Title: Middle-aged women with Rett Syndrome: Longitudinal profile from the British Isles Rett Syndrome Survey and suggestions for care

Running Title: Middle-aged women with Rett Syndrome

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Declarations

Ethics approval and consent to participate

The British Isles Rett Syndrome Survey (BIRSS) was initially maintained with ethics approval from the NHS Multi-Centre Research Ethics Committee for Scotland and, after the move of BIRSS to Cardiff, the NHS Wales Research Ethics Committee 3. Data were collected and stored with the consent of parents or carers.

Consent for publication

Consent to participation in BIRSS explicitly included the goal of reporting the collected and anonymised information in medical journal reports.

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Availability of data and materials

The clinical data analysed for the current study are available from the corresponding author on reasonable request, subject to protection of the identity of the affected individuals.

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Authors' contributions

Anna Hryniewiecka-Jaworska collected the data from 2005, adding this to the previous data collected by Dr Kerr. She documented the consent process for all participants. She extracted the data of all those in BIRSS of > 40 years and drafted the first version of the paper in 2015. Emily Sloper revised the original draft very substantially, before submission, and responded to the reviewers' comments. Angus Clarke was responsible for the ethics committee approval, the oversight of BIRSS and of this research, and also contributing to interpretation of the data and to revising repeated drafts. Hayley Archer assisted with data interpretation and drafting of the paper. All authors have participated in the Cardiff Rett Syndrome Clinic and approved the final manuscript.

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Lay Summary

Women over 40 years of age with Rett Syndrome:

*are usually affected by a less severe, non-progressive form of the condition

*are less likely to have had the diagnosis recognised than children with the same condition

*may experience unrecognised depression

*can be actively helped in multiple ways to lead more fulfilling lives, if the diagnosis is made

Abstract (150 words)

Background and Methods

We report historical information from longitudinal data held in the British Isles Rett Syndrome Survey (BIRSS) concerning women of at least 40 years. This information, including comments on the quality of care, has been provided by families, carers and clinicians.

Results

Information was available on 30 women with a clinical diagnosis of Rett Syndrome (RTT), of whom 24 were <50 years. Twenty-nine women were diagnosed with classic RTT and one with atypical. Of eighteen women tested for *MECP2* mutations, pathogenic variants were identified in fourteen. There was little increase in severity over time.

Conclusions

The study found that: (1) milder phenotypes were common; (2) depression may be under-recognised; (3) menopause does not seem to occur early; (4) nutrition standards from the general population will often be inapplicable; (5) multiple opportunities exist to prevent functional decline through detailed attention to the quality of the medical and social care.

BACKGROUND

Rett syndrome (RTT) is a neurodevelopmental disorder characterised by an apparently healthy first six months of life, then stagnation of development and subsequent regression. The child, usually a girl, becomes withdrawn and sometimes distressed, develops stereotypical hand movements and loses skills including purposeful hand use and communication [Hagberg et al 1983; Neul et al 2010]. She subsequently emerges from regression but remains profoundly affected by dyspraxia, gait ataxia, difficulties with communication and cognition and, perhaps, an element of being “locked-in”. There is relatively limited information available about adult women with RTT, especially about the natural history of RTT in those above 40 years of age. Accordingly, we have extracted historical data from the now inactive British Isles Rett Syndrome Survey (BIRSS).

Multiple factors are likely to contribute to reduced ascertainment among older women in the British Isles, including (i) the relative lack of familiarity with features of RTT among professionals supporting affected adults, (ii) the lower frequency of

121 referral for diagnostic assessment of adults with cognitive impairment, (iii) the shift
122 in residence from family home to social care as parents age, and a shift from
123 predominantly health care provision to social care, with reduced frequency of health
124 service input when a young person with severe cognitive impairment moves into
125 adult services, and (iv) the often limited access of carers and professionals to
126 information about an adult woman's early childhood. For these reasons, much more
127 is known about children with RTT than about adults. The number of adults reported
128 with RTT is much less than the numbers of children; population surveys usually give a
129 peak prevalence in mid-childhood, falling to much lower levels with increasing age.
130 The higher mortality in affected females compared to the general population will
131 also contribute to this effect [Freilinger et al 2010; Kirby et al 2010; Anderson et al
132 2014; Tarquinio et al 2015]. The mortality rate in RTT patients in the UK has been
133 estimated at 1.2% per annum [Kerr et al 1997]. This effect is likely to be more
134 marked in those more severely affected, although data may be skewed by possible
135 underdiagnosis in more mildly affected individuals. Some patients develop additional
136 clinical features, such as gastrointestinal problems of likely autonomic origin, which
137 may blur the clinical picture of RTT [Nielsen et al 2001; Smeets et al 2003; Roze et al
138 2007; Brunetti and Lumsden 2020].
139
140 There are few longitudinal studies of women with RTT and most follow a small
141 number of patients under 40 years of age [Berg et al 2001; Hagberg et al 2001;
142 Hagberg et al 2003; Smeets et al 2003; Hagberg 2005] and consensus statements
143 acknowledge that further experience with older patients is needed [Fu et al 2020].
144 The larger natural history studies also concentrate on younger patients [Anderson et

al 2014; Neul et al 2014; Tarquinio et al 2017], and those studying adult women generally have few patients over 40 years of age [Tarquinio et al 2015; Cianfaglione et al 2016; Bisgaard et al 2021; Peron et al 2022]. Cross-sectional data have also been used in studies on larger populations including older people with RTT [Smeets et al 2003; Cass et al 2003; Halbach et al 2008; Smeets et al2009; Vignoli et al 2012; Neul et al 2024]. A review of published experience indicates aspects of care to address [Lotan et al 2009]. The aim of the present study was to report the available longitudinal data concerning 30 middle-aged survivors known to BIRSS and to note helpful interventions for the health and social care of adults with RTT.

METHODS

Data for thirty women over the age of forty years, about whom information was gathered on at least two occasions, were ascertained from the BIRSS. The BIRSS was established by Dr Alison Kerr in Glasgow in 1990 [Kerr et al 2003] but transferred to Cardiff when Dr Kerr retired in 2005. The original intention from 2005 was to update the patient records every five years, but this was not achieved due to a reduction and subsequent cessation in funding for BIRSS. However, historical data were extracted before the database was discontinued. The data were provided by parents and carers of those affected, collected by postal questionnaire and supplemented by telephone conversations, information from other clinicians and occasionally in person at the Cardiff Rett syndrome clinic.

All patients on whom at least some data were available from >40 years of age, who met the clinical diagnostic criteria for Rett syndrome, and had at least two data collection points for the BIRSS (survey questionnaires) were included in this study, drawing on earlier survey information as well as that from >40 years. Patients did not require a molecular diagnosis to be included. Patients were classified according to the revised diagnostic criteria for Rett syndrome [Neul et al 2010].

