The developmental trajectory of sleep in children with Smith-Magenis syndrome compared to typically developing peers: A three-year follow-up study

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Abstract

Study Objectives: To determine the trajectory of: (i) objective sleep parameters and (ii) caregiver-reported sleep questionnaire scores over three years in children with Smith-Magenis syndrome (SMS) compared to age-matched typically developing (TD) controls. We also aimed to (iii) describe individual profiles of change in sleep parameters over time.

Methods: Week-long, overnight actigraphy and questionnaire data from 13 children with SMS and 13 age-matched TD children were collected at Time 1 and Time 2 (three years later). Independent samples t-tests, paired samples t-tests and Bayesian analyses were used to compare sleep parameters and sleep questionnaire scores between groups at each time point and compare data within groups to assess change over time.

Results: Sleep parameters were consistently more disrupted in the SMS group than the TD group, with significantly reduced sleep efficiency, increased wake after sleep onset and earlier get up times at both time points. This was mirrored in the questionnaire data, with children with SMS evidencing higher scores for overall sleep disturbance, night waking and daytime sleepiness. Whilst TD sleep parameters demonstrated expected developmental changes over three years, in the SMS group sleep parameters and variability between and within children remained largely stable. However, some children with SMS showed substantial variation in sleep parameters over time. Questionnaire scores remained stable over three years in both groups.

Conclusions: Overall, sleep disturbance appears to be a stable feature of SMS, indicative of a divergent sleep trajectory compared to TD peers. Proactive intervention approaches should be considered for poor sleep in SMS.

Keywords: Smith–Magenis syndrome, actigraphy, sleep, intellectual disability, trajectory

Statement of significance

This paper is the first describing the persistence of objectively-defined poor sleep in individuals with Smith-Magenis syndrome (SMS), a rare genetic syndrome which affords insight into the genetic influences on sleep more broadly. In individuals with SMS, stability of all sleep parameters was noted in comparison to age-related changes to bed time and total sleep time seen in the typically developing comparison group and broader literature. Bayes factors were substantial, suggesting that poor sleep in individuals with SMS is persistent over three years. The overall stability of these objectively-defined sleep parameters is further supported by the persistence of subjectively-reported sleep disorder scores, and alludes to the potential role of the retinoic acid induced 1 (RAI1) gene in divergent sleep trajectories. Key implications for intervention are discussed.

Introduction

Smith-Magenis syndrome (SMS) is caused by a variation or deletion to the retinoic acid induced 1 (RAI1) gene on chromosome 17p11.2. and is associated with mild to moderate intellectual disability (ID) and a well-defined behavioural phenotype of sociability, impulsivity and elevated rates of self-injury and aggression [1–3]. Sleep disturbance is widely reported in SMS and has been delineated objectively as extended wake after sleep onset (WASO), reduced total sleep time (TST) and sleep onset latency, and earlier morning waking than age-matched typically developing (TD) peers, [4]. This sleep disturbance has a demonstrable and significant impact on individuals and their caregivers [5]. Although SMS is rare, occurring in 1 in 25,000 live births [6], the population affords a window into the genetics of sleep disturbance because RAI1 is proposed to regulate the circadian locomotor output cycles kaput ('CLOCK') gene, which in turn regulates the central circadian rhythm and several other circadian genes [7]. Therefore, understanding the profile of sleep in this syndrome has the potential to enhance understanding of sleep more broadly and inform bespoke support for people with SMS and their families.

Within paediatric populations, poor sleep is associated with poor cognitive emotional and behavioural outcomes for TD children and children with neurodevelopmental conditions such as autism and/or rare neurogenetic syndromes [8–14]. Given that SMS is associated with ID, and behavioural and emotional difficulties [e.g. 15,16] there is a need to improve sleep in children in this group to mitigate such outcomes. A critical step towards determining the timing and focus of interventions is to describe the longitudinal trajectory of poor sleep in these groups, in comparison to the developmental changes in sleep well-documented in the TD population [17]. If

poor sleep is persistent in SMS, more proactive, bespoke and targeted intervention approaches may be warranted.

Despite the elevated risk of poor sleep in SMS, the developmental trajectory of sleep in this high-risk group has received limited attention in research. Using cross-sectional cohorts and clinical descriptions, both diagnosable sleep disorders and 'general' sleep difficulties are demonstrated to be persistent throughout childhood and into adulthood in SMS [e.g. [18]] whereas these problems are generally transient in TD children [[19,20]]. Cross-sectional data from informant-report diaries and sleep questionnaires suggest that as children with SMS get older they sleep less [[21]], wake more after sleep onset and wake earlier [[22]]. Although subjective methods are useful in providing a broad picture of poor sleep in these groups, they are limited by the caregiver not necessarily seeing the individual at night-time and caregivers' own experience of sleep deprivation [[23]].

In a cross-sectional study that used actigraphy as an objective sleep assessment, Trickett et al. (2019) found no relationship between TST and age in a sample of children with SMS recruited due to a caregiver reported 'sleep problem' [[4]]. This suggests that poor sleep does not improve with age in children with SMS and supports Potocki et al.'s (2000) cross-sectional polysomnography study of twenty-eight individuals with SMS (aged two to 31 years) which found no relationship between age and TST [[24]]. However, a more recent cross-sectional study by Smith et al. (2019) found that WASO and early waking, as defined by actigraphy, reduced with age in individuals with SMS, indicating that some sleep parameters may improve over time [[25]]. Though these objective data are robust, they are limited by their cross-sectional design, and

therefore only demonstrate change (or stability) in sleep patterns without accounting for individual variation. Therefore, prospective longitudinal studies utilising both objective and subjective sleep assessments are required to better evaluate the trajectory of poor sleep in individuals with SMS.

As sleep is a developmental process known to fluctuate through the lifespan [17,26], it is critical to consider change or stability in sleep parameters in individuals with SMS in comparison to TD peers. There are robust data demonstrating that sleep timing alters during typical adolescence with a shift toward a later phase and later bedtime [27]. This shift is associated with a gradual reduction in overall TST as individuals get older [17]. The use of a longitudinal age-matched TD contrast group would allow researchers to quantify the severity of poor sleep in this population at high-risk for poor sleep. Furthermore, the use of a TD contrast group would enable careful evaluation of whether the divergence in sleep parameters in individuals with SMS from TD sleep parameters persists, or whether these differences remit over time.

Objective longitudinal research would also help to elucidate potential underlying mechanisms and risk markers for poor sleep in SMS, which are critical for timely and effective intervention. In SMS, the predominant explanation for poor sleep, particularly early morning waking and excessive daytime sleepiness, is the difference in the secretion pattern of melatonin [21,24]. In comparison to TD individuals, individuals with SMS are reported to have an 'inverted' melatonin secretion pattern, which peaks during the day and falls during the night, thus circadian timing and subsequent sleep parameters are *divergent* in individuals with SMS compared to TD individuals. This inverted pattern has been reported in over 90% of 27 individuals studied cross-

sectionally [21,24] and is thought to be a by-product of dysregulation of the retinoic acid-induced (RAI1) gene, which is either deleted, or, less commonly, mutated in SMS [28]. As the genotype does not vary as the individual with SMS ages, it would be hypothesised that there would be limited variation in sleep parameters (particularly sleep onset latency and get up time) and subjectively reported sleep disorders over the lifespan. However, Smith et al. (2019) found cross-sectional improvements to WASO and reduced early waking in older children with SMS [25]. These objectively derived cross-sectional differences, together with reports of individuals with SMS who experience sleep disturbance *without* the abnormal melatonin secretion pattern [see 29] indicate that sleep disturbance in SMS may not be caused solely by biological differences in melatonin secretion and gene regulation. Stability of objectively measured poor sleep at multiple time points would support a hypothesis of atypical and stable melatonin release as primary to poor sleep in SMS, whilst replication of improvements in sleep parameters would suggest that alternative mechanisms contribute to sleep outcomes and/or that atypical melatonin release is also not stable over development in individuals with SMS. These findings would have significant value more broadly in increasing understanding of the genetic pathways to sleep disturbance.

