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Title: Early manifestation of sleep problems in toddlers with Williams Syndrome using a mixed method longitudinal approach.

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Abstract: Children with neurodevelopmental disorders commonly experience sleep problems. Williams Syndrome (WS), a rare genetic disorder characterised by a complex, uneven cognitive profile, is no exception. Compared with children with typical development (TD), school-aged children with WS experience significant sleep disruption: shorter sleep duration, more night wakings, greater bedtime resistance and excessive daytime tiredness. In children with TD, sleep problems impede optimal daytime functioning. In WS, this could compound existing difficulties. Few studies have examined sleep in very young children with WS and little is known about the early emergence of sleep problems in this population. To date, studies have been based on parent-report and no studies have objectively assessed sleep patterns using longitudinal approach in toddlers with WS. Thus, the current study sought to objectively explore sleep patterns in toddlers with WS. Parents of 38 children (13 WS, 25 TD) completed the Brief Infant Screening Questionnaire and the Medical and Demographics Questionnaire and sleep patterns were assessed using actigraphy. Data were collected longitudinally at ages 18, 24 and 30 months. Significant sleep disturbances were present in WS from 18 months old. Sleep duration, as measured by actigraphy, was significantly shorter in WS at all ages and, furthermore, parents of children with WS reported more night wakings, longer settling times and high levels of parental involvement. Crucially, whereas actigraphy showed developmental improvements in sleep quality in TD, no longitudinal changes were found in WS. Findings could be instrumental in working towards instigating appropriate, timely sleep management in this group, thus improving outcomes for children and their families.

Dear Prof Heaton,

On behalf of all authors, I would like to submit the paper “Early manifestation of sleep problems in toddlers with Williams Syndrome using a mixed method longitudinal approach” for the special issue in memory of Annette Karmiloff-Smith.

Kind Regards,
Dagmara Dimitriou

***Highlights (for review)**

- Longitudinal and objective sleep patterns in young children with Williams Syndrome
- Sleep problems in Williams Syndrome emerge and manifest in early childhood
- Shorter sleep durations in Williams Syndrome; based on objective measures
- Different developmental sleep trajectory in toddlers with Williams Syndrome
- Limited sleep support provided for parents who consider sleep problematic

1 Introduction

In typical development (TD), sleep disturbances are relatively common in the infant and toddler years, with prevalence rates of approximately 30% (Bayer, Hiscock, Hampton, & Wake, 2007; Galland, Taylor, Elder, & Herbison, 2012; Mindell, Owens, & Carskadon, 1999). Longitudinal studies with pre-school children show that sleep difficulties decline with age (Gaylor, Burnham, Goodlin-Jones, & Anders, 2005). It is estimated that around 20% of school-aged children experience sleep problems (Mindell et al., 1999; A Sadeh, Raviv, & Gruber, 2000). In contrast, sleep problems are reported to occur with a substantially higher frequency in school-aged children with neurodevelopmental disorders, with prevalence rates of up to 80% (Bartlett, Rooney, & Spedding, 1985; Esbensen & Schwichtenberg, 2016). There is wide-ranging variability of sleep problem prevalence rates, due to methodological differences; this makes direct comparison between sleep in typical and atypical development difficult. Nevertheless, results from a recent meta-analysis exploring differences in sleep quality and duration between people with and without intellectual disability (ID) confirmed that, in most cases, sleep duration was shorter and of poorer quality in people with intellectual disabilities (Surtees, Oliver, Jones, Evans, & Richards, 2018). Specific difficulties children with ID experience include long sleep latencies, frequent night waking and short sleep durations (Tietze et al., 2012).

Few studies have explored the emergence of sleep problems in ID so little is known about the developmental trajectory of difficulties and the manifestation of problems in early childhood. This should be addressed given the crucial role sleep plays in healthy development and the range of negative outcomes associated with sleep disturbances, including impaired cognitive functioning, behavioural difficulties and emotional dysregulation, in addition to having negative consequences on wider family life (Bayer et al., 2007; A. Sadeh, Gruber, & Raviv, 2002).

1.1 Williams Syndrome

WS is a rare genetic disorder, caused by a hemizygous deletion of around 28 genes on chromosome 7q11.23 (Ewart et al., 1993). Prevalence rates in the UK are approximately 1 in 18,000 live births. The resulting cognitive profile is complex and uneven, with a distinct pattern of strengths and weaknesses; specific strengths

include aspects of language, social interaction and good facial recognition skills, in conjunction with clear difficulties with visuospatial skills and, in most incidences, mild to moderate ID (Martens, Wilson, & Reutens, 2008; Pober, 2010).

Consistent with other neurodevelopmental disorders, studies exploring sleep in individuals with WS indicate that sleep difficulties are highly prevalent. Annaz, Hill, Ashworth, Holley, and Karmiloff-Smith (2011) found that, based on parent-report, 97% of school-aged children experienced sleep problems; these included more night waking, bedtime resistance, restless sleep and insufficient sleep compared with children with TD. Subsequent studies report similar findings, supporting the notion that children with WS experience disturbed sleep. Based on actigraphy and parent-report, Ashworth and colleagues found that children with WS experienced long sleep latencies, short sleep durations and frequent night waking (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013). Polysomnography studies show that children with WS spend more time awake after sleep onset than children with TD (Arens et al., 1998); in addition, individuals with WS experience reduced sleep efficiency and increased slow wave sleep and sleep disruption (Gombos, Bodizs, & Kovacs, 2011; Mason et al., 2011). It has been proposed that sleep disruptions, such as delayed sleep onset and disturbed sleep cycles, may be related to abnormal levels of sleep-related hormones, melatonin and cortisol, which help regulate sleep-wake cycles (Santoro, Giacheti, Rossi, Campos, & Pinato, 2016; Sniecinska-Cooper et al., 2015).