A Simplified Severity Score (SSS) was calculated for all women in the study for each decade of their lives using information in the BIRSS health questionnaire (Table 1). This score, the second, simpler score of the two used by Smeets and colleagues, excludes clinical features not normally present in milder RTT and includes factors considered likely to influence the long-term evolution and severity of RTT [Smeets et al 2009]. The probable score for the early decades of some patients was deduced from the available information.

Insert Table 1 here

The data collected also included patient demographics and antenatal, medical and family history. Feeding difficulties were assessed by calculating a Feeding Difficulty Score, with a maximum score of 8 [Kerr et al 2005].

RESULTS

Of thirty middle aged women with RTT (aged 40 years and over), 29 had Classic RTT and one had atypical RTT. One woman was in her 60s, 5 were in their 50s and 24 were in their 40s (Figure 1).

Figure 1. Ages of patients at time of the last completed survey health questionnaire

Molecular analysis

Eighteen of the 30 women had *MECP2* analysis, of whom 14 (78%) had identified mutations. Eight women had not been tested and no information was available for the remaining four. Among those with identified *MECP2* mutations, six were missense mutations (one Arg133Cys, two Arg306Cys, one Thr158Met, one Pro255Arg and one Pro133His); one was an early truncating mutation (Arg255X), two were late truncating mutations, three were small, intragenic, C- terminal deletions and two were large (exonic) deletions. Those women who did not have a molecular diagnosis instead fulfilled the diagnostic criteria for a clinical diagnosis of RTT. One explanation for the lack of molecular confirmation in some women relates to laboratory practices when their genomic testing was performed. Many were amongst the first patients tested for RTT in the United Kingdom, at which time the detection rate was lower (approximately 80%), likely due to limitations of the technology [Cheadle et al 2000]. Molecular testing was not repeated in this clinic because women were referred from centres across the UK and abroad. Clinical diagnoses were established in person by Dr Kerr before transfer of the survey in 2005, or confirmed at the Cardiff Rett syndrome clinic, or both.

Severity

Where possible, Smeets's simplified severity score (SSS) was calculated for each decade of life [Smeets et al 2009]. It remained below 9 for 19 patients in all decades of their lives. When calculated, the SSS for 24 women (80%) was 9 or below, for three women (10%) was 10, and for three women (10%) was 11 or 12. Very little increase in severity was observed over the decades and, even when the severity increased, the score usually remained below 9 (Figure 2).

Figure 2. Each patient's 'simplified severity score' in each decade of life

Gross motor skills

Two (7%) women never walked and two (7%) lost the ability to walk during their childhood regression. Of those 26 women walking after their childhood regression, two (8%) permanently lost their ability to walk in their 20s and nine (37.5%) of those still walking in their 40's lost that ability during their 40s or 50s. Of the 14 women known to continue to walk, all had an abnormal gait with a stooped posture on a spectrum of ability from walking independently, although with a mildly ataxic gait, to walking but requiring a variable degree of support. Sitting ability was well preserved: 26 of 30 women could sit in their forties, 13 requiring support.

Of the women who could walk, contractures were present in eleven (79%), not present in two (14%) and there was no information for one woman. Information was not specifically recorded about the location of the contractures in this cohort. Four women had corrective operations for contractures including tendon lengthening or

tendonotomies. Hip problems (dislocation, displacement, rotation) were reported in 12 women.

Insert Table 2 here

Hand use

All women could use their hands to some extent before regression. Eleven women (37%) regained hand use and could finger feed throughout their lives. One had a late apparent regression including a loss of her ability to use hand skills in her twenties. Ten women (33%) never regained hand use after regression. Three women lost their ability to finger feed in their thirties, forties and fifties. One woman regained her ability to finger feed in her twenties and lost it again in her forties. Another woman regained her finger feeding in her thirties and was still feeding herself in her forties. Longitudinal information on this was not available for three women but they could not use their hands at one time point: one in her 50's and two in their 40's.

Stereotypies were described in all the women at some point during their lives, especially midline hand movements and hand-to-mouth movements. Although the reports were subjective from parents or carers, stereotypies in later life were described as milder, less intense and sometimes only affecting one hand or manifesting during periods of agitation. In some cases, stereotypies disappeared with age. In several, the ability to use one hand improved when the other hand was held gently.

Speech, understanding and communication

Twenty-eight of the 30 women could use words before regression, with most losing this ability during childhood regression. Of the five women known to recover words after regression, one lost these in her 20s, two in their 30s and two continued to use words at least into their 40s, one including short phrases.

Insert Table 3 here

Information regarding other means of expressive communication was available for 26 of the 30 women. Eleven used meaningful sounds, 24 of 29 women for whom data was available could use facial expressions and eight of 26 women could communicate by gesture (Figure 3A).

Figure 3. Expressive (3A) and receptive (3B) communication ability at final data collection point for all women with RTT

Regarding receptive communication, 15 of 29 women could understand words without gestures, 13 of 27 could understand gestures and 15 of 25 had some understanding in specific contexts. Seventeen of 23 were said to have some appreciation of facial expression (Figure 3B).

With regards to the use of eye contact, 23 women maintained good eye contact, three had poor eye contact and three had no eye contact. One woman, previously

reported to have poor eye contact, regained good eye contact at 62 years after a customised chair was made, which resulted in better positioning of her head.

Epilepsy

Seizures were reported for 18 of 30 women (60%) at some stage during their lives. Ten (33%) had epileptic seizures in middle age, usually generalised tonic-clonic (GTC) or myoclonic seizures, with the seizures being well controlled on medication in nine. Five women had been seizure-free for many years; two remained on carbamazepine and medication was being withdrawn or had been stopped in three others.

One woman with a few GTC seizures per year had not taken regular anticonvulsant medication since 27 years of age. In one patient with ongoing seizures, there was difficulty differentiating between autonomic episodes and epilepsy. Similar difficulties had previously been reported for two further women, now seizure-free.

Scoliosis

All 30 women had scoliosis that progressed slowly throughout their lives but only one was reported as having undergone surgery. This may be because these decisions were made some decades ago. Eighteen women had mild scoliosis and four developed scoliosis beyond the fourth decade. Sixteen of the 18 women with mild scoliosis could walk in early adulthood. Twelve women had severe scoliosis, of whom one never walked and required surgical treatment; all had abnormal muscle tone (hypertonia or dystonia). The other lady who never walked had mild scoliosis.

Breathing

Of the 30 women, 27 intermittently hyperventilated and 25 had breath-holding spells, with or without vacant spells, at some stage. The frequency of hyperventilation episodes decreased in many of the 18 women still affected in middle age; 16 had ongoing vacant spells and they all suffered breath-holding episodes.

Growth

The majority of the women were of short stature, with their height below the 2nd centile. The median weight was approximately the 2nd centile. Ten (one third) were underweight and 37% had a normal BMI (Table 5). However, unusually for RTT, a majority (17/28, 61%) had a normal head circumference, above the 2nd centile, as might be expected in this group with a relatively mild phenotype.