An alternative explanation for poor sleep in SMS is that rather than (or in addition to), the sleep trajectory being divergent due to a known or unknown biological mechanism it is *delayed* compared to TD peers, commensurate with the motor and cognitive delay seen in these groups [e.g. 30,31]. If this hypothesis is correct, the same pattern of changes in sleep parameters over time as reported in the TD literature would be expected in SMS, but occurring later in children's development, perhaps in line with mental-age or neural-age development. Galland et al. (2012)'s

systematic review [17] of cross-sectional changes in 24-hour TST in TD children suggests mean sleep duration reliably reduces with age from new-borns (14.6 hours) to 12-year-olds (8.9 hours). This is likely due initially to the decline in daytime napping over the first five years of life [32] and then later bedtimes and reduction in night sleep throughout childhood. Current cross-sectional subjective sleep data using informant-report measures similar to those synthesised by Galland et al. (2012) [17], suggest sleep parameters in SMS may mirror TD change over time [16,16,21,22] with mixed findings from actigraphy data [4,25]. Longitudinal research is therefore required to consider whether sleep trajectories in SMS are delayed or divergent compared to TD peers and in relation to developmental age to inform intervention for poor sleep in these groups.

Finally, longitudinal research is needed to explore within and between individual variability in sleep parameters over time in individuals with SMS in relation to individual characteristics. This is particularly important in rare syndromes such as SMS, to maximise the use of individual data and harness the strength of small-*N* designs in order to consider change over time [33]. Age-related changes to TST in typical development appear to be moderated by intra-person variability in environmental factors such as school timing and biological circadian phase delay [34,35]. Therefore, poor sleep in SMS may also be influenced by other factors, such as the child's behaviour, sleep environment and other aspects of their sleep hygiene [4,16,36]. The phenotypic facial features of individuals with SMS may also predispose them to sleep disordered breathing [16], which may become more or less difficult as facial characteristics mature with age [37]. Importantly, individuals with SMS show a phenotypic preference for caregiver attention [3] which may lead to multiple interactions with caregivers during the night [5,38]. Over time, these interactions can serve to unintentionally reinforce the child's signalling behaviour at waking

through the process of operant reinforcement, thus prolonging poor sleep [39]. Additionally, SMS is associated with painful health conditions including constipation, reflux and otitis media which can become chronic [18]. These conditions have been associated with poor sleep in TD individuals [40] and chronic pain more broadly is a known correlate of poor sleep in TD children [41]. As our previous work demonstrates, these night-time interactions and painful health conditions may be partly responsible for acute poor sleep in SMS [42]. However, longitudinal research is needed to explore the relationship of child behaviour, pain, and sleep hygiene to long-term poor sleep.

In summary, cross-sectional studies using subjective data collection methods indicate likely persistence of poor sleep in SMS. There is a need for a prospective longitudinal design to evaluate change in sleep parameters over time in this high-risk group, using objective assessment of sleep. Additionally, TD children demonstrate age-related changes in TST and sleep consolidation over time, thus longitudinal changes in these parameters in SMS must be considered in comparison to a TD contrast group to determine whether sleep trajectories are delayed and/or divergent. In this study we conduct a longitudinal follow-up of the cohort described by Trickett et al. (2019) [4] to delineate the developmental trajectory of poor sleep in individuals with SMS using objective measures and contrast the trajectory of change with that of TD children. The aims are:

i) To compare specific actigraphy-defined sleep parameters at Time 1 (T^1) and Time 2 (T^2, three years later) in each group to determine the trajectory of objective sleep parameters in SMS compared to a community sample of age-matched TD controls and determine whether they are delayed and/or divergent in individuals SMS.

ii) To compare caregiver reported sleep questionnaire scores at T^1 and T^2 in both groups to describe the trajectory of subjectively reported sleep disorders in SMS and compare the trajectory to that of TD peers.

iii) To explore individual profiles of change in sleep parameters over time, in relation to chronological and developmental age-expected changes in sleep and reliable change in caregiver-reported sleep disorders, overactivity and impulsivity, pain, sleep hygiene and adaptive functioning.

Methods

Participants

At T^1 (2015-2016), twenty-six participants with SMS and fifty-two TD children were recruited to a longitudinal study of sleep and behaviour (approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham). All children with SMS had a confirmed genetic diagnosis according to caregiver report. The decision was taken to recruit children with SMS with a caregiver reported 'sleep problem' to objectively define poor sleep in these groups (as in Trickett et al., 2019) [4]. Additionally, the recruitment of individuals with a known 'sleep problem' conferred the advantage of considering possible mechanisms of poor sleep. TD children were not required to have a caregiver reported 'sleep problem' to take part at T1, though by T2 some did. This decision was taken to evaluate the putative discrepancies in sleep parameters experienced by individuals with SMS with poor sleep, in comparison to what might be expected in typical development. This approach also enables consideration of how sleep parameters in SMS might differ longitudinally from a typical sleep trajectory.

The full recruitment procedure and T^1 comparison of twenty of these children with SMS and an age-matched sample of twenty TD children, drawn from the wider cohort recruited in 2015-2016, are described in Trickett et al., (2019) [4]. At T^1, 20 children with SMS participated in the actigraphy study and a further three participants had informant-based assessments of sleep. Thirteen of these participants with SMS (Mean age = 11.09, SD = 1.57) and 23 TD children (Mean age = 9.86, SD = 2.89) took part in the follow-up study at T^2 (2018-2019) and are the subject of this paper. Of these, only twelve participants with SMS had actigraphy data available from T^1, thus the longitudinal objective analysis has twelve participants, but longitudinal subjective analysis has thirteen. Supplementary Material 1 provides a summary of recruitment and attrition across both time points in both groups. There were no significant differences in T^1 demographic or sleep characteristics between those who did and did not take part at T^2.

A sample was selected from the TD contrast group and matched to the SMS group. Two matching approaches were trialled, in order to identify ideal matches for children with SMS based on their exact age at time of assessment (within a year) and sex. Due to the over-representation of male participants in the TD group, matching which prioritised sex resulted in all children with SMS being matched to a TD participant of the same sex, but only 7/13 being matched to a child within a year of their exact age. Matching which prioritised age resulted in all children with SMS being matched to a child within a year of their exact age, and only 5/13 *not* matched to a child of the same sex. Therefore, age-based matching was deemed the most appropriate approach in this study, especially given the comparative importance of developmental processes. The finalised matching approach is detailed in Supplementary Material

2. Table 1 describes the participant characteristics of those included in the follow-up study.

[Insert Table 1 here]

Procedure

At T^1, families were contacted via telephone or email to book in a 'study week' where the child was asked to wear a Philips Actiwatch 2 (Philips Respironics) in their typical home environment whilst caregivers completed a sleep diary. All study weeks were completed during school term-time to maintain consistency and because of potential differences in term-time versus school holiday sleep patterns [see [43,44]]. All caregivers were advised that the actiwatch could be worn on the ankle or, preferably, the wrist, and to press the event marker at 'lights out time' and 'get up time'. Participants were encouraged to wear the actiwatch at all times (except for bathing and swimming, which was at caregivers' and teachers' discretion).

At T^2, all participants eligible for follow-up (i.e. aged ≤ 15)[1] were contacted via post with details of the longitudinal sleep study. Participants were booked in for a study week, ideally within two years eleven months and three years one month (1065-1125 days) of their original participation, where school term time allowed for this. The mean follow-up date was 1103 days (range: 1064-1143 days) after initial participation.

[1] Note that ethical approvals only allowed children under the age of 16 to participate at both T^1 and T^2. Therefore, a cohort of children who had been eligible to take part at T^1 were no longer eligible at T^2, and were therefore not approached for the follow-up data collection.

