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ORIGINAL CONTRIBUTION

Longitudinal effects of caregiving on parental well-being: the example of Rett syndrome, a severe neurological disorder

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Abstract

Little longitudinal research has examined parental well-being in those with a child with specific genetic developmental disorder although the associated severe neurological impairments and multiple physical comorbidities likely place substantial burden of caregiving on the parent. We aimed to examine longitudinally the well-being of parents of individuals included in the Australian Rett Syndrome Database over the period from 2002 to 2011 using the Short Form 12 Health Survey. Residential remoteness, the child being a teenager at baseline, having frequent sleep disturbances or behavioural problems, and the type of *MECP2* gene mutation were each associated with later poorer parental physical well-being scores. Being a single parent or on a low income was also associated with later poorer physical well-being, while the child having enteral feeding was associated with later poorer emotional well-being. Both the physical and emotional well-being of the parent improved if the child was living in out-of-home care. Our findings suggest that some opportunities do exist for clinicians to help optimise parental well-being. Being alert to the possibility and need for management of a child's sleep or emotional disturbance is important as is awareness of the additional likely parental burden as the child moves through adolescence into early adulthood and their need for additional support at that time. However, the findings also highlight the complex nature of parental well-being over time in parents of children with a severe neurological disorder and how they may be affected by a range of inter-related family and child factors.

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

Introduction

An increasing body of evidence suggests that caregiving a child with a developmental disorder impacts the emotional well-being of the parent [1]. However, research targeting parents of children with specific genetic disorders remains relatively limited, despite the substantial care burden associated with the neurological impairments and diverse physical comorbidities. Rett syndrome is a rare genetic disorder generally caused by a de novo mutation in the methyl CpG-binding protein 2 (*MECP2*) gene [2]. It mainly affects females and has an estimated cumulative incidence of 1 in 8905 by the age of 32 years [3]. Following seemingly normal development in the first 6 months, the child usually loses communication and/or hand skills from 15 to 30 months of age resulting in severely impaired neurodevelopment [2, 4]. The disorder is commonly accompanied by comorbidities including epilepsy, sleep disturbances, scoliosis, feeding and growth problems, and awake breathing abnormalities [2, 5].

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Two cross-sectional studies have investigated emotional well-being and its determinants among mothers of a child with Rett syndrome [6, 7]. In 2005 using Australian population-based data, we found that mental health scores were markedly lower than population norms and that poorer emotional health was associated with maternal work status (being a full-time homemaker or unemployed) and perceived marital functioning (poorer marital adjustment) [7]. Furthermore, we found that well-being was adversely affected in mothers of children who had a recent bone fracture and also compromised when their child was exhibiting more anxiety and mood disturbances [7]. No relationship with the *MECP2* gene mutation type was observed [7]. Similarly in a UK study ($n=87$) that was not population-based increased severity of behavioural problems and medical conditions were associated with maternal depression and anxiety [6]. Using Australian population data we also found slightly poorer physical health in mothers of individuals with Rett syndrome, associated with their work status (being full-time homemaker or unemployed), and the adequacy of resources available (poorer availability) [7]. Other negative associations with maternal physical health were also identified in relation to the presence of child breathing issues, sleeping disturbances and use of in-home structured therapy [7]. Further, using Australian longitudinal data ($n=170$) we identified an association between use of respite care services and subsequent poorer physical well-being [8].

Children with developmental disabilities usually require lifelong and multidisciplinary supports that evolve over time in relation to the natural history of their condition [9, 10], underlining the importance of investigating the trajectory of parental well-being over the child's lifetime [11, 12]. However, there is a paucity of research examining parental well-being using longitudinal designs [12]. Recently, a UK study examined a change in parental emotional well-being over an average of 16.4 months of follow-up among 50 mothers of individuals with Rett syndrome aged seven to 48 years [13]. Although there was little change in well-being over time, increasing severity of child behavioural problems as well as maternal baseline depression and anxiety status were shown to predict later more severe psychological symptoms in the mother [13]. These findings are consistent with previous studies involving US mothers ($n=92$) of adolescents with developmental disabilities with 3 years of follow-up [14] and Australian mothers ($n=238$) of school-aged children with non-specific intellectual disability with 11 years of follow-up [15]. However, no such association was found over 3 years of follow-up among US mothers ($n=145$) of pre-school children with autism spectrum disorder, where higher levels of maternal self-efficacy were predictors of later fewer depression symptoms [16]. In contrast, another US study found that the physical health of mothers ($n=116$) of pre-school-aged children with developmental disabilities changed little over a 6-year period although it was constantly poorer than those ($n=129$) of mothers of typically developing children [17].

Current longitudinal studies are, therefore, limited either by short length of follow-up or limited range of child ages studied. Using a population-based database with longitudinal data collection, our study examined the trajectory of parental well-being among Australian families caring for a child with Rett syndrome over a period of 9 years. We investigated the longitudinal associations with family and child characteristics using linear mixed-effect regression models. We also compared trends in well-being with age between these parents and the general population.

Methods

Data collection

Data were sourced from the Australian Rett Syndrome Database (ARSD), housed at the Telethon Kids Institute in Perth, Western Australia. The database was established as a national population-based registry of Rett syndrome in 1993, with ongoing ascertainment through the Australian Paediatric Surveillance Unit and the parent group, the Rett Syndrome Association of Australia [18]. Data have been collected from two main sources, clinicians and families [19–21]. Information on child development and symptomatology leading to diagnosis has been provided by clinicians [19–21]. Data on a comprehensive range of family and child characteristics have been collected via family questionnaires in 1996, 2000, 2002, 2004, 2006, 2009 and 2011 [21], developed in accordance with the specific aims of each wave of data collection in collaboration with a family reference group [7]. Parental well-being was measured by the Short Form 12 Health Survey (SF-12) [22] in 2002, 2006, 2009 and 2011. Family questionnaires used for these four waves comprised two parts. Part one included questions about parental demographics such as parental qualification and work status, the place of residence of the affected child, child medical conditions such as epilepsy, sleep disturbances, scoliosis, behavioural problems measured by the Rett Syndrome Behaviour Questionnaire (RSBQ) [23], awake breathing abnormalities, bone fracture, and current function such as feeding ability and mobility as well as access to social support and schooling such as respite care use and parental income. Part two contained questions regarding family structure including information on siblings of the affected child, family function assessed by the McMaster Family Assessment Device (FAD) [24, 25] and parental well-being by the SF-12 [22].

One hundred and seventy-eight of 219 families (81.3%) returned the 2002 questionnaire, 210 of 237 (88.6%) the 2006 questionnaire, 214 of 254 (84.3%) the 2009 questionnaire and 229 of 262 (87.4%) the 2011 questionnaire. There

were 241 families who returned family questionnaires at two or more of the four waves and who were eligible for this study.

Outcome measures: parental well-being

The SF-12 was used to assess parental well-being at all of the four waves in this study [22]. It was originally developed as a self-report screening instrument for measuring individual's physical and mental health status in medical settings [22]. It comprises 12 items that form two scales: physical component summary (PCS); and mental component summary (MCS), calculated based on a norm-referencing method using the US general norms with a mean score of 50 and standard deviation (SD) of ten [22]. Higher scores indicate better health status [22]. Physical and emotional well-being were quantified by the PCS and MCS scores, respectively [22]. The general South Australian norms are available by age and sex [26].