Insert Table 4 here

Insert Table 5 here

Feeding and nutrition

Data regarding feeding and nutrition were available for 28 patients. Nineteen women had minimal to moderate feeding difficulties (feeding score ≤3), nine women had moderate to severe feeding difficulties (feeding score 4-7). Despite this, only three women were fed enterally via tube: two via PEG or PEJ inserted in their fifth decade following aspiration pneumonias, the third via PEG inserted because of

unexplained weight loss in her 30s. Overall, 82% of women in our study had problems with swallowing, chewing, secretions and/or appetite.

Further information was obtained from carers of 22 women with RTT. Two had severe difficulties with maintaining effective mouth closure, two had poor posture affecting feeding, four had difficulty chewing, two had difficulty swallowing, five had excessive secretions, one had poor appetite and two had difficulty drinking.

Mood, behaviour and sleep

Twenty-eight (93%) of the 30 women currently experience or previously experienced episodes of excitement and/or agitation, including ten who had episodes of laughing. Nineteen women demonstrated self-injurious behaviours at some point in their lives. Injurious behaviours towards others were reported in six women; for one this occurred only when she was pre-menstrual. Autistic features were described in one lady who did not relate easily to others and lacked emotional warmth to her family, avoiding eye contact, disliking disruption to her daily routine and preferring repetitive activities such as paper flicking.

Insert Table 6 here

Twenty-five women (83%) had had episodes of unexplained sadness at some point in their lives. Nine women (30%) had unexplained weight loss during adulthood. For one woman, a temporary period of deterioration was reported with transient loss of

mobility and bladder control, cessation of menstruation and apparent depression in her late twenties.

Although not specifically covered in the BIRSS questionnaire, anxiety (including social phobia and agoraphobia) was reported in comments made about five women, either in clinic or in the free text section of the questionnaire. One woman in her 50s had severe mood swings with agitation, treated with imipramine and lithium. One woman had severe anxiety in her 40s, treated with risperidone. One woman required carbamazepine as a mood stabilizer for severe tantrums. Three women were also treated with fluoxetine for low mood and one took 5-hydroxytryptophan.

Grief reactions were described in three women. One woman was described as depressed and 'incredibly upset and frightened' after her grandfather's death. Another became withdrawn, losing her appetite and losing weight in reaction to her father's death. Another woman was described as "very sad when someone sings a song that her mother used to sing to her before she died 17 years previously. That is the only time she seems to cry".

73% of women had experienced sleep difficulties at some point in their lives (Table 7). Eight women were not described as having had sleep difficulties, but it is possible that this may reflect recall bias amongst their carers.

Insert Table 7 here

Menstrual status

Data about menstruation status were available for 27 women. Five women had stopped menstruating (aged 40-53 years at the time of report) and one was peri-menopausal.

General health

Common symptoms included constipation, requiring regular use of laxatives, joint contractures and small cold feet. Gastro-oesophageal reflux, upper and lower respiratory tract infections, aspiration pneumonias and chronic otitis media were also reported. For two women (one in her twenties and another in her thirties), an acute period of deterioration was reported and was associated with obvious distress, loss of mobility and, in one case, loss of bladder control and menstruation. No cause was found; the two women recovered although their mobility was impaired thereafter. Diet-controlled diabetes, kidney stones and urinary tract infections, rheumatoid arthritis, gingivitis, allergy to cats and dogs, asthma, hay fever and eczema, blepharitis and conjunctivitis, rosacea, sebaceous cysts, uterine fibroids, vaginal candidiasis, myopia and hallux valgus were also reported. Data were not specifically collected on objective measures of osteopenia or osteoporosis, as that was not routinely assessed in women with RTT at the time. Three of the women (10%) had experienced one or more fractures.

Insert Table 8 here

DISCUSSION

There was a greater prevalence of milder disease among the older women with RTT in our study, consistent with the findings of others [Smeets et al 2009; Tarquinio et al 2015]. This indicates a survival advantage for the most mildly affected patients [Kerr et al 2003]. Some patients were able to walk, talk and use their hands at least into early middle age. Some features of RTT improved with aging, for example, epilepsy, agitation, sleep and hand stereotypies. However, there was late motor deterioration in some, including development of abnormal muscle tone with loss of walking. Other late-onset deteriorations included loss of speech, increasing feeding difficulties and constipation. The potential to recover skills lost during temporary set-backs in adulthood was demonstrated in some women, as with episodes interpreted as resulting from depression or of uncertain origin. Although the use of words was present in only two women, most achieved some communication by other means. In general, our longitudinal data show a substantial stability in severity over the adult years (Figure 2).

Milder phenotypes have been reported to be more likely in association with specific *MECP2* gene mutations or with favourably skewed X-chromosome inactivation (XCI) [Cheadle et al 2000; Leonard et al 2003; Kerr et al 2006; Smeets et al 2009; Bebbington et al 2010; Halbach et al 2012; Neul et al 2014]. However, caution is recommended in the interpretation of genotype-phenotype relationships, particularly when counselling the parents of newly diagnosed girls, due to the variability in clinical phenotypes. Clinical variability has been documented in natural history studies [Andersson et al 2014; Neul et al 2014; Tarquino et al 2015; Tarquino

et al 2017;] and our own work has demonstrated the poor correlation between severity and X chromosome inactivation in lymphocytes [Archer et al 2007]. These studies reinforce the conclusion that genotypes are useful in providing explanations for established neurodevelopmental phenotypes but are inadequate for the prediction of how the clinical phenotype may evolve in an individual case [Shahbazian and Zoghbi 2001; Weaving et al 2003; Archer et al 2006; Archer et al 2007; Bebbington et al 2008; Halbach et al 2012; Neul et al 2015]. Clinical assessment of the timing and severity of phenotypic manifestations remain the most important prognostic factors [Smeets et al 2003; Schanen et al 2004].

Gross Motor. Gross motor activity, performance and muscle strength generally deteriorate over the years in RTT [Dunn et al 2001; Steffenburg et al 2001; Hagberg 2002; Kerr 2002; Williamson and Christodoulou 2006; Roze et al 2007; Halbach et al 2008; Bisgaard et al 2021]. People with RTT can undergo premature neuromuscular aging and peripheral atrophy is often seen, usually combined with dystonic-rigid signs [Hagberg 2005]. Increased muscle tone, spasms and contractures can also be problematic [Roze et al 2007; Dunn and Macleod 2001]. Abnormal muscle tone, posture and locomotion increase the risk of contractures, malposition and loss of motor function [Larsson et al 2001]. Plantar flexion, peroneal weakness and scoliosis become more prevalent with age [Witt Engerstrom 1992]. While muscle tone may be reduced earlier in life, it is often increased in adults [Kerr and Stephenson 1985]. However, some of those in our study who could walk with little impairment were reported to have near normal muscle tone.

