Title: Surgical fusion of early onset severe scoliosis increases survival in Rett syndrome: a cohort study

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Abstract
AIM Scoliosis is a common comorbidity in Rett syndrome and spinal fusion may be recommended if severe. We investigated the impact of spinal fusion on survival and risk of severe lower respiratory tract infection in Rett syndrome.
METHOD Data were ascertained from hospital medical records, the Australian Rett Syndrome Database, a longitudinal and population-based registry, and from the Australian Institute of Health and Welfare National Death Index database. Cox regression and generalized estimating equation models were used to estimate the effects of spinal surgery on survival and severe respiratory infection respectively in 140 females who developed severe scoliosis (Cobb angle ≥45°) prior to adulthood.
RESULTS After adjusting for mutation type and age of scoliosis onset, the rate of death was lower in the surgery group (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.12-0.74, *P*=0.009) compared to those without surgery. Rate of death was particularly reduced for those with early onset scoliosis (HR 0.17, 95% CI 0.06-0.52; *P*=0.002). There was some evidence to suggest that spinal fusion was associated with a reduction in risk of severe respiratory infection among those with early onset scoliosis (risk ratio 0.41, 95% CI 0.16-1.03, *P*=0.06).
INTERPRETATION With appropriate cautions, spinal fusion confers an advantage to life expectancy in Rett syndrome.

Shortened title:
Spinal fusion in Rett syndrome

What this paper adds

- Survival was improved in those with a severe scoliosis who had surgical compared to conservative management, particularly for those with an earlier onset scoliosis where protective effects on respiratory health were also observed.
- Our findings provide evidence that supports clinical counselling in relation to spinal fusion from which clinicians and families can make their individual decisions.
- Our methods demonstrate the value of well managed databases for the investigation of rare disorders.

Rett syndrome is a rare neurodevelopmental disorder that predominantly affects females[1] and is usually associated with mutations in the Methyl CpG-binding Protein 2 (*MECP2*) gene.[2] Following initial normal or near normal early development, Rett syndrome is characterized by loss of speech and hand function, stereotypical hand movements and gait disturbance as well as the development of comorbidities.[1] Scoliosis is the most common orthopedic complication affecting 75% of girls by age 13 years.[3] In the face of a poor evidence base to guide management of scoliosis in Rett syndrome we assembled an international expert panel and, using available literature mainly on neuromuscular scoliosis management, published the first published guidelines on this topic.[4] Spinal fusion may be considered if the Cobb angle of the scoliosis progresses to greater than 40-50°.[4] Surgery is complex and in Rett syndrome, is performed within the context of problems including epilepsy,[5] increased sensitivity to anesthetics,[6] and poor growth,[1] highlighting the need for a Rett syndrome specific management plan. Multidisciplinary care is essential.

A high fraction of short term complications of spinal fusion mainly related to the respiratory system have been reported[7] but correction of the scoliosis is usually satisfactory with spinal symmetry and sitting balance improved following surgery.[8] Participation in activities of daily living is at least maintained at pre-operative levels with some improvement in some girls.[9] Families recently reported high levels of overall satisfaction particularly in relation to surgical and ICU care.[10] What is not known is how surgical and conservative treatments compare for severe scoliosis in Rett syndrome in relation to subsequent physical health, particularly respiratory infections and long-term survival. As for other rare disorders, relatively little is known about the value of available treatment options.

The Australian Rett Syndrome Database was established in 1993 and is a population-based registry of Rett syndrome cases with information collected from clinicians and families longitudinally. This unique rare disease registry has allowed us to examine the impacts of a number of comorbidities over time[11,12] and now provides capacity to evaluate interventions. The primary objectives for this study were to examine the impacts of spinal fusion on mortality and risk of respiratory infections in girls and women with Rett syndrome and a severe scoliosis. The secondary objective was to investigate differences in the effect of surgery between early and late scoliosis onset subgroups.