Single imputation was employed to manage missing data and conducted separately in each wave [27]. First, 12 items were divided into key and non-key items for each of the PCS and MCS scores according to the strength of a correlation between an item and the score [27]. All the missing items were then replaced by the mean weights among those with no missing data whenever up to three key items were missing for each of the scores regardless of the number of missing non-key items [27].

Of 241 eligible families, the SF-12 scores were obtained by 145 families in 2002; 149 in 2006; 189 in 2009; and 176 in 2011. Those with no SF-12 scores ($n=9$) or with only one SF-12 score ($n=22$) were then excluded. We also excluded data collected from foster mothers ($n=4$) or grandparents ($n=4$) and if questionnaires had been returned by a different family member between the two waves ($n=4$), leaving 198 (82.2% of 241) natural parents for the following analysis.

Independent variables and their definition

Data provided by the natural parents via family questionnaires and clinicians were used to define independent variables which were grouped into family-related and child-related factors. Family-related factors included: three time-constant variables (parental highest qualification, remoteness of residence and birth order); and seven time-variant variables (parental age, parental work status, parental income, number of siblings, family function, place of residence and care arrangements). Child-related factors included: two time-constant variables (child age at baseline and mutation type); and nine time-variant variables (mobility, feeding difficulty, epilepsy, sleep disturbances, scoliosis, mood disturbances, anxiety, awake breathing abnormalities and bone fracture). The independent variables and their definition are summarised in S. Table 1.

Geographical remoteness of residence was measured by the Accessibility/Remoteness Index of Australia (ARIA + 2011) and categorised into three groups; major cities, inner regional and outer regional or remote [28]. Parental income referred to parent's reported annual gross income at which the parent responded a family questionnaire in real terms using Australian dollars, stratified into six groups. Family function was defined based on a score of the General Functioning 12-item (GF-12) subscale of the FAD [24, 25]. Higher scores indicate poorer family function [24, 25]. Using a cut-off score of 2.0 [25], parents were divided into two groups; better and poorer family function. Single parents were assigned to a third group categorised as not applicable (N/A). Care arrangements were categorised as "none" when the affected child lived in parental residence and used no respite services in the previous year, "any respite" when the affected child lived in parental residence and used any form of respite services in the previous year, and "in care" when the affected child was in care.

Child age at baseline was stratified into quartile groups based on child age at which the parent first responded to a family questionnaire across the four waves; younger than 7, 7–11, 11–17 and 17 years or older. The *MECP2* gene mutation type was grouped as C-terminal deletions, early truncating, large deletions, p.Thr158Met, p.Arg133Cys, p.Arg168*, p.Arg294*, p.Arg270*, p.Arg255*, p.Arg306Cys, and p.Arg106Trp mutations. The other mutations were grouped as "other" and those without a *MECP2* mutation or whose mutation was not considered pathogenic were categorised as "negative".

The following child-related factors were based on function or status of the affected child at the time which the parent answered a family questionnaire, apart from bone fracture in the previous 2 years. Feeding difficulty referred to parent's report of feeding ability of the affected child grouped as "no/little" when the child did not need special food preparation, "slight" when the child needed special food preparation (e.g. chopped, pureed) and/or coughed and/or choked with liquids and/or purees more frequently than weekly, and "severe" when the child was tube fed or used a combination of oral and tube feeding. Sleep disturbances were defined according to the child's frequency of night waking as reported by the parent. "Sometimes" referred to waking less than each week and "often" to weekly to daily night waking. Scoliosis was grouped as "no/mild" when the affected child was not diagnosed with scoliosis or had scoliosis with the Cobb angle less than 45°, "severe with surgery" when the child had surgery for scoliosis and "severe without surgery" when the child had scoliosis with the Cobb angle 45° or more yet had not had surgery [29]. The RSBQ was initially developed to discriminate the

behavioural characteristics of Rett syndrome from other severe intellectual disability [23]. Mood disturbances and anxiety were measured by the RSBQ subscales of general mood and fear/anxiety, respectively [23]. Higher scores indicate more severe disturbances of mood and anxiety [23] and scores were stratified into tercile groups; no/mild, moderate and severe. Awake breathing abnormalities were stratified based on parent's report of severity of breathing abnormality in the waking state. "Mild" and "severe" were assigned when a parent reported that the child was experiencing rare or occasional and frequent awake breathing abnormalities, respectively.

Statistical analysis

Descriptive statistics, reported as mean (SD), median (range), or *n* (%) where appropriate, were used to summarise the family-related and child-related factors, as well as the outcome measures. Temporal change of selected independent variables was reported without formal statistical comparison. The following analyses were conducted separately for the PCS and MCS scores.

Linear mixed-effect regression models were used to examine the effects of family-related and child-related factors on well-being scores over time [30]. A base model to investigate univariate effects was constructed including the parental age interaction term as well as each of the family-related and child-related factors. Multivariate linear mixed-effect regression models included the family-related factors shown to be potentially important according to either or both of the fixed intercepts and slopes in the univariate analyses ($p < 0.20$) [31] as well as child age at baseline and mutation type (multivariate model). The family-related factors were parental demographics (parental age, work status, highest qualification, income and remoteness), family function, birth order, number of siblings and place of residence. Care arrangements were not included as a predictor variable since they partially overlap with place of residence, which we considered a more potentially important confounding variable as the effect of daily care on parental well-being would have been limited when the affected child was in care compared with when the child lived together in parental residence. The multivariate effects of family-related and child-related factors were then investigated by adding each of the factors to the multivariate model.

Since the well-being scores change with age in general populations we compared the trends with parental age in the studied population with those in the general population standardising the well-being scores based on the South Australian general norms by age and sex (*z*-scores) [22, 26].

The effect sizes of fixed slopes with their respective 95% confidence intervals (95% CIs) for the linear mixed-effect regression models were reported and demonstrated by an increase of 1 year in parental age. The statistical package Stata 14 (StataCorp LP, College Station, TX) was used for all the analyses.

Ethics approval

Ethics approval for the ARSD has been obtained by the Princess Margaret Hospital for Children Human Research Committee (1909/EP).

Results

One hundred and eighty-three (92.4%) of 198 parents were natural mothers and 15 (7.6%) natural fathers. Table 1 shows the family-related characteristics as well as the PCS and MCS scores of these parents, while the child-related characteristics are demonstrated in Table 2.

Parental median ages increased from 41.2 years (range 26.9–63.6) in 2002 to 48.1 years (range 30.2–72.5) in 2011. Across the waves, the proportion of parents in full-time employment overall decreased from 24.8% in 2002 to 12.6% in 2011. The proportion of individuals living in supported accommodation outside the family home (in care) nearly quadrupled from 4.6 to 17.1% between 2002 and 2011 (Table 1).

More girls and women were being tube fed in 2011 than in 2002 (27.5 vs 15.9%), whereas there was a decrease in the experience of weekly or daily seizures over the four waves. The proportions of those with severe scoliosis with and without surgery almost doubled across the waves (2002: 24.2%, 2011: 43.3%) whereas a history of bone fracture declined approximately by a third (2002: 12.1%, 2011: 7.5%) (Table 2).