Actigraphy Assessment

Using the default settings of medium sensitivity, the actiwatch defined sleep parameters) based on movement in 30 second epochs. Actigraphy data were downloaded to Philips Actiware software and cleaned using information from the caregiver sleep diary and the event marker according to the protocol outlined in Trickett et al., (2019) [4] and Agar et al., (2022) [38]. This protocol was developed to maximise accuracy of the data and remove artefact which can make actigraphy unreliable [45]. For example, sleep intervals would be excluded if the diary suggested that the watch had been removed overnight or adjusted if the diary suggested the child was sedentary rather than asleep in the early evening (see Supplementary Material 3 for the full protocol and Supplementary Material 4 for a summary of key parameters derived from actigraphy). This protocol is intended to standardise and make explicit the visual inspection process that typically occurs as part of cleaning actigraphy [see 46].

All data were cleaned by the first author, and 25% of participants' data were cleaned by a research assistant to assess inter-rater reliability of the cleaning protocol. A two-way mixed-effects model inter-rater reliability analysis [47] was used to assess the absolute agreement of the two raters on each average parameter. Overall intra-class coefficients ranged from .921-.999, thus reliability of the cleaning protocol was excellent.

Informant-Based Measures

At both time points, caregivers completed the Vineland Adaptive Behavior-II Interview [VABS-II; [48]] with a researcher. This was used as a measure of children's adaptive functioning as a proxy for overall ability. In addition, caregivers completed questionnaires about their child's behaviour and characteristics.

The Modified Simonds & Parraga Sleep Questionnaire [MSPQ, [49,50]] was used as a subjective measure of children's poor sleep with questions about the child's sleeping environment, bedtime routine, sleep timings, history of treatment and impact on the family. The MSPSQ has adequate internal consistency and was selected as data relating to diagnosable sleep disorders can be extracted following scoring guidelines outlined by Johnson et al. (2012) [[51]]. Seven subscales can be calculated: Bedtime Resistance, Sleep Onset Delay, Night Waking, Sleep Anxiety, Parasomnias, Sleep-Disordered Breathing and Daytime Sleepiness, with test-retest reliabilities ranging from 0.83 – 1 [[50]]. Additionally, a total score can be derived [[51]], with higher scores indicating poorer sleep. Both total and subscale scores correlate significantly with corresponding scores on the Children's Sleep Habits Questionnaire developed by Owens et al. (2000) [[52]]. In addition, the Family Inventory of Sleep Habits [FISH, [53]] was used as a measure of sleep hygiene, with higher scores indicating better sleep hygiene.

The Non-communicating Children's Pain Checklist – Revised [NCCPC-R, [54]] was used as a measure of pain-related behaviours. The measure is suitable for use with individuals with ID and compromised verbal communication, with excellent psychometric properties [[55]]. Higher scores

suggest the individual is in more pain. In this study, administration was modified so that caregivers rated each behaviour over a week rather than over two hours. This decision was taken to capture chronic but potentially intermittent pain caused by long-term health conditions, rather than bursts of acute pain. Painful health conditions are common in individuals with ID [56,57] and this modified approach has been taken to measure 'typical' pain behaviour in both children and adults with ID previously [58,59].

The Activity Questionnaire [TAQ, 60] was used to measure behavioural features associated with attention deficit hyperactivity disorder in individuals with ID. Scores are pro-rated based on an individual's verbal ability and mobility, producing a total score and subscale scores for 'overactivity', 'impulsivity' and, for verbal participants, 'impulsive speech', with higher scores indicating a greater frequency of attention deficit hyperactivity disorder-like behaviours. The measure has robust inter-rater and test-retest reliability, and good internal consistency [60].

Data analysis

Independent samples t-tests were used to compare objective and subjective sleep data between groups at each time point. Paired samples t-tests were used to compare data at T^1 and T^2 within groups to assess change over time. As some of the sleep parameters defined by actigraphy were not normally distributed, non-parametric Mann Whitney U and Wilcoxon rank tests were used when appropriate. Due to the number of comparisons the alpha level was Bonferroni corrected within each family of tests.

A coefficient of variance (CoV) for TST, WASO and longest period of sleep before wake was calculated for each child and group to consider variability in these parameters between individual children, and within each child's assessment period [e.g. [4,61]]. The CoV between individual children was calculated as the Group standard deviation (SD) of the variable/ Group Mean of the variable. The CoV within each child's assessment period was calculated as the Individual SD of the variable/ Individual Mean of the variable[2].

To quantify the differences in objective parameters and subjectively defined sleep disorder scores between groups and over time, effect sizes were calculated (Cohen's d was calculated for parametric variables and adjusted Cohen's d for non-parametric variables) and Bayesian independent and paired samples t-tests undertaken. Bayesian statistics indicate the extent to which the data support the null hypothesis (that the groups/time points do not differ on a given variable) versus the alternative hypothesis (that the groups/time points differ), by calculating a Bayes Factor. For example, Bayesian analyses allow consideration of the change (alternative hypothesis) or stability (null hypothesis) of sleep parameters over time. This approach also improves confidence in findings drawn from small samples. Jeffreys' (1961) [[62]] guidelines were used to interpret the data as per Surtees et al. (2019) [[63]], a study of actigraphy parameters in a sample of <20 children with autism. These guidelines suggest a Bayes Factor of 1-3 represents 'anecdotal evidence' in favour of the null hypothesis, 3-10 'moderate evidence', 10-30 'strong evidence', 30-100 'very strong evidence' and >100 as 'extreme evidence'. Conversely, $^1/_3$ - 1 represents 'anecdotal evidence' in favour of the alternative hypothesis, $^1/_{10}$ - $^1/_3$ 'moderate

[2] For non-parametric variables a Quartile-based Coefficient of Variance (QCV) was calculated, using the interquartile range and median in place of the SD and mean respectively.

evidence', $^{1}/_{30}$ - $^{1}/_{10}$ 'strong evidence', $^{1}/_{100}$ - $^{1}/_{30}$ 'very strong evidence' and $<^{1}/_{100}$ as 'extreme evidence'.

To address the final exploratory aim, individual changes to sleep parameters in the SMS group were considered in relation to chronological and developmental age-related changes in the TD sample and published normative data. Developmental age was calculated based on average age equivalent for each domain on the VABS-II at each time point. Since many children had an adaptive age equivalent below the minimum age of the TD sample (<4 years), data synthesised by Galland et al. (2012) [17] are also presented as a comparison. In addition, children were classified on each sleep parameter as either having improved or reduced sleep using visual inspection.

Questionnaire scores relating to overactivity and impulsivity, pain, caregiver reported sleep disorders, sleep hygiene and adaptive functioning were considered in relation to individual change over time in specific sleep parameters. Given the small *n*, reliable change indices were calculated for questionnaire and interview data for each participant, using the Leeds Reliable Change Indicator [64]. Reliable change indices consider whether an individual is making reliable improvements or reductions on a given measure over time, beyond what is expected given the known test-retest reliability of the measure. The Cronbach's alpha or intraclass coefficients were taken from the relevant manual or from published literature for each measure entered into the analyses [48,53,55,65,66].

Results

Group differences in actigraphy-defined sleep parameters

Table 2 shows the results of comparisons of actigraphy sleep parameters at T^1 and T^2 for children with SMS compared to age-matched TD peers.

[Insert Table 2 here]

At T^1, sleep was more disrupted in the SMS group than the TD group, with children with SMS experiencing significantly poorer sleep efficiency, less time in bed and less time asleep than their TD peers. Although children in both groups went to bed at a similar time, children with SMS woke two hours earlier than their TD peers, with a trend toward greater WASO. However, there was no difference between the sleep onset latency (SOL) of the two groups. The Bayes factor suggests that the data are more consistent with the null hypothesis (that there is no difference between the SOL of the two groups). The coefficient of variance between children for TST and particularly for WASO was higher in the SMS group (13.8 vs 6.3% and 103.1% vs 34.9%, respectively). The coefficient of variance for longest period of sleep before wake was higher in the TD group (24.2% vs 19.3%). Variability of these parameters for individual children within their own assessment period was also higher in SMS, with the coefficient of variance significantly higher for TST.