Considering the growing evidence supporting a characteristic link between WS and sleep difficulties there is a notable lack of studies investigating sleep in WS in early childhood. This limits the ability for early and targeted sleep intervention to take place in this group. Just two studies have addressed the infant and toddler years. Axelsson, Hill, Sadeh, and Dimitriou (2013) conducted the first study examining sleep in toddlers with WS (*M*=31.67 months). Consistent with older children, they found that, based on parent-report, toddlers with WS had shorter night sleep duration, an increased number and duration of night wakings, took longer to settle, and had later bed times than chronological age-matched children with TD. More recently, and also via parent survey, Abel and Tonnsen (2017) similarly reported shorter night sleep duration in toddlers with WS (*M*=20 months); however, in contrast with the Axelsson et al. (2013) study, night waking frequency did not differ between

toddlers with WS and TD, which could be associated with the younger age group. The limited available evidence suggests that sleep problems in WS may emerge early in childhood; however, results should be treated with caution as parent-report is not always considered reliable.

To date, no studies have objectively assessed sleep in toddlers with WS and no longitudinal studies incorporate these early years. This leaves questions concerning the developmental trajectories of sleep problems in WS and the ability to distinguish between sleep disturbances that are characteristic of the normal sleep maturation process, and genuine sleep problems present in early childhood. Thus, the current study sought to address this knowledge gap by objectively assessing sleep in infants and toddlers with WS, longitudinally from ages 18 to 30 months. The main aim being to determine how early childhood sleep patterns in WS compare with those of TD, identifying how any sleep disturbances change and manifest over time, this will include measures of sleep duration, latency, night waking and parent-reported problematic sleep.

2 Methods

2.1 Participants

Parents of infants and toddlers with WS were contacted, via the Williams Syndrome Foundation, UK database. Of the 17 invited parents, 13 (6 female, 7 male) contributed the final sample (representing 72% of the appropriately aged children registered). Reason for non-participation included: two families being too busy with appointments/surgeries and two families who were unobtainable after repeated contact attempts. A control group of 35 children with TD were approached through word of mouth, of whom 25 (12 female, 13 male) comprised the final sample. Thus, the overall inclusion rate was approximately 70% for both groups. Prior to recruitment, ethical approval was granted by the XX (removed for blind review) Research Ethics Committee, and information was treated in accordance with the General Data Protection Regulation (2016) and the Data Protection Act (2018).

2.2 Procedure

Sleep data were collected longitudinally, at 6 month intervals. Data mostly reflected three time points over the course of one year and encompassed ages 18, 24 and 30 months. In the TD group, age of initial data collection point was 18 months old (*n*=25). Due to the rarity of WS, cross-sectional data and overall sample size were optimised by recruiting participants at any of the targeted age points. Thus, age of initial data collection point ranged and was, 18 months (*n*=8), 24 months (*n*=3) or 30 months old (*n*=2). Data were examined and included where data represented a minimum of five typical days of sleep, unaffected by motion, illness or any other external factor, as recommended by Acebo et al. (1999). Where actigraphy did not reach the minimum five day requirement (see Table 1), this was as a result of participants refusing to wear the watch (14%), illness (36%), technical problems (36%), or parent-report that days were very unusual (14%). Due to the longitudinal nature of the data, differing age of initial data point, and difficulties of research with this age group, data were not always useable. Table 1

Number of days of actigraphy data

	18 months	**24 months**	**30 months**
n	30	30	24
Mean number of days collected (range)	5.83 (0-8)	6.43 (1-9)	6.63 (4-8)
Number of participants with 5+ days data	25	27	23
% of sample	83	90	96
Number of participants with 0-4 days data	5	3	1
% of sample	17	10	4

Table 2 shows final inclusion rates and whether data were useable.

Table 1

Number of days of actigraphy data

	18 months	**24 months**	**30 months**
n	30	30	24
Mean number of days collected (range)	5.83 (0-8)	6.43 (1-9)	6.63 (4-8)
Number of participants with 5+ days data	25	27	23

% of sample	83	90	96
Number of participants with 0-4 days data	5	3	1
% of sample	17	10	4

Table 2

Inclusion rates for each participant at each age

	Williams Syndrome			**Typical Development**		
	18 months	**24 months**	**30 months**	**18 months**	**24 months**	**30 months**
1	X	X	X	X	X	X
2	X	-	-	X	X	-
3	/	X	X	/	-	-
4	X	X	X	X	X	X
5	X	X	X	X	X	X
6	-	X	-	/	X	X
7	X	X	X	X	X	X
8	X	X	X	/	/	X
9	-	-	X	X	X	X
10	-	X	X	/	X	X
11	-	X	-	/	X	-
12	-	-	X	X	X	X
13	-	X	X	/	X	-
14				/	X	X
15				X	X	X
16				X	X	X
17				X	X	-
18				X	X	X
19				X	/	-
20				X	X	-
21				X	X	-
22				X	-	-
23				X	X	-
24				X	X	-
25				X	-	-
26						

X = 5+ nights of useable actigraph data; / = 0-4 nights of actigraph data; - = no data collected

2.2.1 Measures

Sleep was assessed at each data collection point using actigraphy, parent-reported sleep diary and sleep-related questionnaires.

