only published disease criteria available for defining childhood dementia.

For the purpose of this study, the definition and criteria have been modified, based on expert advice, to only include childhood dementia disorders of genetic origin, specifically monogenic disorders (that is, disorders that are a result of a single gene defect). Indeed, these disorders constitute the greatest burden of degenerative cognitive disorders in childhood in Australia and comparable developed nations. Additionally, the monogenic disorders have a predictable incidence and are therefore more reliably modelled. Moreover, this afforded us a clearly defined group of conditions with commonalities in diagnosis, clinical course, and outcome.

This therefore excludes acquired disorders, such as encephalopathies arising from infectious, viral or toxic aetiologies, those related to nutritional deficiencies and, similar to Nunn et al. (2002) and Verity et al. (2010), also excludes static intellectual loss, for example as a result of encephalitis, head injury or hypoxia.

Conditions typically associated with episodic cognitive impairment (often in the context of acute metabolic crises, for example phenylketonuria, homocystinuria, and urea cycle disorders) and otherwise without temporally progressive decline have also been excluded. As have those conditions where primary cognitive decline is considered a consequence of uncontrolled epilepsy (the epileptic encephalopathies). It is acknowledged that overlap exists amongst these clinicopathological classification systems, with some of these genetic disorders assigned to more than one designation. For example, some mitochondrial diseases are considered epileptic encephalopathies and childhood dementia disorders and were included in this analysis.

The inclusion criteria for childhood dementia thus includes any child (under 18 years of age at onset of symptoms) with any illness that fulfils all the following criteria:

- Multiple losses of already attained development skills
- Duration of illness greater than 3 months
- Skill loss most likely due to central nervous system (CNS) dysfunction
- Evidence of generalised (not merely focal) brain dysfunction
- Has a condition which will in the future, in all probability, lead to progressive deterioration as above.
- Is monogenic in origin

We identified over 70 conditions that meet this definition (Appendix 1 and 2). The number of conditions is higher than the 70 listed in the appendices because, for simplicity, we grouped some conditions together rather than defining every subtype, for example the 11 types of childhood onset neuronal ceroid lipofuscinoses (NCLs) and the many types of mitochondrial disease. There are at least 96 nuclear genes, mutations in which cause the 70 conditions, and a multitude of mitochondrial genetic causes. Similarly, we have not accounted for every ultra-rare or novel genetic childhood dementia, as most of these conditions are newly identified with only a small number of cases identified globally.

Given the large number and rarity of each condition, inclusion and exclusion criteria were applied to collate a representative list of childhood dementia disorders that would have sufficient data in order to reliably quantify the burden of illness analysis. Consequently, any condition with insufficient incidence data or a prevalence rate of less than 200 cases reported was excluded.

Of the 70 conditions that met the childhood dementia definition, 32 were excluded due to insufficient data. A total of 38 conditions were therefore included in this analysis. Included and excluded conditions are listed in Appendix 1 and Appendix 2, respectively.

To understand more about the aetiology and pathogenesis of the included conditions, the functional classification was determined for each condition using classifications in the literature and the Orphanet database[4].

2.1.2 Quantifying disease burden

The analysis quantifies disease burden by first forecasting the number of individuals to be born with a disorder that will lead to childhood dementia in Australia over the decade 2021 to 2030. This forecast is based on incidence rates determined from the literature and applied to the projected size of the Australian birth cohort over this period. Next, life expectancy for each of the childhood dementia conditions is compared against that of the general population life expectancy at birth to determine the YLL for a given condition. Disability adjustments, health care costs, NDIS costs and lost productivity costs are all applied to the life expectancy of the given condition. These calculations are described by way of an example in Section 2.2 to follow with reference to the input data used.

[4] https://www.orpha.net/consor/cgi-bin/Disease_Classif.php

It should be noted the costs of any treatments which may be available in Australia for these conditions have not been included. This is because the vast majority of the conditions do not have a reliable, effective and accessible treatment option. For those conditions that do have treatments, most are either only partially effective, not widely accessible in Australia (e.g. chenodeoxycholic acid for cerebrotendinous xanthomatosis) or relatively inexpensive (e.g. penicillamine for Wilson's disease). Four of the conditions have treatments on the Australian Federal Government's Life Savings Drug Program; Gaucher disease, MPS I, MPS II and Late-Infantile Batten disease (CLN2 disease). The costs of these treatments are not publicly available and therefore could not be included in the analysis.

Including the costs of treatments in the analysis would require adjusting the underlying burden of disease estimates to reflect the effectiveness of those treatments. Given the difficulty associated with costing these treatments, the further difficulty associated with measuring the beneficial impact of these treatments on disease burden and the fact only a small minority of patients with childhood dementia are able to access an effective treatment, it was decided to exclude both the costs and potential benefits of any treatments from the analysis, with the exception of adjusting the life expectancy for these few 'treatable' conditions. As such, the disease burden estimated in this study can be understood to reflect the burden of living with and managing the conditions given best available standard of care, rather than the cost of treating them. That is to say, the burden of childhood dementia measured in these analyses broadly reflects the standard of care at the time the data were collected and reported.

2.1.3 Perspective

The analysis takes a societal perspective which means it is designed to capture the burden of childhood dementia across society at large. The analysis includes the following items to quantify the cost and burden of childhood dementia in Australia:

- Healthcare costs
- Indirect costs (i.e. costs of lost productivity of patients and/or their carers)
- Costs to the NDIS
- The impact/burden to the individuals in terms of quality of life
- The impact/burden to the individuals in terms of premature mortality

All costs reported in the analysis are in terms of Australian dollars at 2020 values (AUD2020). Where necessary, future costs were discounted at a rate of 5% per annum consistent with the discount rate typically used in Australian healthcare decision making processes (see Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines for example[5]).

[5] https://pbac.pbs.gov.au/

2.2 Inputs and data sources

This study is based on desktop research and validated with clinical expert opinion. An extensive review of the literature was undertaken to identify relevant outcomes (incidence, life expectancy and costs) for people with childhood dementia, although to the best of our knowledge, no comprehensive studies of all disorders that cause childhood dementia have been undertaken. Review of the literature has revealed that the incidence, life expectancy and costs for each respective childhood dementia in this list varies. Reliance is placed on 'averages' of these outcomes as it was not feasible to capture these variations within this report.

The data is primarily derived from grey literature. In many instances, the primary source for these data have not been verified and, as such, it is possible that there are variations in estimates. The estimates identified were reviewed by clinicians to ensure estimates applied to the analysis were within a reasonable range and likely to be applicable to Australian clinical experience and practice.

2.2.1 Incidence and life expectancy

A broad review of the literature was performed to ascertain incidence estimates and life expectancy estimates of each individual condition included in the analysis. The search was primarily performed by extensive grey literature[6] search including websites of organisations relevant to childhood dementia and hand searching relevant reports. The following literature databases were also employed; PubMed, Embase and Google Scholar. Search terms included incidence, prevalence, proportion, mortality, life expectancy, survival, and the names of each condition. The search was supplemented with advice from local subject matter experts and clinicians.

Where only a subset of patients with a condition met the eligibility criteria, the proportion of those patients were applied to the identified incidence estimate. For example, in Gaucher disease the incidence of all Gaucher disease is 1.69 per 100,000. Of this, 90% have Type 1 Gaucher disease which is not neurodegenerative. Types 2 and 3 which do cause childhood dementia account for 5% of the Gaucher population each, and this proportion was applied to the overall incidence. Where the available information reported a range for either the incidence or life expectancy a simple average was taken.

Estimating the incidence of mitochondrial diseases presented two main challenges, namely the genetic heterogeneity and pleiotropy. There are well over 300 mitochondrial and nuclear genes implicated in mitochondrial disease, and mutations in many of these genes can cause a range of different conditions, often with different ages of onset. The opinion of a subject matter expert was thus sought in Professor David Thorburn at the Murdoch Children's Research Institute, Melbourne, whose laboratory has acted as the national referral centre for the diagnosis of mitochondrial disease in children for over 20 years and has diagnosed more than 700 children. He was able to give an estimate of the incidence of mitochondrial diseases presenting with childhood dementia based on his research group's published and unpublished data.

For the purpose of estimating the impact of life expectancy on subsequent YLL, DALYs and costs, each life expectancy estimate was discounted at rate of 5% per annum to determine the net present value of the costs associated with death at the time it occurs.

The incidence rate and life expectancy for each of the 38 conditions included in the analysis are summarised in Figure 1 and Figure 2, respectively. Full details of these data and citations are provided in Appendix 1.

[6] Gray literature is materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels

