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ORIGINAL PAPER

Comparing Parental Well-Being and Its Determinants Across Three Different Genetic Disorders Causing Intellectual Disability

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Abstract

Using the Short Form 12 Health Survey this cross-sectional study examined parental well-being in caregivers of children with one of three genetic disorders associated with intellectual disability; Down syndrome, Rett syndrome and the CDKL5 disorder. Data were sourced from the Western Australian Down Syndrome (n = 291), Australian Rett Syndrome (n = 187) and International CDKL5 Disorder (n = 168) Databases. Among 596 mothers (median age, years 43.7; 24.6–72.2), emotional well-being was poorer than general female populations across age groups. Multivariate linear regression identified the poorest well-being in parents of children with the CDKL5 disorder, a rare but severe and complex encephalopathy, and negative associations with increased clinical severity irrespective of diagnosis. These findings are important for those providing healthcare and social services for these populations.

Keywords Parental well-being · Down syndrome · Rett syndrome · SF-12 · Intellectual disability · Genetic disorder

Introduction

A growing number of studies have examined parental well-being in families with a child with a developmental disability over the last decade, focusing mainly on mothers with a child with autism spectrum disorder, non-specific intellectual disability or cerebral palsy (Fairthorne et al. 2015). The literature suggests that mothers experienced poorer emotional well-being compared with those without a child with a developmental disability or with the general population (Pousada et al. 2013; Totsika et al. 2011; Zablotsky et al. 2013). Relationships between poor maternal emotional well-being and recurring grief (Gupta 2007; Whittingham et al. 2012), difficulty coping (Minnes et al. 2015; Piazza et al. 2014; Zablotsky et al. 2013), child behavioural and emotional problems (Firth and Dryer 2013; Minnes et al. 2015; Totsika et al. 2011) and child sleep disturbances (Hodge et al. 2013; Lee 2013; Wayte et al. 2012), as well as limited access to or unmet needs for social support (Cantwell et al. 2014; Giallo et al. 2011; Ingersoll and Hambrick 2011; Pousada et al. 2013) have either been identified or postulated.

Genetic disorders account for a substantial proportion of intellectual disability and associated syndromes (Gilissen et al. 2014). Down syndrome is generally caused by an extra partial or whole copy of chromosome 21 (Pangalos et al. 1994) with an approximate prevalence of one per 1000 live births in Western Australia (WA) (Bower et al. 2015). Despite variable severity, an affected child almost always experiences intellectual disability and some comorbidities such as congenital heart disease and may be prone to behavioural problems (Grieco et al. 2015; Thomas et al. 2010). Rett syndrome is a rare genetic disorder mainly affecting females (Neul et al. 2010). It is caused by a mutation in the methyl CpG-binding protein 2 (*MECP2*) gene and has an estimated cumulative risk of diagnosis of 1 in 8905 by the age of 32 years (Fehr et al. 2011). Typically, the child

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develops normally in the first 6 months, but there is subsequent loss of communication and/or hand skills usually between 15 and 30 months, resulting in severe intellectual and physical disabilities (Fehr et al. 2010; Neul et al. 2010). Comorbidities such as epilepsy, autonomic dysfunction, growth and sleep problems and scoliosis also commonly occur (Leonard et al. 2017; Neul et al. 2010). The CDKL5 disorder is a relatively newly recognised entity caused by a mutation in the cyclin-dependent kinase-like 5 (*CDKL5*) gene (Fehr et al. 2013). It was initially identified in children clinically diagnosed with the early-onset seizure variant of Rett syndrome (Evans et al. 2005) or with an epileptic encephalopathy (Kalsheuer et al. 2003). Compared with Rett syndrome, the child is likely to experience more severely impaired neurodevelopment, refractory epilepsy and prominent sleep disturbances (Fehr et al. 2013).

There is generally a paucity of research on parental well-being for those with a child with a genetic developmental disorder. Furthermore, the pathways to achieving a diagnosis for their child and disease-specific family support may be complex (Anderson et al. 2013), resulting in further emotional burden for parents (Tibben 2016). Impaired emotional health has been reported among mothers with a child with Down syndrome (Bourke et al. 2008), Rett syndrome (Cianfaglione et al. 2015; Laurvick et al. 2006), and more recently in those with a child with the CDKL5 disorder (Mori et al. 2017). High stress levels have also been experienced by those with a child with Prader-Willi syndrome (Tvrdik et al. 2014). Determinants often relate to clinical characteristics of the specific disorder. For example, we found that child behavioural and emotional problems, impaired musculoskeletal health and more episodes of illness in the previous year were associated with poorer parental emotional well-being among 363 Western Australian families of children with Down syndrome (Bourke et al. 2008). In a study of 87 British families of children with Rett syndrome, greater severity of medical conditions and behavioural problems were shown to threaten parental emotional well-being (Cianfaglione et al. 2015) while using a population-based Australian cohort we found that a recent bone fracture was one of the major risk determinants of impaired emotional well-being (Laurvick et al. 2006). In contrast, in an international sample of families with children with the CDKL5 disorder (n = 158) we found that increased severity of child sleep disturbances was adversely associated with parental emotional well-being while enteral feeding was a protective factor (Mori et al. 2017).

It is feasible that service provision or specific interventions may ameliorate the burden for families. A US study reported that the provision of a tailored, interdisciplinary programme ameliorated parental distress among 57 parents with children with Prader-Willi syndrome (Tvrdik et al. 2014). Alternatively, our longitudinal study of 170 Australian families of children with Rett syndrome found that use of respite care was not associated with better parental emotional health and was associated with poorer physical health over 2 years of follow-up (Urbanowicz et al. 2011). Similarly, we did not find any positive association between parental physical or emotional well-being and respite care use among those of children with the CDKL5 disorder (Mori et al. 2017). These findings might indicate that although multidisciplinary supports based on individual needs will theoretically reduce the emotional burden of caregiving, the current systems in place may not be adequately structured to support these particular populations of children and their parents.

Several previous studies have therefore examined parental well-being by targeting an individual genetic disorder. However, the commonalities and differences as well as risk and protective factors also need to be investigated across disorders so that our understanding of the impact of everyday caregiving a child with a rare genetic disorder can be better interpreted. This information could help inform an optimal framework for health care and social support delivery to children with these disorders and their families. This cross-sectional study aimed to examine parental well-being among those raising a child with one of three genetic disorders associated with intellectual disability; Down syndrome, Rett syndrome and the CDKL5 disorder. First, we compared parental well-being with that in the general population. Second, we investigated the univariate associations with family, child and socio-environmental characteristics. We then investigated the multivariate associations with child diagnosis, clinical features and socio-environmental characteristics adjusting for family characteristics and child age.

