

Time in bed, sleep quality and associations with cardiometabolic markers in children: the Prevention and Incidence of Asthma and Mite Allergy birth cohort study

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SUMMARY

We investigated associations of time in bed and multiple sleep quality characteristics with cardiometabolic markers in children. Data from the prevention and incidence of asthma and mite allergy study, a population-based prospective birth-cohort study started in 1996–1997 in the Netherlands, were analysed. In total 1481 children aged 11–12 years completed a questionnaire (including questions on sleep) and underwent a medical examination. We measured body mass index, waist circumference, total- and high-density lipoprotein cholesterol, blood pressure and glycated haemoglobin. Results showed that in girls, some sleep characteristics were related to anthropometrics (body mass index, waist circumference) and cholesterol. Girls who had a long time in bed (11–12.5 h) had 0.16 lower body mass index z-score (95% confidence interval –0.31; –0.01) and 0.99 cm smaller waist circumference (95% confidence interval –2.01; –0.13) compared with girls who spent 10–10.5 h in bed. Girls who went to bed late and rose early had 0.16 mm higher total cholesterol (95% confidence interval 0.01; 0.31) and 0.08 mm higher high-density lipoprotein cholesterol (95% confidence interval 0.01; 0.14) than 'early to bed/early rise' girls. Girls with night-time awakenings had 0.14 mm higher total cholesterol (95% confidence interval 0.03; 0.25) than girls without night-time awakenings. Girls who felt sleepy/tired ≥ 1 day per week had 0.10 mm lower high-density lipoprotein cholesterol (95% confidence interval –0.16; –0.04) and 0.17 mm higher total cholesterol/high-density lipoprotein cholesterol ratio (95% confidence interval 0.02; 0.32) than girls who did not feel sleepy. No associations were found for boys. Sleep characteristics were not related to blood pressure and glycated haemoglobin, and effect sizes of the associations in girls were small. Therefore, we consider it premature to propose that improved sleep could reduce cardiovascular risk during childhood.

INTRODUCTION

Studies in adults have shown that inadequate sleep is associated with metabolic syndrome and diabetes (Van Cauter *et al.*, 2008) and with cardiometabolic risk factors,

including weight status (Cappuccio *et al.*, 2010), cholesterol, blood pressure (BP; Bjorvatn *et al.*, 2007) and glucose metabolism (Spiegel *et al.*, 2005).

Because cardiometabolic risk factors track from adolescence into adulthood (Camhi and Katzmarzyk, 2010), it is

important to investigate whether sleep behaviour is also related to cardiometabolic markers in children. In the paediatric population, associations have been described between inadequate sleep and being overweight (Cappuccio *et al.*, 2008), waist circumference (WC; Chaput *et al.*, 2006), insulin resistance (Koren *et al.*, 2011) and systolic BP (Javaheri *et al.*, 2008). However, other studies did not demonstrate associations between sleep and cardiometabolic markers (Archbold *et al.*, 2012; Bayer *et al.*, 2009; Martikainen *et al.*, 2011). Previous studies in children mainly looked at sleep duration. Recently, it was suggested that sleep quality, in addition to sleep duration, might also be important for cardiovascular disease risk in adults (Hoevenaer-Blom *et al.*, 2011). In children, studies on sleep parameters other than duration (sleep efficiency, sleep regularity, duration of slow-wave sleep) are scarce, used different sleep methodologies (actigraph or laboratory polysomnography) and reported conflicting results (Javaheri *et al.*, 2008; Koren *et al.*, 2011; Martikainen *et al.*, 2011).

A sex difference in regular sleep has been acknowledged, with male adolescents sleeping less than females on both schooldays and non-schooldays (Knutson, 2005). The aetiological basis for less sleep in male adolescents is not fully understood and, despite a growing recognition, little systematic research has been done regarding these sex differences in childhood.

We aimed to investigate whether sleep duration and sleep quality influence cardiometabolic markers. For this aim we studied multiple cardiometabolic markers separately in boys and girls at about the age of 12 years from the general population. To assess sleep, we examined time in bed (as an indicator of sleep duration), sleep–wake pattern and characteristics of sleep quality (night-time awakenings, difficulty with getting up in the morning, feeling rested after waking up, and feeling sleepy/tired during the day).

MATERIALS AND METHODS

We used the data from a population-based Dutch birth cohort study: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study. A detailed description of the study design has been published previously (Wijga *et al.*, 2013). In short, pregnant women were recruited from the general population during their first antenatal visit in 1996–1997; the number of children at baseline was 3963. Yearly, around the child's birthday, data were collected by parental questionnaires up to the age of 8 years, and again at the age of 11 years by separate parental and child questionnaires. Additionally, in subgroups of children, extensive medical examinations were performed at the ages of 4, 8 and 12 years. The study protocol was approved by the medical ethics committees of the participating institutes, and all parents gave written informed consent. In total 2651 children completed the child questionnaire at 11 years old (response rate higher than 70%), including for the first time questions on sleep. The parental questionnaire did not contain questions

on child's sleep. All children still in the study ($n = 3202$) were invited to the medical examination at the age of 12 years, and 1511 (47%) of them were willing to participate. Our study population consisted of 1481 children (759 girls and 722 boys) who completed the questionnaire at 11 years old and had data on any of the cardiometabolic markers.