At T^2, group differences in get up time, WASO and sleep efficiency remained significant. Additionally, differences in bedtime between the groups were significant, with children with SMS going to bed one hour twenty-six minutes earlier than their TD peers. Time in bed did not

differ significantly between groups (Bayes factor 2.405, 'anecdotal' evidence in support of the null hypothesis), but there was a trend toward differences in TST (effect size 1.17, Bayes factor .178, 'moderate' evidence in favour of the alternative hypothesis). There were no significant differences between the groups in terms of individual variability within the assessment period. Variability between children in TST (7.1% vs 8.4%) and period of longest sleep before wake (38.6% vs 30.4%) was also similar in both groups. Variability between children was greater for WASO in SMS (84.1% vs 51.9%).

Change over time in actigraphy-defined sleep parameters

To consider the developmental trajectory of poor sleep, actigraphy-defined sleep parameters at T^1 and T^2 in were compared for each group (see Table 3). In the SMS group, children's sleep parameters and variability between and within children remained largely stable over three years. Interpretation of the Bayes factors suggests 'moderate' evidence in favour of the null hypothesis for bedtime, and the coefficient of variance for inter-assessment variability in TST and WASO, suggesting these were particularly stable. However, evidence in favour of the null hypothesis for the other variables was 'anecdotal'. For the twelve children in the SMS-matched TD group, bedtime became significantly later (Bayes factor .001, 'extreme' evidence in favour of the alternative hypothesis) whilst there was no change in children's get up time. Though there was no significant change in children's sleep efficiency, SOL or WASO, TD children did spend less time in bed as they got older and obtained significantly less TST. Levels of variability within and between children remained stable over three years, with 'moderate' Bayes factors. Evidence in favour of the null hypothesis was also 'moderate' for get up time and sleep efficiency in this group, but weaker for WASO and SOL.

[Insert Table 3 here]

Group differences in subjectively defined sleep disorders

Table 4 shows the group comparisons for subjectively defined sleep disorders and sleep hygiene scores. Caregivers of children with SMS reported higher overall MSPSQ scores and higher subscale scores for night waking and daytime sleepiness than caregivers of age-matched TD children at both time points, despite comparable sleep hygiene scores, with 'extreme' evidence for the alternative hypothesis. However, it should be noted that the mean MSPSQ score in both groups at T^1 was above the cut-off of 56 for 'poor sleepers' as suggested by Johnson et al. (2012) [51]. At T^1, children with SMS were also reported to have higher scores on the parasomnias and sleep-disordered breathing subscales but these differences were not significant at T^2. No significant differences were found between groups for bedtime resistance, sleep onset delay and sleep anxiety at either time point. Interpretation of the Bayes factors suggests evidence for the null hypothesis was 'anecdotal' in all cases, except for bedtime resistance and sleep anxiety at T^1 and sleep onset delay at T^2 where evidence for the null hypothesis was 'moderate' (see Table 4).

[Insert Table 4 here]

Change over time in subjectively defined sleep disorders

The results of the analysis of change over time in subjectively defined sleep disorders and sleep hygiene scores are shown in Table 5. In the SMS group, caregiver reported sleep hygiene and sleep disorders were largely stable over time, with no significant differences between T^1 and T^2 scores. In the SMS group, evidence was moderate for the null hypothesis for all scores, except

for the MSPSQ total score and parasomnia subscale score (see Table 5). Age-matched TD peers showed a similar stability of subscale scores. Interpretation of the Bayes factor suggests 'moderate' evidence in favour of the null hypothesis for sleep onset delay, sleep-disordered breathing, daytime sleepiness and night waking but weaker evidence for the stability of the other subscales.

[Insert Table 5 here]

Individual change over time

Given individual variation in objective sleep parameters within the SMS group identified in the CoV analysis, each child's data was compared at T^1 and T^2 in relation to their chronological *and* developmental ages, and the mean TST at each age from the TD contrast group and published normative data, to further consider whether the trajectory of TST is delayed or divergent in SMS. Figure 1 presents the TST of each individual child with SMS at T^1 and T^2 in relation to their chronological age (a) and their developmental age (b). As indicated by red and blue lines in panel (a), though mean TST did not change over three years for the SMS group (see Table 3), it did decrease for some individual children (n=4) and increase for others (n=8). Generally, TST did not fall within the TD confidence intervals and in all cases, children with SMS were receiving less sleep than would be expected for their developmental age (b).

[Insert Figure 1 here]

To consider age-related changes in sleep consolidation, each child's individual WASO was compared at T^1 and T^2 in relation to changes to their chronological and developmental age.

Figure 2 presents the mean WASO of each individual child with SMS at T^1 and T^2 in relation to their chronological age (a) and their developmental age (b). As indicated by red and blue lines in panel (a), though mean WASO did not change over three years for the SMS group (see Table 3), it did decrease for some individual children (n=5) and increase for others (n=7). Some individuals' mean WASO fell within the TD confidence intervals, but generally children with SMS were awake for longer than their chronologically age-matched TD peers (a) and for longer than expected given their developmental age (b).

[Insert Figure 2 here]

In summary, although group means revealed stability of objective sleep parameters and subjectively defined sleep disorders, visual inspection of the data suggests some individual children demonstrated a change in objectively defined TST and WASO.

To address the final aim of the study, change in mean sleep parameters for each child with SMS is summarised in Table 6. Increased TST was generally accompanied by later get up times and earlier bedtimes, rather than reduced WASO. Decreased TST was accompanied by increased SOL and later bedtimes. Reliable change statistics were calculated for each individual participant on factors where individual variability, above and beyond chronological and developmental age, might be associated with a change in sleep parameters. As demonstrated in Table 6 there were no discernible patterns of change observed via visual inspection associated with experiencing an increase or decrease in any objectively defined sleep parameters.

[Insert Table 6 here]

Discussion

This paper demonstrates the three-year trajectory of objectively defined sleep parameters and caregiver reported sleep disorders in SMS, a syndrome at ultra-high risk for poor sleep, in comparison to TD age-matched peers. This was the first longitudinal study to use actigraphy, a validated objective measure of sleep, to compare sleep parameters in children with SMS to TD chronologically age-matched peers. This strengthens the validity of findings and demonstrates the utility of this assessment approach. The use of in-depth analysis to consider group and individual differences in sleep profiles maximises the data derived from a modest sample of participants with an exceptionally rare syndrome. This represents a robust and rigorous approach to phenotype sleep and changes in sleep over time in studies with clinical samples that are often rare and prone to attrition. The results of this study extend previous objective and subjective research suggesting poor sleep is stable in individuals with SMS, and consistently worse than TD peers, by demonstrating no significant change in objective atypical sleep parameters and subjectively defined sleep disorders over three years. This stability contrasts with typical age-expected changes to TST, sleep consolidation and sleep onset and offset times. In particular, children with SMS showed persistent reductions in TST and sleep efficiency, earlier bed and get up times and greater WASO than TD peers, at both T^1 and T^2.

The results of the study demonstrate stability of sleep parameters in children with SMS who were recruited due to a 'sleep problem' three years after initial assessment. In contrast to reductions in TST with age reported in the literature and demonstrated by TD peers, on average children with SMS had stable bedtimes and get up times over three years and did not show a

longitudinal reduction in TST. WASO remained stable in SMS and TD samples but was significantly higher in the SMS group than the TD group at T^2, suggesting sleep does not become more consolidated over time. In the SMS group, average get up times were two hours earlier than TD peers at T^1 and ninety minutes earlier at T^2, demonstrating a statistically significant divergent sleep trajectory in those with SMS recruited for poor sleep. The stability in this subsample contrasts with cross-sectional reports of individuals with SMS waking more and earlier [22] or more and later [25] as they get older, but supports cross-sectional polysomnography and actigraphy data demonstrating no relationship between age and TST [4,24]. The stability of poor sleep in SMS is further supported by the persistence of individuals' subjectively defined sleep disorder scores, with moderate evidence for the null hypothesis on most subscales of the MSPSQ including sleep disordered breathing. Importantly, these differences were noted despite equivalent sleep hygiene scores with the TD group at both time points.