Participants and Methods

Study design and data sources

Families/carers of females registered in the database were recruited from multiple sources including the Australian Paediatric Surveillance Unit (http://www.apsu.org.au/) and were invited to complete an initial questionnaire at registration. They were also asked to participate in up to six follow-up surveys administered in 2000, 2002, 2004, 2006, 2009, and 2011.[12]

Morbidity data used in the study were sourced from the initial and follow-up questionnaires, and supplemented by hospital medical records, densitometry reports, and telephone interviews with families/carers. Medical, including radiological, records were manually interrogated at nine Australian tertiary hospitals (mainly pediatric), where scoliosis surveillance and surgery were performed. Spinal

radiographs were reviewed by spinal surgeons or radiologists and the magnitude of the scoliosis was measured using the method of Cobb.[13]

Study population
Females with clinically[1] or genetically confirmed Rett syndrome who developed severe scoliosis were included in the analyses. The number of cases during the study period determined the sample size. Scoliosis was considered severe if surgical fusion had been undertaken or one or more Cobb angles of at least 45° had been detected at any time during spinal surveillance.

Outcomes
The primary outcome of the study was death from any cause, ascertained through the Australian Rett Syndrome Database and linkage to the Australian Institute of Health and Welfare National Death Index.[14] The International Statistical Classification of Diseases and Related Health Problems 10th Revision codes were used to classify the cause of death. In the analysis, individuals were first observed at the age at scoliosis onset, defined as the age when scoliosis was first diagnosed or first recorded in the database or medical records (if age at diagnosis not available). Observations were censored at the age of death, or, if there was no death record, the age of last contact with families/carers.

The secondary outcome was the occurrence of lower respiratory tract infections (LRTI) after scoliosis onset. At each follow-up questionnaire, LRTI was considered present if one of the following was reported: pneumonia (all-cause), bronchitis or chest infection in the 12-month period before the survey. LRTI was considered severe if one or more days of overnight hospitalization were required. A binary indicator variable for severe LRTI was coded representing the presence or absence of the condition.

Exposure and covariates
Spinal surgery, an exposure variable, was coded as 1 if the operation had been undertaken and coded as 0 otherwise. Potential confounders included mutation type, age at scoliosis onset and age at questionnaire completion. Mutations were grouped as large deletions, C-terminal deletions, early truncating, p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys, and p.Thr158Met. All others were grouped as "other" mutations. Females who were mutation negative or with unknown mutation status were included as "Negative/Unknown". Age at scoliosis onset was also considered a potential effect modifier and was stratified into two groups: younger than 8 years and 8 years or older to classify scoliosis onset as early or late.[15] We described the frequency of gastrostomy insertion before spinal fusion or 18 years if conservatively managed, weight at spinal fusion or 13 years if conservatively managed, ambulation trajectory over the longitudinal observation period and hand function at entry into the database. Walking was categorised as walking independently, able to walk with assistance or unable to walk, at each of the follow-up questionnaires. Using up to six observation points, latent class growth modelling was then used to identify groups of individuals with different patterns of ambulation status over time. We also described the maternal highest attained qualification and residential location according to the Accessibility/Remoteness Index of Australia[16] category for both groups.

Study oversight
Ethics approvals for data access were obtained from the Princess Margaret Hospital for Children, Perth; Royal Perth Hospital, Perth; Women's and Children's Hospital, Adelaide; Royal Children's Hospital, Melbourne; Monash Medical Centre, Melbourne; Sydney Children's Hospitals Network, Sydney; Mater Children's Hospital, Brisbane; and Royal Children's Hospital, Brisbane. Ethics approval was obtained to link the cohort to the National Death Index administered by the Australian Institute of Health and Welfare.

Statistical analyses
Descriptive statistics were reported for all variables by exposure status. For survival analysis, Kaplan-Meier method was used to estimate the survival function for the whole cohort and also for those who were managed conservatively. Those who underwent spinal fusion did not represent a defined group prior to their surgery and cannot be shown separately using this method. Hazard ratios and 95% confidence intervals for differences in mortality associated with spinal fusion were estimated using a Cox regression model in which surgery was included as a time-dependent variable. The proportional hazards assumption was tested and confirmed. Longitudinal data, consisting of whether or not a severe LRTI was present at each questionnaire time point, were examined using log-binomial regression with generalized estimating equations to estimate the effect of spinal surgery on the risk of a severe LRTI, accounting for clustering within individuals. Robust standard errors and exchangeable working correlation structure were used in the model for parameter estimation. Surgery status was based on whether spinal fusion had been performed at the time the questionnaire was completed. The probability, or absolute risk, of at least one severe LRTI during the 12-month observation period prior to survey were estimated based on the recycled predictions approach using the STATA *margins* command. All missing data were considered missing for reasons unrelated to the study outcomes.