Assessment of sleep characteristics

The questionnaire at 11 years old that was completed by the children contained 15 questions on different aspects of sleep, which we used to create indicators of time in bed, sleep–wake pattern and sleep quality (night-time awakenings and daytime outcomes). Questions were adopted from validated questionnaires that had been previously used; this is further described in the supplemental information.

Time in bed and sleep–wake pattern

Usual bedtimes and get-up times on schooldays were reported in nine- (from '<18:30 hours' to '22:30 hours') and eight- (from '<06:00 hours' to '>08:30 hours') answer options. From reported bedtimes and get-up times on schooldays, time in bed on schooldays was calculated. Time in bed was categorized because of previously reported non-linear associations. Because there is a lack of empirical evidence on optimal sleep time for children, we categorized time in bed based on our own data as short (7.5–9.5 h), medium (10–10.5 h, reference) and long (11–12.5 h). The majority of the children were in the reference category (60%).

Because timing of sleep has been considered important for cardiometabolic risk factors, independently of sleep duration (Olds *et al.*, 2011), we classified children into one of four sleep–wake patterns: early to bed/early rise (EE, reference); early to bed/late rise (EL); late to bed/early rise (LE); and late to bed/late rise (LL). Sleep–wake patterns were constructed using median-splits for early or late bedtimes and get-up times (median = 21:00 hours for bedtimes and median = 07:50 hours for get-up times). Medians were calculated for boys and girls combined because medians for bedtimes and get-up times did not differ between genders. After recoding, means of bedtimes and get-up times, respectively, for each sleep–wake pattern were: EE 20:35–07:29 hours; EL 20:42–07:53 hours; LE 21:14–07:32 hours; LL 21:15–07:54 hours.

Sleep quality: night-time awakenings and daytime outcomes

We used four indicators of sleep quality: one variable on night-time awakenings and three variables on daytime outcomes. A composite variable on night-time awakenings was created from two (three category) questions. The original questions asked for 'frequency of night-time awakenings' (almost never, sometimes, almost every night) and 'how long does it take before you fall asleep again' (immediately, a while, very long). The resulting composite variable on night-time awakenings

had two categories (yes/no). 'Yes' was 'Waking almost every night; or waking sometimes, in combination with falling asleep again after a while or after a very long time'. 'No' was 'Waking almost never; or waking sometimes, in combination with falling asleep again immediately'.

Three questions were used as daytime outcomes of sleep quality. 'Difficulty with getting up in the morning' and 'Feeling rested after waking on a schoolday' were each reported in two categories (yes, no). A third question informed on the frequency of feeling sleepy or tired during the day. This was reported in five categories (from 'never' to 'three times a week or more'), and subsequently grouped in two categories: never or sometimes (reference); and at least once a week.

Assessment of cardiometabolic markers

During home visits at the age of 12 years, anthropometry measurements and BP readings were obtained, and blood was drawn for measurement of cholesterol and glycated haemoglobin (HbA1c) by trained staff. Details on these measurements are provided as supplemental information.

Other characteristics

Information included in the child's questionnaire was age at the time of completing the questionnaire, puberty development scale (1–4), and two questions regarding computer time and TV time, which were used to create a composite variable for total screen time (minutes per week). The mother's educational level [low (primary school, lower vocational or lower secondary education), intermediate (vocational education or intermediate/higher secondary education) or high (vocational education and university)] was reported when the child was 1 year old.

Statistical analyses

We performed separate analyses for boys and girls, as we expected *a priori* that associations might differ between genders. Multiple linear regression was conducted to estimate associations between sleep variables and cardiometabolic markers. Potential confounders were identified by literature research and by examining associations between these factors and the exposure variables. The crude model included age of the child at medical examination and at completion of the questionnaire. The full model was additionally adjusted for height, mother's education, puberty development and screen time. Screen time was included as a measure of sedentary behaviour, and also because of its reported independent adverse effect on sleep (Owens *et al.*, 1999). Analyses of systolic and diastolic BP were additionally adjusted for cuff size used in BP measurements. Analyses of HbA1c were also adjusted for storage time of the blood samples. We additionally included body mass index (BMI) z-score and WC separately in the fully adjusted models to investigate to what extent associations between

sleep and cardiometabolic markers were mediated by these factors.

In an additional analysis, we investigated the association between time in bed and being overweight in order to be able to compare our results with those of previous studies, which often reported overweight (and not BMI). We conducted logistic regression, adjusting for the same set of variables as formerly mentioned. Overweight (including obesity) was defined based on international defined cut-off points (Cole *et al.*, 2000). Normal weight children (excluding those classified thin or extremely thin) served as the reference. For all statistical analyses SAS software version 9.3 (SAS Institute, Cary, NC, USA) was used.