Trajectories in parental well-being with parental age by family-related factors and child age at baseline

A decline in the PCS score with parental age was identified in both univariate and multivariate models (see S. Table 2 and Table 3, respectively). Multivariate analyses indicated that the PCS score decreased with parental age, particularly, in single parents, poor family function, when parental income was low, in family with two or more siblings, for parents who lived in inner regional regions, and when the individual with Rett syndrome was aged between 11 and 17 years at baseline. In addition, the score decreased more when the individual lived in the parental residence than when in care. Among those whose child lived in the parental residence, the score declined in those with any respite service use by − 0.25 (95% CI − 0.09, − 0.42; $p < 0.01$) for each increased year of age (Table 3, Fig. 1).

Table 1 Characteristics of family-related factors and SF-12 scores among parents included in the study ($n = 198$)

Time-constant variable	$n = 198$			
Parental qualification, *n* (%)				
Secondary school or less	104 (52.5)			
TAFE/Technical certificate	52 (26.3)			
University degree	42 (21.2)			
Remoteness, *n* (%)				
Major cities	131 (66.2)			
Inner regional	44 (22.2)			
Outer regional/remote	23 (11.6)			
Birth order, *n* (%)				
Firstborn	86 (43.4)			
Later-born	112 (56.6)			
Time-variant variable	2002 cohort ($n = 132$)	2006 cohort ($n = 140$)	2009 cohort ($n = 168$)	2011 cohort ($n = 160$)
SF-12 score, mean (SD)				
PCS	46.6 (10.5)	47.1 (10.2)	46.1 (10.3)	47.3 (10.3)
MCS	46.4 (8.2)	45.5 (9.1)	47.3 (9.0)	45.6 (11.1)
Number of observations	132	140	168	164
Parental age, years, median (range)	41.2 (26.9–63.6)	43.3 (30.9–64.4)	46.5 (28.3–70.2)	48.1 (30.2–72.5)
Number of observations	132	140	168	164
Parental work status, *n* (%)				
Full-time homemaker	59 (48.8)	69 (49.3)	70 (46.7)	72 (50.3)
Part-time employment	32 (26.4)	46 (32.9)	56 (37.3)	53 (37.1)
Full-time employment	30 (24.8)	25 (17.9)	24 (16.0)	18 (12.6)
Number of observations	121	140	150	143
Parental income, *n* (%)				
$70,000 or more	34 (26.0)	44 (31.4)	59 (36.2)	58 (36.3)
$50,000–69,999	30 (22.9)	25 (17.9)	26 (16.0)	33 (20.6)
$40,000–49,999	16 (12.2)	18 (12.9)	17 (10.4)	14 (8.8)
$30,000–39,999	16 (12.2)	12 (8.6)	8 (4.9)	13 (8.1)
$20,000–29,999	17 (13.0)	19 (13.6)	27 (16.6)	21 (13.1)
Less than $20,000	18 (13.7)	22 (15.7)	26 (16.0)	21 (13.1)
Number of observations	131	140	163	160
Number of siblings, *n* (%)				
0	13 (10.6)	10 (7.1)	14 (8.3)	14 (8.5)
1	40 (30.3)	54 (38.6)	57 (33.9)	56 (34.2)
2 or more	78 (59.1)	76 (54.3)	97 (57.7)	94 (57.3)
Number of observations	132	140	168	164
Family function, *n* (%)				
Better	61 (46.2)	69 (49.3)	92 (56.1)	82 (51.6)
Poorer	66 (50.0)	69 (49.3)	70 (42.7)	76 (47.8)
N/A[a] (single parent)	5 (3.8)	2 (1.4)	2 (1.2)	1 (0.6)
Number of observations	132	140	164	159
Place of residence, *n* (%)				
Parental residence	126 (95.5)	136 (97.1)	147 (87.5)	136 (82.9)
In care	6 (4.6)	4 (2.9)	21 (12.5)	28 (17.1)
Number of observations	132	140	168	164
Care arrangements, *n* (%)				
None in the last year	58 (44.3)	27 (19.3)	34 (20.2)	29 (17.7)
Any respite	67 (51.2)	109 (77.9)	113 (67.3)	107 (65.2)
In care	6 (4.6)	4 (2.9)	21 (12.5)	28 (17.1)
Number of observations	131	140	168	164

[a]Not applicable

The MCS score showed little change with parental age in both univariate and multivariate models (see S. Table 2 and Table 3, respectively). Multivariate analyses indicated improved scores when parents lived in outer regional or remote regions or their child with Rett syndrome was in care. Although no difference in trend was observed according to family function, at a median parental age of 45 years the score was lower in parents in poorer functioning families and single parents compared with those who perceived their family relationships as satisfactory by − 4.10 (95% CI − 5.61, − 2.58; $p < 0.01$) and − 5.12 (95% CI − 10.55, 0.30; $p = 0.06$), respectively (result not shown in Table 3). The score declined for each increased year of age when the affected child was aged between 11 and 17 years at baseline, while it increased in the group of 17 years or over at baseline. There was little difference in the trend between those who did or did not use respite services in the previous year (Table 3, Fig. 1).

Trajectories in parental well-being with parental age by *MECP2* mutation type

Trends in the PCS and MCS scores varied by types of the *MECP2* gene mutations (S. Table 3, Table 4, Fig. 2). In the multivariate analysis, the PCS score declined with parental age in those whose child had a p.Arg168* mutation, a C-terminal deletion or a p.Arg294* mutation. In contrast, there was an increase in the score for those with a child with a p.Arg255* mutation, but the estimation was imprecise. The MCS score decreased with parental age when the child had a p.Arg255* or large deletion mutation while the score increased for p.Arg133Cys and other mutation types (Table 4, Fig. 2).

Trajectories in parental well-being with parental age by child comorbidities

The multivariate analyses showed the PCS score declined when the child with Rett syndrome was experiencing weekly to daily night waking or severe anxiety problems (coefficients = − 0.29; 95% CI − 0.46, − 0.11; $p < 0.01$ and − 0.25; 95% CI − 0.44, − 0.07; $p < 0.01$, respectively). Although a downward trend was observed for severe feeding difficulty, weekly to daily epileptic seizures and moderate mood disturbances, little difference was found compared with the least severe groups (Table 5, Fig. 3).

In contrast, when their child with Rett syndrome was tube fed, the MCS score decreased with parental age after adjustment for covariates (coefficient = − 0.20; 95% CI − 0.44, 0.04; $p = 0.10$). While little change was demonstrated in weekly to daily sleep disturbances, there was a difference of − 0.24 (95% CI − 0.49, 0.01; $p = 0.06$) in the score for each increased year of parental age compared with no sleep disturbances (result not shown in Table 5). No variability was found in the trend across the groups of mood disturbances or anxiety. However, at a median parental age of 45 years, the score was lower with moderate and severe mood disturbances compared with no or mild mood disturbances by − 2.13 (95% CI − 3.92, − 0.33; $p = 0.02$) and − 2.71 (95% CI − 4.71, − 0.72; $p < 0.01$), respectively (results not shown in Table 5). There was little difference in the trend when those whose child had a history of bone fracture were compared with those whose child did not (coefficient = − 0.11; 95% CI − 0.39, 0.17; $p = 0.43$) (result not shown in Table 5) (Table 5, Fig. 3).