Methods

Participants

Data were sourced from three databases, all housed at the Telethon Kids Institute in Perth, WA. The WA Down Syndrome 'Needs Opinions Wishes' (NOW) Database was established in 1997 as a state-wide population-based database of Down syndrome by ascertaining school-aged children with Down syndrome (birth years 1980–1991) from the WA Disability Service Commission and the WA Birth Defects Registry (Petterson et al. 2005). Further cases ranging in age from birth to 25 years (birth years 1980–2004) were identified from the Disability Service Commission in 2004 (Petterson et al. 2005) and data on family, child and socio-environmental characteristics were collected in 1997, 2004, 2009 (birth years 1980–1994) and 2011 (birth years 1980–1995) via family questionnaires (Foley et al. 2016). The Australian Rett Syndrome

Database (ARSD) was established as a national population-based register of Rett syndrome in 1993, with ongoing ascertainment through the Australian Paediatric Surveillance Unit and the parent group, the Rett Syndrome Association of Australia (Downs and Leonard 2013). Data on a comprehensive range of family, child and socio-environmental characteristics were longitudinally collected in 1996, 2000, 2002, 2004, 2006, 2009 and 2011 via family questionnaires (Anderson et al. 2014; Downs and Leonard 2013). Clinicians have also provided information on child neurodevelopment and clinical symptoms specifically during the perinatal period to early childhood before the diagnosis was made (Anderson et al. 2014; Downs and Leonard 2013). The International CDKL5 Disorder Database (ICDD) was established as the first structured database of the CDKL5 disorder in 2012 and cases have been recruited through the International Foundation for CDKL5 Research website as well as by contacting families with a child with the CDKL5 disorder, already participating in the Inter-Rett database, an international study of Rett syndrome first established in 2002 (Fehr et al. 2013; Louise et al. 2009). Information collected includes a broad range of data on family, child and socio-environmental characteristics with the aim of increasing knowledge about this recently recognised disorder. The 2004 cohort (n = 363) of the WA Down Syndrome NOW Database was used for this study since the cohort included both young children and adults with Down syndrome, the best match for comparison with those in the other two databases. The 2011 cohort (n = 229) of the ARSD was used for this study as it approximated best with the timing of the administration of the CDKL5 disorder questionnaire (September 2012-April 2016, n = 200). The total study population included families of 792 cases.

In collaboration with family representatives as well as researchers and clinicians family questionnaires have been developed separately for each disorder according to their unique clinical features and taking account of the specific aims of each wave of data collection (Anderson et al. 2014; Downs and Leonard 2013; Fehr et al. 2013; Foley et al. 2016; Robertson et al. 2006).

The 2004 Down syndrome questionnaire comprised two parts. Part one contained 16 sections including questions regarding parental socio-demographics including current financial situation by the Indicators of Social and Family Functioning Reference Instrument (Zubrick et al. 2000) and access to social support, child current and previous comorbid physical conditions, current functioning and behaviour problems respectively by the Functional Independence Measure for Children (WeeFIM) modified to be used when rated by a parent (Leonard et al. 2002), and the Developmental Behaviour Checklist: Primary Carer Version (DBC-P) (Einfeld and Tonge 2002). Part two contained nine sections including parental well-being assessed by the Short Form 12 Health Survey Version 2 (SF-12v2) (Ware et al. 2004) and family structure.

The 2011 Rett syndrome questionnaire consisted of two parts. Part one contained 17 sections including questions relating to parental demographics and current financial situation by the Indicators of Social and Family Functioning Reference Instrument (Zubrick et al. 2000), child medical history principally epilepsy, gastrointestinal conditions, breathing abnormalities, scoliosis and sleep disturbances, current functional ability and access to social support such as respite care. Part two contained nine sections including parental well-being measured by the Short Form 12 Health Survey (SF-12) (Ware et al. 1995) and family structure.

The CDKL5 disorder questionnaire is comprised of three parts. Part one contains 19 sections in relation to child development and medical conditions including current functional ability such as mobility, communication skills and feeding, previous and current medical conditions such as epilepsy, sleep disturbances [measured by the Sleep Disturbance Scale for Children (SDSC) (Bruni et al. 1996)], gastrointestinal illnesses, scoliosis, breathing abnormalities and respiratory conditions, and access to social support including respite and financial aids. Part two contains three sections including parental demographics, family structure and parental well-being assessed by the SF-12v2 (Ware et al. 2004). Part three is a seizure diary.

Measures for Dependent Variable: Parental Well-Being

A parent was defined as the family member who filled in a family questionnaire and who primarily cared for the affected child in this study. Parental well-being was measured by the SF-12 or SF-12v2 as aforementioned (Ware et al. 1995, 2004). The SF-12 was derived from the Short Form 36 Health Survey (SF-36), which was originally developed as a self-reporting screening instrument that assessed and monitored the physical and mental health status of a patient in clinical settings (McHorney et al. 1993; Ware et al. 1995). The Short Form 36 Health Survey Version 2, an updated version of the SF-36, has been widely used to measure maternal well-being across the literature in the field of developmental disabilities (Lee 2013). The SF-12 is considered as an efficient alternative to the SF-36 in diverse medical conditions (McHorney et al. 1993) and has also been validated in Australian (Avery et al. 2004) and other populations with diverse ethnicity (Delate and Coons 2000; Jenkinson et al. 2001). The SF-12v2 is an updated version of the SF-12 and captures more individual variation (Ware et al. 2004). Both versions consist of 12 items asking about individual's health-related quality of life including six each relating to physical and emotional health, which yield norm-referenced scores for two well-being scales; the Physical Component Summary

(PCS) and Mental Component Summary (MCS) (Ware et al. 1995, 2004). Higher scores indicate better well-being (Ware et al. 1995, 2004). The PCS and MCS scores of the SF-12v2 have been shown to be comparable with those of the SF-12 (Ware et al. 2004).