RESULTS

Table 1 shows the general characteristics of the participants according to gender. The mean age at completion of the questionnaire was 11.4 ($\pm$ 0.3) years, while mean age at the moment of medical examination was 12.7 ($\pm$ 0.4) years. The majority of the mothers of the children completed intermediate or higher level of education (82%). This percentage was somewhat higher than in the total PIAMA study population (77%, n = 3807). There was a difference in pubertal development between the genders, with girls being more progressed [puberty development scale (pds) 1.8 ± 0.6] than boys (pds 1.3 ± 0.3). Children on average spent 109 ($\pm$ 68) min in front of a screen (tv or computer) daily, boys 26 (0–30) min more than girls. The prevalence of overweight (including obesity) was 12%. The total group of children who completed the questionnaire at 11 years old (n = 2651) was comparable to the group of children who, in addition to completing the questionnaire, also participated in the medical examination at 12 years old (n = 1511), with respect to mothers educational level, puberty development and prevalence of overweight. The smaller group spent less time (–20 minutes per week) in front of a screen compared with the larger group.

Sleep characteristics

The majority of children (60%) reported 10–10.5 h in bed at night; 33% longer and 7% shorter (Table 1). Of all children, 27% had night-time awakenings, 22% did not feel rested after waking on a schoolday, and 17% felt sleepy/tired during the day at least once a week. About half of the children reported difficulty with getting up in the morning (51%), girls more than boys (56% versus 45%).

Table 2 shows the prevalence of children who reported daytime outcomes ('difficult to get up in the morning'; 'not feeling rested after waking on a schoolday'; or 'sleepy/tired at least once a week'), for categories of time in bed, sleep–wake pattern and night-time awakenings. Night-time awakenings correlated with daytime outcomes, for girls as well for boys (P < 0.01 for all daytime outcomes). For example, 40% of the boys and 34% of the girls reporting night-time awakenings felt

Table 1 General information, sleep characteristics and cardiometabolic markers of the study population (*n* = 1481)

	<i>All children</i>	<i>Girls (n = 759; 51%)</i>	<i>Boys (n = 722; 49%)</i>
General information			
Age (years) at time of questionnaire completion*	11.4 (0.3)	11.4 (0.3)	11.4 (0.3)
Age (years) at medical examination†	12.7 (0.4)	12.7 (0.4)	12.7 (0.4)
Height† (cm)	160 (8)	161 (7)	160 (8)
Mother's education at baseline, <i>n</i> (%)			
Low	264 (18)	125 (17)	133 (18)
Intermediate	622 (41)	325 (43)	286 (40)
High	621 (41)	307 (41)	303 (42)
PDS*	1.5 (0.5)	1.8 (0.6)	1.3 (0.3)
Total screen time* (min·day ⁻¹)	109 (68)	96 (62)	122 (71)
Overweight or obese, <i>n</i> (%)†	180 (12)	87 (12)	93 (13)
Time in bed and sleep–wake pattern*			
Time in bed on schooldays, <i>n</i> (%)			
Short (7.5–9.5 h)	108 (7)	47 (6)	61 (9)
Medium (10–10.5 h)	887 (60)	455 (60)	432 (60)
Long (11–12.5 h)	482 (33)	257 (34)	225 (31)
Sleep–wake pattern on schooldays, <i>n</i> (%)			
Early to bed/Early rise (EE)	448 (30)	239 (31)	209 (29)
Early to bed/Late rise (EL)	385 (26)	205 (27)	180 (25)
Late to bed/Early rise (LE)	283 (19)	138 (18)	145 (20)
Late to bed/Late rise (LL)	361 (24)	177 (23)	184 (26)
Sleep quality*			
Night-time awakenings, <i>n</i> (%)			
No	1080 (73)	551 (73)	529 (74)
Yes	396 (27)	207 (27)	189 (26)
Daytime outcomes			
Getting up in the morning, <i>n</i> (%)			
Not difficult to get up	725 (49)	331 (44)	394 (55)
Difficult to get up	749 (51)	427 (56)	322 (45)
Feeling rested after waking on a schoolday, <i>n</i> (%)			
Yes	1145 (78)	593 (78)	552 (77)
No	329 (22)	165 (22)	164 (23)
Feeling sleepy/tired during the day, <i>n</i> (%)			
Never or sometimes	1228 (83)	631 (83)	597 (84)
At least once a week	243 (17)	126 (17)	117 (16)
Cardiometabolic markers†			
BMI for age z-score	0.12 (1.06)	0.05 (1.05)	0.19 (1.07)
WC (cm)	66.4 (6.7)	66.1 (6.5)	66.8 (6.9)
TC (mm)	4.1 (0.7)	4.1 (0.6)	4.0 (0.7)
HDLC (mm)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)
TC/HDLC ratio	3.1 (0.9)	3.1 (0.8)	3.1 (1.0)
Systolic BP (mmHg)	115 (9)	114 (10)	115 (9)
Diastolic BP (mmHg)	67 (6)	67 (6)	67 (7)
HbA1c (%)	5.1 (0.2)	5.1 (0.3)	5.1 (0.2)

Data are mean (SD) unless otherwise noted.