Actigraphy

Parents were provided with a MotionWatch8 (CamNTech Ltd) actigraphy device, with instructions to attach it to their child's wrist or ankle and for it to be worn continuously for a one week period, as recommended by (Acebo et al., 1999). The actigraphy variables of interest are: time of sleep onset, wake time, assumed sleep

time (time from sleep onset to offset), actual sleep time (assumed sleep minus any periods of wake), night wakings (number and duration), actual sleep percentage (actual sleep time expressed as a percentage of the assumed sleep time), and fragmentation index (an indication of sleep quality). In addition, parents completed a sleep diary recording their child's lights out time, time of sleep onset, getting up time, and any daytime naps or night waking for the duration of the study; they were also asked to report whether each day represented a typical day for their child. These diary parameters were used to support analyses of actigraphy data.

Questionnaires

1. *Medical and Demographics Questionnaire (MDQ)*, developed in the Lifespan Learning and Sleep Laboratory (LiLAS lab), xx (removed for blind review) Institute of Education. Based on parent-report, this is a screening tool to identify possible factors influencing sleep, including information regarding medication use, hospital visits and surgeries, and parent level of education.
2. *Brief Infant Screening Questionnaire (BISQ)*, a 13 item parent-report survey developed to screen for sleep disorders in children aged from 0-3 years old, providing information such as sleep duration, sleep location and night wakings (Sadeh, 2004).

3 Results

Data were analysed using IBM Statistical Package for Social Sciences (SPSS) Version 25. The absence of outliers was assured using Cook's distance; extreme outliers were removed for individual variables where Cook's distance was greater than 1 and the significance of results was impacted. Levene's test was used to assess the assumption of homogeneity of variance. First, appropriate to the small sample size and data not being normally distributed, Spearman's rho correlations were used to measure the association between subjective (parent-report) and objective (actigraphy) sleep measures. Second, group differences were examined using Mann-Whitney U; categorical variables were assessed using chi-square. Third, one-way repeated measures analysis of variance (ANOVA) was used to measure changes in sleep over time.

Group characteristics

Demographic data were collected for all participants, as shown in Table 3. Independent sample t-tests showed no group differences for age at any data collection point. Chi-square analysis was used to assess group differences on the categorical variables gender, ethnicity, parent education and birth order. The groups did not differ on gender $x^2(1) = .000$, $p = 1.00$, ethnicity $x^2 (2) = .75$, $p = .687$, nor birth order $x^2 (1) = 3.39$, $p = .066$. Group differences were observed for parent education level with the TD group associated with at least one parent finishing higher education, compared to neither parent finishing higher education in the WS group $x^2 (1) = 7.98$, $p = .005$. The Index of Multiple Deprivation Decile (IMD) was used as a measure of socioeconomic status based on participants' home postcode; an independent sample t-test showed no differences between the groups ($t(28) = .920$, $p = .365$).

Table 3

Group characteristics

	WS (*n*=13)	**TD (*n*=25)**
Mean age (SD) (months)	25.18 (4.95)	23.58 (4.85)
Age range (months)	17.65-31.56	17.03-32.25
Gender (M/F%)	53.8/46.2	52/48
Birth order (first born/younger sibling%)	38.5/61.5	69.2/30.8
Ethnicity (% white)	92.3	92.3
Ethnicity (% mixed)	7.7	3.8
Ethnicity (% other)	0	3.8
Parent with higher education (%)	**61.5***	**96.2***
Index of Multiple Deprivation Decile (*M*)	6.9	7.7

*$p<.05$

Medical data were also collected for each participant, as shown in Table 4.

Table 4

Group medical history

	Number of children with reported problem (% of total sample)	
	WS	**TD**
Allergies	-	3 (12)

Asthma	-	1 (4)
Cardiac problems	12 (92)	-
Ear infections	1 (8)	-
Gastrointestinal problems	5 (38)	2 (8)
Global developmental delay	4 (31)	-
Had operations	10 (77)	3 (12)
Hernia	5 (38)	-
Hypercalcemia	3 (23)	-
Kidney problem	1 (8)	-
Lung infections	3 (23)	-
Other significant health problems	2 (15)	-

Comparison of actigraphy and parent-reported sleep patterns

Spearman's Rho was used to investigate the similarity between parent-report and actigraphy. This was conducted at all ages for individual groups for time of sleep onset, sleep latency and assumed sleep durations across 24 hours and overnight (Table 5). Results indicated that, in most cases, there was agreement between parent-report and actigraphy; notably, there was significant strong positive associations observed for time of sleep onset in both groups, at all ages.

Table 5

Correlation between parent-report and actigraphy

	18 months		**24 months**		**30 months**	
	WS	**TD**	**WS**	**TD**	**WS**	**TD**
n	**8**	**18**	**10**	**19**	**11**	**13**
Time of sleep onset	**1.0*****	**.89*****	**95*****	**.94*****	**.98*****	**.75****
Latency	.70	.11	**.86***	**.72****	**.86****	**.72****
Assumed 24 hr sleep	.80	**.81****	**.70***	**.79***	**.85****	**.75****
Assumed nighttime sleep	.70	**.92****	**.88****	**.75****	.54	**.78****

*p<.05, **p<.01, ***p<.001

Actigraphy measured sleep variables

Actigraphy measured sleep variables for all age groups, in WS and TD, are reported in Table 6.