Comparisons of trajectories in well-being in parents included in the study with that in general populations

Compared with South Australian population norms, *z*-scores for the PCS and MCS showed little change with parental age in univariate analysis. Multivariate models found that, while there was no downward trend in the z-score for the PCS (coefficient = 0.00; 95% CI − 0.01, 0.02; $p = 0.61$), the MCS declined slightly by − 0.01 (95% CI − 0.03, 0.00; $p = 0.09$) for each increased year of age.

Discussion

The pathway parents of a child with Rett syndrome follow over time is complex and tortuous and passes through many different stages. From welcoming an apparently healthy daughter into the world and caring for a normal child during infancy, they come to realise that their child has a developmental disability; eventually find the cause for this; care for her during childhood when she may be developing additional medical comorbidities requiring various interventions; and finally watch her mature into adulthood with often little knowledge of her likely life expectancy [32, 33]. Our longitudinal study has allowed us to follow these families through the vicissitudes of their lives as their daughter often faces and overcomes new challenges. Cognizant of their experiences, we were prompted to use our unique longitudinal dataset to investigate how this difficult journey might impact on the emotional and physical well-being of these parents. We found that living in a remote area, the child being a teenager at baseline, having frequent sleep disturbances or behavioural problems, and the type of *MECP2* gene mutation were each associated with later poorer parental physical well-being. Being a single parent or on a low income was also associated with later poorer physical well-being, while the child being enterally fed was associated with later poorer emotional well-being. Both the physical and

Table 2 Characteristics of child-related factors among parents included in the study ($n = 198$)

Time-constant variable	$n = 198$			
Child age at baseline, *n* (%)				
Younger than 7 years	44 (22.2)			
7–11 years	51 (25.8)			
11–17 years	53 (26.8)			
17 years or over	50 (25.3)			
Mutation type, *n* (%)				
C-terminal deletion	20 (10.1)			
Early truncating	11 (5.6)			
Large deletion	12 (6.1)			
p.Thr158Met	18 (9.1)			
p.Arg133Cys	17 (8.6)			
p.Arg168*	13 (6.6)			
p.Arg294*	12 (6.1)			
p.Arg270*	11 (5.6)			
p.Arg255*	10 (5.1)			
p.Arg306Cys	9 (4.6)			
p.Arg106Trp	7 (3.5)			
Other	19 (9.6)			
Negative	39 (19.7)			
Time-variant variable	2002 cohort ($n = 132$)	2006 cohort ($n = 140$)	2009 cohort ($n = 168$)	2011 cohort ($n = 160$)
Mobility, *n* (%)				
Independent	48 (36.4)	58 (41.4)	73 (43.5)	71 (43.3)
Assisted	34 (25.8)	24 (17.1)	32 (19.1)	30 (18.3)
Wheelchair-bound	50 (37.9)	58 (41.4)	63 (37.5)	63 (38.4)
Number of observations	132	140	168	164
Feeding difficulty, *n* (%)				
None/Little	30 (22.7)	43 (30.7)	61 (36.3)	42 (26.3)
Slight	81 (61.4)	62 (44.3)	68 (40.5)	74 (46.3)
Severe (tube use)	21 (15.9)	35 (25.0)	39 (23.2)	44 (27.5)
Number of observations	132	140	168	160
Epilepsy, *n* (%)				
None in the last year	51 (38.6)	53 (37.9)	73 (43.5)	70 (42.9)
Yearly/Monthly	28 (21.2)	43 (30.7)	51 (30.4)	46 (28.2)
Weekly/Daily	53 (40.2)	44 (31.4)	44 (26.2)	47 (28.8)
Number of observations	132	140	168	163
Sleep disturbances, *n* (%)				
None	15 (11.4)	17 (12.1)	24 (14.3)	46 (28.8)
Sometimes	69 (52.3)	30 (21.4)	41 (24.4)	35 (21.9)
Often	48 (36.4)	93 (66.4)	103 (61.3)	79 (49.4)
Number of observations	132	140	168	160
Scoliosis, *n* (%)				
No/Mild	100 (75.8)	93 (66.4)	103 (61.3)	93 (56.7)
Severe with surgery	25 (18.9)	26 (18.6)	44 (26.2)	51 (31.1)
Severe without surgery	7 (5.3)	21 (15.0)	21 (12.5)	20 (12.2)
Number of observations	132	140	168	164
Mood disturbances, *n* (%)				
No/Mild	43 (32.6)	40 (28.6)	53 (31.9)	52 (32.5)
Moderate	38 (28.8)	49 (35.0)	58 (34.9)	53 (33.1)
Severe	51 (38.6)	51 (36.4)	55 (33.1)	55 (34.4)

Table 2 (continued)

Time-variant variable	2002 cohort (n = 132)	2006 cohort (n = 140)	2009 cohort (n = 168)	2011 cohort (n = 160)
Number of observations	132	140	166	160
Anxiety, n (%)				
No/Mild	36 (27.3)	29 (20.7)	51 (30.7)	46 (28.0)
Moderate	46 (34.9)	41 (29.3)	50 (30.1)	53 (33.1)
Severe	50 (37.9)	70 (50.0)	65 (39.2)	61 (38.1)
Number of observations	132	140	166	160
Awake breathing abnormalities, n (%)				
Normal rhythm	20 (15.2)	30 (21.4)	48 (28.6)	44 (27.5)
Mild	66 (50.0)	59 (42.1)	68 (40.5)	70 (43.8)
Severe	46 (34.9)	51 (36.4)	52 (31.0)	46 (28.8)
Number of observations	132	140	168	160
Bone fracture, n (%)				
No	116 (87.9)	126 (90.0)	155 (92.3)	148 (92.5)
Yes	16 (12.1)	14 (10.0)	13 (7.7)	12 (7.5)
Number of observations	132	140	168	160

emotional well-being of the parent improved when the child was living in out-of-home care.

A strength of this study is its ability to capitalise on the availability of the population-based longitudinal database which has now been collecting data for 25 years and which has already made a major contribution to the body of knowledge about Rett syndrome [34]. We, nevertheless, acknowledge the limitations inherent in this study. Despite the continued economic growth in Australia, parental income was unfortunately not adjusted for inflation nor was other income such as pensions taken into account possibly resulting in distortion of the effect of parental income on well-being scores. Second, the multivariate models examining the effects of each of the child physical comorbidities did not include the other comorbid conditions. There might have been interactions or confounding relationships between the covariates, distorting the relationships with the well-being scores.

Very few other studies have specifically examined caregiver's well-being in Rett syndrome [13, 35–38]. Aside from those using the Australian Rett Syndrome Database [37, 38], others have depended on parental report rather than a validated diagnosis of Rett syndrome [36], been unrepresentative and not population-based [13, 35, 36], or longitudinal follow-up has been restricted to a period of less than 2 years [13]. In contrast, this study has used population-based and representative data where the diagnosis of Rett syndrome has been validated genetically or clinically from a cohort followed for up to 9 years. Moreover, other studies have all focussed on emotional to the exclusion of physical health [13, 35, 36].