453 Walking skills may be greater than is commonly assumed, with lack of walking
454 resulting from a lack of opportunity and training [Jacobsen et al 2001; Schönewolf-
455 Greulich et al 2017]. Contractures can also represent a potential barrier to continued
456 walking [Kerr and Burford 2001]. Fixed joints become more common with age, with
457 contractures present in 95% of adults in one study [Cass et al 2003]. Many such
458 contractures may be prevented by regular passive exercises through the full range of
459 movement [Kerr 2002]. Abnormal muscle tone and posture can contribute to the
460 development of hip displacement in RTT and screening for this is advised in middle
461 age [Tay et al 2010].
462
463 **Hand Use**. Loss of purposeful hand movement is usually noted in those with RTT,
464 even when less severe [Kerr 2002; Stallworth et al 2019]. Hand stereotypies are a
465 typical manifestation in RTT and often occur early and persist throughout life [Roze
466 et al 2007 Vignoli et al 2009; Stallworth et al 2019]. Reports on the natural history of
467 hand function and description of hand stereotypy in RTT vary [Witt-Engerström
468 1990; Cass et al 2003; Carter et al 2009; Downs et al 2010]. In adult women, hand
469 stereotypies tend to involve the hands being held apart, whereas in younger girls
470 they are typically held together [Kerr et al 1987; Cass et al 2003] suggested this may
471 result from restriction of movement or possibly a lower level of arousal or agitation.
472 Despite stereotypies, many of the women who survived to middle-age had some use
473 of their hands, mostly in finger-feeding. Regaining this ability in later life has been
474 reported, although it was not seen in our cohort and can easily be lost when not
475 encouraged [Jacobsen et al 2001; Schönewolf-Greulich et al 2017], as seen in one
476 woman reported here, when self-feeding was discouraged in residential care.

Speech was uncommon in the women reported here, as elsewhere [Halbach et al 2013], although there was substantial ability to communicate. Speech is possible among older women with mild phenotypes, being most probable in those with missense and late truncating mutations including C-terminal deletions [Nielsen et al 2001; Zappella et al 2001; Kerr et al 2006]. Cognitive and communication skills do not appear to decline with age and may improve [Hagberg 2002; Cass et al 2003; Halbach et al 2008; Halbach et al2013]. Eye contact is frequently well-preserved in adulthood [Hagberg et al 2001; Hagberg 2005; Halbach et al 2008; Schönewolf-Greulich et al 2017]. Women cared for at home are more likely to be reported as communicating effectively [Didden et al 2010], possibly representing a greater awareness in the families of the women's abilities. Carers of women with RTT, both at home and in residential facilities, should encourage communication and decision-making by the women [Schönewolf-Greulich et al 2017]. This may require attention to appropriate seating and head support to enable eye contact.

It is possible that older women with better quality preserved speech are less likely to have been diagnosed with RTT and are absent from our study for that reason.

Epilepsy . As we also found, epilepsy has previously been reported to be less prevalent in later life, often with complete resolution of seizures [Steffenburg et al 2001; Hagberg 2002; Hallbach et al 2013]. The differentiation of non-epileptic vacant spells and epileptic seizures remains problematic in middle-aged women, and therefore the incidence of epilepsy may be over-reported in this age-group [Julu et al

2001; Glaze et al 2010; Tarquinio et al 2017; Henriksen et al 2018]. Video EEG monitoring could help provide definitive information and avoid the inclusion of other non-epileptic events such as vacant spells, episodic laughing, crying or staring [Glaze et al 1998; Pintaudi et al 2010]. In our study, most middle-aged patients continued to take anti-epileptic medications despite having had no seizure for years, consistent with other reports [Cass et al 2003; Halbach et al 2013; Tarquinio et al 2017].

Regular review of anti-epileptics is important in RTT; withdrawal should be considered in those who have been seizure free for a significant time [Steffenburg et al 2001; Hagberg 2002; Halbach et al 2013; Tarquinio et al 2017]. This is especially important because osteoporosis has been reported in RTT [Budden et al 2003; Motil et al 2008]; the prolonged use of anti-epileptic medications can contribute to this [Leonard et al 2010].

Osteopenia and osteoporosis. Only 10% of the women in this report had a history of fractures but the failure of BIRSS to have collected data on osteopenia or osteoporosis is disappointing. Periodic screening for low bone density should be considered in all adult women with RTT as osteopenia can be present from a young age [Motil et al 2008]. Other risk factors for osteoporosis frequently present in adult RTT women include a sedentary life, nulliparity, low body weight, prolonged use of depot contraceptives and inadequate sun exposure, as well as long-term antiepileptic medication [Ryan et al 2002; Zysman et al 2006; Motil et al 2008]. The risk of fractures in RTT is greater than in the general population and fractures can be

missed by carers due to communication difficulties and the apparently high pain threshold of many RTT patients [Downs et al 2008].

Scoliosis was present in all women in our study. To prevent progression of scoliosis and improve seated position and walking ability, early surgical intervention is usually recommended [Kerr et al 2003; Thorey et al 2007; Downs et al 2009; Bisgaard et al 2021]. Surgery is most beneficial when the woman is well-nourished and active [Kerr et al 2003]. In our study, only one woman with severe scoliosis was managed with corrective surgery. Given that the women included in the study were often from other regions or countries, we cannot comment on why the others were not managed surgically.

Breathing. In line with the findings in this study, breathing dysrhythmias such as apnoeas, hyperventilation and breath-holding spells are common in RTT but have been shown to decrease in adulthood [Witt Engerström 1990; Cass et al 2003; Halbach et al 2013; Tarquinio et al 2018]. However, either the failure to initiate inspiration or episodes of prolonged inspiration can persist in many adult women [Witt Engerstrom 1992]. Valsalva breathing patterns are also characteristic and can lead to a sudden fall in blood pressure, fainting and abdominal bloating [Kerr et al 2002; Witt Engerstrom 1992].