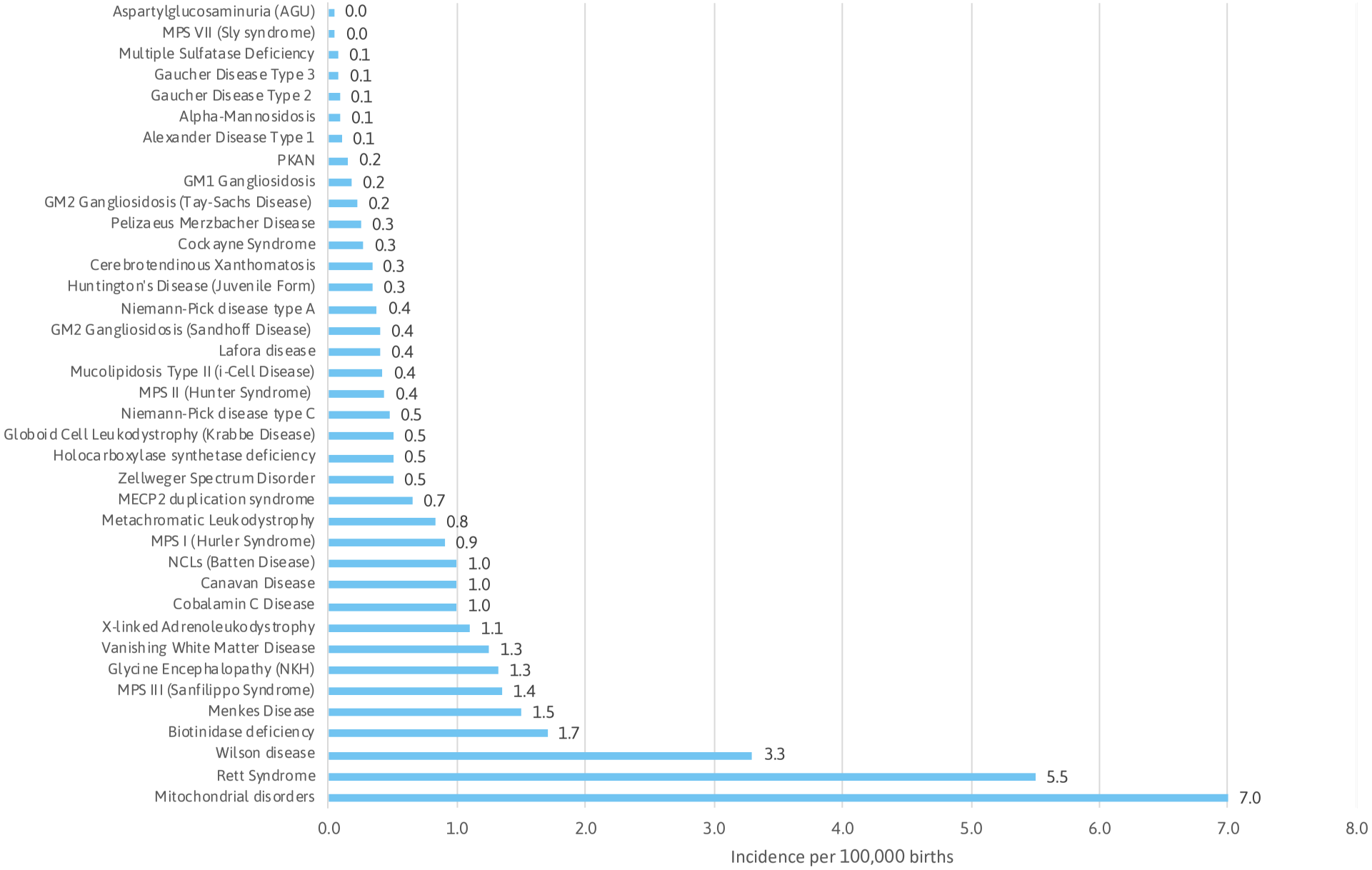

Figure 1 Incidence per 100,000 births of each of the childhood dementia disorders included in the analysis

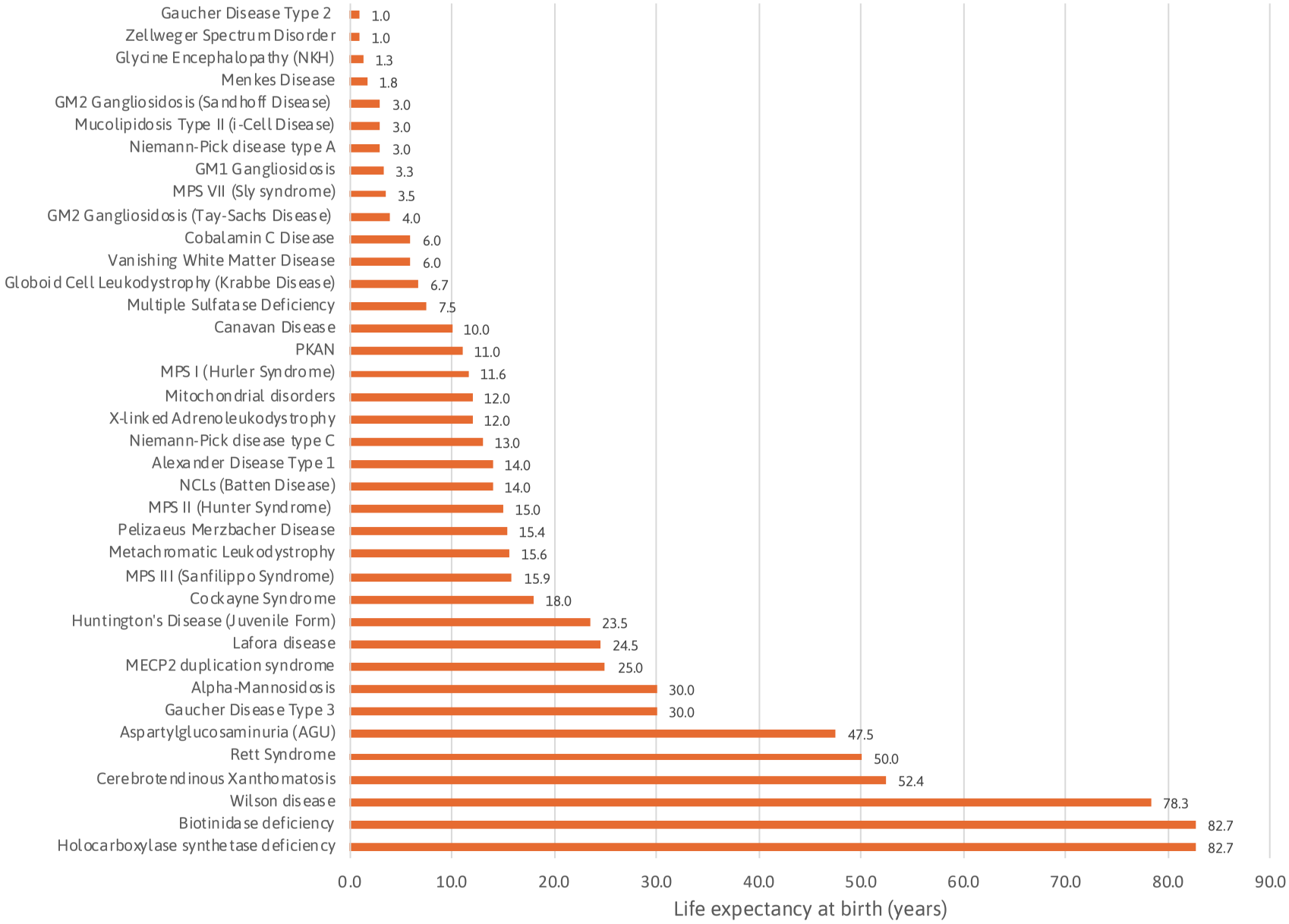

Figure 2 Life expectancy at birth (years) for each of the childhood dementia disorders included in the analysis

The number of births for each respective condition is projected from 2021 to 2030 to calculate the total number of births and incidence per 100,000 of childhood dementia. Population projections of total Australian births were derived from the Australian Bureau of Statistics (ABS) population projections (Series B) [7] This was applied to the incidence per 100,000 estimates to project the incidence for each condition from 2021 to 2030. The incidence projections were summed to calculate the total births of all childhood dementia disorders in each year. An example of this calculation for Alexander disease type 1 in the year 2021 is presented in Table 1. The total births from 2021 to 2030 are calculated by summing the total births in each year.

TABLE 1 Calculation of the total number of births with childhood dementia, 2021. Example using Alexander disease type 1 in the year 2021[a]

Row	Outcome	Incidence	Source
A	Birth cohort	342,397	ABS
B	Incidence per 100,000 (from the literature)	0.1	Table 15
C	Expected number of births with Alexander disease type 1	0.3	A x B
D	Total births, 2021	122.1	Sum of C for all 39 conditions included in the analysis a

2.2.2 Prevalence

The prevalence of children and persons expected to be living with childhood dementia is estimated for the years 2021 to 2030. As incidence estimates, not prevalence, were collected from the literature for each condition, the prevalence of each childhood dementia is calculated from incidence and life expectancy estimates.

The incidence and life expectancy data from the literature (Appendix 1) were used to derive a prevalence to incidence factor. For example, if the life expectancy of a given condition is 10 years. Then, on average, there will be ten birth cohorts alive at any given point in time and the prevalence to incidence factor would be 10. However, given that birth cohorts are growing over time it is necessary to adjust this factor.

The prevalence factor for each year of life expectancy is calculated as a function of the probability that a person is alive in any given year multiplied by the relative size of the total birth population noting that for each year a person is alive, the total birth population size also increases so that the relative contribution that patient makes to the overall prevalence diminishes with time. Based on historical birth growth rates from 2000-2018 (ABS 2011[8]), the annual birth cohort growth is estimated to be approximately 1.5%. Consequently, for each year a patient is alive, the relative contribution of the prevalence decreases by the same factor. For example, the number of people alive today with a condition which has a life expectancy at birth of three years is equal to the number of people born this year (i.e. incidence), the number of people born last year (1.5% smaller cohort) and the number of people born the year before that (1.5% smaller cohort again).

Table 1 Abbreviations: Australian Bureau of Statistics
a. List of all conditions presented in Appendix 1

[7] https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3222.02017%20(base)%20-%202066?OpenDocument
[8] https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3301.02018?OpenDocument

The prevalence to incidence factor for a given life expectancy is calculated as the sum of the birth cohort factor for each year a patient is expected to be alive. For each condition, the prevalence factor is determined according to the corresponding life expectancy and multiplied by the expected number of births in any given year (derived from the incidence data as described above).

$$P{:}I\ factor = \sum_{i=0}^{n-1} \frac{1}{(1+g)^i}$$

Where:
n = life expectancy
g = annual growth rate on the birth cohort

Equation 1 Estimating prevalence from incidence and life expectancy data

Taking the example of Alexander disease type 1 presented previously, the life expectancy of 14 years equates to a prevalence factor of 12.731. Based on the incidence, the number of children born with Alexander disease type 1 in 2021 is 0.3 meaning the analysis would estimate 4 people living Alexander disease type 1 in Australia in the year 2021 (Table 2).

TABLE 2 Example calculation of prevalence for Alexander disease type 1 in the year 2021

Row	Parameter	Value	Source
A	Life expectancy	14 years	Table 16
B	Prevalence factor	12.731	Calculated as described above
C	Expected number of births	0.3	Incidence x Birth cohort
D	Estimated prevalence	4	Row B x Row C

The prevalence factor is applied to the total births to determine the prevalence of each condition in each respective year. The sum of the prevalence of the total childhood dementia cohort for each year was calculated to derive the total prevalence of childhood dementia from 2021 to 2030.