Measures for Independent Variables

Data collected in the 2004 Down syndrome family questionnaire, the 2011 Rett syndrome questionnaire and the CDKL5 disorder questionnaire (administered during the period from November 2012 till April 2016) were used to measure independent variables for Down syndrome, Rett syndrome and the CDKL5 disorder, respectively. The independent variables were grouped into: family-related factors (parental age, highest qualification and current work status, and the number of siblings and birth order of the affected child); child-related factors (child age, diagnosis, clinical severity, disrupted sleep and frequency of hospitalisations); and socio-environmental factors (place of residence, respite use, financial hardship and attending day activities). Parental highest qualification referred to the highest educational qualification a parent had obtained by the time when the parent completed a questionnaire, categorised as no higher than secondary school, technical certificate or university degree. Data for parental age, highest qualification and current work status were not available when the primary caregiver was a grandparent or a sibling (n = 6). The independent variables and how they were defined are summarised in Table 1.

Child disrupted sleep was categorised based on a degree of current disrupted sleep [an item of the DBC-P (Einfeld and Tonge 2002)] in Down syndrome, a frequency of night waking over the previous 2 years (a customised question) in Rett syndrome or a frequency of night waking over the last 6 months [an item of the SDSC (Bruni et al. 1996)] in the CDKL5 disorder. 'Severe' was defined either when the parent reported child disrupted sleep was a major problem in Down syndrome or when child's night waking occurred more frequently than weekly in Rett syndrome and the CDKL5 disorder. 'Mild' was assigned when a child presented disrupted sleep, which was not severe. For respite use 'formal' respite included services provided by public or private organisations and 'informal' respite referred to any service offered by other family members, friends and neighbours to parents with a child who lived in the family home. Financial hardship was grouped according to the parent's current experience of financial hardship. 'Yes' was assigned when the parent reported being currently unable to save money for parents of children with Down syndrome and Rett syndrome [the Indicators of Social and Family Functioning Reference Instrument (Zubrick et al. 2000)], or being having

Table 1 Independent variables and their measurement

Independent variable	Measurement
Family-related factor	
Parental age	Parent's age at which the parent completed a questionnaire
Parental highest qualification	The highest educational qualification a parent had obtained by the time when the parent completed a questionnaire (no higher than secondary school, technical certificate, university degree)
Parental current work status	Parent's current work status (full-time homemaker, part-time employment, full-time employment)
Number of siblings	Number of any other siblings of the affected child (e.g. natural siblings, adopted siblings) (0, 1, 2 or more)
Birth order	The order which the affected child was born within a family (firstborn, later-born)
Child-related factor	
Child age	Age of the affected child at which the parent completed a questionnaire
Diagnosis	Diagnosis received by the affected child (Down syndrome, Rett syndrome, CDKL5 disorder)
Clinical severity	Severity of clinical features of the affected child (mild, moderate, severe)
Child disrupted sleep	Parent's perceived degree of disrupted sleep or frequency of night waking of the affected child (not present, mild, severe)
Frequency of hospitalisations	Total number of reported hospitalisations in the previous year (one and 0.5 time for each overnight and day admission, respectively)
Socio-environmental factor	
Place of residence	Place where the affected child lived most of the time (family home, outside home)
Respite use	Use of respite services in the previous year among parents with children who lived in the family home (none, formal only, informal only, both)
Financial hardship	Parent's current experience of financial hardship (Yes/No)
Attending day activities	Participation in day care, school or day occupation for the affected child aged 6 years or older and parent's perceived satisfaction with the current arrangement [satisfactory, neither satisfactory or unsatisfactory, unsatisfactory, none (stay at home)]

difficulty finding the funding to meet the child's needs (a customised question) in the CDKL5 disorder.

Child Clinical Severity

Because clinical characteristics inevitably vary across the three diagnoses, a clinical severity score was constructed separately for each diagnosis. Individuals with each diagnosis were then categorised into tercile groups according to the severity levels within that diagnosis; mild, moderate and severe.

The Kerr scale, extensively used in the past by ourselves and others, often with minor modifications, was used to assess clinical severity of Rett syndrome in this study (Bebbington et al. 2012, 2010; Colvin et al. 2003; Halbach et al. 2016, 2012; Kerr et al. 2001; Scala et al. 2007). Six of 20 items (head circumference during the first year, present head circumference, muscle tone, joint contractures, peripheral circulation of extremities and intellectual ability) were excluded because: there were missing data for the first two items; no data were collected on the next three; and the last was considered unimportant as severe intellectual impairment is one of the main characteristics of Rett syndrome. For items on scoliosis (spine posture), gastrostomy placement (oro-motor difficulty) and epilepsy data from previous questionnaires were also used to ensure accurate and maximal data. An average of the sum score of the remaining 14 items was then obtained for those with no more than two missing items. Since no specific criteria exist for mild, moderate and severe clinical groups the clinical severity was defined within our population by stratifying the individuals into tercile groups; mild, moderate and severe.

For Down syndrome and the CDKL5 disorder, a measure was developed selecting items based on the potential for strong associations with clinical severity. Seventeen items were constructed in Down syndrome: 14 organ groups of physical conditions (cardiac, gastroenterological, ear, eye, orthopaedic, respiratory, immunological, dermatological, neurological, psychiatric, haematology/oncology, endocrine, autoimmune and others); mobility; communication skills; and behavioural problems. Each group of physical conditions was rated on a three-point Likert scale, in which zero was assigned to never having occurred, one to having occurred in the past (not present) and two to being present currently. Two items (locomotion and communication) of the modified WeeFIM were used for scoring motor and communication abilities obtaining the average score (Leonard et al. 2002; Ottenbacher et al. 1999). Because locomotion and communication abilities are generally acquired by the age of two years (Baumer et al. 2013), those aged younger than 2 years (n = 25) were assigned with a probable future ability level based on data among those aged 2 years or older. The DBC-P was used for scaling behavioural problems obtaining the mean item score (Einfeld and Tonge 2002; Taffe et al. 2008). The DBC-P targets children aged 4 years or older and was not administered to these young children. Since our data did not show any major change in severity with age apart from a very minor downward trend the average score among those aged 3.8 years or older (n = 248) was imputed to those with younger than 3.8 years of age (n = 39). A weighted sum score was then obtained considering likely differences in the impact on the overall clinical severity with the weight of: three for cardiac and haematology/oncology conditions; two for respiratory, immunological, neurological and autoimmune conditions, and behavioural problems; and one for the other ten items. Using the sum score those with no more than two missing items were stratified into tercile groups; mild, moderate and severe, where those with one (n = 24) and two (n = 4) missing items were assigned to the tercile groups created among those with no missing item adding the potential score(s) of the missing item(s) to the responded total score. Items contributing to the clinical severity scale for Down syndrome and their measurement, and correlation coefficients among the items are summarised in Tables A.1 and A.2 of the Online Appendix, respectively.