Growth. Adults with RTT tend to be short [Tarquinio et al 2012]: the average adult height is approximately 136 cm, i.e. 30 cm below the population mean [Holm 1986;

547 Percy 1992]. Adults with RTT usually also have small hands and feet, often with
548 shorter fourth digits, especially the metatarsals [Kerr et al 1995; Kerr 2002].
549
550 The proportion of women with RTT who have short stature or are underweight
551 increases with age [Holm et al 1986; Percy 1992], with the progressive loss of muscle
552 and bone mass [Motil et al 2008; Smeets et al 2009]. Their BMI may therefore be
553 low despite a normal fat mass and the use of general population nutrition standards
554 will often be inappropriate. Skin fold measurements or bioelectrical impedance
555 analysis to estimate body composition may be more useful [Letellier et al 2010]. It is
556 important to tailor nutritional strategies to the specific needs of individual women,
557 who do not always require increased calorie intake but may require
558 supplementation with specific vitamins and minerals, including calcium, Vitamin D
559 and iron [Zysman et al 2006; Schwartzman et al 2008; Tarquinio et al 2012].
560
561 **Feeding difficulties**, especially fluid intake, tend to worsen with age because of
562 increased tongue muscle tone [Kerr 2002]. Adult women have been reported to have
563 more problems with breathing and are more likely to be constipated, especially if
564 fluid intake is limited; these can both interfere with feeding [Halbach et al 2008].
565 Gastro-oesophageal reflux, toothache, oral thrush, change in daily routine and
566 depression may also be considered when loss of appetite is reported in adult
567 patients [Kerr 2002], but it can arise for no clear reason [Cass et al 2003].
568
569 **Mood**. After adolescence, mood has been reported as likely to improve [Sansom et
570 al 1993; Halbach et al 2013], contrasting with the findings in this study and two

previous studies [Cianfaglione et al 2016; Hryniewiecka-Jaworska et al 2016]. Depression is not commonly reported [Sansom et al 1993; Kerr 2002], although it may be under-reported and therefore under-treated [Hryniewiecka-Jaworska et al 2016]. Unexplained changes of appetite, weight loss, sleep disruption, injury to others, fear, restlessness, crying and/or anxiety may be signs of depression or bereavement reactions when no other medical explanation is found. Adult women with RTT may be exposed to numerous stressful events: leaving school, loss of school friendships, change of services, moving away from home and family, and the loss of grandparents, parents, carers or co-residents, any of which could trigger depressive reactions.

Other Health Problems. Women with RTT may also experience a range of common health problems. However, the health issues found to be more common in people with RTT include undiagnosed depression [Hryniewiecka-Jaworska et al 2016], osteoporosis, abnormal thyroid function and diabetes [Cooke et al 1995], and iron deficiency anaemia [Schwartzman et al 2008]. In contrast with a previous study of adults with intellectual disability, women in our study did not experience early menopause [Martin et al 2003].

Limitations

The authors acknowledge that there were limitations to the study, particularly relating to the qualitative nature of the data. The data were collected retrospectively and relied on parent, carer or clinician recall. It is possible that the Simplified Severity Score of Smeets et al [2009] did not reliably capture the range of

595 possible symptoms, potentially resulting in the omission of some details pertaining
596 to the women's health or the decline in their health. There was no specific funding
597 available for the study. Therefore it was not possible to review patients clinically
598 during each decade of their life, particularly given their geographical distribution.
599 Finally, the molecular data available could not be confirmed for every woman and
600 relied on evidence from clinic letters and reports or parental recall. Those without a
601 molecular diagnosis were included on the basis of a clear clinical diagnosis in keeping
602 with the diagnostic criteria, which are purely clinical [Neul et al 2010]. Although
603 unlikely, we acknowledge the possibility of an alternative diagnosis in some patients.
604

605 **CONCLUSION**

606

607 This study provides novel information on the natural history of RTT in women over
608 40 years. They typically have a milder course than usual, with little evidence except
609 of slow progression. Furthermore, demonstrable improvements are often found in
610 features such as hand stereotypies, sleep disturbance, epilepsy and agitation.
611

612 Whilst middle-aged women with RTT experience the same health issues as other
613 women, they also have particular health needs to consider. Most women lacked
614 regular, systematic clinical review and monitoring for Rett-specific complications,
615 particularly in the management of epilepsy and nutrition. Annual health checks for
616 people with intellectual disability have been implemented in England and Wales and
617 can improve health and quality of life [Felce et al 2008]. Such health checks would

also provide an opportunity to address common health problems in middle-aged women with RTT.

Given the variability in care for adults with RTT, further studies and standard of care guidelines could help to improve the quality of physical and mental health care available. In the meantime, the authors have proposed some recommendations in Table 9 to support the care of middle-aged women with RTT. Additional guidance for Rett syndrome clinical services is also available (Sloper et al 2024).

Insert Table 9 here.

REFERENCES

Anderson, A., Wong, K., Jacoby, P., Downs, J., & Leonard, H. 2014. Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet J Rare Dis*; 9 87

Archer H, Evans J, Leonard H, Colvin L, Ravine D, Christodoulou J, Williamson S, Charman T, Bailey ME, Sampson J, de Klerk N, Clarke A. 2007. Correlation between clinical severity in patients with Rett syndrome with a p.R168X or p.T158M MECP2 mutation, and the direction and degree of skewing of X-chromosome inactivation. *J Med Genet;* 44(2):148-152

642 Archer HL, Whatley SD, Evans JC, Ravine D, Huppke P, Kerr A, Bunyan D, Kerr B,
643 Sweeney E, Davies SJ, Reardon W, Horn J, MacDermot KD, Smith RA, Magee A,
644 Donaldson A, Crow Y, Hermon G, Miedzybrodzka Z, Cooper DN, Lazarou L, Butler R,
645 Sampson J, Piltz DT, Laccone F, Clarke AJ . 2006. Gross rearrangements of the MECP2
646 gene are found in both classical and atypical Rett syndrome patients. *J Med Genet;*
647 43(5):451-6.
648
649 Bebbington A, Anderson A, Ravine D, Fyfe S, Pineda M, de Klerk N, Ben-Zeev B,
650 Yatawara N, Percy A, Kaufmann WE, Leaonard H. 2008. Investigating genotype-
651 phenotype relationships in Rett syndrome using an international data set.
652 *Neurology*; 11; 70(11):868-875.
653
654 Bebbington A, Percy A, Christodoulou J, Ravine D, Ho G, Jacoby P, Anderson A,
655 Pineda M, Ben Zeev B, Bahi-Buisson N, Smeets E, Leonard H. 2010. Updating the
656 profile of C-terminal *MECP2* deletions in Rett syndrome. *J Med Genet*; 47(4):242-248
657
658 Berg M, Hagberg B. 2001. Rett Syndrome: Update of a 25-year follow-up
659 investigation in western Sweden – Sociomedical aspects. *Brain & Development*; 23.
660 Supplement 1: 224–226.
661
662 Bisgaard AM, Wong K, Højfeldt AK, Larsen JL, Schönewolf-Greulich B, Rønde G,
663 Downs J, Stahlhut M. 2021. Decline in gross motor skills in adult Rett syndrome;
664 results from a Danish longitudinal study. *Am J Med Genet A*; 185(12):3683-3693.
665

Brunetti S and Lumsden D. 2020. Rett Syndrome as a movement and motor disorder – A narrative review. *European Journal of Paediatric Neurology*; 28: 29-37

Budden SS, Gunnes ME. 2003. Possible mechanisms of osteopenia in Rett Syndrome: Bone histomorphometric studies. *J Child Neurol*; 18(10): 698–702.