Crude estimates, in addition to estimates that were adjusted for potential confounders, are presented for both analyses. Furthermore, the relationships between the effects of spinal fusion surgery and age at scoliosis onset were investigated by adding an interaction term to the multivariate models. The relative excess risks due to interaction and 95% confidence intervals were determined based on calculations described by Rothman.[17]

All statistical analyses were conducted using STATA version 13 (StataCorp LP).

Results
As at 5 November 2014, the families of 394 females, born since 1976 and with a confirmed diagnosis of Rett syndrome, had provided data to the database. Of those, 73 (18.5%) individuals had died and 261 (66.2%) girls and women had a scoliosis. The median age at scoliosis onset was 8 years 9 months (Interquartile range (IQR) 5 years 11 months - 11 years 7 months) and 232 cases (88.9%) had data on scoliosis severity and/or spinal fusion. Severe scoliosis was identified in 140 cases (60.3%) of whom slightly fewer than half (48.6%) developed severe scoliosis prior to eight years of age (Table 1).

Thirty-seven (26%) of the 140 females with severe scoliosis were deceased at the time of the study and the majority of deaths related to respiratory issues. Table 1 shows the characteristics of those with severe scoliosis who did or did not undergo spinal fusion. The distributions of mutation type, age at scoliosis onset, gastrostomy insertion, weight and functional abilities were similar between groups. Maternal highest attained qualification and Accessibility/Remoteness Index of Australia category were also similar between groups.

Scoliosis surgery was performed in 98 (69%) of the 140 females with severe scoliosis at a median age of 13 years 3 months (IQR 11 years 5 months - 14 years 10 months). The Cobb angle at time of surgery was available for 87 cases (89%) and the mean value was 73° (Standard deviation 18°, range 41-126°).

As shown in Figure 1, the estimated survival probability of all with severe scoliosis was 77.4% at 20 years of age and 59.6% at 30 years of age (median survival time: 38 years and 2 months). When observation periods related to surgery were omitted (the censor age for those with spinal fusion was replaced with the age at surgery), the probability of survival in those with scoliosis who had not had surgery was 59.4% at 20 years and 47.6% at 30 years (median survival time: 21 years and 10 months). In the surgery group one of 98 individuals died peri-operatively and another died 8 months after surgery due to multiple comorbidities. After adjusting for mutation type and age of scoliosis onset, the rate of death was lower in the surgery group (Hazard ratio [HR] 0.30; 95% confidence interval [CI] 0.12,0.74; *P*=0.009) compared to those without surgery (Table 2). Considering the interaction between age of scoliosis onset and surgery, spinal fusion had a strong protective effect against all-cause mortality in those who had early onset scoliosis (HR 0.17; 95% CI 0.06,0.52; *P*=0.002). On the other hand, a weaker effect was observed in individuals with late onset scoliosis although there was lack of evidence in our data of a reduction in mortality (HR 0.60; 95% CI 0.18,2.03; *P*=0.41) (Table 3).

Among those with severe scoliosis, the response fractions of the six follow-up questionnaires were 100% (2000), 81% (2002), 92% (2004), 91% (2006), 89% (2009) and 89% (2011). The average prevalence of having experienced one or more severe LRTIs within the 12 months prior to each questionnaire was 13.4% and 9.1% in the no surgery and surgery groups respectively (15.0% vs. 5.5% for those with earlier onset scoliosis). Adjusted for all potential confounders, spinal fusion was associated with some reduction in risk of a severe LRTI but the evidence to suggest such an association is weak (Risk ratio [RR] 0.70; 95% CI 0.35,1.41; *P*=0.31, absolute risk [AR] – no surgery group 0.14; 95% CI 0.07,0.21, AR – surgery group 0.10; 95% CI 0.05,0.14) (Table 2). Stratified by onset age, we have found some evidence to support the finding that spinal fusion was associated with a large reduction in risk of a severe LRTI among those with early onset scoliosis (RR 0.41; 95% CI 0.16,1.03; *P*=0.06, AR-no surgery 0.14; 95% CI 0.04,0.24, AR-surgery 0.06; 95% CI 0.01,0.10). However there was little evidence of an effect of surgery on risk of severe LRTI in those with late onset scoliosis (RR 1.05; 95% CI 0.50,2.24; *P*=0.89, AR-no surgery 0.13; 95% CI 0.05,0.20, AR-surgery 0.13; 95% CI 0.05,0.21) (Table 3).