Sleep onset and latency.

Group differences in time of sleep onset were only present at 24 months; children with WS fell asleep significantly later than children with TD (U = 52.00, p =.035). Sleep latency was measured using parent-reported lights out time and actigraphy measured sleep onset time. Sample size varied from overall actigraphy sample size due to incomplete sleep diaries resulting in the five night minimum requirement not being met; sample size is as follows: 18 months (WS=5, TD=18), 24 months (WS=7, TD=18), 30 months (WS=10, TD=12). No between group differences were observed at any age.

Sleep duration.

Children with WS had significantly shorter assumed sleep durations across 24 hours than children with TD at ages 18 months (U = 32.50, p =.029), 24 months (U = 9.00, p=.002) and 30 months (U = 28.50, p =.036). Actual 24 hour sleep duration was also significantly shorter in WS at ages 24 months (U = 21.50, p =.029) and 30 months (U = 18.00, p =.005). Group differences in overnight sleep duration were only observed at 24 months (U = 30.00, p =.006), with the TD group sleeping for almost an hour longer than the WS group (M=57 minutes).

Daytime sleep.

Daytime sleep duration was significantly shorter in WS at age 30 months (U = 24.00, p =.005), this is to be expected as children with WS had significantly fewer naps than children with TD at 30 months (U = 25.50, p =.007), see Table 7.

Sleep quality.

Sleep quality was mostly comparable between groups; no group differences were observed for actual sleep percentage at any age. Children with TD were found

to experience more night wakefulness at both 18 months (U = 20.00, p =.009) and 24 months (U = 43.00, p =.035) than children with WS.

Table 6

Actigraphy measured sleep patterns (M (SD)) and Mann-Whitney U test results showing group differences at each age

	18 months		**24 months**		**30 months**	
	WS	**TD**	**WS**	**TD**	**WS**	**TD**
	(n=8)	**(n=20)**	**(n=10)**	**(n=18)**	**(n=11)**	**(n=13)**
Age, months	18.47 (0.58)	18.45 (0.83)	24.64 (0.41)	24.62 (0.85)	30.56 (0.56)	30.67 (1.02)
Time of sleep onset (hh:mm)	20:29 (1:07)	19:51 (0:40)	**21:05*** (1:42)	**19:54*** (0:35)	20:07 (0:48)	20:08 (0:47)
Sleep latency (hh:mm)	0:28 (0:18)	0:24 (0:10)	0:39 (0:30)	0:36 (0:15)	0:22 (0:11)	0:37 (0:24)
Assumed 24hr sleep (hh:mm)	**11:22*** (1:04)	**12:24*** (0:45)	**11:05*** (0:21)	**11:59*** (0:37)	**10:51*** (0:43)	**11:32*** (0:32)
Assumed daytime sleep (hh:mm)	01:28 (0:28)	01:31 (0:23)	01:28 (0:39)	01:23 (0:26)	**0:19*** (0:26)	**01:04*** (0:36)
Assumed nightime sleep (hh:mm)	10:23 (0:41)	10:50 (0:38)	**09:48*** (0:54)	**10:45*** (0:27)	10:32 (0:47)	10:27 (0:41)
Actual 24 hr sleep (hh:mm)	09:04 (1:07)	09:34 (1:10)	**08:47*** (0:44)	**09:43*** (0:49)	**08:49*** (0:35)	**09:35*** (0:33)
Actual sleep %	79.48 (5.74)	76.39 (8.86)	79.48 (5.53)	78.73 (5.79)	81.13 (4.94)	82.30 (4.86)
Night waking	**38.45*** (4.25)	**45.62*** (5.85)	**36.79*** (4.04)	**42.77*** (7.74)	39.34 (5.82)	38.48 (7.24)
Night waking duration (mm:ss)	03:13 (00:38)	03:19 (01:05)	03:15 (00:47)	03:14 (00:48)	03:02 (00:34)	02:55 (00:45)
Fragmentation	46.04 (8.83)	50.00 (11.55)	46.82 (6.41)	45.68 (8.34)	42.94 (6.75)	38.53 (6.23)

*p<.05, **p<.01

N.b. Sample size for daytime sleep is shown in Table 7

Table 7

Number of daytime naps (M (SD)) and Mann Whitney U test results showing group differences at each age

	18 months	**24 months**	**30 months**

	WS	TD	WS	TD	WS	TD
	(n=7)	**(n=21)**	**(n=10)**	**(n=19)**	**(n=11)**	**(n=13)**
Number of daytime naps	0.90 (0.42)	1.03 (0.13)	0.72 (0.42)	0.87 (0.28)	**0.24*** (0.33)	**0.67*** (0.34)

**p*<.05

Night waking.

In direct contrast with actigraphy data, parent-report found children with WS to have significantly higher numbers of night waking than children with TD at ages 18 months (U = 40.00, p =.004), 24 months (U = 18.00, p<.001) and 30 months (U = 19.00, p =.002) as shown in *Figure 1: Average number of parent-reported night wakingFigure 1*. In addition, parents of children with WS also reported longer durations spent awake between the hours of 22:00 and 06:00 at all ages; 18 months (U = 30.00, p =.003), 24 months (U = 39.50, p.005) and 30 months (U = 19.00, p =.013), as shown in Table 8.