Taken together, data from these objective and subjective sleep assessments suggest poor sleep does not naturally remit over time in children with SMS and thus proactive intervention approaches should be considered for poor sleep in this group. The stability of the objective and subjective sleep data in individuals with SMS itself is not typical, as highlighted by reductions in time in bed and TST and later bedtimes in the matched TD contrast group [and wider TD literature, see 17]. This suggests a divergent sleep trajectory in SMS compared to TD peers, rather than a delay in the emergence of a typical sleep profile. This hypothesis is further supported by the notable disparity between the TST of individuals with SMS and those observed at equivalent developmental ages by Galland et al. (2012) [17], suggesting there is not a 'delay' in the acquisition of sleep consolidation in this group. However, it should be noted that, whilst not

'typical', the lack of age-expected reduction in TST in SMS may be a positive finding, given that children were already sleeping less than TD peers at T^1, with SMS TST below the 95% confidence intervals of the TD mean at each chronological age. Therefore, further reduction in TST over time would not be beneficial for children with SMS.

The stability of the early get up time in the SMS group across three years, coupled with relatively short and stable SOL provides further support for a *divergent* sleep trajectory in SMS; a stable but inverted melatonin secretion pattern which causes individuals to feel sleepy in the day and more awake after 3am [21,24]. This is likely due to the downstream effects of RAI1 dysregulation to the CLOCK and other circadian genes [7]. Furthermore, stability of the average bedtime in the SMS group (with moderate Bayes factor) suggests children now need to go to bed earlier than is typical, arguably because they feel tired much earlier than TD peers. Additionally, it may be that caregivers are still keen to implement earlier bedtimes for children with SMS than what might be considered 'typical', given the profile of early waking and the significant difficulties associated with caring for people with SMS and keeping them safe overnight [5].

However, it should be noted that though data based on group means revealed stability of objective sleep parameters and subjectively defined sleep disorders, visual inspection of the data suggests some individual children demonstrated a change in objectively defined TST and WASO which is likely to be significant to those children and their caregivers. Interestingly, a substantial proportion of children with SMS demonstrated an increase in TST at T^2 with some experiencing later get up times, reduced WASO and SOL and earlier bedtimes. This suggests that while the group means for these parameters are stable (and indeed for some individual children become

markedly poorer over time) there is individual variability in parameters and the possibility of clinically meaningful improvements over time.

Additionally, the data highlighted substantial intra-individual and inter-individual variation in sleep parameters within individuals with the same genetic syndrome. Variability between children in WASO for example was much greater in the SMS group than the TD group at both time points, suggesting waking is more problematic for some children than others. To consider which factors might be associated with these individual differences, reliable change statistics for several measures relating to child melatonin use, behavioural and adaptive characteristics and possible indicators of pain in relation to changes in sleep parameters were conducted. However, no obvious pattern of reliable improvements or deteriorations associated with changes in sleep parameters could be identified from the exploratory reliable change indices, and the relatively small sample size prevented other inferential statistical approaches. Of particular note is the suggestion that exogenous melatonin use is not accompanied by sustained improvement or worsening in sleep parameters in either group. This is particularly surprising given the number of children in this study taking exogenous melatonin to improve sleep, and the reported disruption to the endogenous melatonin cycle in individuals with SMS [21]. A further limitation of the study is that without the use of polysomnography it is not possible to rule out the influence of periodic limb movements and sleep-related breathing difficulties on sleep parameters in SMS [67]. However, polysomnography may not be accessible for many individuals with SMS due to anxiety around sleeping in an unfamiliar environment, or tolerating the equipment required [68]. It is therefore not yet clear why some individuals' TST or WASO might increase over three years while others' decrease, but future research should aim to better characterise these changes

utilising more objective measures of children's overnight breathing, movement, behavioural and pain-related characteristics and circadian rhythm analyses, in addition to actigraphy. Understanding this variability is likely to be of great importance to families who cite sleep as a key informational need, and is crucial for improving syndrome-related interventions [5].

It is acknowledged that whilst the longitudinal design enabled researchers to consider the trajectory of sleep parameters and subjectively defined sleep disorders in a high-risk rare syndrome, this approach did limit the sample to those who were able and motivated to take part in a comprehensive at-home sleep assessment, twice. Several families were not able to commit to such an extensive study having already participated three years previously, and one participant with SMS whose family did want to participate again struggled to tolerate the actiwatch three years later. Therefore, the data presented here may reflect the sleep profiles of only the most motivated families, or the children with the least sensory difficulties or 'challenging' behaviour at bedtime. However, given the range of reliable gains and declines on several measures of child behaviour and adaptive ability, alongside individual changes to sleep parameters, this seems somewhat unlikely. Retention of TD children across both timepoints was also a challenge, with only twenty-three complete actigraphy assessments at both T^1 and T^2 and seventeen of these from male participants. As age was the priority variable for matching, this therefore meant that a disproportionate number of males were included in the control sample and 5 females with SMS had to be matched to males. This imbalance in participants' sex may have influenced the extent of the differences between the SMS and TD groups. Further research should explore the potential role of sex differences in sleep parameters in SMS. Furthermore, the design of the study, a longitudinal analysis of sleep in *children* with SMS, meant that it was not possible to consider

individuals under the age of 4 or over 15 at either time point. Therefore, the data do not reflect poor sleep at every age of childhood, and some older children recruited at T^1 could not be included at T^2, limiting the sample size and application of the findings to change over time in children aged 4-15 only. Further research should investigate the sleep profiles of both younger and older individuals with SMS to delineate a sleep trajectory across the full lifespan.

The size of the sample was modest, due to the rarity of the syndrome and some attrition over the 3-year data collection period, which did limit the analysis approaches that could be undertaken in this study (for example, planned regression analyses could not be conducted to predict changes to sleep parameters at T^2). The remaining frequentist analyses should be interpreted with appropriate caution until future studies have replicated these findings in larger samples. However, a key strength of the present study is the application of Bayesian approaches, which allow quantification of the support for the null versus alternative hypotheses even in small samples. Bayesian statistics have recently been applied to sleep research in individuals with autism [see [63]] and may be beneficial for future studies of other neurodevelopmental conditions where recruitment and retention of large sample sizes may be particularly difficult.

In conclusion, this study is the first to compare the longitudinal sleep trajectory of children with SMS to TD age-matched controls using objective actigraphy data. Comparison of sleep parameters revealed poorer sleep at both time points in the SMS group, and stability of parameters over three years. This stability, in contrast to TD age-related changes to TST, sleep consolidation, bedtime and get up time, suggests a divergent sleep trajectory in SMS. This may be driven by a biological change, such as an altered circadian rhythm [[21,24]]. The objective data

are further supported by the stability of caregiver reported sleep disorders in SMS, which were elevated compared to TD peers. However, for some individual children substantial improvements to TST, WASO and SOL are noted, alongside changes to bedtimes and get up times. These changes did not seem to be associated with specific child behaviours or adaptive functioning. Taken together, these findings suggest that poor sleep is not transient in individuals with SMS, thus proactive intervention is warranted.

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Figures

Figure 1. Changes in TST for children with SMS over three years. Each line depicts a child with SMS's TST at T^1 and T^2. The black line indicates the mean TST of children in the TD contrast group at each age, with 95% confidence intervals plotted in grey. In panel (a) sleep trajectory is considered in relation to individuals' chronological age. The red lines represent children with SMS who showed a decrease in mean TST over three years, and the blue lines those who showed an increase in mean TST. In panel (b) sleep trajectory is considered in relation to individuals' nearest developmental age, according to the VABS-II. The blue lines represent children whose developmental age increased over three years, and the red lines those who evidence a regression in developmental age over three years. Two participants are not depicted – one whose VABS-II data were missing at T^1 and one who evidenced no change in developmental age over three years. The dashed black line represents data reported at each age by Galland et al. (2012), reflecting observed TST for children younger than four.