2.2.3 Years of life lost

The YLL measures the years of potential life lost due to early death. YLL considers the age at which deaths occur by giving greater weight to deaths at younger age and lower weight to deaths at older age (WHO 2017). Given the reduced life expectancy in childhood dementia, the YLL is calculated.

To determine the YLL, the discounted life expectancy of any given person in the general population is calculated using the same 5% discount rate. Given an average life expectancy in the general population of 82.65 years (based on the average life expectancy at birth estimated in 2016-2018; ABS data[9]), the discounted life expectancy is estimated to be 19.65.

The discounted life expectancy for each childhood dementia disorder is then subtracted from the discounted life expectancy in the general population to derive the YLL for each individual childhood dementia included in the analysis. The discounted YLL is applied to the projected birth estimates to derive the total YLL estimate for each disorder for each year from 2021 to 2030.

The YLL estimate for each disorder is summed to determine the total YLL across all childhood dementia disorders from 2021 to 2030. An example of these calculations for Alexander disease type 1 in the year 2021 is presented in Table 3.

TABLE 3 YLL estimates: example method of Alexander disease type 1 in the year 2021

Row	Outcome	Incidence	Source
A	Life expectancy	14.0	Table 15
B	Discounted life expectancy	9.9	14 years discounted at 5% per year
C	YLL (discounted)	9.8	19.65^- B
D	Incidence (projection)	0.3	Table 1
E	YLL projections	3.3	C x D
F	Total YLL in 2021 (all childhood dementia)	1,033.8	Sum of all E*

Table 3 Abbreviations: YLL, years of life lost
*List of all conditions presented in Table 15

^ discounted life expectancy: average life expectancy in the general population of 82.65 years discounted at 5%
[9] https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3302.0.55.001Main+Features12016-2018?OpenDocument

2.2.4 Disability adjusted life years

To measure the quality of life associated with childhood dementia a DALY weight is assigned to each condition. A DALY measures time spent in a state that is less than optimal health, referred to as 'disability'. A number of health states have been assigned a DALY weight by the WHO (2017). These DALYs represent the time lost per year because of the 'disability'.

According to WHO[10], "One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population."

The Global Burden of Disease (GBD) study (2010) undertook a comprehensive estimation of disability weights through a large-scale empirical investigation. Respondents from the general population were surveyed on judgements about health loss associated with many causes of disease and injury. Estimates of disability weights for 220 health status were derived from 13,902 individuals in household surveys in five countries. This was supplemented by an open-access web-based survey of 16,328 people. These weights were revised in the Global Health Estimates (GHE) (2015) update of 30,660 respondents in four European countries.

The GHE (2015) update did not include a health state directly applicable to childhood dementia. As such, after reviewal of the list of health states included in the GHE (2015) it was advised by expert clinicians that the definitions of 'intellectual disability' were most applicable to childhood dementia disorders as a whole. There were four health states associated with intellectual disability. The GHE (2015) DALY estimate and definition of these health states is presented in Table 4.

The severity of childhood dementia in the included conditions in Table 11 varies across conditions and over an individual's lifetime. To account for the varying severity levels an average of the four intellectual disability health state DALY estimates was calculated. The average of 0.312 is used to assign a weighting of the severity of disability in childhood dementia.

[10] https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158

TABLE 4 Health state weights used in the WHO Global Health Estimates

Health state	GHE 2015	Definition
Intellectual disability - mild	0.127	Has low intelligence and is slow in learning at school. As an adult, the person can live independently, but often needs help to raise children and can only work at simple supervised jobs.
Intellectual disability - moderate	0.293	Has low intelligence, and is slow in learning to speak and to do even simple tasks. As an adult, the person requires a lot of support to live independently and raise children. The person can only work at the simplest supervised jobs.
Intellectual disability - severe	0.383	Has very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.
Intellectual disability - profound	0.444	Has very low intelligence, has almost no language, and does not under-stand even the most basic requests or instructions. The person re-quires constant supervision and help for all activities.
Average	0.312	

2.2.5 Years of life lost to disability

The YLD extends the concept of YLL to include years of 'healthy' life lost due to being in a state of poor health or disability (WHO 2017).

To estimate the YLD, the discounted life expectancy is applied to the average DALY (see Table 4) to derive the YLD for each condition. This is projected over the next 10 years by applying the YLD to the total births of each condition. The YLD estimate for each condition is summed to determine the total YLD from 2021 to 2030. An example of these calculations for Alexander disease type 1 in the year 2021 is presented in Table 5.

TABLE 5 YLD estimates: example method of Alexander disease type 1 in the year 2021

Row	Outcome	Incidence	Source
A	Life expectancy	14.0	Table 16
B	Discounted life expectancy	9.9	14 years discounted at 5% per year
C	DALY weight	0.31	Table 4
D	YLD (discounted)	3.1	B x C
E	Incidence (projection)	0.3	Table 1
F	YLD projections	1.1	D x E
G	Total YLD (in 2021)	425.6	Sum of F values for all conditions*

Table 4: Abbreviations: GHE, Global Health Estimates; WHO, World Health Organisation
Source: WHO 2017 Annex Table D; Annex Table C

Table 5: Abbreviations: DALY, disability adjusted life year; YLD, years of life lost to disability
*List of all conditions presented in Table 15

2.2.6 Costs

The costs considered in this analysis include both direct costs, comprising costs of medical services and professional care required for the individual patient and management of their disease; and indirect costs defined as those associated with each condition and the subsequent impact on work-related and other productivity.

The estimation of the annual healthcare and indirect costs presented in this section employs a bottom-up approach whereby an average cost per person is derived from the available literature and applied across all relevant childhood dementia disorders considered in this paper.

2.2.6.1 Annual healthcare costs

No publicly available data sources have been identified for healthcare expenditures for all childhood dementia disorders in Australia or elsewhere. However, it is reasonable to assume that the healthcare resource utilisation would be greater among those with childhood dementia disorders compared to the general paediatric population.

A pragmatic search of the literature identified three key sources (Wyatt et al., 2012; Imrie et al., 2009 and Hendrie et al., 2011) identifying resource utilisations and costs of childhood dementia patients and/or carers.

Wyatt and colleagues (2012) undertook a longitudinal cohort study of people with lysosomal storage disorders measuring the effectiveness and cost of then-available enzyme replacement therapies (ERT) and substrate reduction therapies (SRT) for six individual conditions, three of which are considered to cause childhood dementia and are relevant to this paper: mucopolysaccharidosis (MPS) type I and II, and Niemann-Pick disease type C (NPC). Gaucher disease was not considered relevant to this assessment on the basis that 97% (145/150) of the Gaucher disease patients in the Wyatt study (Wyatt et al., 2012) had type 1 which is not considered a childhood dementia.

The proportion of MPS II patients who are considered to have childhood dementia is 60% - 80% (Guffon et al., 2015; Orphanet 2019[11]). The costs of all MPS II patients in the Wyatt study (Wyatt et al., 2012) are included as these costs were not separated out by the mild and severe form. This will underestimate the overall healthcare costs in MPS II, given that 20% - 40% of MPS II patients have a mild form that does not meet the childhood dementia criteria.

In addition to the assessment of the cost of ERT and SRT, the direct costs of care derived from self-reported or parent-reported retrospective data on health service and social care use were collated over the preceding 1 2 months.

For hospital resource use, data included the number of days in hospital and reasons for inpatient stays and the number of and reasons for outpatient attendances, day hospital admissions and accident and emergency attendances.

For services and care professionals used outside of hospital, data for 20 different types of service providers (e.g. GPs, district nurses, occupational therapists, and social workers, etc) were recorded including the number of contacts, duration of contact, whether or not the visit/care was provided at home; and, if the service was paid for privately, the amount paid per attendance/use.

The total costs were calculated by multiplying the number of episodes of each type of service use by the appropriate reference cost, for each episode of care (NHS reference costs: NSRC 2009–2010) or by the mean number of contact hours reported per episode and the hourly cost to the public sector for the different types of health and social care professional (Unit Costs of Health and Social Care 2010).

[11] https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=131&disease=Mucopolysaccharidosis-type-2&search=Disease_Search_Simple

A retrospective, cross-sectional cohort study based on responses from patients and/or their carers (n=18) enrolled through a UK NPC database which aimed at assessing the direct medical costs, the direct non-medical costs, and the indirect costs in terms of inability to work was also identified (Imrie et al., 2009). Resource use and direct medical, direct non-medical costs were evaluated using data collected via postal survey in October 2007. A Medical Resource Use questionnaire, designed to assess healthcare use associated with NPC collected information related to tests, medications, home visits, consultations, hospitalisations and other services provided by health professionals, residential care and out-of-pocket non-medical resources.

Unit costs for resources that were paid by the NHS or otherwise publicly funded were taken where possible. If no published unit costs were available, costs were estimated based on Manchester Children's Hospital, expert opinion or professional associated websites. All unit costs were in 2007 British pounds.

An Australian study conducted by Hendrie and colleagues (Hendrie et al., 2011), was the third included study, measuring the use and cost of health sector and related services in Rett syndrome. Families (n=170) were asked to report on the use and cost of the following services over a typical year: medical practitioner visits, therapy services out of school and paid home and community services, medical tests, hospital admissions, prescription and non-prescription medication, therapeutic devices and short and long term residential care.

Where the costs reflected market prices (e.g. dental services), no adjustment was made to these costs. For resources that were publicly provided, or the cost did not reflect market prices (e.g. prescription medication), unit costs were obtained from official sources such as the Pharmaceutical Benefits Scheme and the National Hospital Cost Database collection. The cost of therapeutic devices and special equipment were converted to an equivalent annual cost using a 5% discount rate and estimates of their usual life span. All costs were expressed in 2004/05 Australian dollars.