Discussion

Using population-based infrastructure for the study of a rare disorder, we recently investigated survival in Australian females with Rett syndrome born since 1976 and

found slightly more than three quarters survived to 20 years of age.[18] In the current study, we investigated survival in the subset that had developed a severe scoliosis. At 20 years, survival was lower for those who did not undergo a spinal fusion (59.4%) compared to all of those with severe scoliosis. In Rett syndrome, the type of genetic mutation influences general clinical severity[19] and many other aspects of health such as epilepsy.[5] Taking into account the effects of genotype and age of scoliosis onset, spinal fusion was associated with an estimated 70% better likelihood of survival at any point in time during the observation period.

The study cohort was stratified by age of scoliosis diagnosis, a surrogate for severity of scoliosis. In doing so, better survival following spinal fusion was observed particularly in those with earlier than later onset scoliosis. Within the conservatively managed group, an earlier onset of scoliosis was associated with poorer survival than later onset scoliosis, highlighting the very high risks for children with both a neurodevelopmental disability and early onset scoliosis. During growth and development, the spine grows in synchrony with the rib cage and lungs such that progressive scoliosis with an early onset is associated with the development of a restrictive respiratory deficit.[20] Spinal fusion in Rett syndrome reduces the magnitude of scoliosis enabling straighter posture[8] and potentially impacts positively on any restrictive respiratory deficit.[20]

A secondary effect of a reduced restrictive respiratory deficit could be reduced frequency of LRTIs. There was no difference overall in the risks of having a severe LRTI in those who were managed conservatively or surgically but when stratified, spinal fusion protected against severe LRTI in those with an early but not a later onset scoliosis. Whilst the effect was moderately evident in our data, the magnitude of change was large. The notion of protected respiratory health suggests a potential mechanism for reduced mortality in those who were most vulnerable and contributes evidence to the thesis of a causal relationship beyond association.[17] Spinal fusion conferred an advantage to life expectancy overall but particularly in those with the more severe phenotype who also demonstrated better respiratory health. This is important information for clinicians to discuss with families when deciding whether or not to proceed with spinal fusion surgery, a process that is often extremely stressful to parents.[10]

Two large US databases found perioperative mortality following surgical treatment for scoliosis in children to be rare but highest in children with scoliosis of neuromuscular origin compared to idiopathic and congenital scoliosis.[21,22] In the current study, one of 98 patients died in the immediate postoperative period consistent with the US reports. Spinal fusion has other risks including wound infection and neurological, respiratory and gastrointestinal complications,[23] and clinical counseling with families must carefully attend to these known risks.

The randomized controlled trial is the gold standard study design for testing the efficacy of interventions but its application is not feasible or ethical for all research questions.[24] A randomized controlled trial is unlikely to be appropriate to assess the role of spinal fusion in children with a severe neuromuscular scoliosis because it is best practice surgical management and long-term outcomes are necessary. Observational studies are generally viewed as having less validity but well-designed observational studies have found similar results to well-designed randomized

controlled trials.[24] Rett syndrome is a rare neurological disorder and cohort study design could not take place without the necessary infrastructure in place. The strengths of the Australian Rett Syndrome Database include population-based nationwide ascertainment processes since 1993 and longitudinal tracking of outcomes. Other strengths include the large dataset derived from multiple clinical and family sources over time, capacity to assess confounders and access to death registry data. No differences in socioeconomic status as measured by maternal education or remoteness of geographic location were observed between the treatment and comparison groups. Where no previous literature existed, we have conducted a cohort study design with spinal fusion as the exposure and multiple design strategies that strengthened the study. We have provided an example of innovative methods for studying a rare disorder using observational data.

We acknowledge that Rett syndrome is in general a fragile condition. Epilepsy is frequently refractory[5] and the rate of fracture is four times that of the general female population.[11] Each of these comorbidities is associated with periods of poor health that could potentially influence survival. Some girls with a severe scoliosis would not have been medically fit for fusion surgery but distribution of mutations, a marker of clinical severity,[19] was similar in the surgically and conservatively treated groups. The children in the treatment and comparison groups were also similar in the frequency of gastrostomy insertion, and their growth and functional abilities. These comparisons suggest that improved survival was less likely to be due to medical frailty, but rather the differences in survival were more likely to relate to spinal fusion.