Figure 2. Changes in WASO for children with SMS over three years. Each line depicts a child with SMS's WASO at T^1 and T^2. The black line indicates the mean WASO of children in the TD contrast group at each age, with 95% confidence intervals plotted in grey. In panel (a) changes to WASO are considered in relation to individuals' chronological age. The red lines represent children with SMS who showed an increase in mean WASO over three years, and the blue lines those who showed a decrease in mean WASO. In panel (b) WASO trajectory is considered in relation to individuals' nearest developmental age, according to the VABS-II. The blue lines represent children whose developmental age increased over three years, and the red lines those who evidence a regression in developmental age over three years. Two participants are not depicted – one whose VABS-II data were missing at T^1 and one who evidenced no change in developmental age over three years.

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Table 1. *Participant characteristics for each sub-sample*

Objective analysis	SMS (n=12)	TD (n=12)
Mean age (SD)	11.27 (1.50)	10.83 (1.88)
Number of males	5	10
Number of females	7	2
Mode family income	£45,001-£55,000	£65,001 or more
Number taking sleep medication	8*	0
Mean nights of actigraphy (SD)	6.25 (1.74)	7.58 (0.67)
Subjective analysis	**SMS (n=13)**	**TD (n=13)**
Mean age (SD)	11.10 (1.57)	10.65 (1.91)
Number of males	6	11
Number of females	7	2
Mode family income	£45,001-£55,000	£65,001 or more
Number taking sleep medication	9*	0

* All these children were taking melatonin regularly, one child was also taking chloral hydrate, and another was taking alimemazine. One child was taking melatonin 'occasionally' and is not included in this total. Only three children (in both the objective and subjective analysis) were not taking any sleep medication.

Table 2. *Actigraphy-defined sleep parameters, test statistics, p values, effect sizes and Bayes factor for children with SMS and age-matched TD peers at Time 1 and Time 2. Significant differences between groups appear in bold.*

	Time 1						Time 2					
Sleep Parameter	SMS (n = 12)	TD (n=12)	t/U score	*p* value*	Effect size	Bayes factor	SMS (n = 12)	TD (n=12)	t/U score	*p* value*	Effect size	Bayes factor
Bedtime (hh:mm) Mean *(SD)*	20:11 (0:55)	20:46 (0:52)	1.622	.119	0.75	1.219	**19:59 (0:57)**	**21:45 (1:07)**	**4.178**	**<.001**	**1.77**	**.013**
Get up time (hh:mm) Mean *(SD)*	**05:01 (1:14)**	**07:01 (0:42)**	**4.924**	**<.001**	**1.94**	**.003**	**05:38 (0:50)**	**07:04 (0:36)**	**4.829**	**<.001**	**2.00**	**.003**
Sleep onset latency (mins) Median (*IQR)*	7.55 (3.05-17.73)	7.56 (4.23-17.32)	69.000	.887	0.07	3.408	14.11 (10.16-27.05)	13.24 (9.70-20.21)	64.000	.671	0.19	3.345
Wake after sleep onset (mins) Median *(IQR)*	70.37 (51.34-123.91)	54.08 (39.81-58.68)	35.000	.033	1.00	.417	**97.04 (51.13-132.64)**	**47.66 (32.92-61.47)**	**24.000**	**.005**	**1.37**	**.062**
Period of longest sleep before wake (mins) Median *(IQR)*	53.42 (48.90-59.22)	62.63 (55.12 - 70.26)	43.000	.101	0.73	1.269	54.16 (46.41-67.31)	55.31 (51.83-68.65)	66.500	.755	0.13	3.438
Time in bed (hh:mm) Mean (*SD*)	**08:49 (01:23)**	**10:15 (0:32)**	**3.336**	**.005**	**1.37**	**.073**	09:39 (0:51)	09:19 (0:52)	-.947	.354	0.39	2.405
Sleep efficiency (%) Mean *(SD)*	**79.13 (6.58)**	**86.69 (3.53)**	**3.508**	**.003**	**1.47**	**.052**	**75.67 (6.25)**	**85.75 (4.48)**	**4.538**	**<.001**	**1.85**	**.006**
Total sleep time (hh:mm) Mean *(SD)*	**07:00 (0:58)**	**08:53 (0:33)**	**5.811**	**<.001**	**2.39**	**<.001**	07:16 (0:31)	07:58 (0:40)	2.859	.009	1.17	.178
CoV in total sleep time within	**10.70 (8.04-20.64)**	**6.70 (5.03-7.83)**	**24.000**	**.005**	**1.37**	**.203**	10.89 (6.27-14.33)	7.66 (4.99-8.16)	50.000	.219	0.54	1.567

assessment period (%) Median *(IQR)*												
Quartile based CoV in wake after sleep onset within assessment period (%) Median *(IQR)*	36.65 (17.94-48.54)	30.16 (16.15-35.53)	53.000	.291	0.46	2.080	28.14 (20.50-45.30)	20.99 (17.40-29.81)	53.000	.291	0.46	1.767
Quartile based CoV in period of longest wake within assessment period (%) Mean *(SD)*	21.95 (6.32)	19.37 (8.28)	-.859	.400	0.35	2.566	31.90 (12.03)	24.47 (12.40)	-1.490	.151	0.61	1.427

Table 3. *Change over time of actigraphy-defined sleep parameters, test statistics, p values, effect sizes and Bayes factor for children with SMS and age-matched TD peers. Significant differences appear in bold.*

	SMS (n=12)						TD (n=12)					
Sleep Parameter	Time 1	Time 2	t/Z score	*p* value*	Effect size	Bayes factor	Time 1	Time 2	t/Z score	*p* value*	Effect size	Bayes factor
Bedtime (hh:mm) Mean *(SD)*	20:11 (0:55)	19:59 (0:57)	.858	.409	0.25	3.314	**20:46 (0:52)**	**21:45 (1:07)**	**-6.781**	**<.001**	**0.88**	**.001**
Get up time (hh:mm) Mean *(SD)*	05:01 (1:14)	05:38 (0:50)	-2.088	.061	0.49	.812	07:01 (0:42)	07:04 (0:36)	-.529	.607	0.07	4.081
Sleep onset latency (mins) Median (*IQR)*	7.55 (3.05-17.73)	14.11 (10.16-27.05)	-2.315	.021	1.07	.391	7.56 (4.23-17.32)	13.24 (9.70-20.21)	-1.255	.209	0.53	2.668
Wake after sleep onset (mins) Median *(IQR)*	70.37 (51.34-123.91)	97.04 (51.13-132.64)	-1.098	.272	0.46	2.600	54.08 (39.81-58.68)	47.66 (32.92-61.47)	-1.804	.071	0.79	.989
Period of longest sleep before wake (mins) Median *(IQR)*	53.42 (48.90-59.22)	54.16 (46.41-67.31)	-.235	.814	0.10	3.427	62.63 (55.12-70.26)	55.31 (51.83-68.65)	-1.569	.117	0.67	2.539
Time in bed (hh:mm) Mean (*SD*)	08:49 (01:23)	09:39 (0:51)	-2.290	.043	0.73	.607	**10:15 (0:32)**	**09:19 (0:52)**	**5.115**	**<.001**	**1.30**	**.009**
Sleep efficiency (%) Mean *(SD)*	79.13 (6.58)	75.67 (6.25)	1.843	.092	0.54	1.137	86.69 (3.53)	85.75 (4.48)	1.549	.583	0.67	3.355
Total sleep time (hh:mm) Mean *(SD)*	07:00 (0:58)	07:16 (0:31)	-1.005	.336	0.34	2.936	**08:53 (0:33)**	**07:58 (0:40)**	**4.485**	**.001**	**1.50**	**.022**
Coefficient of variance in total sleep time within assessment period (%) Median *(IQR)*	10.70 (8.04-20.64)	10.89 (6.27-14.33)	-.863	.388	0.36	3.945	6.70 (5.03-7.83)	7.66 (4.99-8.16)	-.549	.583	0.23	3.602

Quartile based coefficient of variance in wake after sleep onset within assessment period (%) Median *(IQR)*	36.65 (17.94-48.54)	28.14 (20.50-45.30)	-.863	.388	0.36	3.283	30.16 (16.15-35.53)	20.99 (17.40-29.81)	-.628	.530	0.26	3.412
Quartile based coefficient of variance in period of longest wake within assessment period (%) Mean *(SD)*	21.95 (6.32)	31.90 (12.03)	-2.879	.015	1.04	.250	19.37 (8.28)	24.47 (12.40)	-1.628	.132	0.48	1.502