The estimated annual costs of care for children for each disease presented in the three studies (Wyatt et al., 2012; Imrie et al., 2009 and Hendrie et al., 2011) are summarised in Table 6 below. The total mean annual costs of care were inflated to 2020 Australian dollars on the 21st July 2020 via Inflation tool[12] and xe.com[13]

TABLE 6 Estimated annual care costs of childhood dementia identified in the literature

Disease subtype	Mean cost	Year	Source	Inflated to 2020[a]	Total mean cost (AUD)[b]
MPS I	£18,600	2009/10	Wyatt 2012	£22,718	$40,728
MPS II	£7,600	2009/10	Wyatt 2012	£9,283	$16,642
NPC	£4,240	2009/10	Wyatt 2012	£5,179	$9,285
NPC	£18,088	2007	Imrie 2009	£23,784	$42,645
Rett syndrome	$21,158	2004/05	Hendrie 2011	$30,199	$30,199
Overall mean cost					$27,900

Table 6 Abbreviations: AUD, Australian dollar; MPS, mucopolysaccharidosis; NPC, Niemann-Pick disease type C
a. Inflation to 2020 dollars on the 21st July 2020 (inflation tool.com)
b. Conversion to AUD on the 21st July 2020 (xe.com)

[12] https://www.inflationtool.com/
[13] https://www.xe.com/

The mean annual cost of care across all five estimates as presented in Table 6 was estimated to be $27,900 and is applied to all remaining childhood dementia disorders.

The lifetime costs of treatment for each disease were subsequently calculated to be the annual costs of care multiplied by the discounted life expectancy for each condition. Applying these costs to the expected number of births for each year provides an estimate of the total costs of care for each disease for each year in the model. An example of such calculation is provided for Alexander disease type 1 for the year 2021 below (Table 7).

The health care cost attributable to childhood dementia overall was then calculated as the sum across all conditions for each year.

TABLE 7 Example calculation of lifetime costs of healthcare for Alexander disease type 1 for a child born in 2021

Parameter	Cost	Source
Annual cost of care	$27,900	Table 6
Discounted life expectancy	9.9	14 years discounted at 5% per year
Expected number of births in 2021	0.3	Based on an incidence of 0.1 per 100,000
Total cost	$94,560	Annual cost x discounted LE x Number of births

Abbreviations: LE, life expectancy

2.2.6.2 Annual indirect costs

The indirect costs aimed to quantify the costs incurred due to lost productivity arising from reduced participation in the workforce by the individual and the carer. The estimated indirect costs were derived from Imrie et al., 2009, described above. As indirect costs occur because of patients and/or carers not being able to work, the data were collected for adult respondents only.

Of the 11 adult patient respondents, seven (64%) reported being unemployed due to their disease; two (18%) were employed, including one part time and one full time worker. Of the 13 carers who responded to the questionnaire, seven (54%) were not currently in paid work due to their caring responsibilities; three carers (23%) had reduced their working hours to part time, and two other employed carers (15%) had taken an average of 2 days' leave in the last 3 months.

These results were converted to an estimated loss of earnings using the Annual Survey of Hours and Earnings (ASHE) from 2007 and the Office for National Statistics (ONS).

The indirect costs of NPC from productivity losses due to reduced working hours, absenteeism and unemployment, were high for both patients and carers. The mean (SD) indirect cost per patient across the entire cohort was £10,008 (£11,736) and £1,632 (£4,356) for carers per year with a total annual indirect cost of £11,640 equating to $27,433 Australian 2020 dollars per year (Table 8). Productivity losses associated with carer unemployment were not calculated because it was not known whether the respondents had needed to give up employment due to their caring responsibilities. This likely explains the lower indirect costs to the caregiver, relative to the patient. The indirect costs incurred by carers of individuals with childhood dementia are therefore likely underestimated.

TABLE 8 Estimated indirect costs of Niemann-Pick disease type C

Indirect costs	Monthly, £	Annual, £	Inflated to 2020[a]	Annual costs (AUD[b])
Productivity losses – patient	£834	£10,008	£13,156	$23,587
Productivity losses – carer	£136	£1,632	£2,145	$3,846
Total				$27,433

The lifetime costs of care for each disease were subsequently calculated to be the annual costs of care multiplied by the discounted life expectancy for each condition. Applying these costs to the expected number of births for each year provides an estimate of the total costs of care for each disease for each year in the model. An example of such a calculation is provided for Alexander disease type 1 for the year 2021 in Table 9.

TABLE 9 Example calculation of lifetime costs of indirect costs for Alexander disease type 1 in the year 2021

Parameter	Cost	Source
Annual cost of care	$27,433	Table 8
Discounted life expectancy	9.9	14 years discounted at 5% per year
Expected number of births in 2021	0.3	Based on an incidence of 0.1/100,000
Total cost	$92,976	Annual cost x discounted LE x Number of births

Table 8 Abbreviations: AUD, Australian dollar

a. Inflation to 2020 dollars on the 21st July 2020 (inflation tool.com)

b. Conversion to AUD on the 21st July 2020 (xe.com)

Table 9 Abbreviations: LE, life expectancy

As per the estimate of the lifetime health care costs, the lifetime caregiver costs for each syndrome was calculated as the annual indirect cost multiplied by the discounted life expectancy and expected number of births for each syndrome. The sum of the indirect costs for all conditions was calculated to derive the total indirect costs of childhood dementia overall for each year.

2.2.6.3 Value of a statistical life year

The indirect costs applied above measure the lifetime income-loss for an individual and their carer due to disease morbidity. They are a measure of productivity losses and although useful, human life is viewed as more than earnings. They do not capture the value of unpaid work and the opportunity cost of excess mortality in childhood dementia. To capture this, a "value of a statistical life year" (VSLY) is used. A VSLY is an estimate of the value of a year of healthy human life. It estimates how much society is willing to pay to reduce the risk of death.

In Australia, the Office of Best Practice Regulation (OBPR) recommends that departments and agencies use the estimate of $151,000 for the VSLY (Abelson, 2007). The OBPR uses ABS Wage Price Index data to express these estimates in 2019 dollars, giving a VSLY of $213,000 (Department of the Prime Minister and Cabinet, 2019). This is applied to the total YLL across all conditions to determine the total opportunity cost of premature mortality associated with childhood dementia. Unlike the indirect costs associated with productivity loss presented above which are applied to the years an individual with childhood dementia is alive, these costs are applied to the YLL which represent the years an individual would be alive if they did not have the condition.

2.2.6.4 Costs to the National Disability Insurance Scheme

The NDIS in Australia is a funding stream designed to support eligible people with permanent and significant intellectual, physical, sensory, cognitive or psychosocial disability, according to their needs, so that their skills and independence improves over time.

The quarterly NDIS data release from December 2019 was used to determine the NDIS spend on patients with intellectual disabilities as a proxy for those with childhood dementia on the basis that the disability support required would be the same and that children with childhood dementia would likely fall into this NDIS category.

The number of patients receiving funding as of the 31st December and the estimated annual spend are summarised in Table 10.

TABLE 10 Estimated NDIS annual spend on patients with intellectual disabilities as of 31st December 2019

Patient group	N	Average annual spend	Total spend
0-6	3,246	$27,000	$87,642,000
7-14	13,401	$29,000	$388,629,000
15-18	7,758	$55,000	$426,690,000
Adult patients	54,587	$123,826	$6,759,263,000
All ages	78,992	$97,000	$7,662,224,000

Table 10 Abbreviations: NDIS, National Disability Insurance Scheme
Source: Data derived from https://data.ndis.gov.au/data-downloads

Using the age specific costs, the cumulative NDIS spend over a patient's lifetime was estimated with cumulative costs applied to each childhood dementia syndrome depending on life expectancy. For example, a patient with Alexander disease with a life expectancy of 14 years, would be expected to receive $392,000 (7x$27,000+7x$29,000) of NDIS funding over their lifetime ($289,262 after discounting).

The lifetime cost is applied to the corresponding expected number of births for each syndrome to derive the NDIS cost for each syndrome for each year of the analysis. The total cost of childhood dementia to the NDIS equal to the sum of costs across all syndromes each year.

2.2.7 Data sources and limitations

The paucity of health care resource utilisation and cost data in the literature means that little is known regarding the true costs of care for the majority of childhood dementia disorders. The costs presented in this section in relation to the direct health care costs are reliant on three sources limited to only a small handful of disorders which may not be an accurate representation of all childhood dementia disorders which vary greatly in their aetiology, clinical presentation and lived experience.

While it is acknowledged that the costs of health care reported in all three studies reflect the total expenditure incurred by a patient in any given year rather than the incremental cost of treatment due to the condition itself, the healthcare costs in otherwise healthy children is expected to be so low that it is unlikely to grossly alter the results. It is also likely that these studies do not capture all expenditure on healthcare services relevant to each disease and that different syndromes may require other healthcare services such as allied health, not captured in this study. This may have resulted in an underestimation of direct costs employed in the analysis presented in this paper.

The indirect costs of care were based on a single study describing the costs attributable to the loss of productivity with NPC from both patients and carers. The costs of care from a caregiver perspective is directly linked to the life expectancy of the patient thus the cost is likely to vary considerably between the different disorders. As the life expectancy of untreated patients with NPC is limited to 12 years of age, this is considered to be a reasonable representation of the life expectancy of childhood dementia disorders overall among those disorders where no disease modifying treatments are available[14]. The indirect costs estimated in Imrie (2009) were primarily made up of loss productivity from the individual as it was not known whether the respondents had needed to give up employment due to their caring responsibilities. This underestimates the total indirect costs due to productivity loss from carers.

[14] It is noted that biotionidase deficiency and holocarboxylase were assumed to have a normal life expectancy when treated

3 RESULTS

3.1 Incidence and life expectancy

A total of 70 conditions were reviewed and fit the defined set of disease criteria for childhood dementia (Nunn et al., 2002; Verity et al., 2010).

Of those, 32 were excluded due to insufficient data (See Appendix 2). A total of 38 conditions were therefore included in this analysis.

The incidence and life expectancy estimates, as derived from the literature, for all conditions included in the analysis are presented in Table 11. The references for each input are presented in Appendix 1. The calculated YLL and YLD for each condition are also presented in Table 11.

The incidence of all childhood dementia disorders ranges from 0.05 (Aspartylglucosaminuria) to 7.00 (mitochondrial disorders) per 100,000.

The life expectancy ranges from 1 (Gaucher disease type 2 and Zellweger Spectrum Disorder) to a normal life expectancy of 83 years (Biotinidase deficiency and Holocarboxylase synthetase deficiency). It is noted that the life expectancy of Biotinidase deficiency and Holocarboxylase synthetase deficiency is in the treated population where life expectancy is assumed to be normal.