Although compared with population norms, there was a slight downward trend as well as being associated cross-sectionally [7] with lower scores, emotional well-being of parents of children with Rett syndrome changed little over up to 9 years of follow-up, consistent with results from a UK study [13]. These results may represent the development of some parental resilience [10, 39] as suggested by findings from other studies of developmental disability [14, 15]. In contrast, parental physical well-being deteriorated with age, particularly in single parents and those with low income, consistent with the known effects of social disparity on physical health [40, 41]. On the other hand, although a predictor of poorer physical well-being we found that dwelling in outer regional or remote regions was associated with improved emotional well-being of a parent. This is consistent with previous Australian studies finding better emotional well-being, but not physical health, for those living in remote regions, who reported stronger social networks and cohesion compared with those from urban cities [42, 43].

Poorer family function or being a single parent was identified as a major predictor of both subsequent poorer physical and emotional well-being in our study. Greater access to informal supports including those provided by family members has been shown to ease parenting stress among parents of individuals with mild intellectual disability [44], and reduce the emotional and physical burden of caregiving in parents of children with muscular dystrophy [45]. In particular, partner support was perceived critical for caring for a child with chronic illness by reducing the burden of daily care and strengthening family relationships [46]. These and our findings suggest that both single parents and dysfunctional families could be highly vulnerable to the burden of care and require additional both emotional and physical supports.

Although it can also be associated with persistent guilt and anxiety [47], our findings in keeping with others [47–49]

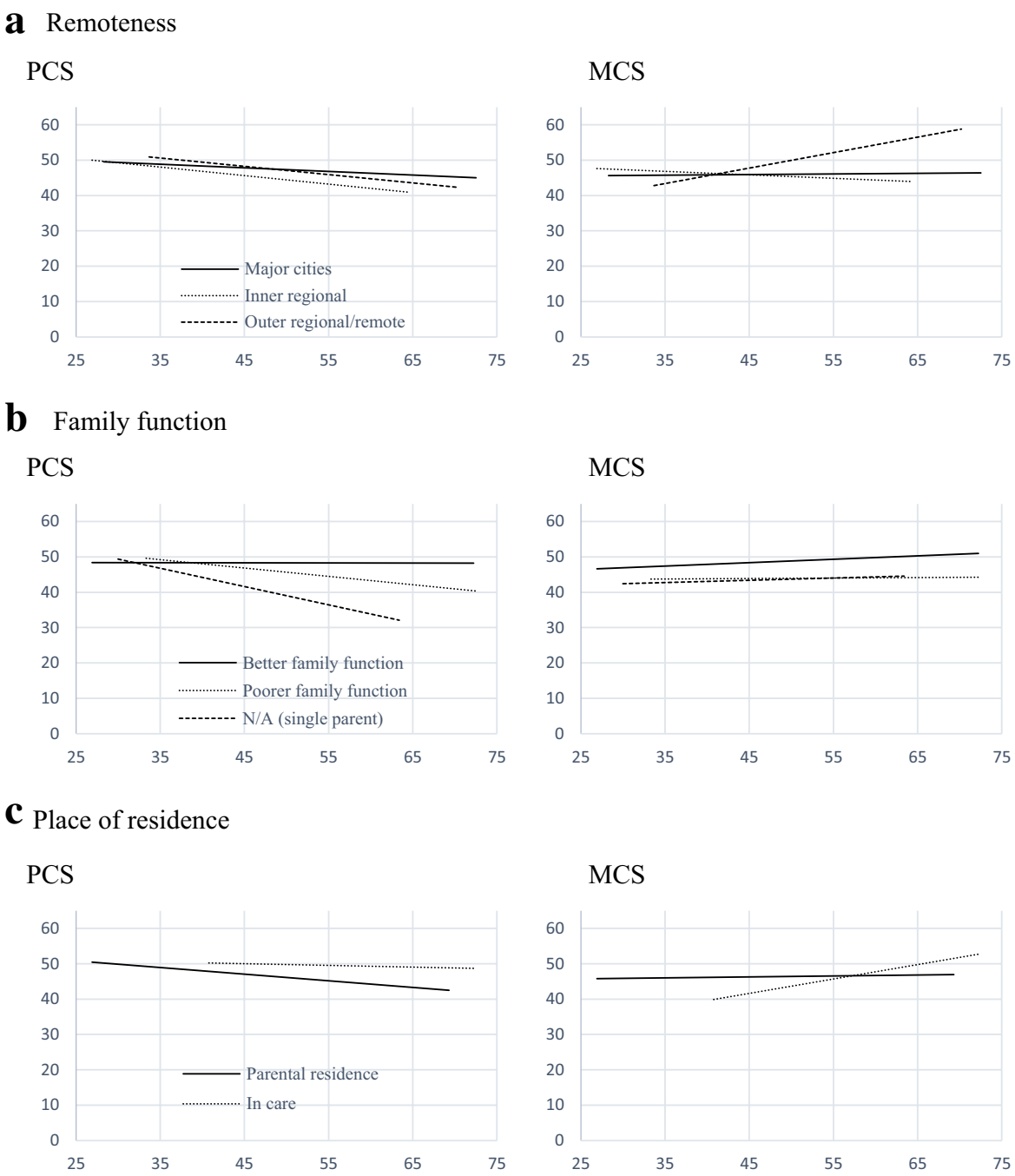
Table 3 Changes in SF-12 scores over time shown by intercept coefficients and the 95% CI of linear mixed-effects regression models for family factors and child age at baseline in a multivariate model ($n = 185$)[b,c]