Table 4. *Subjectively defined sleep disorders and sleep hygiene scores, test statistics, p values, effect sizes and Bayes factor for children with SMS and age-matched TD peers at Time 1 and Time 2. Significant differences appear in bold.*

	Time 1						Time 2					
Sleep Questionnaire Score	SMS (n = 13)	TD (n=13)	t/U score	*p* value*	Effect size	Bayes factor	SMS (n = 13)	TD (n=13)	t/U score	*p* value*	Effect size	Bayes factor
Bedtime Resistance Mean *(SD)*	12.38 (4.29)	12.08 (2.99)	-.212	.834	0.08	3.527	12.31 (4.99)	10.31 (3.75)	-1.155	.259	0.45	2.071
Sleep Onset Delay Mean *(SD)*	2.08 (.95)	1.77 (1.17)	-.736	.469	0.29	2.864	2.08 (.95)	1.85 (1.14)	-.559	.582	0.22	3.152
Sleep Anxiety Mean *(SD)*	10.69 (3.22)	11.23 (1.79)	.527	.603	0.21	3.199	11.08 (4.11)	8.69 (2.84)	-1.720	.098	0.68	1.094
Night Waking Median *(IQR)*	**8.00 (6.5-8)**	**4.00 (2-4.5)**	**3.000**	**<.001**	**2.86**	**<.001**	**7.00 (7-8)**	**4.00 (2-4.5)**	**0.000**	**<.001**	**3.23**	**<.001**
Parasomnias Mean *(SD)*	**24.92 (7.44)**	**17.08 (5.48)**	**-3.060**	**.005**	**1.20**	**.118**	22.15 (6.28)	16.15 (4.65)	-2.767	.011	1.09	.206
Sleep Disordered Breathing Mean *(SD)*	10.00 (3.27)	6.92 (2.36)	-2.753	.011	1.08	.211	8.85 (2.76)	6.69 (2.39)	-2.124	.044	0.84	.614
Daytime Sleepiness Mean *(SD)*	**7.08 (1.67)**	**2.92 (1.75)**	**-6.208**	**<.001**	**2.43**	**<.001**	**7.00 (1.63)**	**3.38 (1.66)**	**-5.598**	**<.001**	**2.20**	**.001**
Modified Simonds and Parraga Sleep Questionnaire Total Mean *(SD)*	**88.54 (11.02)**	**59.61 (15.74)**	**-5.427**	**<.001**	**2.13**	**.001**	**83.62 (9.06)**	**54.69 (13.53)**	**-6.404**	**<.001**	**2.51**	**<.001**
Family Inventory of Sleep Habits Total Mean *(SD)*	46.46 (5.29)	50.46 (3.95)	2.186	.039	0.86	.557	45.23 (4.42)	47.77 (5.05)	1.364	.185	0.54	1.679

Table 5. *Change over time in subjectively defined sleep disorders and sleep hygiene scores, test statistics, p values, effect sizes and Bayes factor for children with SMS and age-matched TD peers.*

	SMS (n=13)						TD (n=13)					
Sleep Questionnaire Score	Time 1	Time 2	t/Z score	*p* value*	Effect size	Bayes factor	Time 1	Time 2	t/Z score	*p* value*	Effect size	Bayes factor
Bedtime Resistance Mean *(SD)*	12.38 (4.29)	12.31 (4.99)	.068	.947	0.02	4.816	12.08 (2.99)	10.31 (3.75)	1.735	.108	0.52	1.340
Sleep Onset Delay Mean *(SD)*	2.08 (.95)	2.08 (.95)	<.001	1.000	0.00	4.827	1.77 (1.17)	1.85 (1.14)	-1.000	.337	0.07	3.047
Sleep Anxiety Mean *(SD)*	10.69 (3.22)	11.08 (4.11)	-.534	.603	0.11	4.218	11.23 (1.79)	8.69 (2.84)	2.649	.021	1.07	.349
Night Waking Median *(IQR)*	8.00 (6.5-8)	7.00 (7-8)	-.250	.803	0.10	4.686	4.00 (2-4.5)	4.00 (2-4.5)	-.574	.566	0.23	4.581
Parasomnias Mean *(SD)*	24.92 (7.44)	22.15 (6.28)	1.459	.170	0.40	1.893	17.08 (5.48)	16.15 (4.65)	1.209	.250	0.18	2.495
Sleep Disordered Breathing Mean *(SD)*	10.00 (3.27)	8.85 (2.76)	1.015	.330	0.38	3.008	6.92 (2.36)	6.69 (2.39)	.415	.686	0.10	4.447
Daytime Sleepiness Mean *(SD)*	7.08 (1.67)	7.00 (1.63)	.154	.880	0.05	4.772	2.92 (1.75)	3.38 (1.66)	-.683	.508	0.27	3.876
Modified Simonds and Parraga Sleep Questionnaire Total Mean *(SD)*	88.54 (11.02)	83.62 (9.06)	1.946	.076	0.49	1.005	59.61 (15.74)	54.69 (13.53)	2.086	.059	0.34	.822
Family Inventory of Sleep Habits Total Mean *(SD)*	46.46 (5.29)	45.23 (4.42)	.925	.373	0.25	3.250	50.46 (3.95)	47.77 (5.05)	2.604	.023	0.59	.374

Table 6. *Reliable change in child characteristics from T^1 to T^2 in relation to increases or decreases in mean TST, mean WASO, mean Bed Time, mean Get Up Time and mean Sleep onset Latency in the SMS group.*

	Exact Age at T^2	Mean change in Total Sleep Time	Mean change in Wake After Sleep Onset	Mean change in Bedtime	Mean change in Get up Time	Mean Change in SOL	Melatonin T1	Melatonin T2	TAQ	NCPCC-R	MSPSQ	FISH	VABS Communication	VABS Daily Living Skills	VABS Socialisation	VABS Motor
PPT1	12.21	+02:05:26	+69.29	-01:28:18	+01:44:56	+2	~	~	O	-	O	-	O	O	O	+
PPT2	10.48	+00:56:18	-21.73	-00:51:27	+00:27:11	+1.3	N	N	-	-	O	O	M	M	M	M
PPT3	10.38	+00:50:37	+6.29	-00:00:53	+01:03:04	+3.48	Y	Y	+	O	O	O	O	+	O	O
PPT4	10.99	+00:32:19	+37.8	-01:06:50	+00:21:27	+11.13	Y	Y	O	+	O	O	O	O	O	O
PPT5	9.94	+00:28:20	+64.5	-00:10:20	+01:22:50	-3.48	N	Y	-	+	O	O	O	O	-	O
PPT6	14.99	+00:27:06	+21.9	-00:36:26	+00:20:32	-1.9	Y	Y	+	+	O	O	O	O	O	O
PPT7	11.84	+00:25:26	+55.5	-00:09:17	+01:37:47	+22.5	Y	Y	+	+	O	O	O	-	O	O
PPT8	12.07	+00:14:33	-16.5	+00:41:00	+00:49:40	+11.11	Y	Y	-	-	+	O	O	O	O	O
PPT9	10.87	-00:20:37	-62.43	-00:50:49	-01:55:19	+4.87	Y	Y	O	+	O	O	-	O	-	O
PPT10	8.99	-00:28:25	-10.16	+00:35:20	+00:20:10	+11.42	N	N	O	O	O	-	-	+	-	O
PPT11	11.76	-00:46:37	+19.44	+00:44:45	+01:32:46	+3.88	Y	Y	+	O	O	O	-	O	-	-
PPT12	10.67	-01:18:05	-8.38	+00:51:42	-00:19:48	-0.43	N	N	-	O	O	O	+	O	O	O

Y= Yes, N = No, ~ = Occasional melatonin use. O = no reliable change, - = reliable decline, + = reliable improvement. M = missing data. Note: variables where an 'increase' or 'decrease' would be associated with greater TST are indicated in green, and variables where an 'increase' or 'decrease' would be associated with reduced TST are indicated in red. Similarly, 'earlier' bedtimes and 'later' get up times theoretically increase TST, while 'later' bedtimes and 'earlier' get up times reduce TST. It is acknowledged that there are circumstances where these changes could otherwise be problematic (i.e. oversleeping, or going to bed before dinner) but they are presented in this way to provide a simple overview of the data.