Nine items were constructed for the CDKL5 disorder: epilepsy; feeding difficulty; gastroenterological problems; respiratory conditions; abnormal breathing patterns; spinal posture; sleep disturbances; gross motor ability; and communication skills. The first six items were graded on a three-point Likert scale, where zero was assigned to no problem, one to mild and two to severe symptoms. For epilepsy, 'no problem' referred to never or well-controlled, 'mild symptoms' to monthly or weekly and 'severe symptoms' to daily seizures based on the parent's report of seizure frequency. For feeding difficulty, 'no problem' referred to none, 'mild symptoms' to being orally fed yet requiring special food preparation and 'severe symptoms' to having received gastrostomy placement. For gastroenterological problems and abnormal breathing patterns, 'no problem' referred to never, 'mild symptoms' to having had the condition in the past (but not present) and 'severe symptoms' to currently having the condition. For respiratory conditions, 'no problem' referred to never, 'mild symptoms' to having had hospital admissions due to respiratory illnesses and 'severe symptoms' to requiring special equipment, such as a suction machine, at home to maintain respiratory health. Spinal posture was categorised into no deviation or having a diagnosis of scoliosis or kyphosis, rated zero or one, respectively. The average score for the Disorders of Initiating and Maintaining Sleep subscale from the SDSC was used for measuring sleep disturbances (Bruni et al. 1996). Individuals were then stratified into quartile groups, in which zero was assigned to those in the 1st quartile, one to those in the 2nd quartile, two to those in the 3rd quartile and three to those in the 4th quartile. Gross motor ability and communication skills were rated on

a three-point Likert scale. For the former, zero was assigned to those requiring no assistance to walk forward ten steps, one to those requiring some assistance and two to those requiring maximal assistance or unable to perform the task. For the latter, zero was assigned to those who could use sign or spoken language to communicate, one to those using complex gestures or vocalisations, and two to those using no or simple communication (Fehr et al. 2016). Those aged younger than 2 years (n = 29) were assigned with a probable future ability level based on data among those aged 2 years or older as data were not available for these children and our previous study has shown that the skills are highly likely to be severely impaired in the CDKL5 disorder (Fehr et al. 2016, 2015). Using the sum score those with no more than one missing item were stratified into tercile groups; mild, moderate and severe, where those with one missing item (n = 19) were assigned to the tercile groups created among those with no missing item adding the potential score of the missing item to the responded total score. Items contributing to the clinical severity scale for the CDKL5 disorder and their measurement, and correlation coefficients among the items are summarised in Tables A.3 and A.4 of the Online Appendix, respectively.

Procedure

The PCS and MCS scores were obtained for 646 families (81.6% of 792): 291 (45.1% of 646) were from the WA Down Syndrome NOW Database; 187 (28.9%) from the ARSD; and 168 (26.0%) from the ICDD. The questionnaire response fractions were 291 of 363 (80.2%) for the WA Down Syndrome NOW Database, 187 of 229 (81.7%) for the ARSD and 168 of 200 (84.0%) for the ICDD. 576 (89.2% of 646) questionnaires were completed by a natural mother, 42 (6.5%) by a natural father, 14 (2.2%) by an adoptive mother, 5 (0.8%) by a grandparent, 3 (0.5%) each by a stepmother and a foster mother, 1 (0.2%) by a sibling and 2 (0.3%) by either of natural parents. Missing SF-12 and SF-12v2 data were managed by a single imputation method employed separately for each diagnosis (Perneger and Burnand 2005).

A Chi square test of independence and linear regression were performed to investigate differences in family-related, child-related and socio-environmental factors across three diagnoses when they are categorical and continuous variables, respectively.

The following statistical analyses were then performed separately for each of the PCS and MCS scores. Ninety-two percent of respondents were mothers and their mean scores were compared with US female norms by age group. Differences were assessed using two sample t-tests assuming unequal variance. Those in the age groups of 18–24 years and 65–74 years were excluded from this comparison because of small sample sizes (n = 2 and 6, respectively).

The univariate associations between the well-being scores and family-related, child-related and socio-environmental factors were examined using linear regression models. The regression assumptions of independence uniform variance, linearity and normality of errors were tested using studentised residual plots fitted with a lowess smoothing function (Cleveland 1979) and normal quantile plots. Collinearity was examined using the variance inflation factor (Kleinbaum et al. 1988) and none of the independent variables met or exceed ten. Child sex was not included in the models because Rett syndrome and the CDKL5 disorder predominantly affect females. A reference group of each of the factors which were categorical or binary variables was selected according to either the proportion (i.e. a group accounting for the largest proportion) or phenotypic severity (i.e. a group of the least severe phenotype). To investigate associations between the well-being scores and child diagnosis, clinical features (clinical severity, child disrupted sleep and frequency of hospitalisations) and socio-environmental factors, a multivariate linear regression model that first included the family-related factors found to be potentially important in the univariate analyses ($p < 0.20$) (Rothman et al. 2008) as well as child age was developed (base model). The association with child diagnosis was investigated by adding child diagnosis to the base model. Because the child diagnosis was related to the well-being scores as well as the clinical features and socio-environmental factors, it was also included in the base model and each of the clinical features and socio-environmental factors was added to the model to investigate the associations. The effect sizes with their respective 95% confidence intervals (95% CIs) for the linear regression models were reported. The statistical package Stata 14 (StataCorp LP, College Station, TX) was used for all the analyses.

Ethics Approval

Ethical approval for analyses of data from the WA Down syndrome NOW Database, the ARSD and the ICDD has been obtained by the Princess Margaret Hospital for Children Human Research Committee (1003/EP), the Princess Margaret Hospital for Children Human Research Committee (1909/EP) and the University of Western Australia Human Research Committee (RA/4/1/5024), respectively.