	PCS		MCS	
	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
Parental qualification				
Secondary school or less	− 0.20 (− 0.38, −0.02)	0.03	0.08 (− 0.08, 0.24)	0.35
TAFE/technical certificate	− 0.30 (− 0.54, −0.06)	0.01	− 0.19 (−0.41, 0.03)	0.09
University degree	− 0.01 (− 0.31, 0.29)	0.93	− 0.04 (−0.32, 0.25)	0.80
Remoteness				
Major cities	− 0.12 (− 0.28, 0.04)	0.15	− 0.00 (− 0.15, 0.15)	0.99
Inner regional	− 0.42 (− 0.69, −0.14)	< 0.01	− 0.22 (− 0.47, 0.04)	0.10
Outer regional/remote	− 0.37 (− 0.78, 0.04)	0.08	0.35 (− 0.04, 0.73)	0.08
Birth order				
Firstborn	− 0.19 (− 0.39, 0.00)	0.05	− 0.02 (− 0.20, 0.16)	0.84
Later-born	− 0.20 (− 0.37, − 0.02)	0.03	− 0.02 (− 0.18, 0.15)	0.86
Parental age	−0.20 (− 0.34, − 0.05)	< 0.01	− 0.02 (− 0.15, 0.12)	0.81
Parental work status				
Full-time homemaker	− 0.19 (− 0.36, − 0.03)	0.02	− 0.04 (− 0.19, 0.12)	0.62
Part-time employment	− 0.26 (− 0.49, −0.04)	0.02	− 0.00 (− 0.22, 0.22)	0.99
Full-time employment	− 0.09 (− 0.39, 0.22)	0.59	0.06 (− 0.23, 0.35)	0.69
Parental income				
$70,000 or more	− 0.21 (− 0.45, 0.03)	0.08	− 0.07 (− 0.30, 0.15)	0.53
$50,000–69,999	− 0.24 (− 0.52, 0.03)	0.09	0.13 (− 0.14, 0.40)	0.35
$40,000–49,999	− 0.05 (− 0.38, 0.29)	0.79	0.01 (− 0.31, 0.33)	0.95
$30,000–39,999	0.00 (− 0.32, 0.32)	1.00	0.09 (− 0.22, 0.40)	0.57
$20,000–29,999	− 0.45 (− 0.73, −0.17)	< 0.01	− 0.10 (− 0.37, 0.17)	0.47
Less than$20,000	− 0.12 (− 0.36, 0.12)	0.31	− 0.05 (− 0.27, 0.17)	0.66
Number of siblings				
0	− 0.28 (− 0.61, 0.05)	0.09	0.10 (− 0.21, 0.40)	0.54
1	− 0.03 (− 0.26, 0.19)	0.79	− 0.00 (− 0.22, 0.21)	0.99
2 or more	− 0.26 (− 0.43, − 0.09)	< 0.01	− 0.05 (− 0.21, 0.11)	0.56
Family function				
Better	− 0.09 (− 0.26, 0.08)	0.28	0.03 (− 0.13, 0.19)	0.71
Poorer	− 0.28 (− 0.46, −0.10)	< 0.01	− 0.07 (− 0.24, 0.10)	0.42
N/A[a] (single parent)	− 0.68 (− 1.14, − 0.21)	< 0.01	− 0.08 (− 0.54, 0.38)	0.73
Place of residence				
Parental residence	− 0.20 (− 0.35, − 0.06)	< 0.01	− 0.03 (− 0.17, 0.10)	0.65
In care	− 0.04 (− 0.53, 0.45)	0.86	0.28 (− 0.20, 0.75)	0.26
Care arrangements				
None	− 0.08 (− 0.29, 0.13)	0.46	− 0.04 (− 0.25, 0.16)	0.67
Any respite	−0.25 (− 0.42, −0.09)	< 0.01	− 0.02 (− 0.17, 0.14)	0.85
In care	− 0.02 (− 0.51, 0.47)	0.94	0.28 (− 0.20, 0.76)	0.25
Child age at baseline				
Younger than 7 years	0.11 (− 0.22, 0.44)	0.50	− 0.10 (− 0.41, 0.22)	0.55
7–11 years	− 0.27 (− 0.56, 0.02)	0.07	− 0.00 (− 0.28, 0.28)	1.00
11–17 years	− 0.37 (− 0.60, − 0.13)	< 0.01	− 0.19 (− 0.41, 0.02)	0.08
17 years or over	− 0.09 (− 0.38, 0.19)	0.52	0.29 (0.02, 0.55)	0.03

[a]Not applicable

[b]Positive and negative values show positive and negative changes in the SF-12 scores for each increase of one year in parental age, respectively. Zero represents no change in the score over time

[c]Multivariate linear mixed-effect regression models included parental qualification, remoteness, birth order, parental age, parental work status, parental income, number of siblings, family function, place of residence, child age at baseline and mutation type



[a] Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

Fig. 1 Changes in predicted SF-12 score over time by main family-related factors (multivariate model; $n = 185$). **a** Remoteness. **b** Family function. **c** Place of residence. Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

suggest that placement in out-of-home care may reduce the physical and emotional toll on parents. It is interesting that the child being a teenager at baseline was associated with later poorer physical well-being. At this time the child is likely to be growing and becoming heavier to handle. Compounded by the likely presence of scoliosis the physical burden of caring for the child's needs may well be increasing and impacting on mother's own health. Thus, it is important

Table 4 Changes in SF-12 scores over time shown by intercept coefficients and the 95% CI of linear mixed-effects regression models for child's mutation type in a multivariate model ($n = 185$)[a,b]

	PCS		MCS	
	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
C-terminal deletion	− 0.27 (− 0.69, 0.16)	0.22	0.10 (− 0.29, 0.48)	0.62
Early truncating	− 0.21 (− 0.65, 0.24)	0.36	− 0.20 (− 0.60, 0.21)	0.35
Large deletion	− 0.09 (− 0.58, 0.39)	0.71	− 0.25 (− 0.70, 0.20)	0.28
p.Thr158Met	− 0.12 (− 0.50, 0.25)	0.52	− 0.09 (− 0.44, 0.25)	0.60
p.Arg133Cys	0.06 (− 0.41, 0.54)	0.79	0.34 (− 0.10, 0.78)	0.13
p.Arg168*	− 0.28 (− 0.68, 0.12)	0.17	− 0.15 (− 0.51, 0.21)	0.43
p.Arg294*	− 0.26 (− 0.73, 0.20)	0.26	− 0.20 (− 0.63, 0.22)	0.34
p.Arg270*	− 0.16 (− 0.73, 0.40)	0.57	− 0.06 (− 0.59, 0.46)	0.82
p.Arg255*	0.25 (− 0.37, 0.86)	0.43	− 0.33 (− 0.89, 0.24)	0.25
p.Arg306Cys	− 0.12 (− 0.63, 0.39)	0.65	0.20 (− 0.27, 0.67)	0.40
p.Arg106Trp	− 0.02 (− 0.57, 0.54)	0.95	0.11 (− 0.39, 0.61)	0.67
Other	− 0.19 (− 0.56, 0.17)	0.29	0.34 (0.01, 0.67)	0.05
Negative	− 0 .44 (− 0.74, − 0.15)	< 0.01	− 0.16 (− 0.43, 0.12)	0.27

[a]Positive and negative values show positive and negative changes in the SF-12 scores for each increase of one year in parental age, respectively. Zero represents no change in the score over time

[b]Multivariate linear mixed-effect regression models included parental qualification, remoteness, birth order, parental age, parental work status, parental income, number of siblings, family function, place of residence, child age at baseline and mutation type

that adequate attention is given to providing for carers the necessary physical supports such as hoists and modified vehicles, and that an extra pair of hands is available to assist with the more demanding caring tasks including maintaining the child's physical activity levels. Respite also aims to support parents with a child with disability, still living in the family home, in coping with care demands and facilitating their own social lives [50, 51]. However, we found, as previously [8], that respite care use was actually associated with later worsening parental physical well-being as its use may merely reflect other unmet needs of families who are facing barriers to accessing and securing services [52–54] and in the meantime accumulating further physical burden from daily care.

This is the first study to investigate any relationship between parental well-being and genotype in Rett syndrome. Some of the associations we found could be explained by the variation in clinical severity associated with different genotypes [5, 55–60] and the subsequent impact on the caregiver. For instance, there was only an improvement in parental emotional well-being over time for mothers of those with four mutation types and previous research has shown that in three of these, p.Arg133Cys [55, 56], C-terminal deletions [57, 58] and p.Arg306Cys, the phenotype is generally mild compared with those such as p.Arg255* and large deletions where the trend was in the opposite direction. The improvement in emotional health over time, therefore, is not unexpected given the likely lower burden on the family when the child has a mild mutation [55, 56], especially a p.Arg133Cys mutation, compared for example with the more severe phenotype conferred by a large deletion [59].