Nevertheless, the findings of the current study need to be interpreted within an appreciation that Rett syndrome is a complex medical disorder and that integrated clinical care across medical and surgical specialties would seem advisable. It was not possible to define precisely the age of scoliosis onset, rather the data of necessity described the age of diagnosis to approximate scoliosis onset. The Australian Rett Syndrome Database data collection includes multiple aspects of health and wellbeing for both the child and family and our questionnaire data describing episodes of severe LRTI was restricted to the 12-month period prior to each questionnaire to limit participant burden. A binary variable was defined as to the presence of a severe LRTI having occurred or not which although a relatively crude measure, was more valid than frequency of severe LRTIs.

Conclusion

A progressive and severe scoliosis is of immediate clinical concern to neurologists, pediatricians and spinal surgeons and guides the decision to proceed with surgery. Using a nationwide longitudinal database for a rare disorder, we have conducted the first study to investigate survival and a respiratory health outcome following surgical management of scoliosis in females with Rett syndrome. Survival was improved in those who had surgical compared to conservative management of their scoliosis, particularly for those with an earlier onset scoliosis where there was also potential to protect against lower respiratory infections. Clinical counselling can now be based on a framework of evidence from which clinicians and families can then make their own individual decisions. We believe that the database we have developed for Rett syndrome provides a model that could be replicated for many other rare disorders, which cumulatively affect a substantial proportion of the population but for whom treatments are poorly investigated. With appropriate cautions with regard to the

fragility of Rett syndrome, ameliorating the effects of severe scoliosis with spinal fusion surgery is likely to confer benefits to the child.

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References

1 Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK, RettSearch C. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010; **68**: 944-50.

2 Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics* 1999; **23**: 185-8.

3 Ager S, Fyfe S, Christodoulou J, Jacoby P, Schmitt L, Leonard H. Predictors of scoliosis in Rett syndrome. *J Child Neurol* 2006; **21**: 809-13.

4 Downs J, Bergman A, Carter P, Anderson A, Palmer GM, Roye D, van Bosse H, Bebbington A, Larsson EL, Smith BG, Baikie G, Fyfe S, Leonard H. Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. *Spine (Phila Pa 1976)* 2009; **34**: E607-17.

5 Bao X, Downs J, Wong K, Williams S, Leonard H. Using a large international sample to investigate epilepsy in Rett syndrome. *Dev Med Child Neurol* 2013; **55**: 553-8.

6 Tofil NM, Buckmaster MA, Winkler MK, Callans BH, Islam MP, Percy AK. Deep sedation with propofol in patients with Rett syndrome. *J Child Neurol* 2006; **21**: 210-3.

7 Gabos PG, Inan M, Thacker M, Borkhu B. Spinal fusion for scoliosis in Rett syndrome with an emphasis on early postoperative complications. *Spine (Phila Pa 1976)* 2012; **37**: E90-4.

8 Larsson EL, Aaro S, Ahlinder P, Normelli H, Tropp H, Oberg B. Long-term follow-up of functioning after spinal surgery in patients with Rett syndrome. *Eur Spine J* 2009; **18**: 506-11.

9 Marr C, Leonard H, Torode I, Downs J. Spinal fusion in girls with Rett syndrome: post-operative recovery and family experiences. *Child Care Health Dev* 2015.

10 Downs J, Torode I, Ellaway C, Jacoby P, Bunting C, Wong K, Christodoulou J, Leonard H. Family satisfaction following spinal fusion in Rett syndrome. *Dev Neurorehabil* 2014.

11 Downs J, Bebbington A, Woodhead H, Jacoby P, Jian L, Jefferson A, Leonard H. Early determinants of fractures in Rett syndrome. *Pediatrics* 2008; **121**: 540-6.

12 Wong K, Leonard H, Jacoby P, Ellaway C, Downs J. The trajectories of sleep disturbances in Rett syndrome. *J Sleep Res* 2014: doi: 10.1111/jsr.12240.

13 Cobb JR. *Outline for the study of scoliosis.* Ann Arbor, MI: American Academy of Orthopaedic Surgeons; 1948.

14 Kelman C. The Australian National Death Index: an assessment of accuracy. *Aust NZ J Publ Heal* 2000; **24**: 201-3.

15 Fernandes P, Weinstein SL. Natural history of early onset scoliosis. *J Bone Joint Surg Am* 2007; **89 Suppl 1**: 21-33.