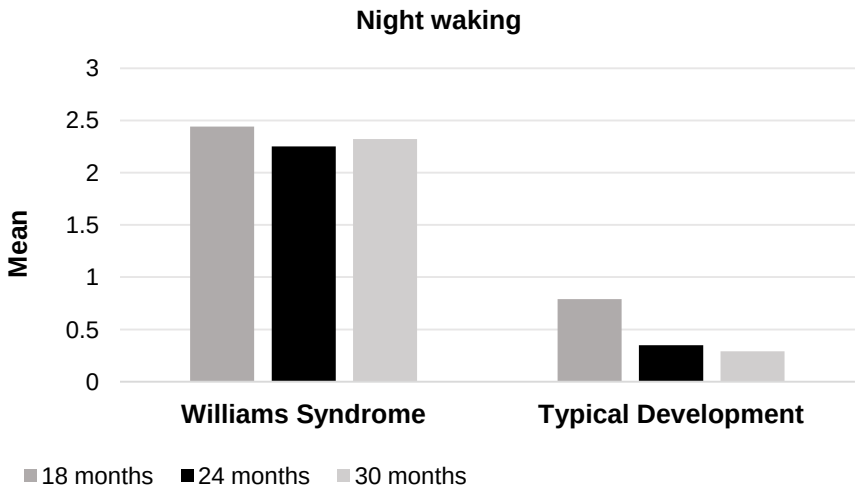

Figure 1: Average number of parent-reported night waking

Parent-reported sleep problems, based on BISQ

Parents were asked to record if they considered their child's sleep to be problematic and whether, if problems occurred, they were regarded small or serious. As expected in the toddler years, sleep problems, at any level, were reported in high frequency and were present in around 40% of the entire sample (18 months: 40.6%, 24 months: 28.1%, 30 months: 41.7%). Despite problems being more frequently

reported by parents of children with WS (Table 8), a significant association was only found between parent-reported sleep problem and group at 30 months old, with sleep problems more frequently reported in WS (x^2 (1) = 4.03, *p* =.045); there was a trend towards significance at 24 months (x^2 (1) = 3.44, *p* =.054). In addition, where children with TD were reported to have problems, with the exception of one case (5%), these were considered small; in children with WS, sleep problems were also primarily considered to be small but in five cases (29%) these were considered serious problems.

Parental input.

Parental input encompassed children requiring assistance to fall asleep, co-sleeping, or moving to a parent's bed during the night. Significant associations were found between levels of parental involvement and group; WS was significantly associated with high levels of parental input at 18 months (x^2 (1 *n* = 32) = 6.00, *p* =.014), 24 months (x^2 (1, *n* = 32) = 12.64, *p* .001) and trending towards significance at 30 months (x^2 (1, *n* = 23) = 3.63, *p* =.057). Parents of children with WS also reported that it took longer for them to put their child to sleep than parents of children with TD at ages 18 months (*U* = 17.50, *p* =.002) and 24 months (*U* = 35.00, *p* =.016), see Table 8. High levels of parental input were also significantly associated with the presence of a parent-reported sleep problem across the entire sample, at ages 18 months (x^2 (1, *n* = 32) = 6.35, *p* .012), 24 months (x^2 (1, *n* = 32) = 10.37, *p* .001) and 30 months (x^2 (1, *n* = 23) = 9.67, *p* .002).

Table 8

Parent-reported sleep difficulties and Mann Whitney U test results showing group differences at each age

	18 months		**24 months**		**30 months**	
	WS	**TD**	**WS**	**TD**	**WS**	**TD**
	(n=8)	**(n=24)**	**(n=10)**	**(n=21)**	**(n=11)**	**(n=13)**
Parent-reported sleep problem (%)	5 (62.5)	8 (33.3)	5 (50.0)	4 (18.2)	7 (63.6)	3 (23.1)
Number of parent-reported night wakings (*M*(SD))	**2.44*** (2.23)	**0.79*** (1.05)	**2.25**** (1.65)	**0.35**** (0.52)	**2.32*** (2.38)	**0.29*** (0.69)
How long to put child to sleep	**0:49***	**0:17***	**1:16***	**0:23***	0:25	0:27

(hh:mm)	(0:21)	(0:13)	(1:15)	(0:31)	(0:11)	(0:25)
How much time spent awake between 22:00-06:00 (hh:mm)	**0:33*** (0:24)	**0:09*** (0:15)	**0:42*** (0:43)	**0:09*** (0:21)	**0:28*** (0:29)	**0:03*** (0:08)

*p<.05, **p<.01

Parent-reported sleep support

Professional assistance.

Despite high frequencies of parent-reported sleep problems only seven families had received any professional assistance with their child's sleep (TD 3, WS 4) and there was no group difference present. Chi-square analysis revealed no association between receiving professional assistance and parent-perceived sleep problems.

Medication.

At 30 months old two children with WS were using melatonin to assist sleep. In both cases parents reported their child to have a sleep problem, one a serious problem and one a small problem. Significant results did not change with the removal of these participants, thus they were included in all data analyses. No children with TD were reported to take medication to help with sleep.

Developmental trajectories of sleep

Sleep duration.