Results

The characteristics of family-related, child-related and socio-environmental factors among 646 families in the analyses are shown in Table 2. Parents of a child with the CDKL5 disorder were younger, more highly educated and more likely to be in full-time employment compared with

Table 2 Characteristics of family-related, child-related and socio-environmental factors by child diagnosis (n = 646)

Factor	Overall (n = 646)	Down syndrome (n = 291)	Rett syndrome (n = 187)	CDKL5 disorder (n = 168)
Parental age in years median (range)	43.7 (24.6–75.7)	44.8 (24.8–75.7)	46.0 (25.8–72.2)	38.0 (24.6–63.7)
Number who responded	625	282	179	164
Parental highest qualification, n (%)				
No higher than secondary school	238 (38.6)	125 (43.7)	82 (47.4)	31 (19.8)
Technical certificate	147 (23.9)	76 (26.6)	40 (23.1)	31 (19.8)
University degree	231 (37.5)	85 (29.7)	51 (29.5)	95 (60.5)
Number who responded	616	286	173	157
Parental current work status, n (%)				
Full-time homemaker	282 (45.9)	137 (48.2)	79 (47.9)	66 (40.0)
Part-time employment	164 (26.7)	59 (20.8)	64 (38.8)	41 (24.9)
Full-time employment	168 (27.4)	88 (31.0)	22 (13.3)	58 (35.2)
Number who responded	614	284	165	165
Number of siblings, n (%)				
0	79 (12.3)	22 (7.6)	20 (10.7)	37 (22.3)
1	195 (30.4)	56 (19.4)	70 (37.4)	69 (41.6)
2 or more	368 (57.3)	211 (73.0)	97 (51.9)	60 (36.1)
Number who responded	642	289	186	166
Birth order, n (%)				
Firstborn	251 (39.3)	91 (31.5)	83 (45.1)	77 (46.4)
Later-born	388 (60.7)	198 (68.5)	101 (54.9)	89 (53.6)
Number who responded	639	289	184	166
Child age in years, median (range)	11.7 (0.0–35.7)	13.0 (0.3–25.1)	16.7 (2.6–35.7)	5.9 (0.0–34.7)
Number who responded	646	291	187	168
Child sex, n (%)				
Female	459 (71.1)	129 (44.3)	187 (100.0)	143 (85.1)
Male	187 (29.0)	162 (55.7)	0 (0.0)	25 (14.9)
Number who responded	646	291	187	168
Clinical severity, n (%)				
Mild	175 (27.9)	77 (27.2)	59 (32.1)	39 (24.2)
Moderate	193 (30.7)	93 (32.0)	54 (29.4)	46 (28.6)
Severe	260 (41.4)	113 (39.9)	71 (38.6)	76 (47.2)
Number who responded	628	283	184	161
Child disrupted sleep, n (%)				
Not present	264 (44.8)	187 (77.6)	52 (28.3)	25 (15.2)
Mild	117 (19.9)	36 (14.9)	37 (20.1)	44 (26.8)
Severe	208 (35.3)	18 (7.5)	95 (51.6)	95 (57.9)
Number who responded	589	241	184	164
Frequency of hospitalisations, n (%)				
0	438 (70.0)	237 (82.0)	128 (70.3)	73 (47.1)
1–3	168 (26.8)	49 (17.0)	47 (25.8)	72 (46.5)
4 or more	20 (3.2)	3 (1.0)	7 (3.9)	10 (6.5)
Number who responded	626	289	182	155
Place of residence, n (%)				
Family home	617 (95.5)	286 (98.3)	167 (89.3)	164 (97.6)
Outside home	29 (4.5)	5 (1.7)	20 (10.7)	4 (2.4)
Number who responded	646	291	188	168
Respite use[a], n (%)				
None	218 (36.2)	138 (49.1)	39 (23.4)	41 (26.5)
Formal only	203 (33.7)	71 (25.3)	101 (60.5)	31 (20.0)

Table 2 (continued)

Factor	Overall (n = 646)	Down syndrome (n = 291)	Rett syndrome (n = 187)	CDKL5 disorder (n = 168)
Informal only	89 (14.8)	47 (16.7)	8 (4.8)	34 (21.9)
Both	93 (15.4)	25 (6.9)	19 (11.4)	49 (31.6)
Number who responded	603	281	167	155
Financial hardship, n (%)				
No	331 (55.4)	145 (52.0)	93 (57.4)	93 (59.6)
Yes	266 (44.6)	134 (48.0)	69 (42.6)	63 (40.4)
Number who responded	597	279	162	155
Attending day activities[b], n (%)				
Satisfactory	286 (70.3)	153 (68.9)	76 (71.0)	57 (73.1)
Neither	57 (14.0)	38 (17.1)	12 (11.2)	7 (9.0)
Unsatisfactory	46 (11.3)	26 (11.7)	12 (11.2)	8 (10.3)
None (stay at home)	18 (4.4)	5 (2.3)	7 (6.5)	6 (7.7)
Number who responded	407	222	107	78

[a]Among parents whose child lived in a parental residence (n = 617)

[b]Among parents with children aged 6 years or older (n = 481)

those of children with Down syndrome or Rett syndrome [coefficient = − 2.77; 95% CI − 3.57, − 1.96; p < 0.001, X^2(4, N = 616) = 51.63; p < 0.001 and X^2(4, N = 614) = 31.59; p < 0.001, respectively]. Similarly, their child was younger and more likely to be the only child (coefficient = − 1.97; 95% CI − 2.71, − 1.23; p < 0.001 and X^2(4, N = 642) = 66.80; p < 0.001, respectively). Children with Down syndrome were more likely to be later-born compared with those with Rett syndrome or the CDKL5 disorder [X^2(4, N = 639) = 13.49; p = 0.001]. Disrupted sleep and one or more hospitalisations in the previous year were reported to be highest among children with the CDKL5 disorder [X^2(4, N = 589) = 198.50; p < 0.001 and X^2(4, N = 626) = 59.98; p < 0.001, respectively]. More children with Rett syndrome lived outside a parental residence than did those with Down syndrome or the CDKL5 disorder [X^2(2, N = 646) = 23.75; p < 0.001]. Formal respite services were used most frequently by families of children with Rett syndrome, and informal and both formal and informal respite by families of children with the CDKL5 disorder [X^2(6, N = 603) = 128.07; p < 0.001]. Those with children with Down syndrome were least likely to be using respite services. Compared with those with Down syndrome more children with Rett syndrome and CDKL5 disorder did not attend day activities [X^2(6, N = 407) = 9.14; p = 0.166] (Table 2).