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDLC, high-density lipoprotein cholesterol; PDS, puberty development scale; TC, total cholesterol; WC, waist circumference.

*Around the age of 11 years.

†Around the age of 12 years.

sleepy/tired at least 1 day a week, while this was 17% for boys and girls without night-time awakenings ($P < 0.0001$).

In girls, time in bed seemed to be correlated with daytime outcomes. Girls with short time in bed reported unfavourable daytime outcomes more frequently than girls with medium or long time in bed. For example, 40% of girls with short time in bed reported not to 'feel rested after waking on a schoolday', while this was 15% for girls with medium time in bed.

In boys, the sleep–wake pattern seemed to be correlated with daytime outcomes. Boys with a LL pattern more often had unfavourable daytime outcomes than boys with the EE pattern. Among boys with a LL pattern, 54% reported 'difficulty to get up in the morning', and 21% reported not to 'feel rested after waking on a schoolday', while this was 38% and 12%, respectively, for boys with a EE pattern.

Table 2 Prevalence (%) of daytime sleepiness for categories of sleep duration, sleep-wake pattern and night-time awakenings

	<i>Daytime outcomes</i>					
	<i>Difficult to get up in the morning</i>		<i>Feeling rested after waking</i>		<i>Sleepy/tired during the day</i>	
	<i>'Yes'</i>		<i>'No'</i>		<i>'At least once a week'</i>	
	<i>Girls</i>	<i>Boys</i>	<i>Girls</i>	<i>Boys</i>	<i>Girls</i>	<i>Boys</i>
Time in bed at schooldays						
Short (7.5–9.5 h)	64	38	40	12	36	27
Medium (10–10.5 h)	55	43	15	16	20	22
Long (11–12.5 h)	58	50	15	19	23	23
<i>P</i> -value*	0.57	0.34	<0.01 [†]	0.96	0.66	0.49
Sleep-wake pattern at schooldays						
Early to bed/Early rise (EE)	53	38	14	12	23	19
Early to bed/Late rise (EL)	59	50	14	19	21	26
Late to bed/Early rise (LE)	54	38	20	13	20	26
Late to bed/Late rise (LL)	59	54	21	21	24	22
<i>P</i> -value*	0.03 [†]	<0.001 [†]	0.53	0.04 [†]	0.27	0.40
Night-time awakenings						
No	53	43	13	12	17	17
Yes	64	52	26	30	34	40
<i>P</i> -value*	<0.001 [†]	<0.01 [†]	<0.001 [†]	<0.001 [†]	<0.001 [†]	<0.001 [†]

**P*-values were calculated for associations between sleep variables (rows) and daytime sleepiness (columns) using chi-square tests, within girls and boys separately.

[†]*P* < 0.05.

Associations between sleep and cardiometabolic markers

Time in bed, sleep–wake pattern, night-time awakenings or daytime outcomes did not significantly decrease, or increase, BP and HbA1c in the crude analysis, or after adjustment for other study factors in boys and girls (Table 3 and 4). Among girls, after adjustment we observed significant associations between measures of sleep and anthropometric outcomes (BMI, WC) and cholesterol levels (Table 3). Girls with long time in bed (11–12.5 h) had 0.16 lower BMI *z*-score [95% confidence interval (CI) –0.31; –0.01] and 0.99 cm smaller WC (95% CI –2.01; –0.13) compared with girls with medium time in bed (10–10.5 h) on schooldays. Girls who went to bed late at night and rose early in the morning (LE pattern) had 0.16 mm higher total cholesterol (TC; 95% CI 0.01; 0.31) and 0.08 mm higher high-density lipoprotein cholesterol (HDL; 95% CI 0.01; 0.14) compared with girls with an EE pattern. Girls who had night-time awakenings had 0.14 mm higher TC (95% CI 0.03; 0.25) than girls who did not have night-time awakenings. Girls who felt sleepy or tired at least once a week had 0.10 mm lower HDL (95% CI –0.16; –0.04) and 0.17 mm higher TC/HDL ratio (95% CI 0.02; 0.32) than girls who were not feeling sleepy during the day. Among boys, time in bed, sleep–wake pattern, night-time awakenings or daytime outcomes did not significantly increase or decrease any of the cardiometabolic markers, in the crude analysis, or after adjustment for other study factors (Table 4).

Additionally we included BMI *z*-score and WC separately in the fully adjusted model to investigate whether associations between sleep and cardiometabolic markers in girls were mediated by BMI or WC. Out of a total of seven associations, two associations with cholesterol attenuated and were no longer significant after adjustment. The association with HDL in girls with a LE pattern was no longer significant after adjusting for WC ($\beta = 0.07$; 95% CI 0.00; 0.13). The association with TC/HDL ratio in girls who felt sleepy at least once a week was no longer significant after adjusting for WC ($\beta = 0.12$; 95% CI –0.02; 0.26) or BMI ($\beta = 0.14$; 95% CI –0.00; 0.29). The other associations did not alter (data not shown). In an additional analysis with overweight (at 12 years old) instead of BMI as outcome variable, we found that the odds of being overweight decreased for girls with a long time in bed by 56% [odds ratio (OR) = 0.44, 95% CI 0.24; 0.79] compared with girls with a medium time in bed. In boys, a long time in bed was not associated with lower risk of overweight.