The incidence and life expectancy of all childhood dementia disorders is estimated to be 35.67 per 100,000 and 27.81 years, respectively. The prevalence of all children living with childhood dementia from 2021 to 2030 is estimated to be 1,396 to 1,545 and the prevalence of all persons (children and adults) living with childhood dementia from 2021 to 2030 is estimated to be 2,273 to 2,516.

In an average year (between 2021 to 2030) the YLL due to childhood dementia premature mortality is 1,096 year. The YLD due to disability associated with childhood dementia disorders is 451 years. The estimated YLL and YLD in the year 2021 are presented in Figure 3 and Figure 4, respectively. Aspartylglucosaminuria (AGU) and Gaucher disease type 2 have the lowest YLL and YLD estimated in 2021 respectively. The highest YLL and YLD in 2021 is in mitochondrial disorders and Rett syndrome, respectively.

TABLE 11 Incidence and life expectancy of all childhood dementia disorders included in the analysis

Condition	Incidence per 100,000	Life expectancy	YLL	YLD
Lysosomal disorders of lipid metabolism and transport*				
Gaucher disease type 2	0.08	1.00	18.69	0.30
Gaucher disease type 3	0.08	30.00	4.27	4.79
Globoid cell leukodystrophy (Krabbe disease)	0.50	6.72	14.05	1.74
GM1 Gangliosidosis	0.18	3.30	16.67	0.93
GM2 Gangliosidosis (Tay-Sachs disease)	0.22	4.00	16.10	1.11
GM2 Gangliosidosis (Sandhoff disease)	0.40	3.00	16.92	0.85
Metachromatic leukodystrophy	0.83	15.60	8.99	3.32
Multiple sulfatase deficiency	0.07	7.5	13.52	1.91
Niemann-Pick disease type A	0.38	3.00	16.92	0.85
Niemann-Pick disease type C	0.47	13.00	10.25	2.93
Glycoproteinosis*				
Alpha-mannosidosis	0.09	30.00	4.27	4.79
Aspartylglucosaminuria (AGU)	0.05	47.50	1.62	5.62
Mucolipidosis type II (i-cell disease)	0.42	3.00	16.92	0.85
Mucopolysaccharidoses*				
MPS I (Hurler syndrome)	0.90	11.60	11.00	2.69
MPS II (Hunter syndrome)	0.43	15.00	9.27	3.24
MPS III (Sanfilippo syndrome)	1.35	15.90	8.85	3.36
MPS VII (Sly syndrome)	0.05	3.5	16.51	0.98
Other lysosomal diseases*				
Neuronal Ceroid Lipofuscinoses (CLNs, or Batten disease); 14 subtypes (except those that are adult onset CLN 4, 11, 13)	1.00	14.00	9.75	3.09
Other disorders of lipid metabolism and transport				
Cerebrotendinous xanthomatosis	0.34	52.40	1.20	5.75
Disorders of amino acid and other organic acid metabolism				
Canavan disease	1.00	10.00	11.92	2.41
Glycine encephalopathy / Nonketotic hyperglycinemia (NKH)	1.32	1.34	18.38	0.39
Holocarboxylase synthetase deficiency	0.50	82.65^	0.01	6.12

Condition	Incidence per 100,000	Life expectancy	YLL	YLD
Vitamin-responsive inborn errors of metabolism				
Biotinidase deficiency	1.70	82.65^	0.01	6.12
Cobalamin C deficiency (Cbl-C)	1.00	6.00	14.57	1.58
Disorders of mineral absorption and transport				
Menkes disease	1.50	1.75	18.01	0.51
Wilson disease	3.30	78.30	0.08	6.10
Peroxisomal disease				
X-linked adrenoleukodystrophy (subset with childhood dementia)	1.10	12.00	10.78	2.76
Zellweger spectrum disorder	0.50	1.00	18.69	0.30
Other Inborn errors of metabolism				
Mitochondrial disorders (subset with childhood dementia)	7.00	12.00	10.78	2.76
Lafora disease	0.40	24.50	5.70	4.35
Leukodystrophies not otherwise categorised				
Alexander disease type 1	0.10	14.00	9.75	3.09
Pelizaeus Merzbacher disease	0.25	15.4	9.08	3.29
Vanishing white matter disease	1.25	6.00	14.57	1.58
Neurodegeneration with brain iron accumulation				
Pantothenate kinase-associated neurodegeneration (PKAN)	0.15	11.00	11.34	2.59
Neurodegenerative diseases not otherwise categorised				
Cockayne syndrome	0.27	18.00	7.96	3.64
Huntington's disease (juvenile form)	0.34	23.50	6.00	4.25
MECP2 duplication syndrome	0.65	25.00	5.55	4.39
Rett syndrome	5.50	50.00	1.39	5.69
ALL CHILDHOOD DEMENTIA	**35.67***	**27.81**	**1,096***	**451***
Prevalence of all childhood dementia 2021-2030				
All children				1,396 to 1,545
All persons				2,273 to 2,516

Abbreviations: MPS, Mucopolysaccharidosis; NCL, Neuronal Ceroid Lipofuscinoses; NKH, Non-Ketotic Hyperglycinemia PKAN, Pantothenate kinase-associated neurodegeneration

*Annual average, see Table 14 for results from 2021 to 2030

^Assumes early detection and lifelong treatment. Note there are cases where response to treatment is not satisfactory

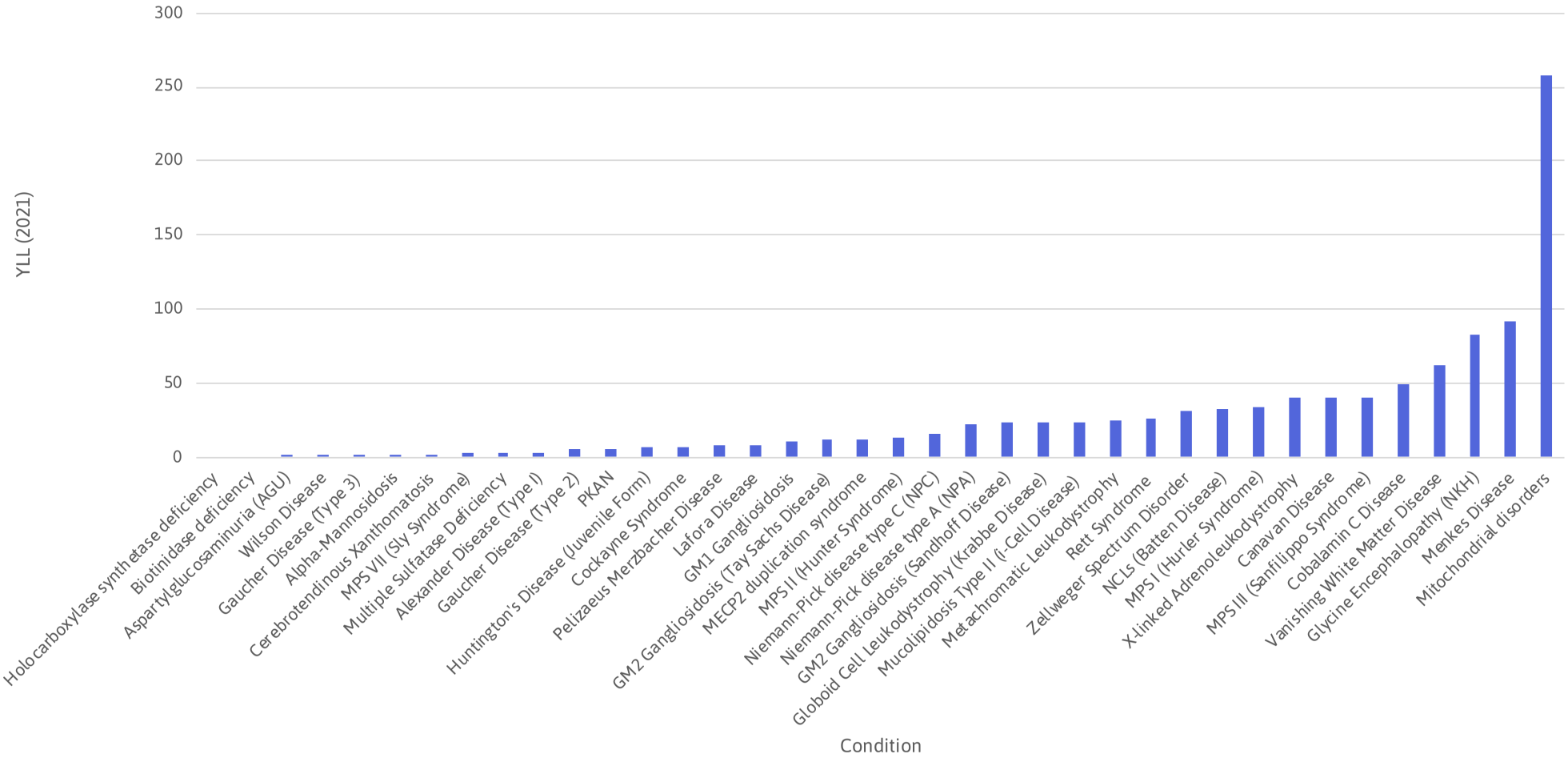

Figure 3 Years of life lost accrued for those born with a childhood dementia disorder in 2021