Comparisons of Parental Well-Being Scores Among Mothers of This Study with US Female Population

Among 596 mothers, the mean PCS and MCS scores were 50.6 (SD 9.4; range 14.3–72.7) and 44.5 (SD 10.9; range 2.6–66.8), respectively. Compared with US female norms, the mean PCS score was slightly higher by 1.93 points (95% CI 1.13, 2.74; p < 0.001) overall. Within age strata the mean PCS score was higher in the 35–44 year age group only by 1.28 points (95% CI 0.09, 2.47; p = 0.034). The mean MCS score was lower by 3.90 points (95% CI 2.98, 4.82; p < 0.001) overall and across the age groups (Table 3).

Associations Between Parental Physical Well-Being and Family-Related, Child-Related and Socio-environmental Factors

The univariate analysis identified that the PCS score declined with parental age by − 0.24 points (95% CI − 0.32, − 0.16; p < 0.001) for each increased year of age. Compared with those with secondary education or less, parents had higher scores by 2.83 points (95% CI 0.95, 4.72; p = 0.003) if they had a technical certificate and by 3.21 points (95% CI 1.55, 4.87; p < 0.001) if a university degree. Full-time employees had a mean score 2.35 points (95% CI 0.62, 4.08; p = 0.008) higher than full-time homemakers. Parents whose affected child had two or more siblings had lower scores than those whose affected child was the only child by − 2.12 points (95% CI − 4.40, 0.16; p = 0.068) (Table 4).

In the multivariate analyses, adjusting for family-related factors and child age, an association between the PCS score and child diagnosis was observed. Compared with parents of children with Down syndrome the regression coefficients were 2.54 points (95% CI 0.71, 4.36; p = 0.006) lower for Rett syndrome. After further adjustment for child diagnosis, there was still an association between the mean score and child clinical severity. Parents with children with moderate and severe clinical severity had slightly lower scores compared with those with a child with milder severity by − 1.71 points (95% CI − 3.58, 0.16; p = 0.073) and − 1.71 points

Table 3 Comparisons of parental well-being scores among mothers of this study with US female norms by age group (n = 596)

	This study		US female norms		Difference in means (95% CI)	*t*-statistics, p
	n	Mean (SD)	n	Mean (SD)		
PCS score						
Overall	583[a]	50.65 (9.38)	4135	48.72 (9.63)	1.93 (1.13, 2.74)	$t = 4.64$, $p < 0.001$
25–34 years	99	52.73 (8.09)	631	52.71 (9.13)	0.02 (−1.74, 1.78)	$t = 0.02$, $p = 0.982$
35–44 years	230	52.54 (8.05)	839	51.26 (8.29)	1.28 (0.09, 2.47)	$t = 2.12$, $p = 0.034$
45–54 years	189	49.08 (9.92)	887	48.20 (8.61)	0.79 (−0.74, 2.32)	$t = 1.02$, $p = 0.311$
55–64 years	57	46.21 (11.16)	663	46.28 (8.68)	−0.07 (−3.10, 2.96)	$t = -0.05$, $p = 0.963$
MCS score						
Overall	583[a]	44.53 (10.91)	4141	48.43 (9.55)	−3.90 (−4.82, −2.98)	$t = -8.20$, $p < 0.001$
25–34 years	99	42.50 (11.73)	632	47.22 (12.14)	−4.72 (−7.24, −2.20)	$t = -3.70$, $p < 0.001$
35–44 years	230	44.42 (11.18)	839	47.59 (9.45)	−3.17 (−4.76, −1.58)	$t = -3.93$, $p < 0.001$
45–54 years	189	45.12 (10.11)	890	49.64 (7.91)	−4.52 (−6.06, −2.98)	$t = -5.78$, $p < 0.001$
55–64 years	57	46.78 (10.42)	664	50.14 (8.15)	−3.36 (−6.19, −0.53)	$t = -2.37$, $p = 0.021$

The mean PCS and MCS scores were 47.32 (SD 8.61) and 32.98 (SD 23.13) in the aged 18–24 year group (n = 2) and 48.81 (SD 6.67) and 50.09 (SD 11.95) in the aged 65–74 year group (n = 6), respectively;

[a]Parental age was missing for 13 mothers

(95% CI −3.26, 0.04; p = 0.055), respectively. The negative association with no participation in day activities also remained, albeit non-significant (coefficient = −4.59; 95% CI −9.48, 0.29; p = 0.065, compared with satisfactory participation). The association with financial hardship became more pronounced; on average the score was 1.66 points (95% CI 0.20, 3.12; p = 0.026) lower among those who reported financial hardship than those who did not report financial hardship (Table 4).

Associations Between Parental Emotional Well-Being and Family-Related, Child-Related and Socio-environmental Factors

In the univariate analysis the MCS score increased with parental age by 0.13 points (95% CI 0.04, 0.23; p = 0.008) for each increase in year for age. Parents in part-time employment on average scored 2.54 points (95% CI 0.43, 4.65; p = 0.018) higher than full-time homemakers. Compared with parents of an only child, other parents had higher scores, by 4.59 points (95% CI 1.76, 7.41; p = 0.002) when the affected child had one other sibling, and by 5.39 points (95% CI 2.77, 8.02; p < 0.001) when two or more siblings. Parents had lower scores when the child was firstborn compared with when later-born by −2.00 points (95% CI −3.74, −0.28; p = 0.024) (Table 5).

In the multivariate analyses, an association between the MCS score and child diagnosis was observed. The parents of a child with the CDKL5 disorder had lower mean scores than those of a child with Down syndrome (coefficient = −3.18; 95% CI −5.56, −0.79; p = 0.009). After further adjustment for child diagnosis, the association with child clinical severity remained; the mean score declined with the level of child clinical severity with the linear regression coefficients of −2.27 (95% CI −4.67, 0.01; p = 0.056) for moderate and −3.82 (95% CI −5.81, −1.45; p = 0.001) for severe severity compared with a milder severity. Compared with those whose children did not have disrupted sleep, those whose children had sleep disturbances had lower scores by −4.91 points (95% CI −7.55, −2.26; p < 0.001) if mild, and by −5.52 points (95% CI −8.07, −2.97; p < 0.001) if severe. Parents who used both formal and informal respite care had lower scores compared with those who used none of the services by −3.68 points (95% CI −6.52, −0.84; p = 0.011). Those who reported financial hardship scored 3.99 points (95% CI 2.17, 5.82; p < 0.001) lower on average compared with those who did not report financial hardship. Compared with parents who perceived their child's need were being met under the current arrangements, lower scores were identified, by −5.93 points (95% CI −11.37, −0.49; p = 0.033) for those whose child did not attend day activities, by −6.31 points (95% CI −9.69, −2.93; p < 0.001) for those whose child participated in the activities but who felt dissatisfied, and by −3.21 points (95% CI −6.27, −0.14; p = 0.040) for those wo were neither satisfied or dissatisfied about the arrangements (Table 4).