DISCUSSION

This study in 11–12-year-old children shows that sleep characteristics were not associated with BP and HbA1c; and that in girls, but not in boys, some sleep characteristics were associated with anthropometric outcomes (BMI, WC) and cholesterol levels. More specifically, in girls, longer time in bed was associated with lower BMI and WC; night-time

Table 3 Multiple regression analysis of sleep characteristics and cardiometabolic markers, in girls ($n = 759$)

	BMI z-score	WC (cm)	TC (mmol)	HDLC (mmol)	TC/HDL ratio	Systolic BP (mmHg)	Diastolic BP (mmHg)	HbA1c (%)
	$n = 765$ β (95% CI) †	$n = 757$ β (95% CI) †	$n = 627$ β (95% CI) †	$n = 627$ β (95% CI) †	$n = 627$ β (95% CI) †	$n = 720$ β (95% CI) †‡	$n = 720$ β (95% CI) †‡	$n = 620$ β (95% CI) †§
Time in bed and sleep-wake pattern								
Time in bed on schooldays								
Short (7.5–9.5 h)	–0.13 (–0.44; 0.18)	–0.42 (–2.23; 1.39)	–0.01 (–0.22; 0.21)	0.07 (–0.03; 0.17)	–0.18 (–0.44; 0.08)	1.25 (–1.76; 4.26)	–0.68 (–2.71; 1.36)	< –0.01 (–0.09; 0.09)
Medium (10–10.5 h) (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Long (11–12.5 h)	–0.16 (–0.31; –0.01)*	–0.99 (–1.87; –0.11)*	–0.06 (–0.16; 0.05)	<0.01 (–0.05; 0.05)	–0.04 (–0.17; 0.09)	–0.02 (–1.50; 1.48)	0.39 (–0.62; 1.41)	–0.01 (–0.06; 0.03)
Sleep-wake pattern on schooldays								
Early to bed/Early rise (EE) (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Early to bed/Late rise (EL)	–0.17 (–0.35; 0.01)	–1.00 (–2.08; 0.07)	0.05 (–0.08; 0.18)	0.03 (–0.03; 0.10)	–0.03 (–0.19; 0.12)	–0.90 (–2.71; 0.92)	–0.30 (–1.53; 0.93)	–0.01 (–0.07; 0.04)
Late to bed/Early rise (LE)	–0.03 (–0.24; 0.18)	–0.03 (–1.28; 1.21)	0.16 (0.01; 0.31)*	0.08 (0.01; 0.14)*	–0.10 (–0.28; 0.08)	0.65 (–1.43; 2.74)	–0.28 (–1.70; 1.13)	–0.01 (–0.07; 0.05)
Late to bed/Late rise (LL)	< 0.01 (–0.19; 0.19)	–0.23 (–1.35; 0.89)	0.07 (–0.06; 0.20)	0.04 (–0.02; 0.11)	–0.03 (–0.19; 0.13)	–0.76 (–2.65; 1.13)	–0.32 (–1.61; 0.96)	–0.02 (–0.08; 0.03)
Sleep quality								
Night-time awakenings								
No (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.03 (–0.13; 0.19)	0.44 (–0.49; 1.38)	0.14 (0.03; 0.25)*	0.02 (–0.03; 0.07)	0.05 (–0.09; 0.19)	–0.83 (–2.39; 0.74)	–0.44 (–1.50; 0.62)	–0.01 (–0.05; 0.04)
Daytime outcomes								
Getting up in the morning								
Not difficult to get up (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Difficult to get up	–0.01 (–0.16; 0.13)	0.02 (–0.81; 0.86)	–0.02 (–0.12; 0.08)	<0.01 (–0.04; 0.05)	–0.03 (–0.15; 0.10)	–0.45 (–1.84; 0.95)	–0.60 (–1.54; 0.35)	–0.02 (–0.06; 0.02)
Feeling rested after waking on a schoolday								
Yes (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
No	–0.29 (–0.48; –0.10)	–1.01 (–2.12; 0.10)	–0.04 (–0.17; 0.10)	0.01 (–0.05; 0.07)	–0.10 (–0.27; 0.06)	–1.43 (–3.30; 0.44)	–1.02 (–2.28; 0.24)	–0.01 (–0.06; 0.05)
Feeling sleepy/tired during the day								
Never or sometimes (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
At least once a week	0.09 (–0.08; 0.26)	0.76 (–0.25; 1.77)	–0.10 (–0.22; 0.03)	–0.10 (–0.16; –0.04)*	0.17 (0.02; 0.32)*	–1.19 (–2.88; 0.49)	–0.34 (–1.48; 0.80)	0.01 (–0.04; 0.06)

BMI, body mass index; BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; HDLC, high-density lipoprotein cholesterol; TC, total cholesterol; WC, waist circumference.