Carter P, Dawns J, Bebbington A, Williams S, Jacoby P, Kaufman W, Leonard H. 2009. Stereotypical hand movements in 144 subjects with Rett Syndrome from the population-based Australian database. *Movement disorders*; 25(3): 282-8

Cass H, Reilly S, Owen L, Wisbeach A, Weeks L, Slonims V, Wigram T, Charman T. 2003. Findings from a multidisciplinary clinical case series of females with Rett Syndrome. *Developmental Medicine and Child Neurology*; 45(5): 325–337.

Cheadle JP, Gill H, Fleming N, Maynard J, Kerr A, Leonard H, Krawczak M, Cooper DN, Lynch S, Thomas N, Hughes H, Hulten, M, Ravine D, Sampson JR, Clarke A. 2000. Long read sequence analysis of the MECP2 gene in Rett Syndrome patients: Correlation of disease severity with mutation type and localisation. *Human Molecular Genetics;* 9: 1119–1129.

Cianfaglione, R., Clarke, A., Kerr, M., Hastings, R. P., Oliver, C., and Felce, D. 2016. Ageing in Rett syndrome. *Journal of Intellectual Disability Research*; 60: 182–190.

690 Cooke DW, Naidu S, Plotnick L, Berkovitz GD. 1995. Abnormalities of thyroid function
691 and glucose control in subjects with Rett syndrome. *Hormone Research*; 43(6):273-8.
692
693 Didden R, Korziliius H, Smeets E, Green VA, Lang R, Lancioni GE, Curfs LM. 2010.
694 Communication in individuals with Rett syndrome: an assessment of form and
695 functions. *Journal of Developmental and Physical Disabilites;* 22(2): 105-118
696
697 Downs J, Bebbington A, Jacoby P, Williams AM, Ghosh S, Kaufmann W, Leonard H.
698 2010. Level of purposeful hand function as a marker of clinical severity in Rett
699 syndrome. *Developmental Medicine and Child Neurology*; 52(9): 817-23.
700
701 Downs J, Bebbington A, Woodhead H, Jacoby P, Jian L, Jefferson A, Leonard H.
702 2008.Early determinants of fractures in Rett syndrome. *Paediatrics*; 121(3): 540-6
703
704 Downs J, Bergman A, Carter P, Anderson A, Palmer GM, Rove D, van Hosse H,
705 Bebbington A, Larsson EL, Baike G, Fyfe S, Leonard H. 2009. Guidelines for
706 management of scoliosis in Rett syndrome patients based on expert consensus and
707 clinical evidence. *Spine;* 34(17): E607-17
708
709 Dunn HG, Macleod PM. 2001. Rett Syndrome: Review of biological abnormalities.
710 *Canadian Journal of Neurological Science*; 28: 16–29.
711

712 Felce D, Baxter H., Lowe K., Dunstan F., Houston H., Jones G., Felce J, Kerr M. 2008.
713 The impact of repeated health checks for adults with intellectual disabilities. *Journal*
714 *of Applied Research in Intellectual Disabilities*; 21: 585–596
715
716 Freilinger M, Bebbingtnon A, Lanator I, de Klerk N, Dunkler D, Seidl R, Leonard H,
717 Ronen GM. 2010. Survival with Rett syndrome: comparing Rett's original sample
718 with data from the Australian Rett Syndrome Database. *Developmental Medicine &*
719 *Child Neurology*; 52: 962-965
720
721 Fu C, Armstrong D, Marsh E, Lieberman D, Motil K, Witt R, Standridge S, Nues P, Lane
722 J, Dinkel T, Coenraads M, von Hehn J, Jones M, Hale K, Suter B, Glaze D, Neul J, Percy
723 A, Benke T. 2020. Consensus guidelines on managing Rett syndrome across the
724 lifespan. *BMJ Paediatr Open*; 13;4(1):e000717.
725
726 Glaze DG, Percy AK, Skinner S, Motil KJ, Neul JL, Barrish JO, Lane JB, Geerts SP,
727 Annese F, Graham J, McNair L, Lee HS. 2010. Epilepsy and the natural history of Rett
728 Syndrome. *Neurology*; 74(11):909-12
729
730 Glaze DG, Schultz RJ, Frost JD. 1998. Rett Syndrome: characterization of seizures
731 versus non seizures. *Electroencephalography and Clinical Neurophysiology*;
732 106(1):79-83.
733
734 Hagberg B. 2002. Clinical manifestations and stages of Rett Syndrome. *Mental*
735 *Retardation and Developmental Disabilities*; Research Reviews 61–65.

736

737 Hagberg B. 2005. Rett Syndrome: Long-term clinical follow-up: Experiences over four
738 decades. *J Child Neurol*; 20(9): 722–727.

739

740 Hagberg B, Aicardi J, Dias K, Ramos O. 1983. A progressive syndrome of autism,
741 dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of
742 35 cases. *Ann Neurol* 14: 471 – 479.

743

744 Hagberg B, Berg M, Steffenburg U. 2001. Three decades of sociomedical experiences
745 from west Swedish Rett females 4-60 years of age. *Brain* **&** *Development*; 23
746 Supplement 1: S 28–31.

747

748 Hagberg B, Erlandsson A, Kyllerman M, Larsson G. 2003. Odd MECP2-mutated
749 variant-long-term-follow up profile to age 25. *Eur J Paed Neurology*; 7: 417–421.

750

751 Halbach NSJ, Smeets EEJ, Schrander-Stumpel CTRM, van Schrojenstein Lantman de
752 Valk HHJ, Maaskant MA, Curfs LMG. 2008. Aging in people with specific genetic
753 syndromes: Rett syndrome. *Am J Med Genet*; 146A:1925–1932.

754

755 Halbach NSJ, Smeets EEJ, van den Braak N, van Roosendaal KEP, Blok RMJ,
756 Schrander-Stumpel CTRM, Frijns JP, Maaskant MA, Curfs LMG. 2012. Genotype–
757 phenotype relationships as prognosticators in Rett syndrome should be handled with
758 care in clinical practice. *Am J Med Genet Part A*; 158A:340–350.