Irrespective of the *MECP2* gene mutation type, we found relationships between feeding difficulty, sleep disturbances and behavioural problems (mood disturbances and anxiety) and later parental physical or/and emotional well-being. Deteriorating emotional well-being was observed for parents whose child was partly or totally tube fed. We previously reported that experience of gastrostomy placement was generally perceived satisfactory by families of children with Rett syndrome because it improved the physical health of the child and reduced the caregiver burden relating to food and medication administration [61]. Further, in a study of the CDKL5 disorder, a *MECP2*-related disorder associated with a severe early onset epileptic encephalopathy, we found an association of gastrostomy feeding with better parental emotional well-being but poorer physical well-being [54]. However, our recent longitudinal study with 2207 person-years of observation showed no improvement in parenting physical or emotional health, measured by a PCS or MCS score, respectively, was observed following gastrostomy placement among 296 Australian parents of a child with Rett syndrome [62]. Variability in the findings might have been explained by a complex nature of a genetic disorder accompanying multiple physical comorbidities which may collectively affect parental well-being.

Parental emotional well-being declined over time when the child suffered frequent night waking or had severe mood disturbances. Physical well-being also deteriorated among parents whose child had frequent night waking or severe anxiety. Previous research showed increased severity of child behaviour problems predicted later poorer

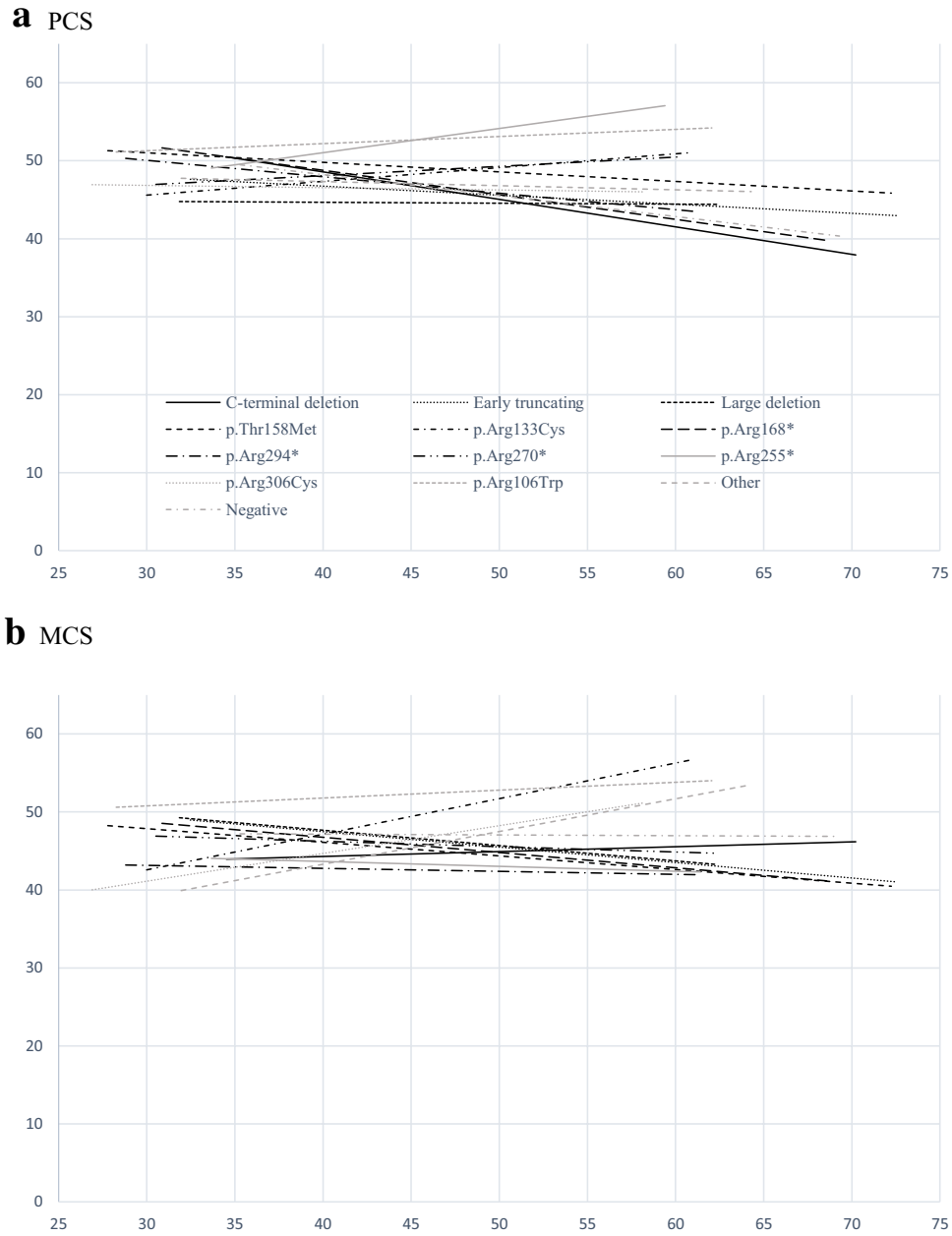


Fig. 2 Changes in predicted SF-12 scores over time by mutation types (multivariate model; $n = 185$). **a** PCS. **b** MCS. Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

[a] Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

emotional well-being of the parent in autism spectrum disorder [16], non-specific intellectual disability [15] and Rett syndrome [13], and physical well-being in developmental delays [17]. Using cross-sectional designs, child sleep disturbances were risk determinants of parental emotional well-being in autism spectrum disorder [63], developmental disabilities [11], cerebral palsy [64] and the CDKL5 disorder [54]. The findings suggest that child sleep and behavioural problems could have both cross-sectional and longitudinal negative effects on parental well-being across different developmental disabilities and that these are important areas for clinicians and service providers to target to optimise well-being for the whole family.

Conclusion

Using a long-standing population-based database this longitudinal study has provided a greater insight into parental well-being and its determinants for families caring for