†All analyses were adjusted for age at completion of the questionnaire, age at medical examination, height, mother's education, puberty and screen time.

‡Analyses of BP were additionally corrected for cuff size.

§Analyses of HbA1c were additionally corrected for storage time.

* $P < 0.05$.

Table 4 Multiple regression analysis of sleep characteristics and cardiometabolic markers, in boys ($n = 722$)

	BMI z-score	WC (cm)	TC (mmol)	HDLc (mmol)	TC/HDLc ratio	Systolic BP (mmHg)	Diastolic BP (mmHg)	HbA1c (%)
	$n = 722$ β (95% CI) [†]	$n = 718$ β (95% CI) [†]	$n = 633$ β (95% CI) [†]	$n = 633$ β (95% CI) [†]	$n = 633$ β (95% CI) [†]	$n = 683$ β (95% CI) ^{†,‡}	$n = 683$ β (95% CI) ^{†,‡}	$n = 626$ β (95% CI) ^{†,§}
Time in bed and sleep-wake pattern								
Time in bed on schooldays								
Short (7.5–9.5 h)	–0.06 (–0.36; 0.24)	–0.39 (–2.23; 1.45)	–0.15 (–0.35; 0.04)	0.03 (–0.07; 0.12)	–0.22 (–0.51; 0.08)	–0.81 (–3.34; 1.71)	0.08 (–1.87; 2.04)	0.03 (–0.04; 0.10)
Medium (10–10.5 h) (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Long (11–12.5 h)	–0.01 (–0.18; 0.16)	–0.04 (–1.09; 1.01)	–0.06 (–0.17; 0.05)	0.02 (–0.04; 0.07)	–0.14 (–0.31; 0.02)	0.92 (–0.49; 2.33)	0.22 (–0.87; 1.31)	0.03 (–0.01; 0.07)
Sleep–wake pattern on schooldays								
Early to bed/Early rise (EE) (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Early to bed/Late rise (EL)	0.02 (–0.19; 0.24)	–0.11 (–1.41; 1.19)	–0.06 (–0.20; 0.08)	0.02 (–0.05; 0.08)	–0.16 (–0.37; 0.05)	0.34 (–1.41; 2.10)	–0.09 (–1.45; 1.26)	0.03 (–0.02; 0.08)
Late to bed/Late rise (LE)	–0.05 (–0.28; 0.18)	–0.45 (–1.86; 0.97)	–0.08 (–0.23; 0.08)	0.01 (–0.05; 0.08)	–0.12 (–0.35; 0.11)	–0.70 (–2.60; 1.21)	0.26 (–1.21; 1.73)	–0.01 (–0.07; 0.04)
Late to bed/Late rise (LL)	0.07 (–0.14; 0.28)	–0.18 (–1.49; 1.13)	<0.01 (–0.14; 0.15)	–0.02 (–0.09; 0.04)	0.08 (–0.13; 0.29)	0.28 (–1.48; 2.04)	0.51 (–0.85; 1.87)	< –0.01 (–0.05; 0.05)
Sleep quality								
Night-time awakenings								
No (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.08 (–0.09; 0.26)	0.54 (–0.56; 1.64)	0.08 (–0.04; 0.19)	0.02 (–0.04; 0.07)	0.01 (–0.17; 0.19)	–0.27 (–1.76; 1.21)	–0.17 (–1.31; 0.97)	–0.02 (–0.06; 0.03)
Daytime outcomes								
Getting up in the morning								
Not difficult	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Difficult to get up	–0.06 (–0.22; 0.10)	–0.03 (–0.99; 0.93)	–0.07 (–0.17; 0.03)	< –0.01 (–0.05; 0.04)	–0.09 (–0.24; 0.07)	–0.61 (–1.91; 0.69)	–0.41 (–1.42; 0.59)	–0.01 (–0.05; 0.03)
Feeling rested after waking on a schoolday								
Yes (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
No	0.10 (–0.12; 0.31)	1.06 (–0.24; 2.36)	0.08 (–0.06; 0.22)	0.01 (–0.05; 0.07)	0.04 (–0.18; 0.25)	–1.26 (–3.04; 0.51)	–0.30 (–1.67; 1.08)	–0.02 (–0.07; 0.03)
Feeling sleepy/tired during the day								
Never or sometimes (ref.)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
At least once a week	0.10 (–0.09; 0.29)	0.92 (–0.23; 2.07)	0.08 (–0.04; 0.21)	0.01 (–0.04; 0.07)	0.03 (–0.16; 0.21)	–1.06 (–2.61; 0.50)	0.27 (–0.93; 1.47)	–0.01 (–0.05; 0.04)

†All analyses were adjusted for age at completion of the questionnaire, age at medical examination, height, mother's education, puberty and screen time.

‡Analyses of BP were additionally corrected for cuff size.