759

760 Halbach NSJ, Smeets EEJ, Steinbusch C, Maaskant MA, van Waardenburg D, Curfs
761 LMG. 2013. Aging in Rett syndrome: a longitudinal study. *Clin Genet*; 84: 223–229.
762
763 Henriksen MW, Breck H, von Tetzchner S, Paus B, Skjeldal OH, Brodtkorb E. 2018.
764 Epilepsy in classic Rett syndrome: Course and characteristics in adult age. *Epilepsy*
765 *Res*; 145:134-139.
766
767 Holm VA. 1986. Physical growth and development in patients with Rett Syndrome.
768 *Am J Med Genet*; Supplement 1:119–126.
769
770 Hryniewiecka-Jaworska A, Foden E, Kerr M, Felce D, Clarke AJ. 2016. Prevalence and
771 associated features of depression in women with Rett Syndrome. *J Intellectual*
772 *Disability Research*; 60(6):564-70
773
774 Jacobsen K, Viken A, von Tetzchner S. 2001. Rett syndrome and aging: A case study.
775 *Disability and Rehabilitation*; 23(3–4): 160–166.
776
777 Julu PO, Kerr AM, Apartopoulos F, Al-Rawas S, Witt-Engerström I, Engerström L,
778 Jamal GA, Hansen S. 2001. Characterisation of breathing and associated central
779 autonomic dysfunction in the Rett disorder. *Archives of Disease in Childhood*; 85(1):
780 29–37.
781

782 Kerr A. 2002. Rett Disorder. In P. Howlin and O. Udwin (eds) *Outcomes in*
783 *Neurodevelopmental and Genetic Disorders*. Cambridge: Cambridge University Press;
784 241–271.
785
786 Kerr A, Archer HL, Evans JC, Prescott RJ, Gibbon F. 2006. People with MECP2
787 mutation-positive Rett disorder who converse. *J Intellectual Disability Research*; 50
788 (5): 386-394
789
790 Kerr A.M, Armstrong DD, Prescott RJ., Doyle D, Kearney DL, 1997. Rett Syndrome:
791 analysis of death in the British Survey. *European Child & Adolescent Psychiatry;* 6
792 Suppl 1:71-74
793
794 Kerr AM, Burford B. 2001. Towards a full life with Rett disorder. *Paediatric*
795 *Rehabilitation*; 4(4):157–168.
796
797 Kerr AM, Mitchell JM, Robertson PE. 1995. Short fourth toes in Rett syndrome: a
798 biological indicator. 1995. *Neuropediatrics*; 26(2):72-4
799
800 Kerr AM, Montague J, Stephenson JB. 1987. The hands, and the mind, pre- and
801 post-regression, in Rett syndrome. *Brain & Development;* 9(5): 487–490.
802
803 Kerr AM, Prescott R. 2005. Predictive value of the early clinical signs in Rett Disorder.
804 *Brain & Development*; 27 Suppl 1:20-24.
805

Kerr AM, Stephenson JBP. 1985. Rett's syndrome in the west of Scotland. *Brit Med J*; 291: 579-582

Kerr AM, Webb P, Prescott RJ, Milne Y. 2003. Results of surgery for scoliosis in Rett syndrome. *Journal of Child Neurology*; 18:703-708.

Kirby RS, Lane JB, Childers J, Skinner SA, Annese F, Barrish JO, Glaze DG, MacLeod P, Percy AK. 2010. Longevity in Rett Syndrome: Analysis of the North American Database. The Journal of Pediatrics; 156 (1): 135-138

Larsson G, Witt-Engerström I. 2001. Gross motor ability in Rett syndrome – the power of expectation, motivation and planning. *Brain and Development*; 23(1): 77–81.

Leonard H, Downs J, Jian L, Bebbington A, Jacoby P, Nagarajan L, Ravine D, Woodhead H. 2010. Valproate and risk of fracture in Rett syndrome. *Arch Dis Child;* 95(6):444-8.

Leonard H, Colvin L. Christodoulou J, Schiavello T, Williamson S, Davis M, Ravine D, Fyfe S, de Klerk N, Matsuishi T, Kondo I, Clarke A, Hacwell S, Yamashita Y. 2003. Patients with the R133C mutation: is their phenotype different from patients with Rett syndrome with other mutations? *J Med Genet* doi: 10.1136/jmg.40.5.e52

Letellier ME, Ciusset JM, Denjean A, Gottrand F, Hankard R. 2010. Assessing change in body composition in children with Duchenne muscular dystrophy: Anthropometry and bioelectrical impedance analysis versus dual- energy X-ray absorptiometry. *Clinical Nutrition*; 29(5): 633-8

Lotan M, Merrick J, Kandel I, Morad M. 2009. Aging in persons with Rett syndrome: an updated review. *Scientific World Journal*; 10:778-87.

Martin DM, Kakumani S, Martin MS, Cassidy G. 2003. Learning disabilities and the menopause. *Journal of the British Menopause Society*; 9(1):22-6.

Motil KJ, Schultz RJ, Wong WW, Glaze DG. 1998. Increased energy expenditure associated with repetitive involuntary movement does not contribute to growth failure in girls with Rett syndrome. *The Journal of Pediatrics*; 132(2):228-33.

Motil KJ, Ellis KJ, Barrish JO, Caeg E, Glaze DG. 2008. Bone mineral content and bone mineral density are lower in older than in younger females with Rett syndrome. *Pediatric Research*; 64(4): 435-9

Neul JL, Benke TA, Marsh ED, Suter B, Fu C, Ryther RC, Skinner SA, Lieberman DN, Feyma T, Beisang A, Heydemann P, Peters SU, Ananth A, Percy AK 2024. Clinical Features and Disease Progression in Older Individuals with Rett Syndrome. *Genes*. 15(8):1107. https://doi.org/10.3390/genes15081107

Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke A, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK; RettSearch Consortium. 2010. Rett syndrome: revised diagnostic criteria and nomenclature. *Annals of Neurology*; 68(6): 944-50

Neul JL, Lane JB, Lee HS, Geerts S, O Barrish J, Annese F, Baggett LM, Barnes K, Skinner S, Motil KJ, Glaze DG, Kaufmann WE, Percy AK. 2014. Developmental delay in Rett syndrome: data from the natural history study. *J Neurodev Disord*; 6(1): 20.

Nielsen JB, Ravn K, Shwartz M. 2001. A 77-year old woman and preserved speech variant among the Danish Rett patients with mutations in MECP2. *Brain Development*; Supplement 11: 230–232.

Percy AK. 1992. Neurochemistry of the Rett Syndrome. *Brain and Development*; 14: Supplement: 57–62.

Peron A, Canevini MP, Ghelma F, Arancio R, Savini M, Vignoli A. 2022. Phenotypes in adult patients with Rett syndrome: results of a 13-year experience and insights into healthcare transition. *Journal of Medical Genetics*; 59**:** 39-45

Pintaudi M, Calevo MG, Vignoli A, Parodi E, Aiello F, Baglietto MG, Hayek Y, Buoni S, Renieri A, Russo S, Cogliati F, Giordano L, Canevini M, Veneselli E. 2010. Epilepsy in Rett syndrome: Clinical and genetic features. *Epilepsy and Behavior*; 19(3):296-300.