Discussion

Caring for a child with each of these genetically caused disorders placed an emotional burden on the parents in our study. Emotional well-being was lower compared with the US female population in all age groups, while there was

Table 4 Univariate and multivariate regression coefficients for PCS score (n = 646)

Model	Univariate regression		Multivariate regression[a]	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Parental age	−0.24 (−0.32, −0.16)	<0.001	–	–
Parental highest qualification				
No higher than secondary school	Reference	–	–	–
Technical certificate	2.83 (0.95, 4.72)	0.003		
University degree	3.21 (1.55, 4.87)	<0.001		
Parental current work status				
Full-time homemaker	Reference	–	–	–
Part-time employment	−0.89 (−2.64, 0.85)	0.315		
Full-time employment	2.35 (0.62, 4.08)	0.008		
Number of siblings				
0	Reference	–	–	–
1	−1.15 (−3.60, 1.30)	0.358		
2 or more	−2.12 (−4.40, 0.16)	0.068		
Birth order				
Firstborn	Reference	–	–	–
Later-born	−0.57 (−2.07, 0.92)	0.450		
Child age	−0.24 (−0.33, −0.15)	<0.001	–	–
Diagnosis				
Down syndrome	Reference	–	Reference	–
Rett syndrome	−2.78 (−4.46, −1.10)	0.001	−2.54 (−4.36, −0.71)	0.006
CDKL5 disorder	3.10 (1.37, 4.84)	<0.001	1.46 (−0.45, 3.37)	0.133
Clinical severity				
Mild	Reference	–	Reference	–
Moderate	−2.28 (−4.20, −0.36)	0.020	−1.71 (−3.58, 0.16)	0.073
Severe	−1.66 (−3.46, 0.13)	0.070	−1.71 (−3.46, 0.04)	0.055
Child disrupted sleep				
Not present	Reference	–	Reference	–
Mild	−0.01 (−2.10, 2.09)	0.996	−1.36 (−3.52, 0.79)	0.215
Severe	0.12 (−1.62, 1.87)	0.890	−0.27 (−2.35, 1.80)	0.796
Frequency of hospitalisations	0.13 (−0.49, 0.75)	0.684	−0.26 (−0.90, 0.37)	0.416
Place of residence				
Family home	Reference	–	Reference	–
Outside home	−5.25 (−8.72, −1.77)	0.003	0.46 (−4.92, 5.83)	0.868
Respite use				
None	Reference	–	Reference	–
Formal only	−2.03 (−3.77, −0.30)	0.022	−0.73 (−2.59, 1.13)	0.442
Informal only	2.27 (0.03, 4.51)	0.047	1.06 (−1.19, 3.32)	0.354
Both	1.27 (−0.94, 3.47)	0.260	0.86 (−1.43, 3.15)	0.462
Financial hardship				
No	Reference	–	Reference	–
Yes	−0.99 (−2.48, 0.48)	0.184	−1.66 (−3.12, −0.20)	0.026
Attending day activities				
Satisfactory	Reference	–	Reference	–
Neither	−1.15 (−3.96, 1.65)	0.419	−0.72 (−3.47, 2.04)	0.610
Unsatisfactory	−1.10 (−4.17, 1.97)	0.480	−1.26 (−4.30, 1.78)	0.416
None (stay at home)	−6.38 (−11.07, −1.68)	0.008	−4.59 (−9.48, 0.29)	0.065

[a]Adjusted for parental age, highest qualification and current work status, number of siblings, birth order and child age; multivariate models for child clinical severity, disrupted sleep and frequency of hospitalisations, place of residence, respite use, financial hardship and attending day activities further adjusted for child diagnosis

Table 5 Univariate and multivariate regression coefficients for MCS score (n = 646)

Model	Univariate regression		Multivariate regression[a]	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Parental age	0.13 (0.04, 0.23)	0.008	–	–
Parental highest qualification				
No higher than secondary school	Reference	–	–	–
Technical certificate	0.59 (−1.67, 2.86)	0.609		
University degree	−0.04 (−2.03, 1.95)	0.969		
Parental current work status				
Full-time homemaker	Reference	–	–	–
Part-time employment	2.54 (0.43, 4.65)	0.018		
Full-time employment	0.96 (−1.13, 3.06)	0.366		
Number of siblings				
0	Reference	–	–	–
1	4.59 (1.76, 7.41)	0.002		
2 or more	5.39 (2.77, 8.02)	<0.001		
Birth order				
Firstborn	Reference	–	–	–
Later-born	2.00 (0.27, 3.74)	0.024		
Child age	0.11 (0.01, 0.22)	0.035	–	–
Diagnosis				
Down syndrome	Reference	–	Reference	–
Rett syndrome	0.47 (−1.52, 2.46)	0.644	0.48 (−1.80, 2.78)	0.682
CDKL5 disorder	−3.66 (−5.72, −1.61)	<0.001	−3.18 (−5.56, −0.79)	0.009
Clinical severity				
Mild	Reference	–	Reference	–
Moderate	−1.85 (−4.07, 0.38)	0.104	−2.33 (−4.67, 0.01)	0.051
Severe	−3.41 (−5.49, −1.32)	0.001	−3.63 (−5.81, −1.45)	0.001
Child disrupted sleep				
Not present	Reference	–	Reference	–
Mild	−4.59 (−6.94, −2.24)	<0.001	−4.91 (−7.55, −2.26)	<0.001
Severe	−4.48 (−6.45, −2.52)	<0.001	−5.52 (−8.07, −2.97)	<0.001
Frequency of hospitalisations	−0.86 (−1.58, −0.13)	0.020	−0.54 (−1.33, 0.25)	0.181
Place of residence				
Family home	Reference	–	Reference	–
Outside home	1.22 (−2.86, 5.29)	0.557	−0.42 (−7.14, 6.30)	0.902
Respite use				
None	Reference	–	Reference	–
Formal only	0.16 (−1.92, 2.23)	0.882	−0.09 (−2.40, 2.21)	0.936
Informal only	−1.61 (−4.29, 1.06)	0.237	−0.50 (−3.29, 2.30)	0.726
Both	−4.18 (−6.82, −1.55)	0.002	−3.68 (−6.52, −0.84)	0.011
Financial hardship				
No	Reference	–	Reference	–
Yes	−4.09 (−5.83, −2.35)	<0.001	−3.99 (−5.82, −2.17)	<0.001
Attending day activities				
Satisfactory	Reference	–	Reference	–
Neither	−1.86 (−4.81, 1.09)	0.216	−3.21 (−6.27, −0.14)	0.040
Unsatisfactory	−4.95 (−8.18, −1.73)	0.003	−6.31 (−9.69, −2.93)	<0.001
None (stay at home)	−5.62 (−10.55, −0.68)	0.026	−5.93 (−11.37, −0.49)	0.033

