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Are some children genetically predisposed to poor sleep? A polygenic risk study in the general population

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Background: Twin studies show moderate heritability of sleep traits: 40% for insomnia symptoms and 46% for sleep duration. Genome-wide association studies (GWAS) have identified genetic variants involved in insomnia and sleep duration in adults, but it is unknown whether these variants affect sleep during early development. We assessed whether polygenic risk scores for insomnia (PRS-I) and sleep duration (PRS-SD) affect sleep throughout early childhood to adolescence. **Methods:** We included 2,458 children of European ancestry (51% girls). Insomnia-related items of the Child Behavior Checklist were reported by mothers at child's age 1.5, 3, and 6 years. At 10–15 years, the Sleep Disturbance Scale for Children and actigraphy were assessed in a subsample ($N = 975$). Standardized PRS-I and PRS-SD (higher scores indicate genetic susceptibility for insomnia and longer sleep duration, respectively) were computed at multiple p-value thresholds based on largest GWAS to date. **Results:** Children with higher PRS-I had more insomnia-related sleep problems between 1.5 and 15 years ($B_{\text{PRS-I} < 0.001} = .09$, 95% CI: 0.05; 0.14). PRS-SD was not associated with mother-reported sleep problems. A higher PRS-SD was in turn associated with longer actigraphically estimated sleep duration ($B_{\text{PRS-SD} < 5e08} = .05$, 95% CI: 0.001; 0.09) and more wake after sleep onset ($B_{\text{PRS-SD} < 0.005} = .25$, 95% CI: 0.04; 0.47) at 10–15 years, but these associations did not survive multiple testing correction. **Conclusions:** Children who are genetically predisposed to insomnia have more insomnia-like sleep problems, whereas those who are genetically predisposed to longer sleep have longer sleep duration, but are also more awake during the night in adolescence. This indicates that polygenic risk for sleep traits, based on GWAS in adults, affects sleep already in children. **Keywords:** Insomnia; sleep duration; polygenic risk score; GWAS; childhood sleep; actigraphy.

Introduction

Problems with falling asleep, frequent awakenings, or insufficient sleep are reported in about 30% of children in the age range of 1–12 years (Allen, Howlett, Coulombe, & Corkum, 2016). These sleep problems tend to persist into adulthood (Hysing et al., 2020). Sleep problems pose a health concern on their own, but poor sleep is also recognized as a potentially modifiable risk factor for adverse health outcomes.

While environmental factors undoubtedly play an important role in the development of problematic sleep, an increasing number of studies show that genetic predisposition determines a considerable portion of the interindividual variability in sleep patterns. In recent meta-analyses of twin studies, we estimated a heritability of 40% for insomnia (Barclay, Kocevska, Bramer, Van Someren, & Gehrman, 2021), 44% for sleep quality, and 46% for sleep duration (Kocevska et al., 2021). This shows that the interindividual variability in sleep traits is under substantial genetic control. Based on common genetic variations from genome-wide association studies (GWAS) in adults, a SNP-based heritability of 7.0% (Jansen et al., 2019) and 9.8% (Dashti et al., 2019) has been estimated for insomnia and sleep duration, respectively. These estimates are comparable with SNP-based heritability of other psychiatric traits [e.g. 8.9% for depression (Howard et al., 2019) and 8.8% for anxiety (Levey et al., 2020)]. Such estimates are indicative of a substantial influence of common genetic variants on the interindividual variation in sleep.

Recent large genome-wide association studies (GWASs) in adults have identified 202 genetic loci

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associated with insomnia (Jansen et al., 2019) and 78 with self-reported habitual sleep duration (Dashti et al., 2019). Based on these studies, one can calculate quantitative polygenic risk scores (PRS), which represent individuals' genetic susceptibility for insomnia and sleep duration, as estimated by the additive effects of multiple alleles using summary statistics from GWAS. Using this method, the polygenic propensity for good or poor sleep has been shown to correlate with sleep parameters in independent samples of adults (Dashti et al., 2019; Jansen et al., 2019).

Polygenic risk studies are increasingly utilized to model genetic susceptibility for psychiatric problems and disorders across development (Ronald, 2020). For example, polygenic risk for depression, anxiety, and neuroticism as determined in adults was shown to predict depression trajectories already during adolescence (Kwong et al., 2021; Lussier et al., 2021). In addition, a recent cross-sectional study showed that polygenic risk for ADHD and depression in adults is related to sleep disturbances in 9- to 10-year-olds (Ohi et al., 2021). Another study in the same sample showed that polygenic risk for insomnia is cross-sectionally associated with difficulty initiating and maintaining sleep (Ma, Chen, Lu, & Tong, 2021). Furthermore, two studies have shown that genetic variants for circadian preference identified in adults are associated with objective sleep timing from infancy (Morales-Muñoz et al., 2021) to childhood and adolescence (Merikanto et al., 2018) and predict individual developmental sleep trajectories from childhood onwards (Merikanto et al., 2018). It is, however, unknown whether the identified genetic variants for insomnia and sleep duration in adults affect sleep in early childhood and whether these associations extend into adolescence. Specifically, we studied whether genetic variants that predispose adults to insomnia and longer sleep duration are associated with the corresponding sleep characteristics across early childhood and in adolescence.