16 Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC). Canberra, ACT: Commonwealth of Australia; 2011.

17 Rothman KJ. Measuring interactions. Epidemiology: An Introduction. Oxford: University Press; 2002. 168-80.

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

19 Bebbington A, Anderson A, Ravine D, Fyfe S, Pineda M, de Klerk N, Ben-Zeev B, Yatawara N, Percy A, Kaufmann WE, Leonard H. Investigating genotype-phenotype relationships in Rett syndrome using an international data set. *Neurology* 2008; **70**: 868-75.
20 Sponseller PD, Yazici M, Demetracopoulos C, Emans JB. Evidence basis for management of spine and chest wall deformities in children. *Spine (Phila Pa 1976)* 2007; **32**: S81-90.
21 Pugely AJ, Martin CT, Gao Y, Ilgenfritz R, Weinstein SL. The incidence and risk factors for short-term morbidity and mortality in pediatric deformity spinal surgery: an analysis of the NSQIP pediatric database. *Spine (Phila Pa 1976)* 2014; **39**: 1225-34.
22 Reames DL, Smith JS, Fu KM, Polly DW, Jr., Ames CP, Berven SH, Perra JH, Glassman SD, McCarthy RE, Knapp RD, Jr., Heary R, Shaffrey CI, Scoliosis Research Society M, Mortality C. Complications in the surgical treatment of 19,360 cases of pediatric scoliosis: a review of the Scoliosis Research Society Morbidity and Mortality database. *Spine (Phila Pa 1976)* 2011; **36**: 1484-91.
23 Sharma S, Wu C, Andersen T, Wang Y, Hansen ES, Bunger CE. Prevalence of complications in neuromuscular scoliosis surgery: a literature meta-analysis from the past 15 years. *Eur Spine J* 2013; **22**: 1230-49.
24 Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; **342**: 1887-92.
25 Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* 2012; **41**: 514-20.

Table 1. Characteristics of 140 girls and women with Rett syndrome and severe scoliosis

	No surgery (N=42)	Surgery (N=98)	Overall (N=140)
Age at death or last contact [years, median (range)]	15.6 (7.2-36.7)	21.0 (10.0-38.2)	19.4 (7.2-38.2)
Mutation[a], n (%)			
C-terminal	1 (2%)	8 (8%)	9 (6%)
Early truncating	3 (7%)	6 (6%)	9 (6%)
Large deletion	6 (14%)	8 (8%)	14 (10%)
p.Arg106Trp	1 (2%)	4 (4%)	5 (4%)
p.Arg133Cys	2 (5%)	4 (4%)	6 (4%)
p.Arg168*	4 (10%)	9 (9%)	13 (9%)
p.Arg255*	4 (10%)	6 (6%)	10 (7%)
p.Arg270*	4 (10%)	9 (9%)	13 (9%)
p.Arg294*	1 (2%)	5 (5%)	6 (4%)
p.Arg306Cys	1 (2%)	1 (1%)	2 (1%)
p.Thr158Met	3 (7%)	11 (11%)	14 (10)
Other	5 (12%)	10 (10%)	15 (11%)
Negative/Unknown	5 (12%)	10 (10%)	15 (11%)
Not tested	2 (5%)	7 (7%)	9 (6%)
Age at scoliosis onset[b], n (%)			
Younger than 8 years	18 (43%)	50 (51%)	68 (49%)
8 years or older	24 (57%)	48 (49%)	72 (51%)
Ever had gastrostomy§[c]			
Yes	15 (36%)	30 (31%)	45 (32%)
No	27 (64%)	68 (69%)	95 (68%)
Weight# [kg, mean (SD)][d]	28.1 (11.0%)	30.2 (8.4%)	29.7 (9.1%)
Ambulation trajectory[e]			
Independent	4 (10%)	10 (10%)	14 (10%)
Assisted	5 (12%)	13 (13%)	18 (13%)
Wheelchair	25 (60%)	47 (48%)	72 (51%)
Deteriorating	7 (17%)	17 (17%)	24 (17%)
Missing	1 (2%)	11 (11%)	12 (9%)
Hand function (Percy score)[f]			
0 acquired and conserved	3 (7%)	8 (8%)	11 (8%)
1 acquired and partially conserved	10 (24%)	34 (35%)	44 (31%)
2 acquired and lost all acquisition	21 (50%)	38 (39%)	59 (42%)
3 never acquired	4 (10%)	12 (12%)	16 (11%)
Missing	4 (10%)	6 (6%)	10 (7%)
Maternal highest attained qualification[g], n (%)			
Primary/high school	11 (26%)	22 (22%)	33 (24%)
Completed high school	5 (12%)	14 (14%)	19 (14%)
Trade/Technical qualification	5 (12%)	13 (13%)	18 (13%)
Advanced diploma/Bachelor degree	12 (29%)	22 (22)	34 (24)
Grad diploma/Postgrad degree	1 (2%)	10 (10%)	11 (8%)
Missing	8 (19%)	17 (17%)	25 (18%)
ARIA+ 2011 category[h], n (%)			
Major Cities of Australia	26 (62%)	60 (61%)	86 (61%)
Inner Regional Australia	11 (26%)	24 (24%)	35 (25%)
Outer Regional Australia	4 (10%)	6 (6%)	10 (7%)
Remote Australia	1 (2%)	3 (3%)	4 (3%)
Very Remote Australia	0	1 (1%)	1 (1%)
Missing	0	4 (4%)	4 (3%)
Cause of death (n=37), n (%)			
Lower respiratory tract infection	5 (31%)	5 (24%)	10 (27%)
Asphyxiation	8 (50%)	5 (24%)	13 (35%)
Respiratory failure	2 (13%)	2 (10%)	4 (11%)
Seizure	0	1 (5%)	1 (3%)
Other	0	2 (10%)	2 (5%)
No information	1 (6%)	6 (29%)	7 (19%)