§Analyses of HbA1c were additionally corrected for storage time.

awakenings with higher TC, late to bed and early risers with higher TC and HDLC; and feeling sleepy/tired during daytime with lower HDLC and higher TC/HDLC ratio. It cannot be ruled out that the associations we found in girls were chance findings due to multiple comparisons. No specific sleep characteristic showed consistent associations with the cardiometabolic markers.

Strengths and limitations

Important strengths of our study include the large number of sleep parameters, multiple objectively measured cardiometabolic markers, ability to adjust simultaneously for several important confounders, and the large study population, allowing stratifying for gender. Our study offers insight not only in characteristics of sleep at night, but also in consequences of sleep during the day.

We used self-reported sleep data, which may be subject to misclassification due to reporting error. Some have suggested the use of objective sleep measurement (actigraphy or polysomnography) instead of self-reported data. However, self-reported sleep duration was found to correlate reasonably well with actigraphy and performed better than parental report in estimating sleep duration (Short *et al.*, 2013). In addition, actigraphy has low specificity for detecting nighttime awakenings (Sadeh, 2011); both methods are unfeasible for use in studies with many participants, and both methods cannot be used to assess experienced sleepiness during the day.

Time in bed was used as an indicator for sleep duration, and this probably overestimates actual sleep duration. Moreover, variation of sleep duration could exist within children who reported a short or long time in bed; thus, this may be a source of random error. It is possible that some of the children may have or had sleep apnea or sleep-disordered breathing (SDB), which would likely impact their sleep and cardiometabolic markers. However, the prevalence of moderate SDB (apnea–hypopnea index ≥ 5) was previously found to be low (1.2% in US children from the general population; Bixler *et al.*, 2009). We assume that in our population the prevalence of SDB was comparably low and did not substantially influence on our results.

The time lapse between completing the questionnaire and attending the medical examination was approximately 1 year. However, for some children this lapse was smaller, and 16 children completed the questionnaire only after undergoing the medical examination. Differences in time lapse could have introduced random errors in the case that sleep affected the cardiometabolic markers ‘instantly’. We consider it more likely that sleep acts on these markers over a longer period of time.

Assessment of pubertal development was an important strength of our study. However, data on pubertal development were obtained at the same time as the sleep data, and assessment of pubertal development was not repeated at the time of the medical examination. It is possible that some of

the children entered puberty after assessment of sleep, and their progressed maturity may have influenced the outcomes.

Children in the PIAMA cohort were recruited from the general population, but children of ethnic and lower educated mothers were underrepresented. Loss to follow-up and selective no-show to the medical examination has occurred especially among participants of lower socio-economic status (SES). Mothers of children in the current study population were higher educated compared with mothers of the total PIAMA population. Studies that have investigated childhood sleep behaviour in relation to SES have shown that children of lower SES have later sleep onset and shorter sleep duration, and that the association between sleep duration and BMI or overweight was in the same direction, but stronger, for children of lower SES (O’Dea *et al.*, 2012). Although behavioural aspects of sleep (e.g. chosen bed-times) may be related to SES, we consider it unlikely that the association between sleep and cardiometabolic markers would be markedly different in children from lower educated mothers.

Previous studies

Many previous studies in children specifically related sleep duration to weight status. Two meta-analyses found that children sleeping <10 h had 58–89% greater odds of being obese (Cappuccio *et al.*, 2008; Chen *et al.*, 2008). However, these analyses were performed on mainly the same studies, and there is still considerable heterogeneity in effects reported by individual studies. In our study, long sleep duration decreased the risk of being overweight in girls, but not in boys. The number of children defined as short sleepers in our study sample was small, and it is possible that findings for these children were non-significant due to lack of power. However, because effect estimates were small we do not expect that associations would have become significant when we would have had a larger sample. Our results are in line with several other studies that did not find a significant association, including two recent studies in very large populations: one US study of over 81 000 children aged 6–11 years (Hassan *et al.*, 2011); and one with a longitudinal design of 13 568 adolescents aged 12–18 years (Calamaro *et al.*, 2010), which found short sleep duration was not significantly predictive of obesity. Both were not included in meta-analyses mentioned earlier.

Our findings are in line with one previous study in children of a wide age range, showing that sleep duration was not associated with BP, TC and HDLC (Hitze *et al.*, 2009). Another study in obese adolescents measured sleep duration extensively by parental report, self-report and actigraphy, and found no associations with BMI, WC, BP and glucose with all methods (Sung *et al.*, 2011).

Studies in children relating sleep characteristics, other than sleep duration, to cardiometabolic markers are scarce. One previous study related self-reported sleep–wake pattern to weight status in 9–16 year olds (Olds *et al.*, 2011). This study

found that LL adolescents had significantly higher BMI z-scores (0.66 versus 0.45, $P = 0.0015$), and were 1.47 times more likely to be overweight or obese than EE adolescents. In our study, LL boys had higher BMI z-scores of 0.07, but not significantly. While the previous study adjusted for age, the study did not measure pubertal stage and did not stratify by sex; possibly explaining the difference in results. Another study comparing normal weight and overweight children found that they did not differ in self-reported sleep quality (Beebe *et al.*, 2007). We could not identify other studies in children that assessed self-reported sleep quality in relation to cardiometabolic markers.