[a]Adjusted for parental age, highest qualification and current work status, number of siblings, birth order and child age; multivariate models for child clinical severity, disrupted sleep and frequency of hospitalisations, place of residence, respite use, financial hardship and attending day activities further adjusted for child diagnosis

little difference in physical well-being. Although it enables the parents to know what to expect for their child and access diagnosis-specific family support (Moeschler et al. 2014), the establishment of a definite diagnosis can be associated with intense emotions such as anger, fear and isolation, followed by recurring grief, particularly in the case of a rare genetic disorder (Glenn 2015), which may provide a partial explanation for the finding.

Parental well-being varied across the diagnoses irrespective of family-related factors and child age. Parents of children with Rett syndrome reported the poorest physical well-being, whereas emotional well-being was poorest among parents of children with the CDKL5 disorder. Compared with these generally more severe diagnoses, parents of children with Down syndrome had relatively better parental physical and emotional well-being. This finding indicates that the care burden on parental well-being may be greater with increasing levels of impaired motor and intellectual ability and greater complexity of comorbidities.

This was underpinned by the finding of a negative association between parental well-being and child clinical severity irrespective of child diagnosis, family-related factors or child age. In this study, given the complex nature of genetic disorders we determined clinical severity in the broad context encompassing neurodevelopmental impairment and diverse physical comorbidities. Although the methodologies used to measure clinical severity in Down syndrome and the CDKL5 disorder were developed specifically for this study, we believe that their inclusion was an important component of the analyses because it allowed us to measure and compare child clinical severity and its association with parental well-being across child diagnoses.

Child disrupted sleep was adversely related to parental emotional well-being irrespective of child diagnosis and consistent with previous studies with autism spectrum disorder and cerebral palsy (Hodge et al. 2013; Lee 2013; Wayte et al. 2012). This suggests that child's sleep problems can be risk determinants of parental emotional well-being across conditions associated with developmental disabilities.

A negative association between the use of both formal and informal respite care services and parental emotional well-being was observed in this study. To support families with a child with intellectual disability, respite services should be provided in a way that ensures the flexibility to address specific family needs (Chan et al. 2012). However, there may be difficulty accessing and securing the appropriate service (Whiting 2012), particularly, when the child has a severe disability (Ingersoll and Hambrick 2011). The needs for respite care services might not have been met for some parents in this study who received both formal and informal respite care services, creating an additional emotional burden on the parents. However, there might have been reverse causality, in which poor parental emotional well-being resulted in an increased demand for respite care and thereby the extensive service use. This needs to be further investigated by using a longitudinal and/or qualitative design.

Financial hardship and lack of participation in or unmet needs for day care, school or day occupation for an affected child were negatively associated with parental emotional well-being. For parents with a child with a disability, participation itself is perceived as meaningful contribution to a community helping develop a more inclusive community and support other families with children with disabilities (Woodgate et al. 2012). However, parents may face multiple challenges in accessing an educational service that satisfies their perceived needs for their child, that has sufficient understanding of the child's disability and has structural flexibility (Piskur et al. 2016). These may also be complicated by other challenges including their own health and financial hardship (Rehm et al. 2013). Further investigation into what leads to satisfactory participation in the day activities is warranted.

There are several limitations of this study. Firstly, this study used a cross-sectional design, which enabled us to identify associations, rather than causation. Secondly, there were differences in family residence and recruitment across three databases. The WA Down Syndrome NOW Database and the ARSD are population-based consisting solely of Australian (Downs and Leonard 2013; Petterson et al. 2005), whereas the ICDD relies on voluntary participation and has a high proportion of families living in the US (Fehr et al. 2013). Although the ICDD is a growing worldwide database, such differences may have led to some variability in family, child and socio-environmental characteristics. Thirdly, the disparity we identified in mental health for our Australian mothers in comparison to the normative population may have been somewhat conservative because the norms provided in one Australian population study were slightly higher than the generally used and well accepted US SF-12 norms (Avery et al. 2004; Ware et al. 2004). However, we felt the latter were most appropriate to use in this study, given our CDKL5 population was international and included parents from 33 different countries. Fourthly, since families were recruited based on the year of birth of the affected child in the WA Down Syndrome NOW Database we were unable to include Down syndrome parents with an adult child aged older than 25 years in the analysis. However, only a minority of parents of children with Rett syndrome (17.6%) and the CDKL5 disorder (3.6%) in this study cared for a child aged over 25 years also. Lastly, the methodology for assessing clinical severity in Down syndrome and the CDKL5 disorder was developed specifically for this study and the measurement validity has not been verified.

Conclusion

Parental well-being in the field of a genetic developmental disability is an important topic. Yet there has been difficulty conducting research examining caregiving burden on parents because these disorders are generally rare and there are few population-based or international registers from which to source participant families. Poor parental emotional well-being has been identified and we have highlighted areas that require further investigation. Access to respite, funding and education or post-school programs as well as severity and complexity of clinical features were determinants of parental well-being in this caregiver population. These should be further investigated to help develop the optimal framework for the delivery of health care and social services in order to enhance parental well-being for families with a child with a rare yet severe and complex disorder.

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Authors' Contributions HL and JD provided access to study data; YM, JD, JH and HL conceived and designed the research plan; YM undertook the analysis with input from KW; all authors interpreted the data; YM drafted the paper and all authors edited and read the manuscript and agreed to it being submitted for publication.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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