ARIA, Accessibility/Remoteness Index of Australia; n, number of observations
Fisher's exact (2-sided) test of equal proportions between no surgery and surgery groups: [a] P=0.974; [b] P=0.461; [c] P=0.560; [e] P=0.490; [f] P=0.608, [g] P=0.702, [h] P=0.843
Two sample t-test with unequal variances: [d] Difference=2.1 kg, 95% CI -2.7,6.9 kg, P=0.374
§ any gastrostomy surgery before fusion surgery or 18 years if conservatively managed
# at fusion surgery or at 13 years of age if fusion surgery was never performed
Note: The percentages within each category may not sum to 100 due to rounding.

Table 2. Unadjusted and adjusted effect estimates of spinal surgery on mortality and risk of severe lower respiratory tract infection for Rett syndrome girls and women with severe scoliosis

	Unadjusted		Adjusted	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
All cause death (N=140)				
No surgery	1.00		1.00	
Surgery	0.59 (0.28,1.26)	0.175	0.30 (0.12,0.74)	0.009
	RR (95% CI)	***P* value**	**RR (95% CI)**	***P* value**
Severe LRTI (N*=459)				
No surgery	1.00		1.00	
Surgery	0.62 (0.38,1.02)	0.059	0.70 (0.35,1.41)	0.314

* Repeated measures over 6 questionnaire time points, each female could have contributed from 1 to 6 measures
HR, hazard ratio; LRTI, lower respiratory tract infection; RR, risk ratio; CI, confidence interval
HRs are adjusted for mutation type and age at scoliosis onset
RRs are adjusted for mutation type, age at scoliosis onset and age at questionnaire ascertainment

Table 3. Modification of the effect of spinal surgery on mortality and risk of severe lower respiratory tract infection by age at scoliosis onset in girls and women with Rett syndrome with severe scoliosis