We therefore assessed whether children's polygenic risk scores (PRS) for self-reported insomnia (PRS-I) and sleep duration (PRS-SD) as determined in adults are associated with sleep in childhood and adolescence. We performed the study in a large sample (n = 2,458) of children from the general population that have been followed throughout adolescence. Sleep was assessed by mother reports at 1.5, 3, 6, and 10–15 years of age, and by actigraphy at age 10–15 years. We hypothesized that genetic susceptibility for poor sleep in adulthood (i.e. higher PRS-I) will be associated with more sleep problems across childhood. We also hypothesized that genetic susceptibility for longer sleep duration (i.e. higher PRS-SD) will be associated with longer sleep duration as measured with actigraphy.

Methods

This study was embedded in the Generation R Study, a population-based birth cohort in Rotterdam, The Netherlands (Kooijman et al., 2016). Briefly, pregnant women with an expected delivery date from April 2002 to January 2006 were recruited to study early determinants of development and health in childhood and beyond. From this birth cohort, genotype data of sufficient quality were available for 2,829 children of Western European ancestry (out of 5,756 in total). Sleep was reported by mothers at ages 1.5, 3, and 6 years, and in a random subsample, more detailed sleep assessments were performed at age 10–15 years (n = 1,143), including actigraphy (Koopman-Verhoeff et al., 2019). The final study sample includes 2,458 children of European ancestry with genotype and sleep data on at least one of four time points between 1.5 and 15 years (Table 1). The Medical Ethics Committee of the Erasmus University Medical Center approved all study procedures, and all participants provided written informed consent.

Genotyping and imputation

In the Generation R Study, DNA samples were collected from cord blood, or by venipuncture at 6 years of age. Individuals were genotyped using Illumina HumanHap 610 or 660 – single-nucleotide polymorphism (SNP) arrays depending on collection time (Illumina, San Diego, CA). Others have previously reported further details on genotype procedures in Generation R (Medina-Gomez et al., 2015). Quality control of the genotype- and individual-level data was conducted using PLINK (version 1.9) and has been described previously (Purcell et al., 2007). Briefly, exclusions of single-nucleotide polymorphisms (SNPs) were made if departure from Hardy–Weinberg equilibrium (HWE) was more significant than $p < 10^{-7}$, minor allele frequency (MAF) was <1%, or if a SNP was not successfully genotyped in the least 97.5% of the population (SNP call rate < 97.5%). We then performed prephasing using Shapeit2 (Delaneau, Zagury, & Marchini, 2013) and imputation with Minimac3 (Das et al., 2016) using the University of Michigan Imputation Server (Das et al., 2016). Genotypes were imputed to the Haplotype Reference Consortium release 1.1 reference panel (McCarthy et al., 2016). Prior to analyses, we excluded SNPs with low imputation quality (info score <0.3); this resulted in a total of 6,147,370 variants. The samples were merged with the three genotyped panels from the HapMap Phase II release 22 build 36 (International HapMap, 2005). Pairwise identity-by-state (IBS) relations were calculated for each pair of individuals using PLINK, and genomic components equivalent to principal components (PCs) were derived from this IBS matrix by multidimensional scaling (MDS). Participants that deviated more than 4 standard deviations (SDs) from the CEU panel mean value in any of the first four genomic components were defined as non-Northwestern European ancestry (Medina-Gomez et al., 2015) and excluded from the analysis. In addition, to correct for potential residual population stratification or cryptic relatedness, we further adjusted the models for 4 genomic principal components.

Polygenic risk score computation

We used imputed genotype data that passed quality control to compute PRSs based on largest GWAS of insomnia (n = 1,331,010) and sleep duration (n = 44,611). Participants qualifying for insomnia answered '*usually*' on the question 'Do you usually have trouble falling asleep at night, or do you wake up in the middle of the night?' or '*yes*' to the question 'Have you ever been diagnosed with, or treated for insomnia?'. For sleep duration, participants answered the question 'About how many hours of sleep do you get per 24 hours?' in hour