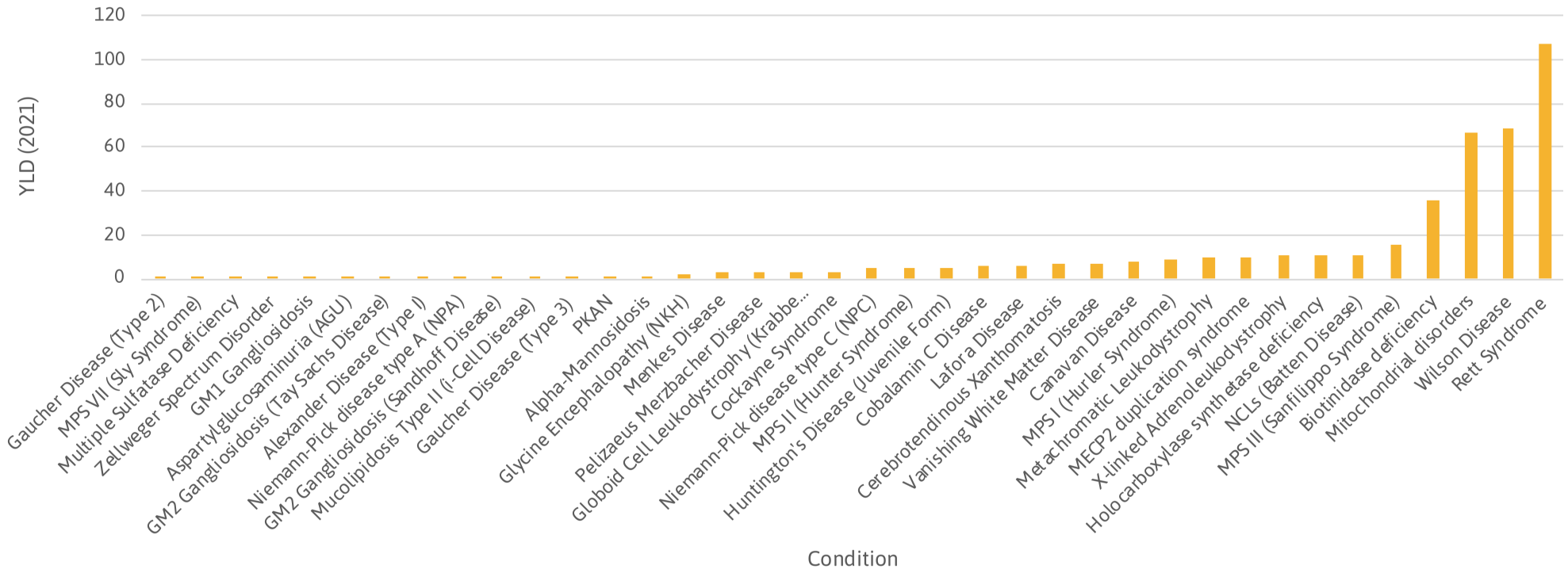

Figure 4 Years of life lost to disability accrued by those born with a childhood dementia disorder in 2021

3.2 Characteristics of the population

Accepted aetio-pathological classifications of disease were employed in this work to group the conditions (Table 11 and Table 12). However, it is acknowledged that there are often differing and overlapping historical classifications. Additionally, some disorders can be allocated to more than one group, in these cases, preference was given for inclusion within the appropriate aetiological category. For example, metachromatic leukodystrophy was classified as a 'lysosomal disorder of lipid metabolism and transport' rather than a leukodystrophy which is a more general descriptor for conditions that affect the white matter of the brain.

The largest proportion of births belong to the lysosomal disease category (21.0%) followed by mitochondrial disorders (19.6%). Third most frequent is the group of "other neurodegenerative conditions" which includes disparate conditions such as Rett syndrome and Juvenile Huntington's disease (19.0%) (Table 12).

To date, most of the disorders identified in this report lack any effective treatment, beyond symptom management and palliative interventions (such as medications to manage seizures and behaviour, physiotherapy, occupational therapy, speech therapy and gastrostomy for feeding difficulty).

Some of the disorders have treatments that aim to ameliorate the underlying defect; mostly dietary restrictions, simple supplementation with certain vitamins, minerals or amino acids to ameliorate the aberrant biochemical pathway. For the majority, success of these treatments is variable and, at best, may only slow disease progression.

Treatment strategies for the lysosomal diseases include pharmaceutical chaperones, substrate reduction therapies (e.g. Miglustat) and enzyme replacement therapies (ERT) to replace the dysfunctional protein. While five ERT products are currently approved for clinical use, four are delivered via intravenous route and are not effective for the central nervous system aspects of these diseases. The fifth product which targets a variant of Batten disease (CLN2), Brineura® (TGA approved in 2018), is delivered via direct intraventricular infusion and has been shown to slow progression of motor and language deficits (Schultz et al., 2018). Its long-term effectiveness however remains unknown.

Additionally, bone marrow transplant (haematopoietic stem cell transplant) is employed at a limited number of paediatric centres for some disorders including metachromatic leukodystrophy, Krabbe disease, Hurler and Hunter syndromes and X-linked adrenoleukodystrophy but benefit is variable and needs to be weighed against the significant risks that can lead to death (Boelens et al., 2014).

There are multiple gene therapy technologies in clinical trial that show promise for some childhood dementia disorders but none have been granted regulatory approval as yet.

With timely diagnosis, less than five percent of the conditions causing childhood dementia could be considered to have currently available treatments with a close to normal life expectancy upon treatment, including Wilson disease, biotinidase deficiency and holocarboxylase synthetase deficiency. These patients however are not completely symptom free with variable treatment responses recognised in these disorders.

TABLE 12 Childhood dementia functional classifications

Aetiopathological classification	% of births
Lysosomal diseases (including disorders of lipid metabolism and transport, mucopolysaccharidoses and glycoproteinosis and others)	21.0%
Mitochondrial disorders	19.6%
Neurodegenerative diseases not otherwise categorised	19.0%
Disorders of mineral absorption and transport	13.5%
Disorders of amino acid and other organic acid metabolism	7.9%
Vitamin-responsive inborn errors of metabolism	7.6%
Peroxisomal disease	4.5%
Leukodystrophies not otherwise categorised	4.5%
Other inborn errors of metabolism	1.1%
Other disorders of lipid metabolism and transport	1.0%
Neurodegeneration with brain iron accumulation	0.4%

The 38 included childhood dementia disorders were grouped by aetiopathological classifications and incidence data used to calculate the number of births in each category.

3.3 Costs

The total cost of childhood dementia in Australia was estimated for the healthcare and indirect costs, opportunity costs as well as the cost of the NDIS as presented in Table 13.

The total cost of childhood dementia to the Australian economy is estimated to be approximately $3.9 billion over the period 2021 to 2030.

TABLE 13 Estimated total costs attributable to childhood dementia in Australia between 2021 and 2030

Year	Healthcare costs	Indirect costs	Cost of life year lost (VSLY)	NDIS expendi-ture	Total cost of childhood dementia
2021	$38,091,430	$37,453,553	$220,183,176	$70,750,462	$366,478,621
2022	$38,732,449	$38,083,837	$223,888,511	$71,941,080	$372,645,877
2023	$39,322,404	$38,663,913	$227,298,679	$73,036,854	$378,321,850
2024	$39,861,073	$39,193,561	$230,412,395	$74,037,370	$383,504,399
2025	$40,350,792	$39,675,080	$233,243,162	$74,946,968	$388,216,003
2026	$40,793,676	$40,110,547	$235,803,200	$75,769,573	$392,476,996
2027	$41,190,280	$40,500,509	$238,095,723	$76,506,219	$396,292,731
2028	$41,544,164	$40,848,467	$240,141,310	$77,163,518	$399,697,459
2029	$41,865,118	$41,164,047	$241,996,549	$77,759,654	$402,785,368
2030	$42,165,491	$41,459,390	$243,732,822	$78,317,563	$405,675,266
Total costs	**$403,916,877**	**$397,152,904**	**$2,334,795,527**	**$750,229,262**	**$3,886,094,570**
Average annual cost	**$40,391,688**	**$39,715,290**	**$233,479,553**	**$75,022,926**	**$388,609,457**

3.4 Summary

The overall results are presented in Table 14. It is estimated that from 2021 to 2030 there will be a total of 1,294 childhood dementia births in Australia, with an average 129 births a year. The prevalence of all children living with childhood dementia from 2021 to 2030 is estimated to be 1,396 to 1,545 and the prevalence of all persons (children and adults) living with childhood dementia from 2021 to 2030 is estimated to be 2,273 to 2,516.

The YLL and YLD from 2021 to 2030 are estimated to be 10,961 and 4,513, respectively.

From 2021 to 2030, the total health care cost of childhood dementia was estimated to be $404 million with an average annual cost of $40 million. Over the ten-year period from 2021 to 2030 considered in the analysis, indirect costs are expected to account for $397 million with an annual average cost of $40 million. The costs to the NDIS are estimated to be $750 million incurred from 2021 to 2030. When applying the VSLY (2019) of $213,000 per YLL the opportunity cost of life years lost over the next ten years is estimated to be $2.3 billion with an annual average of $234 million.

The split of healthcare, indirect and NDIS costs incurred by childhood dementia is illustrated in Figure 5. Majority of costs associated with childhood dementia are in the NDIS, with a relatively equal split between healthcare and indirect costs.

Table 13 Abbreviations: NDIS, National Disability Insurance Scheme; VSLY, value of a statistical life year

TABLE 14 Total births and costs of all childhood dementia disorders in Australia

Outcome	2021 to 2030	Annual average
Australian birth cohort	3,630,736	363,074
Total childhood dementia births	1,295	129
Incidence per 100,000	35.67	35.67
Prevalence		
Children living with childhood dementia: 2021 to 2030		1,396 to 1,545
Persons living with childhood dementia: 2021 to 2030		2,273 to 2,516
Years of life lost	10,961	1,096
Life expectancy	27.81	27.81
Years of life lost due to disability	4,513	451
Costs to the healthcare system	$403,916,877	$40,391,688
Indirect costs	$397,152,904	$39,715,290
Costs of life year lost	$2,334,795,527	$233,479,553
Cost to National Disability Insurance Scheme	$750,229,262	$75,022,926
Total cost of childhood dementia	**$3,886,094,570**	**$388,609,457**

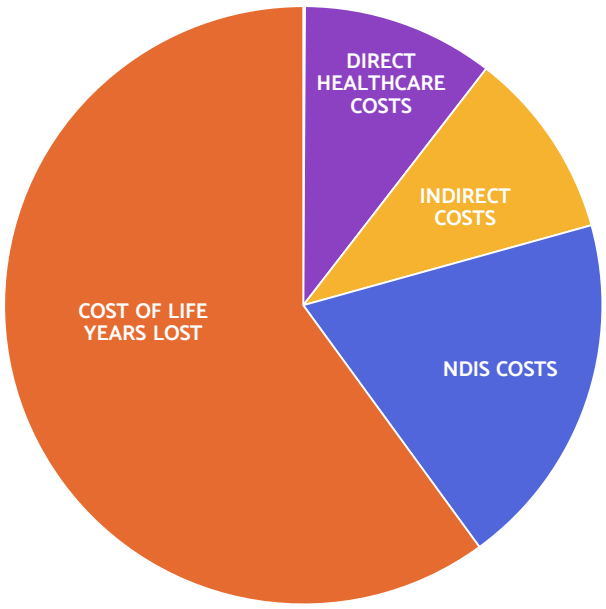

Figure 5 Costs of childhood dementia

4 DISCUSSION

Childhood dementia represents an important challenge to our healthcare system and society at large. Dementia is typically assumed to be a disease of adulthood and old age, however, tragically, children are affected too. Suffering progressive cognitive decline, multiple loss of already attained developmental skills, and a severely shortened life, children often die before adulthood, some in early childhood and infancy. The average life expectancy determined in this study was 28 years.