Repeated measures ANOVA demonstrated that total sleep duration across 24 hours reduced in children with TD between ages 18 and 24 months $F(1,14) = 5.15$, $p = .040$, 24 and 30 months $F(1, 11) = 11.09$, $p = .007$, and, therefore, between 18 and 30 months $F(2,16) = 10.25$, $p = .001$. No changes were found in the WS group. There were no changes in overnight sleep durations in either group, thus the reduction in sleep durations over 24 hours in the TD group was driven by a reduction in daytime sleep duration. Results indicated that significant reductions in daytime sleep occurred between 24 and 30 months in both TD $F(1,8) = 5.42$, $p = .048$ and in WS $F(1,6) = 41.40$, $p = .001$.

Sleep quality.

Improvements in sleep quality were found in the TD group between ages 18 to 30 months (Figure 2), with a reduction in both sleep fragmentation and actigraphy measured night waking ($F(2,12) = 7.54$, $p = .008$, $F(2,12) = 4.16$, $p = .042$, respectively) and an increase in actual sleep percentage ($F(2,12) = 4.68$, $p = .031$). There were no observed differences in the WS group.

There were no changes in number of parent-reported night wakings in either group.

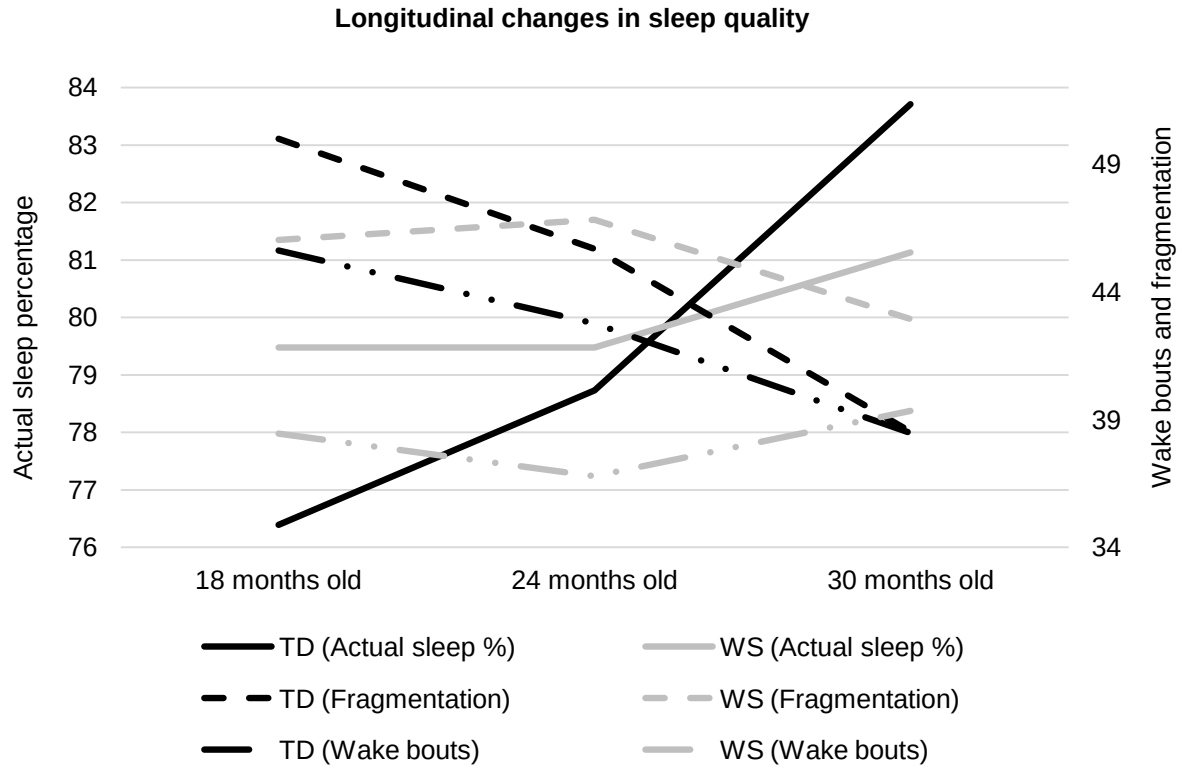

Figure 2: Developmental changes in sleep quality, based on group means.

Individual changes in sleep patterns.

In addition to longitudinal sleep changes according to group, sleep was also assessed individually. TD WS

Figure 3 shows the changes in sleep fragmentation for individual participants, separated by group. **Error! Reference source not found.** demonstrates changes in 24 hour sleep durations.