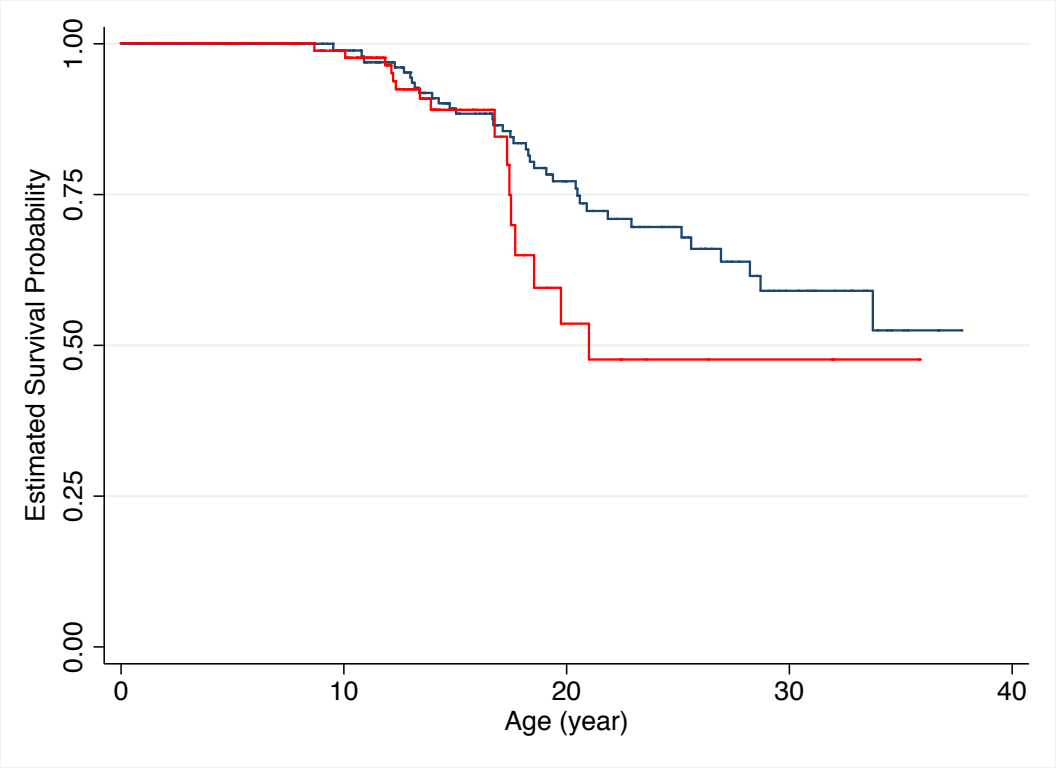
	Conservative management		Surgical management		HR (95% CI) for surgery within age at scoliosis onset strata (baseline conservative management)
All cause death	**N deceased/survived**	**HR (95% CI) *P* value**	**N deceased/survived**	**HR (95% CI) *P* value**	
Onset age < 8 years	11/7	1.0	12/38	0.17 (0.06,0.52) *P*=0.002	0.17 (0.06,0.52) *P*=0.002
Onset age >= 8 years	5/19	0.12 (0.04,0.42) *P*=0.001	9/39	0.07 (0.02,0.28) *P*<0.001	0.60 (0.18,2.03) *P*=0.411
Severe LRTI	**N* with/without severe LRTI**	**RR (95% CI) *P* value**	**N* with/without severe LRTI**	**RR (95% CI) *P* value**	**RR (95% CI) for surgery within age at scoliosis onset strata (baseline conservative management)**
Onset age < 8 years	16/91	1.0	7/120	0.41 (0.16,1.03) *P*=0.058	0.41 (0.16,1.03) *P*=0.058
Onset age >= 8 years	10/77	0.89 (0.36,2.20) *P*=0.794	17/121	0.93 (0.29,3.00) *P*=0.910	1.05 (0.50,2.24) *P*=0.889

Measure of effect modification on additive scale: RERI (95% CI) = [All cause death] 0.78 (0.54,1.02); *P* <0.001 [Severe LRTI] 0.64 (-0.08,1.36); *P* = 0.081
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI) = [All cause death] 3.43 (0.80,14.73); *P* = 0.096 [Severe LRTI] 2.60 (0.88,7.67); *P* = 0.083
HRs are adjusted for mutation type and age at scoliosis onset
RRs are adjusted for mutation type, age at scoliosis onset and age at questionnaire ascertainment

HR, hazard ratio; LRTI, lower respiratory tract infection; RR, risk ratio; RERI, relative excess risk due to interaction; CI, confidence interval
* Repeated measures over 6 questionnaire time points, each female could have contributed from 1 to 6 measures
The results were presented as recommended by Knol and VanderWeele[25]

Figure 1. Kaplan-Meier survival curves of females with Rett syndrome and severe scoliosis (n=140)

Footnote: The estimated survival probability of all with severe scoliosis (blue curve) was 77.4% at 20 years of age and 59.6% at 30 years of age. When observation periods related to surgery were omitted, the probability of survival in those with scoliosis who had not had surgery (red curve) was 59.4% at 20 years and 47.6% at 30 years.


Estimated Survival Probability
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
Age (year)