Although our results partly conflict with previous literature on associations among child and adolescent sleep duration and BMI, our findings are consistent with most studies on childhood sleep and other cardiometabolic risk factors. Moreover, the majority of previous studies only assessed sleep duration, while other sleep parameters as in our study have been reported scarcely, especially daytime outcomes. It is therefore important for further studies to explore other sleep characteristics besides sleep duration, to gain insight into aspects of sleep most relevant to cardiometabolic risk. These studies should assess relations of sleep with multiple cardiometabolic outcomes and not overweight solely.

CONCLUSION

We report novel results on the relation between different sleep characteristics and multiple cardiometabolic markers. We observed some significant associations between indicators of sleep duration and quality, and anthropometric outcomes (BMI, WC) and cholesterol levels in girls. However, effect sizes were small and probably not clinically relevant, associations were not observed in boys, and were inconsistent across specific characteristics of sleep or cardiometabolic markers. The associations do not point in the direction of an increased or decreased cardiovascular risk. Therefore, we consider it premature to propose that improved sleep could reduce cardiovascular risk during childhood.

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FINANCIAL DISCLOSURE

The authors have no financial relationships to disclose.

CONFLICT OF INTEREST

No conflicts of interest declared.

AUTHOR CONTRIBUTIONS

Study concept and design: NEB, AHW, and HAS. Statistical analysis and drafting of the manuscript: NEB. Critical revision of the manuscript for important intellectual content: NEB, HAS, MBMB, BB, GHK, JCDJ, MK, LVR, and AHW. Obtained funding: BB, AHW and HAS. Study supervision: AHW and HAS.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Assessment of sleep characteristics and cardiometabolic markers.

SUPPLEMENTAL INFORMATION

Assessment of sleep characteristics

The two questions concerning the usual bedtime and get up time during schooldays, from which sleep duration and sleep-wake pattern were calculated, were adopted from the Munich Chronotype Questionnaire. This questionnaire was validated against two sleep-logs. Correlations with sleep logs for sleep midpoint, were: Morningness-Eveningness Questionnaire, MEQ: $r = -.73$; and Composite Scale of Morningness, CSM : $r = -.62$ (Roenneberg et al., 2003).

The question on feeling sleepy or tired during the day was adopted from a validated questionnaire, including Likert-type response options (never; rarely; sometimes; often; very often) (Spilsbury et al., 2007).

The questions on night-time awakenings, sleep latency after awakenings and feeling rested after waking had been used in a previous study which showed good internal consistency; Cronbach's alphas for this study were .70, .77, and .77 at T1, T2 and T3 respectively (Meijer et al., 2010). These variables are also criteria for insomnia as provided in the DSM IV (American Psychiatric Association, 1994).

Assessment of cardiometabolic markers

During home visits, when the child was aged 12 years, trained staff measured height, weight, waist circumference, and blood pressure, and blood samples were drawn. Body weight was measured at the nearest 0.1kg and height (cm) was measured at one decimal. Both anthropometric variables were measured while only wearing underwear. BMI for age and sex Standard Deviation Scores (SDS, z-scores) were calculated using the reference growth curves of the Dutch Fourth Nation-wide Growth Study carried out in 1997 (Fredriks et al., 2000). Waist circumference (cm) was measured twice and rounded to one decimal. The mean of the two measurements was calculated and used in analyses.

Blood pressure readings were obtained while children were asked to rest, without talking, for ≥ 5 minutes in the seated position before the first oscillometric BP measure was taken from the nondominant upper arm using an Omron M6 Monitor. Depending on arm circumference, 17 to 22 cm or 22 to 32 cm cuffs were used. The mean of two subsequent measures taken at 5-minute intervals

was used. If two consecutive measures differed by >5 mm Hg, another measurement was taken. The averages of (2 or 3) systolic and diastolic measurements were calculated and used in analyses.

Blood samples in the tubes designated for serum cholesterol measurement were allowed to clot at room temperature for at least 30 minutes, then cooled at 4°C until maximum 24 hours after blood drawing. Samples were then cooled to -20°C, and stored at -80°C for a median 128 days (IQR 73-167) before they were centrifuged for 10 minutes and analysed. Total and high-density lipoprotein (HDL) cholesterol were measured and the ratio between total and HDL cholesterol was calculated (TC/HDL ratio). Serum total and HDL cholesterol concentrations were determined enzymatically using Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis).

For analysis of HbA1c, erythrocytes from blood samples were stored at -20°C for a mean period of 144 days (range 29-364) prior to assay. A 5 µl cell mass was lysated and HbA1c was measured by ion-exchange chromatography using the Adams A1c, HA-8160 HPLC Auto analyser (Menarini Diagnostics Benelux, Valkenswaard, The Netherlands). This analyser was standardized on Diabetes Control and Complications Trial (DCCT) standards.

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