877 Roze E, Cochen V, Sangla S, Bienveneu T, Roubergue A, Leu-Semenescu S, Vidaihet
878 M. 2007. Rett Syndrome: An overlooked diagnosis in women with stereotypic hand
879 movements, psychomotor retardation, Parkinsonism, and dystonia? *Movement*
880 *Disorder*; 22(3): 387–389.
881
882 Ryan PJ, Singh SP, Guillebaud J. 2002. Depot medroxyprogesterone and bone mineral
883 density. *The Journal of Family Planning and Reproductive Health Care*; 28(1):12-15
884
885 Sansom D, Krishnan VH, Corbett J, and Kerr A. 1993. Emotional and behavioural
886 aspects of Rett syndrome. *Developmental Medicine and Child Neurology; 35*(4): 340–
887 345.
888
889 Schanen C, Houwink EJ, Dorrani N, Lane J, Everett R, Feng A, Cantor RM, Percy A.
890 2004. Phenotypic manifestations of MECP2 mutations in classical and atypical Rett
891 syndrome. *Am J Med Genet;* 126(2): 129–140.
892
893 Schönewolf-Greulich B, Stahlhut M, Larsen JL, Syhler B, Bisgaard AM. 2017.
894 Functional abilities in aging women with Rett syndrome - the Danish cohort. *Disabil*
895 *Rehabil*; 39(9): 911-918.
896
897 Schwartzman F, Vitolo MR, Shwartzman JS, Morais MB. 2008. Eating practices,
898 nutritional status and constipation in patients with Rett syndrome. *Arquivos de*
899 *Gastroenterologia*; 45(4):284-9.
900

Shahbazian MD, Zoghbi HY. 2001. Molecular genetics of Rett syndrome and clinical spectrum of MECP2 mutations. *Current Opinion in Neurology*; 14(2):171-6.

Sloper E, Hunt M, Clarke AJ. Review of a specialist Rett syndrome clinic from 2003 to the COVID pandemic: clinic experience and carer perspectives. Orphanet J Rare Dis. 2024 Dec 20;19(1):477

Smeets EE, Chenault M, Curfs LM, Schrander-Stumpel C T, Frijns J P. 2009. Rett syndrome and long-term disorder profile. *Am J Med Genet;* 149A (2):199-205

Smeets EE, Pelc, K., & Dan, B. 2012. Rett Syndrome. *Molecular Syndromology; 2*(3-5), 113-127.

Smeets EE, Shollen E, Moog U, Matthijis G, Herbergs J, Smeets H, Curfs L, Shrander-Stumpel C, Fryns J P. 2003. Rett Syndrome in adolescent and adult females: Clinical and molecular genetic findings. *Am J Med Genet;* 122A: 227–233.

Stallworth JL, Dy ME, Buchanan CB, Chen CF, Scott AE, Glaze DG, Lane JB, Lieberman DN, Oberman LM, Skinner SA, Tierney AE, Cutter GR, Percy AK, Neul JL, Kaufmann WE. 2019. Hand stereotypies: Lessons from the Rett Syndrome Natural History Study. *Neurology*; 28;92(22):e2594-e2603.

Steffenburg U, Hagberg G, Hagberg B. 2001. Epilepsy in a representative series of Rett Syndrome. *Acta Paediatrica*; 90: 34–39.

925

926 Tarquinio DC, Motil KJ, Hou W, Lee HS, Glaze DG, Skinner SA, Neul JL, Annese F,
927 McNair L, Barrish JO, Geerts SP, Lane JB, Percy AK. 2012. Growth failure and
928 outcome in Rett syndrome: specific growth references. *Neurology*;16;79(16):1653-
929 61.

930

931 Tarquinio DC, Hou W, Berg, A., Kaufmann, WE, Lane, JB., Skinner, SA., Motil, KJ, Neul,
932 JL, Percy, AK, Glaze, DG. 2017. Longitudinal course of epilepsy in Rett syndrome and
933 related disorders. *Brain;* 140*:* 306-318.

934

935 Tarquinio DC, Hou W, Neul JL, Berkmen GK, Drummond J, Aronoff E, Harris J, Lane JB,
936 Kaufmann WE, Motil KJ, Glaze DG, Skinner SA, Percy AK. 2018. The course of awake
937 breathing disturbances across the lifespan in Rett syndrome. *Brain Dev*;;40(7):515-
938 529.

939

940 Tarquinio DC, Hou W, Neul JL, Kaufmann WE, Glaze DG., Motil KJ, Skinner SA, Lee HS,
941 Percy AK. 2015. The Changing Face of Survival in Rett Syndrome and MECP2-Related
942 Disorders. *Pediatric neurology*; 53(5), 402-11.

943

944 Tay G, Graham H, Graham HK, Leonard H, Reddinough D, Baikie G. 2010. Hip
945 displacement and scoliosis in Rett syndrome- screening is required. *Developmental*
946 *Medicine and Child Neurology*; 52(1): 93-98

947

948 Thorey F, Jager M, Seller K, Wild A, Adam RA, Krauspe R. 2007. How to prevent small
949 stature in Rett Syndrome- associated collapsing spine syndrome. *Journal of Child*
950 *Neurology*; 22(4): 443-6
951
952 Vignoli A, La Briola F, Canevini M. P. 2009. Evolution of stereotypies in adolescents
953 and women with Rett syndrome. *Movement Disorders*; 24(9):1379-83.
954
955 Vignoli A, Briola FL, Peron A, Turner K, Savini M, Cogliati F, Russo S, Canevini MP.
956 2012. Medical care of adolescents and women with Rett syndrome: An Italian study.
957 *Am J Med Genet*; 158A:13–18.
958
959 Weaving LS, Williamson SL, Bennetts B, Davis M, Ellaway CJ, Leonard H, Thong MK,
960 Delatycki M, Thompson EM, Laing N, Christodoulou J. 2003. Effects of MECP2
961 mutation type, location and X-inactivation in modulating Rett syndrome phenotype.
962 *Am J Med Genet* ;118A (2):103-14.
963
964 Williamson SL, Christodoulou J. 2006. Rett Syndrome: New clinical and molecular
965 insights. *European Journal of Human Genetic*; 14:896-903
966
967 Witt-Engerström I. 1990. Rett syndrome in Sweden. Neurodevelopment--disability—
968 pathophysiology. *Acta Paediatrica Scandinavica;* Supplement, 369: 1–60.
969
970 Witt-Engerstrom I. 1992. Age-related occurrence of signs and symptoms in Rett
971 Syndrome. *Brain Development*; Supplement: 11–20.

Zappella M, Meloni I, Longo I, Hayek G, Renieri A. 2001. Preserved speech variants of the Rett Syndrome: Molecular and clinical analysis. *American Journal of Medical Genetics*; 104(1): 14–22

Zysman L, Lotam M, Ben-Zeev B. Osteoporosis in Rett Syndrome: A study on normal values. 2006. *The Scientific World Journal*; 6:1619-30

FIGURE LEGENDS

Figure 1:

Ages of patients at time of the last completed survey health questionnaire (years)

Figure 2:

Each patient's 'simplified severity score' in each decade of life (Smeets et al 2009)

Figure 3: *Communication ability at final data collection point for all women with RTT*

Figure 3A:

Expressive communication ability at final data collection point for all women with RTT

Figure 3B:

Receptive communication ability at final data collection point for all women with RTT