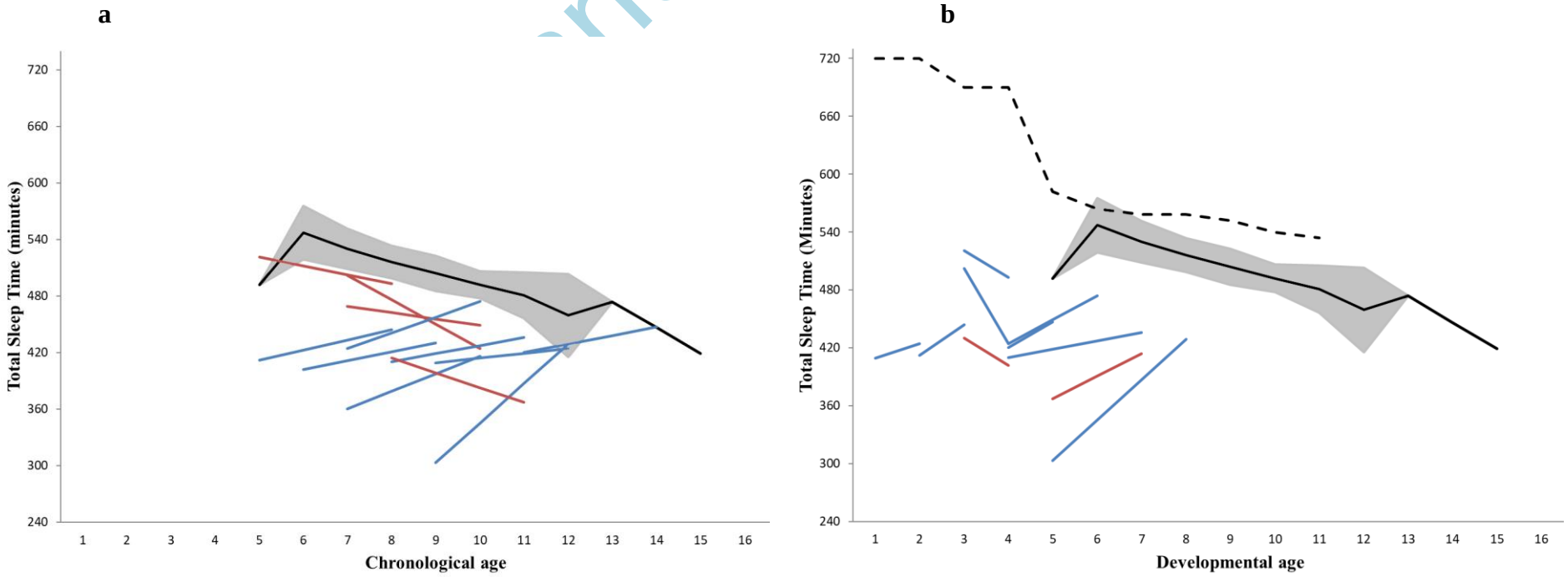

Figure 1. Changes in TST for children with SMS over three years. Each line depicts a child with SMS's TST at T^1 and T^2. The black line indicates the mean TST of children in the TD contrast group at each age, with 95% confidence intervals plotted in grey. In panel (a) sleep trajectory is considered in relation to individuals' chronological age. The red lines represent children with SMS who showed a decrease in mean TST over three years, and the blue lines those who showed an increase in mean TST. In panel (b) sleep trajectory is considered in relation to individuals' nearest developmental age, according to the VABS-II. The blue lines represent children whose developmental age increased over three years, and the red lines those who evidence a regression in developmental age over three years. Two participants are not depicted – one whose VABS-II data were missing at T^1 and one who evidenced no change in developmental age over three years. The dashed black line represents data reported at each age by Galland et al. (2012), reflecting observed TST for children younger than four.

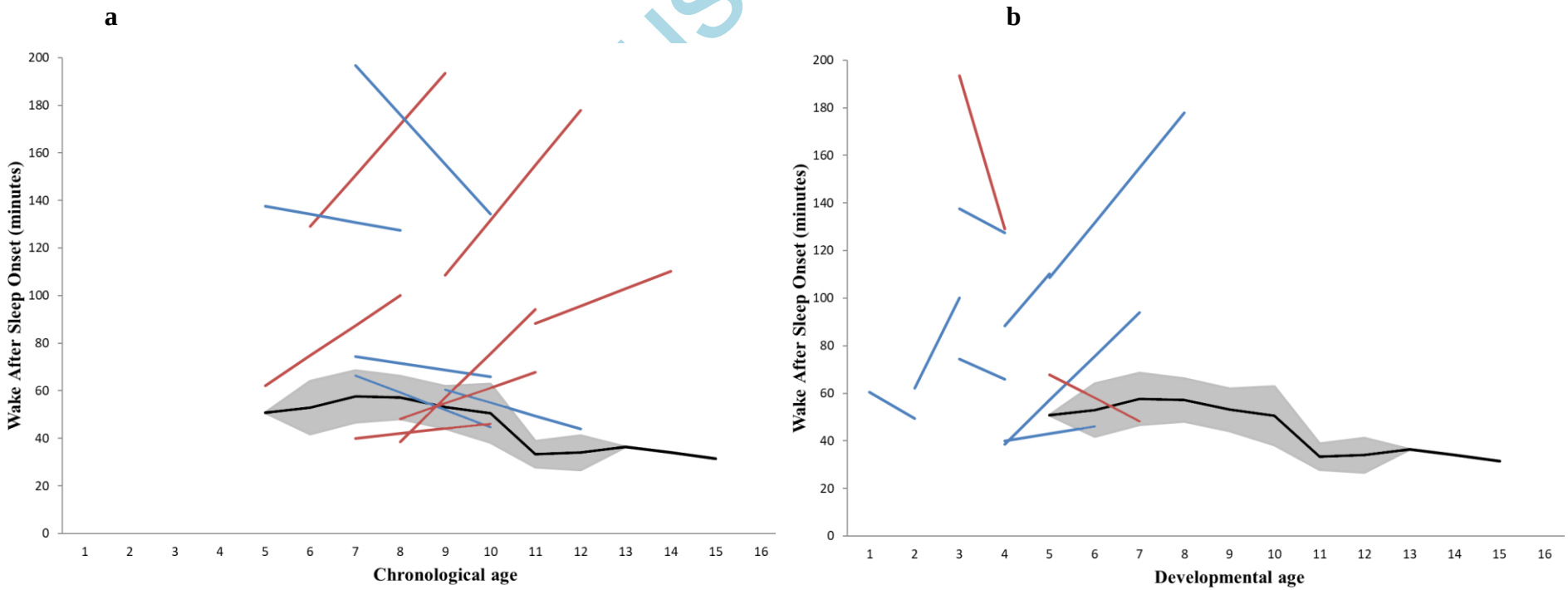

Figure 2. Changes in WASO for children with SMS over three years. Each line depicts a child with SMS's WASO at T^1 and T^2. The black line indicates the mean WASO of children in the TD contrast group at each age, with 95% confidence intervals plotted in grey. In panel (a) changes to WASO are considered in relation to individuals' chronological age. The red lines represent children with SMS who showed an increase in mean WASO over three years, and the blue lines those who showed a decrease in mean WASO. In panel (b) WASO trajectory is considered in relation to individuals' nearest developmental age, according to the VABS-II. The blue lines represent children whose developmental age increased over three years, and the red lines those who evidence a regression in developmental age over three years. Two participants are not depicted – one whose VABS-II data were missing at T^1 and one who evidenced no change in developmental age over three years.