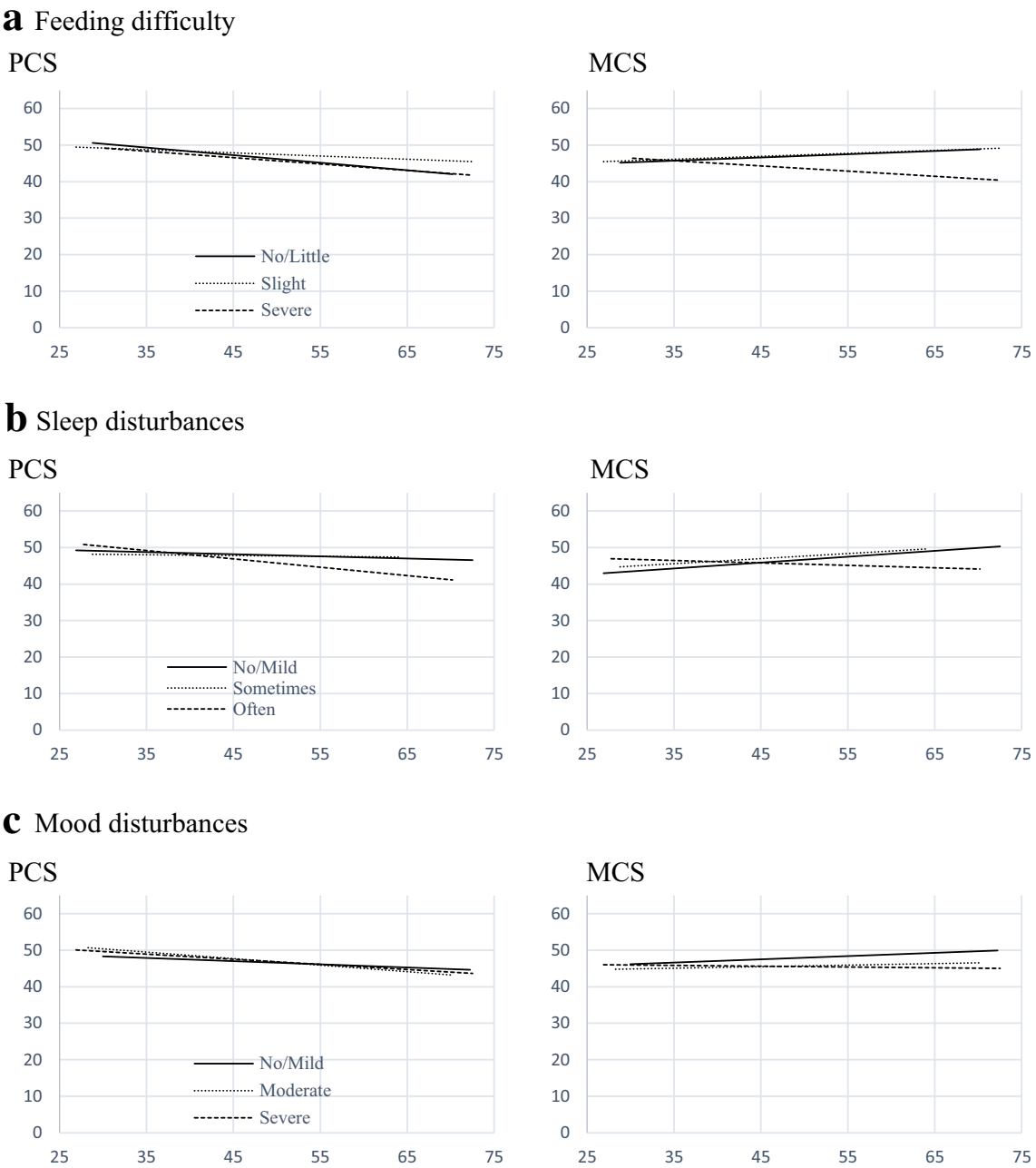
Table 5 Changes in SF-12 scores over time shown by intercept coefficients and the 95% CI of linear mixed-effects regression models for child comorbidities in a multivariate model ($n = 185$)[a,b]

	PCS		MCS	
	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
Mobility				
Independent	− 0.17 (− 0.38, 0.04)	0.12	− 0.08 (− 0.28, 0.12)	0.46
Assisted	− 0.24 (− 0.48, 0.01)	0.06	0.19 (− 0.04, 0.42)	0.10
Wheelchair-bound	− 0.19 (− 0.39, 0.02)	0.08	− 0.10 (− 0.29, 0.09)	0.31
Feeding difficulty				
No/Little	− 0.25 (− 0.47, − 0.04)	0.02	0.05 (− 0.15, 0.25)	0.63
Slight	− 0.14 (− 0.31, 0.04)	0.12	0.04 (− 0.12, 0.20)	0.62
Severe (tube use)	− 0.27 (− 0.52, − 0.01)	0.04	− 0.20 (− 0.44, 0.04)	0.10
Epilepsy				
None in the last year	− 0.20 (− 0.39, −0.01)	0.04	0.04 (− 0.14, 0.22)	0.66
Yearly/Monthly	− 0.09 (− 0.30, 0.12)	0.40	− 0.03 (− 0.23, 0.17)	0.77
Weekly/Daily	− 0.27 (− 0.49, − 0.05)	0.01	− 0.05 (− 0.26, 0.15)	0.61
Sleep disturbances				
None	− 0.10 (− 0.34, 0.13)	0.38	0.13 (− 0.09, 0.36)	0.24
Sometimes	− 0.11 (− 0.31, 0.09)	0.29	0.06 (− 0.13, 0.25)	0.55
Often	− 0.29 (− 0.46, −0.11)	< 0.01	− 0.11 (− 0.27, 0.06)	0.20
Scoliosis				
No/Mild	− 0.24 (− 0.40, − 0.08)	< 0.01	− 0.04 (− 0.20, 0.11)	0.58
Severe with surgery	− 0.27 (− 0.58, 0.03)	0.08	− 0.02 (− 0.31, 0.27)	0.88
Severe without surgery	− 0.25 (− 0.61, 0.11)	0.18	0.16 (− 0.19, 0.50)	0.38
Mood disturbances				
No/Mild	− 0.18 (− 0.38, 0.02)	0.08	0.04 (− 0.15, 0.23)	0.68
Moderate	− 0.23 (− 0.42, − 0.04)	0.02	− 0.01 (− 0.19, 0.17)	0.93
Severe	− 0.18 (− 0.38, 0.02)	0.07	− 0.09 (− 0.28, 0.10)	0.35
Anxiety				
No/Mild	− 0.12 (− 0.32, 0.09)	0.27	0.02 (− 0.17, 0.22)	0.83
Moderate	− 0.17 (− 0.36, 0.01)	0.07	0.00 (− 0.18, 0.18)	0.97
Severe	− 0.25 (− 0.44, − 0.07)	<0.01	− 0.08 (− 0.26, 0.10)	0.37
Awake breathing abnormalities				
Normal rhythm	− 0.23 (− 0.45, − 0.00)	0.05	0.11 (− 0.11, 0.32)	0.31
Mild	− 0.19 (− 0.37, − 0.01)	0.04	− 0.07 (− 0.24, 0.10)	0.45
Severe	− 0.19 (− 0.39, 0.01)	0.07	− 0.06 (− 0.25, 0.13)	0.56
Bone fracture				
No	− 0.19 (− 0.34, − 0.04)	0.01	− 0.00 (− 0.14, 0.13)	0.95
Yes	− 0.22 (− 0.52, 0.07)	0.13	− 0.12 (− 0.40, 0.17)	0.41

[a]Positive and negative values show positive and negative changes in the SF-12 scores for each increase of one year in parental age, respectively. Zero represents no change in the score over time

[b]Multivariate linear mixed-effect regression models included parental qualification, remoteness, birth order, parental age, parental work status, parental income, number of siblings, family function, place of residence, child age at baseline and mutation type

a child with Rett syndrome. As observed in the general population, physical well-being deteriorated over up to 9 years of follow-up. Emotional well-being showed a slight decline in contrast to the general population. This similarity suggests that many parents found strategies and resources to cope despite the burden of Rett syndrome. Identifying protective factors for the health of parents with a child with severe disability is an important topic of future research. Nevertheless, our findings demonstrate that the trajectory of parental well-being for these families is complex and affected by a range of family and child characteristics. Remoteness, child age at baseline, and the *MECP2* gene mutation type, sleep disturbances and behavioural problems of the affected child each influenced



[a] Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

Fig. 3 Changes in predicted SF-12 score over time by main child-related factors (multivariate model; $n = 185$). **a** Feeding difficulty. **b** Sleep disturbances. **c** Mood disturbances. Axial and horizontal lines represent a predicted SF-12 score and parental age as a unit of year, respectively

later parental physical and emotional well-being. Family function and parental income also affected later physical well-being of a parent, while child feeding difficulty was associated with poorer emotional well-being. The study has highlighted the importance of a longitudinal approach to investigating this complex and dynamic concept of caregiving and parental well-being in the field of developmental disabilities.

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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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