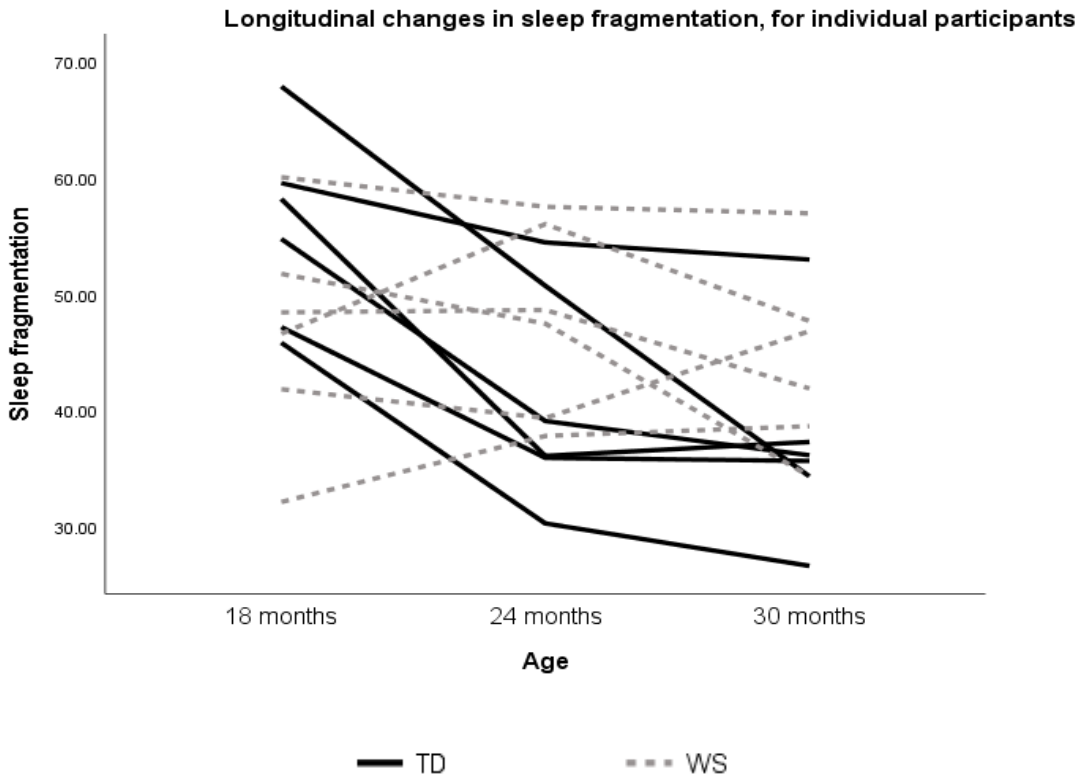

Figure 3: Individual developmental changes in sleep fragmentation level.

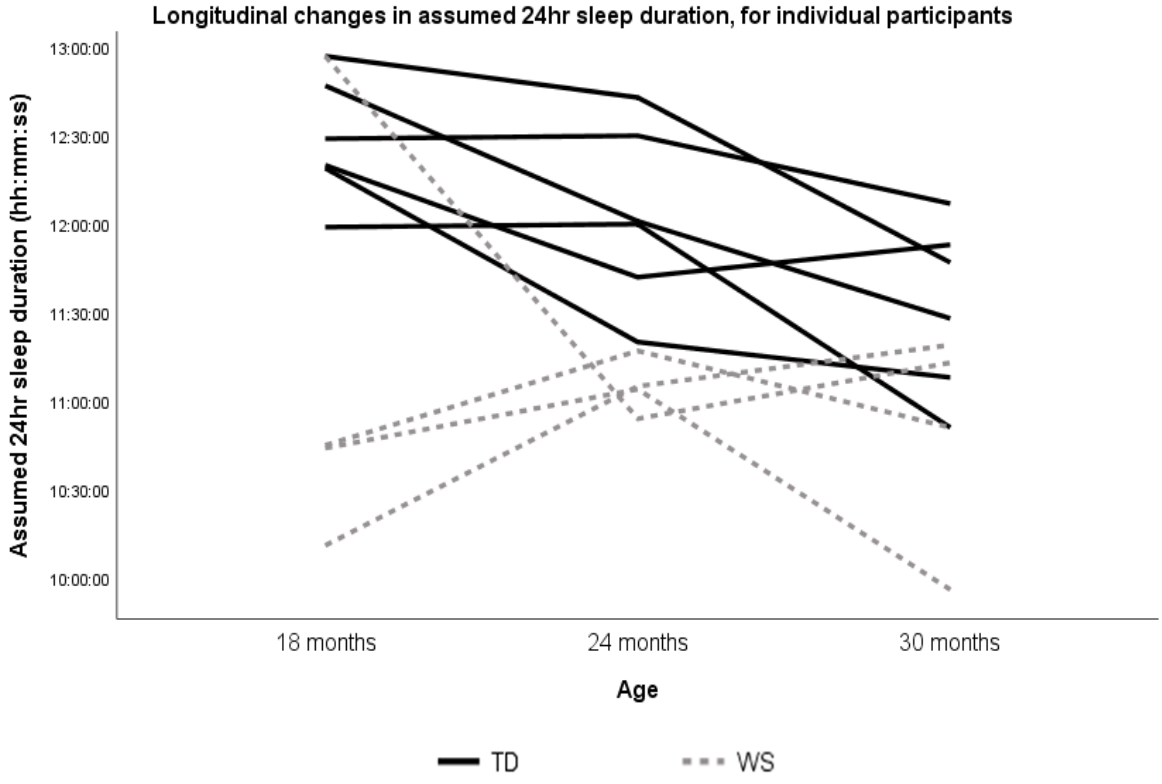

Figure 4: Individual developmental changes in assumed sleep duration across 24 hours.

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4 Discussion

This is the first study to both objectively and longitudinally explore sleep in toddlers with WS. From a sample of close to three quarters of infants and toddlers registered on the WS Foundation UK database, findings indicate that children with WS experience significant sleep disturbances as early as 18 months old. Actigraphy measurement provides evidence that, from 18 months old, children with WS experience significantly shorter sleep durations than children with TD; consistent with parent-report studies in this age-group conducted by Axelsson et al. (2013) and Abel and Tonnsen (2017).