Dementia in childhood has long been recognised by the medical community but as a collective group of disorders, childhood dementia has received little attention to date. The analysis undertaken in this report defines and identifies the Australian population affected by childhood dementia and estimates the resultant direct and indirect costs incurred to the Australian economy currently and over the next decade.

We identified more than 70 disorders that cause childhood dementia. This list is not exhaustive and there are likely children without a definitive diagnosis (syndromes without a name) and other ultrarare conditions with insufficient published literature available to determine if they fit the criteria. Furthermore, with advances in genomic technology, new childhood dementia disorders are being identified among the pool of undiagnosed cases, contributing to this ever-expanding group of conditions. This current list is therefore dynamic and must be curated over time to ensure the incidence and prevalence of childhood dementia is accurately captured.

Analysis of the functional classification of the disorders showed that lysosomal and mitochondrial diseases were the largest groups, accounting for 21% and 19.6% of childhood dementia respectively. The range of aetiologies and pathologies demonstrates the vulnerability of the brain and neuropsychological processes, and highlights the remarkable complexity in cause, diagnosis and treatment of childhood dementia. Importantly however, and central to the purpose of this report, this analysis identifies numerous overlapping disease mechanisms within and between the subgroups of childhood dementia disorders highlighting potential common therapeutic targets and exciting opportunities for research and development.

Indeed, the vast majority of childhood dementia disorders lack effective therapeutic intervention beyond symptom management. Where treatments are available, efficacy is variable and at best, generally only slow the rate of disease progression, highlighting the dire unmet clinical need for childhood dementia patients and their families.

Although each individual condition is considered rare or ultra-rare, with low incidence and therefore low costs to society and the healthcare system, as a collective the cumulative incidence of childhood dementia disorders in Australia is estimated to be 36 per 100,000. In 2021 it is estimated that there will be 2,273 persons living with childhood dementia in Australia. The total costs, including healthcare costs, indirect costs (from productivity loss and opportunity costs) and costs to the NDIS in an average year are estimated to be $389 million.

The YLL is an estimate of the average years a person would have lived if he or she had not died prematurely. Individuals with childhood dementia have, on average, a life expectancy of 28 years, compared to the Australian general population life expectancy of 83 years (ABS 2020[15]). This analysis found that the burden of premature mortality associated with childhood dementia over the next 10 years is 10,961 lost life years, with an annual average of 1,096 life years.

As used by some Australian Government Departments an approach based on the VSLY, which is understood as the marginal dollar value of a year of healthy human life, is used to measure the opportunity cost of the premature mortality in childhood dementia. The VSLY attempts to incorporate these dimensions by estimating how much society is willing to pay to reduce the risk of death. Using the estimate of $213,000 recommended by the OBPR for VSLY (measured in AUD2019), the total cost of life years lost in childhood dementia is estimated to be $2.3 billion over the next ten years with an annual average of $234 million.

The severity of symptoms in childhood dementia means full time care is often required and employment for the individual as well as carers is not plausible. This analysis indicates that these indirect costs, due to productivity loss, to the carers and the individual over the next ten years equate to a total of $397 million, with an annual average of $40 million.

The NDIS provides funding to an estimated 500,000 Australians who have permanent and significant disability. The type of supports that the NDIS may fund include: daily personal activities, transport to enable participation in daily life activities, workplace help, therapeutic supports, help with household tasks, help in equipment assessment, set up and training, home modifications, mobility equipment and vehicle modifications (NDIS[16]). In an average year, it is estimated that the NDIS costs, attributed to childhood dementia, is $75 million, accumulating to $750 million over ten years.

This is the first paper to attempt to quantify the burden of illness in a range of conditions that cause childhood dementia. Although the overall incidence and costs of some conditions have been measured, a combined analysis of all childhood dementia disorders was not feasible with the data available. This analysis does not include an exhaustive list of all of the conditions that cause childhood dementia, thereby underestimating the total incidence and costs. There were 32 conditions initially included in this analysis that were excluded (see Appendix B) due to insufficient data. More conditions, that were not identified, are expected to meet the inclusion criteria. The costs attributed to childhood dementia are therefore expected to be higher than the estimates provided in this analysis.

Another potential limitation of this analysis is the static approach. It does not capture the burden of disease over a lifetime. The progressive nature of childhood dementia means that the severity, and therefore the associated costs of care, are likely to change throughout an individual's lifetime. Reliance is placed on 'averages' of these outcomes as it was not feasible to capture the variations within this report.

The rarity and severity of these conditions means that there is limited high quality, up to date evidence measuring the burden of childhood dementia. The incidence and life expectancy estimates were derived from differing studies and online databases. The inconsistency may affect the comparability of data. Given that the included conditions are rare, quantifying the incidence and life expectancy in small patient groups may not always be accurate.

[15] https://www.abs.gov.au/ausstats/abs@.nsf/mf/3302.0.55.001#:~:text=In%202016%2D2018%2C%20life%20expectancy,and%201.2%20years%20for%20females.

[16] https://www.ndis.gov.au/understanding/what-ndis

To account for the lack of robust data, assumptions were made throughout this analysis, particularly relating to cost inputs. Three studies, encompassing four conditions, quantified resource use and healthcare costs and only one study measuring productivity losses in one condition were identified and applied to all conditions in this analysis. This analysis applied averages despite the variance in disease severity across conditions and within an individual's lifetime. Furthermore, it is likely that individuals in Australia incur out-of-pocket costs to access treatments and other health care resources to manage childhood dementia. This could include travelling overseas for treatment or importing treatments themselves. These costs are not measured and therefore could not be captured in this analysis. Not including these out-of-pocket costs underestimates the total burden of childhood dementia.

The indirect costs incurred by carers were derived from one study measuring costs in adults with NPC (Imrie et al., 2009). The costs were primarily made up of loss productivity from the individual, and only a small proportion were made up from the carer as it was not known whether the respondents had needed to give up employment due to their caring responsibilities. This underestimates the total indirect costs due to productivity loss from carers. There is currently insufficient reliable data to estimate what the incremental cost of caring for an individual with childhood dementia is. More robust research on the indirect costs experienced by carers is required to quantify the full burden of childhood dementia.

Opportunities for future research also extend to include the list of excluded conditions. Continual monitoring and updating of data on all childhood dementia could result in a more robust estimate of the rates and costs associated. High quality, up to date studies collecting data on the incidence, life expectancy and costs of each individual condition are required to provide a more comprehensive analysis.

The direct costs included in this analysis were limited to the Australian healthcare system where possible or included costs derived from other sources with similar healthcare systems in place. Consequently, it may not necessarily be appropriate to extrapolate the results of this analysis to other settings where universal healthcare is not established. This could be a worthwhile avenue for future research and investigation. Nevertheless, it would be reasonable to predict the global impact of childhood dementia on healthcare systems and economies around the world would be substantial.

The total cost of childhood dementia, estimated at $389 million annually, may be considered low in comparison to other conditions affecting children. A number of other conditions that have been analysed in Australia are estimated to cost up to $28 billion annually, such as autism at $9.7 billion (Synergies 2011), ADHD at $20.4 billion (Deloitte Access Economics 2019), cerebral palsy at $1.47 billion (Access Economics 2007) and epilepsy at $12.3 billion (Deloitte Access Economics 2019). The low incidence and life expectancy of childhood dementia accounts for the overall low costs in comparison to other conditions The relatively low cost of childhood dementia to the healthcare system is a consequence of the short life expectancy of the population and the lack of treatment options the healthcare system is able to provide. The burden of childhood dementia is therefore disproportionately met by the patients themselves, support services and carers. The largest cost item for childhood dementia – outweighing all other costs in our study combined – is the opportunity cost associated with premature mortality.

Importantly, and promisingly, there exist on the horizon for patients with childhood dementia encouraging emergent therapies including gene transfer and editing technologies. These treatments have the potential to significantly improve patient outcomes and reduce the burden of these conditions on patients and their carers. The relatively low cost of childhood dementia to the healthcare system and to governments identified in our study suggests there is opportunity for investment in these treatments as they emerge and importantly, in the infrastructure and processes, including newborn screening, to ensure these treatments reach patients when they are most effective.

Our study has identified relatively low financial costs to the healthcare system and to the NDIS, but relatively high opportunity costs associated with childhood dementia. Given the relatively small incidence of these conditions, there is substantial opportunity for investment in these conditions – either in research or in effective treatments themselves – to greatly improve outcomes for patients, their carers and families – with minimal financial impost to government budgets.