Parents of children with WS also reported more disrupted sleep, with more night waking, longer durations of night wakefulness, longer settling times, and a higher frequency of parents' considering their child's sleep to be problematic; this supports previous findings in this age group (Axelsson et al., 2013) but was not reflected in actigraphy data. Significant group differences in actigraphy measured night waking were present at 18 months old and 24 months old but it was the children with TD, not WS, who experienced more night waking. No other group differences were observed in sleep quality at these ages, thus longer total sleep duration in TD (M=1.02, M=0.54, respectively) could be a factor; young children typically experience short intervals of wakefulness at the end of a sleep cycle, with familiar surroundings and an ability to self-soothe resulting in a return to sleep (Davis, Parker, & Montgomery, 2004).

Findings from both parent-report and objective sleep studies indicate that in older children with WS sleep quality is poorer than in TD (Martens, Seyfer, Andridge, & Coury, 2017; Mason et al., 2011; Sniecinska-Cooper et al., 2015); difficulties include delayed sleep onset, restless sleep and frequent night waking. In the present study, parent-report also indicates that sleep quality is poorer in toddlers with WS than in TD, but there was notable disparity between objective and subjective measures; however, such differences have previously been documented in studies of WS. Ashworth et al. (2013) found no significant relationships between parent-report and actigraphy for number and duration of night wakings or sleep fragmentation in children from ages six to 12 years old, despite agreement on measures of sleep duration and sleep latency. This is consistent with the current findings, which also

showed agreement between measures of parent-report and actigraphy for sleep duration at all ages and sleep latency at ages 24 and 30 months.

Despite previous validity studies reporting adequate estimates of sleep by actigraphy (Martin & Hakim, 2011; A. Sadeh, 2011, 2015) the ability of actigraphy to detect periods of wakefulness in children with neurodevelopmental disorders has been questioned. Paquet, Kawinska, and Carrier (2007) compared actigraphy with PSG concluding that, in clinical populations with fragmented sleep, the use of actigraphy is limited. A notion supported by Sitnick, Goodlin-Jones, and Anders (2008), who caution that, in a study of preschool-aged children with typical and atypical development, actigraphy does not depict night wakings well, compared with videosomnography. This may go some way towards explaining the discrepancy between parent-reported night wakings and actigraphy data in the current study. An additional factor is that WS is significantly associated with co-sleeping; parents may be more aware of night wakings and disturbances if they are sharing a bed with their child. Furthermore, movement levels may not be enough to constitute an actigraphy recorded night waking if parents are able to soothe their child back to sleep, with a cuddle or patting their back.

Findings from the current study revealed that the level of parental involvement in children's sleep, including co-sleeping, is associated with whether parents viewed their child's sleep to be problematic, with high levels of involvement indicative of a problem. It is worth noting that there is a distinct lack of definitive and age-appropriate criteria for defining sleep problems, thus individual differences between parent-perception of sleep problems will be present. Goodlin-Jones et al. (2009) note that the potential of heightened stress levels in parents of children with a neurodevelopmental disorder may impact their experience of their child going to bed, falling asleep, and waking during the night. This is certainly conceivable in the current study in view of the high levels of medical difficulties present in the children with WS (Table 4). Nevertheless, a high frequency of all parents viewed their child's sleep to be problematic; it was only from 24 months old that there was an association between WS and parent-reported sleep problems, which could reflect differences in developmental sleep trajectories between the groups.

Cross-sectional actigraphy results suggest that sleep quality is comparable between WS and TD in the toddler years but, when taking a developmental approach, the evidence shows that sleep problems characteristic in older individuals with WS may begin to emerge as early as 18 months old. In the current study, not only are sleep durations typically shorter in WS in these early years but, unlike in TD, sleep quality does not improve with age. Whereas sleep difficulties may be expected to decline with age in children with TD, supported by reductions in sleep fragmentation and night waking and an increase in actual sleep percentage between ages 18 to 30 months in the current findings, this was not the case for children with WS. Thus, the apparent difference in the developmental sleep trajectory may reflect sleep problems in WS manifesting in early childhood.

A noticeable discrepancy from studies with older children with WS, is that sleep latency in the toddler years does not differ from that in TD, this is supported by results from the current sample and findings from Abel and Tonnsen (2017). However, this difference may be due to methodological approach; in the current study parents of children with WS reported long settling times, in the region of three times as long in children of 18 and 24 months, which was consistent with the Axelsson et al. (2013) study.

This study is the first to provide evidence of sleep problems in toddlers with WS using objective measures. Limitations include the small sample size, partly reflective of the rarity of WS but further diminished by the longitudinal study design and the challenges of testing young children. Data were used to explore both longitudinal and cross-sectional sleep patterns, introducing bias by representing data from the same population at different time-points; ideally separate samples would represent cross-sectional and longitudinal data but the low-incidence rate of WS makes this challenging.

Despite the above-mentioned limitations this study provides novel information regarding how and when sleep problems may begin to emerge in WS. Overall, the findings indicate that sleep in toddlers with WS is different to TD. Difficulties are present as early as 18 months old, with shorter total sleep durations, more parent-reported sleep disruption and a differing developmental sleep trajectory than in TD. Specific knowledge of sleep in this age group will be fundamental for the introduction

of targeted sleep support which will contribute to optimising long-term outcomes for children with WS and their families. Additional work is needed to replicate findings in bigger samples and explore how sleep problems may affect early cognitive and behavioural development, which could be achieved applying a cross-country approach.

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