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APPENDIX 1: INCLUDED CONDITIONS

TABLE 15 Incidence data input references

Condition	Incidence per 100,000	Source
Lysosomal disorders of lipid metabolism and transport*		
Gaucher disease (type 2)	0.1	Meikle et al. et al. (1999), Orphanet (accessed 13/07/2020)
Gaucher disease (type 3)	0.1	Meikle et al. et al. (1999), Orphanet (accessed 13/07/2020)
Globoid cell leukodystrophy (Krabbe disease)	0.5	Meikle et al. (1999)
GM1 Gangliosidosis	0.2	Brunetti-Pierri et al. (2008), Meikle et al. (1999)
GM2 Gangliosidosis (Tay-Sachs disease)	0.2	Meikle et al. (1999), Smith et al. (2012)
GM2 Gangliosidosis (Sandhoff disease)	0.4	Meikle et al. (1999), Smith et al. (2012)
Metachromatic leukodystrophy	0.8	Meikle et al. (1999)
Multiple sulfatase deficiency	0.1	Meikle et al. (1999)
Niemann-Pick disease type A (NPA)	0.4	Meikle et al. (1999)
Niemann-Pick disease type C (NPC)	0.5	Meikle et al. (1999)
Glycoproteinosis*		
Alpha-mannosidosis	0.1	Meikle et al. (1999)
Aspartylglucosaminuria (AGU)	0.05	Meikle et al. (1999)
Mucolipidosis type II (i-cell disease)	0.4	Meikle et al. (1999)
Mucopolysaccharidoses*		
MPS I (Hurler syndrome)	0.9	Meikle et al. (1999)
MPS II (Hunter syndrome)	0.4	Meikle et al. (1999)
MPS III (Sanfilippo syndrome)	1.4	Meikle et al. (1999)
MPS VII (Sly syndrome)	0.05	Meikle et al. (1999)

Other lysosomal diseases*		
Neuronal ceroid lipofuscinoses (Batten disease); 14 subtypes (except those that are adult onset CLN 4, 11, 13)	1.0	Johnson et al. (2019)
Other disorders of lipid metabolism and transport		
Cerebrotendinous xanthomatosis	0.3	Salen and Steiner (2017)
Disorders of amino acid and other organic acid metabolism		
Canavan disease	1.00	Orphanet (accessed 1/05/20)
Glycine encephalopathy	1.3	Coughlin et al (2017)
Holocarboxylase synthetase deficiency	0.5	Donti et al. (2016)
Vitamin-responsive inborn errors of metabolism		
Biotinidase deficiency	1.7	Wolf et al. (1991)
Cobalamin C disease	1.0	Martinelli et al. (2011)
Disorders of mineral absorption and transport		
Menkes disease	1.5	Ojha and Prasad (2016)
Wilson disease	3.3	Członkowska et al. (2018)
Peroxisomal disease		
X-linked adrenoleukodystrophy (subset with childhood dementia)	1.1	Engelen et al. (2012), Berger et al. (2014) (calculated from incidence and 35-40% of boys develop Cerebral Adrenoleukodystrophy in childhood)
Zellweger spectrum disorder	0.5	Genetics Home reference (accessed 10/07/20)

Other Inborn errors of metabolism		
Lafora disease	0.4	Jansen and Andermann (2007)
Mitochondrial disorders (subset with childhood dementia)	7.0	Skladal et al. (2003), Gorman et al. (2016) and unpublished data (personal communication with Prof. David Thornburn) which indicates that ~70% of children with mitochondrial disease have an encephalopathy
Leukodystrophies not otherwise categorised		
Alexander disease (type I)	0.1	NORD (accessed 10/07/20)
Pelizaeus Merzbacher disease	0.3	Orphanet (accessed 10/07/20)
Vanishing white matter disease	1.3	Hamilton et al. (2018)
Neurodegeneration with brain iron accumulation		
Pantothenate kinase-associated neuro-degeneration (PKAN)	0.2	Kurian and Hayflick (2018)
Neurodegenerative diseases not otherwise categorised		
Cockayne syndrome	0.3	Kleijer et al. (2008)
Huntington's disease (juvenile form)	0.3	Orphanet et al. (accessed 10/07/20)
MECP2 duplication syndrome	0.7	Giudice-Nairn et al. (2019)
Rett syndrome	5.5	Fehr et al. (2011)

NORD, National Organization of Rare Disorders
Orphanet: www.orpha.net
*Lysosomal disease

TABLE 16 Life expectancy data input references

Condition	Life Expectancy	Source
Lysosomal disorders of lipid metabolism and transport*		
Gaucher disease (type 2)	1	Mignot et al. (2006)
Gaucher disease (type 3)	30	Gilbert-Barness et al. (2017)
Globoid cell leukodystrophy (Krabbe disease)	6.72	Bascou et al. (2018)
GM1 gangliosidosis	3.3	Regier & Tifft (2013), Meikle et al. (1999)
GM2 gangliosidosis (Tay-Sachs disease)	4	Kaback et al. (1999)
GM2 gangliosidosis (Sandhoff disease)	3	Orphanet (accessed 10/07/20)
Metachromatic leukodystrophy	15.6	Mahmood et al. (2010), Genetics Home Reference (accessed 15/07/2020) https://ghr.nlm.nih.gov/condition/metachromatic-leukodystrophy
Multiple sulfatase deficiency	7.5	Sabourdy et al. (2015)
Niemann-Pick disease type A (NPA)	3	OMIM (accessed 10/07/20)
Niemann-Pick disease type C (NPC)	13	Bianconi et al. (2019)
Glycoproteinosis*		
Alpha-mannosidosis	30	Wall et al. (1998), Malm and Nilssen. (2008) (calculated an average)
Aspartylglucosaminuria (AGU)	47.5	Arvio and Mononen (2016)
Mucolipidosis type II (i-cell disease)	3	Edmiston et al. (2019)
Mucopolysaccharidoses*		
MPS I (Hurler syndrome)	11.6	Moore et al. (2008)
MPS II (Hunter syndrome)	15	Genetic Home References (accessed 10/07/20)
MPS III (Sanfilippo syndrome)	15.9	Zelei et al. (2018) (estimated from the life expectancy and proportion)
MPS VII (Sly syndrome)	3.5	Zielonka et al. (2017)

Other lysosomal diseases*		
Neuronal ceroid lipofuscinoses (NCLs or Batten disease); 14 subtypes (except those that are adult onset CLN 4, 11, 13)	14	Mole and Cotman (2016), Mole and Williams (2013) (calculated average)
Other disorders of lipid metabolism and transport		
Cerebrotendinous xanthomatosis	52.4	Pilo-de-la-Fuente et al. (2011)
Disorders of amino acid and other organic acid metabolism		
Canavan disease	10	Orphanet (accessed 10/07/20)
Glycine encephalopathy	1.34	Hoover-Fong et al. (2004)
Holocarboxylase synthetase deficiency	82.65	Assume normal life expectancy with treatment*
Vitamin-responsive inborn errors of metabolism		
Biotinidase deficiency	82.65	Assume normal life expectancy with treatment
Cobalamin C disease	6	Fischer et al. (2014)
Disorders of mineral absorption and transport		
Menkes disease	1.75	Ojha and Prasad (2016)
Wilson disease	78.3	Członkowska et al. (2018)
Peroxisomal disease		
X-linked adrenoleukodystrophy (subset with childhood dementia)	12	Engelen et al. (2012) (Life expectancy based on mean age of onset 7 years and mortality 3-5 years from age of onset)
Zellweger spectrum disorder	1	Rare Diseases (accessed 10/07/20)
Other Inborn errors of metabolism		
Lafora disease	24.5	Ibrihim et al. (2020) (life expectancy based on age of onset 11-18 years. Death 10 years later)
Mitochondrial disorders (subset with childhood dementia)	12	Darin et al. (2001)

Leukodystrophies not otherwise categorised		
Alexander disease (type I)	14	Prust et al. (2011)
Pelizaeus Merzbacher disease	15.4	Maertens and Dyken (2007) (estimated from the life expectancy and prevalence of different forms)
Vanishing white matter disease	6	Hamilton et al. (2018)
Neurodegeneration with brain iron accumulation		
Pantothenate kinase-associated neurodegeneration (PKAN)	11	Dangel et al. (2020)
Neurodegenerative diseases not otherwise categorised		
Cockayne syndrome	18	MedScape (accessed 10/07/20)
Huntington's disease (juvenile form)	23.5	Solberg et al. (2018) (Life expectancy based on average age of onset 6 years + patients surviving 10-15 years from onset of symptoms)
MECP2 duplication syndrome	25	Friez et al. (2006)
Rett syndrome	50	Anderson et al. (2014)

*Lysosomal disease
Abbreviations: OMIM, Online Mendelian Inheritance in Man
NORD, National Organization of Rare Disorders
Orphanet: www.orpha.net

APPENDIX 2: EXCLUDED CONDITIONS

The following conditions were identified as disorders causing childhood dementia but insufficient data was available for their inclusion in the analysis.

Lysosomal diseases

→ Lysosomal disorders of lipid metabolism and transport

- Combined saposin (prosaposin) deficiency
- Farber disease
- GM2 gangliosidosis - AB variant
- Saposin A deficiency
- Saposin B deficiency
- Saposin C deficiency

→ Glycoproteinosis

- α-N-acetylgalactosaminidase deficiency (Schindler disease (type I))
- Beta-mannosidosis
- Fucosidosis (type I and II)
- Galactosialidosis (cathepsin A mutation)
- Mucolipidosis type I (sialidosis)
- Mucolipidosis type IV

→ Other lysosomal diseases

- Sialic acid storage disease

Other disorders of lipid metabolism and transport

- Abetalipoproteinaemia

Disorders of amino acid and other organic acid metabolism

- Glutathione synthetase deficiency
- Sulfite oxidase deficiency

Vitamin-responsive inborn errors of metabolism

- Biotin-thiamine-responsive basal ganglia disease
- Cerebral folate deficiency
- Molybdenum cofactor deficiency
- SLC5A6 deficiency

Other Inborn errors of metabolism

- Congenital disorders of glycosylation (subset of e.g. CDG1E, CDG1J, CDG2A)

Leukodystrophies not otherwise categorised

- POLR3-related leukodystrophies

Neurodegeneration with brain iron accumulation

- Beta-propeller protein-associated neurodegeneration (BPAN)
- Coenzyme A synthase protein-associated neurodegeneration (COASY)
- Fatty acid hydroxylase-associated neurodegeneration (FAHN)
- Kufor-Rakeb syndrome
- Mitochondrial membrane protein-associated neurodegeneration (MPAN)
- Woodhouse-Sakati syndrome (DCAF17)

Neurodegenerative diseases not otherwise categorised

- Giant axonal neuropathy
- Huntington disease-like variants (particularly HDL3)
- Infantile neuroaxonal dystrophy
- Juvenile Parkinson's disease PARK19A (DNAJC6)