Table 1 Sleep characteristics of the included participants

Characteristics	*n*	Age, years mean (IQR)	Mean ± *SD*	Median (IQR)
Mother-reported sleep problems				
Child Behavior Checklist				
At 1.5 years (range 0–10)	2,099	1.5 (1.4–1.6)	1.5 ± 2.0	1.1 (0–2.0)
At 3 years (range 0–10)	2,026	3.0 (2.9–3.1)	1.6 ± 1.9	1.1 (0–2.0)
At 6 years (range 0–9)	2,111	6.3 (6.0–6.9)	1.0 ± 1.6	1.1 (0–2.0)
Sleep Disturbance Scale for Children				
At 10–16 years (range 5–21)	1,018	12.6 (11.6–14.4)	9.2 ± 2.6	9 (7.0–11.0)
Actigraphy at 10–15 years				
TST, hr	975	12.6 (11.6–14.4)	7.6 ± 0.8	7.6 (7.1–8.0)
SOL, min	974	12.6 (11.6–14.4)	40.1 ± 44.6	31.0 (16.8–58.8)
WASO, min	975	12.6 (11.6–14.4)	22.3 ± 3.6	22.3 (20.1–24.8)
Sleep diary at 10–15 years				
TST, hr	935	12.6 (11.6–14.4)	9.2 ± 0.85	9.3 (8.7–11.4)
SOL, min	956	12.6 (11.6–14.4)	25.2 ± 17.7	20.6 (13.3–32.2)
WASO, min	943	12.6 (11.6–14.4)	53.5 ± 61.0	33.3 (11.1–77.8)

IQR, interquartile range; *SD*, standard deviation; SOL, sleep onset latency; *T*, time point; TST, total sleep time; WASO, wake after sleep onset.

increments. PRS-I and PRS-SD were created using PRSice-2 (Choi, Mak, & O'Reilly, 2020). This software calculates individual PRSs by summing up all the SNP alleles associated with the trait carried by the participants weighted by the SNP allele effect size estimated in a previous GWAS. Polygenic scoring was performed in clumped variants according to linkage disequilibrium using an $r^2 < .10$ cutoff within a 300-kb window. We calculated PRSs for each trait based on six different *p*-value thresholds (pTs) with pT < 5e.08 (genome-wide significant, including 233 SNPs for insomnia and 91 SNPs for sleep duration), pT < 0.001 (2,304 SNPs for insomnia and 1,194 SNPs for sleep duration), pT < 0.005 (14,955 SNPs for insomnia and 13,896 SNPs for sleep duration), pT < 0.01 (22,096 SNPs for insomnia and 24,008 SNPs for sleep duration), pT < 0.05 (58,154 SNPs for insomnia and 79,330 SNPs for sleep duration), pT < 0.1 (89,232 SNPs for insomnia and 139,722 SNPs for sleep duration), and pT < 0.5 (233,472 SNPs for insomnia and 463,611 SNPs for sleep duration), as recommended (Choi et al., 2020). In addition, optimal *p*-value threshold was considered from the model where PRS explained highest % of the variance (R^2) in the outcome, as estimated by PRSice-2. Higher scores of PRS-I indicate higher risk for insomnia, whereas higher PRS-SD scores indicate higher genetic predisposition for longer sleep duration. All PRSs were standardized to a mean of 0 and a standard deviation of 1.

Mother-reported sleep problems

Child Behavior Checklist (CBCL). At ages 1.5, 3, and 6 years, children's sleep problems were quantified with the Sleep Problems scale, one of the empirically derived scales of the CBCL/1½–5 (Achenbach & Rescorla, 2000). The Sleep Problems scale comprises seven questions about sleep problems including items on dyssomnia (has trouble falling asleep; sleeps less than most children during the day and/or night; and wakes up often during the night) and parasomnia (nightmares and talks or cries out in sleep). Guided by a previous factor analysis (Kocevska et al., 2017; Mulder et al., 2019), we based the sleep problems score only on the dyssomnia questions, as the two types of sleep problems likely have different (genetic) etiology.

Sleep Disturbance Scale for Children. During home visits organized for the actigraphy data (age 10–15 years) collection, a structured interview was performed with a parent. Parents reported if their children experienced difficulties initiating or maintaining sleep, a subscale of the Sleep Disturbance Scale for Children (Bruni et al., 1996). Items were scored on a five-point Likert scale. Responses were summed per subscale; the total score had moderate internal consistency (α = .64); higher scores indicate more sleep problems.

Actigraphy. In a subsample of 975 genotyped children, sleep was assessed at age 10–15 years using actigraphy (GENEActiv; Activinsights, UK). The first actigraphy data collection started nearly 1 year after the 10-year assessment (n = 665), and the second was conducted nearly 1 year after the 13-year assessment (n = 310); these assessments included no repeated measurements (Blok et al., 2022). No differences in the study associations were identified between the two age groups. Children wore the actigraphy watch and kept a sleep diary for nine subsequent days (five school days and four weekend days) on their nondominant wrist (Koopman-Verhoeff et al., 2019). The GGIR R-package was used for processing including autocalibration with gravity as reference, detection of atypical values, and nonwear (Van Hees et al., 2014). The algorithm is using an accelerometer-derived arm angle averaged over 5-s epochs to detect sleep. If there is no arm movement larger than 5° for at least 5 min, this will be classified as a period of sustained inactivity or sleep (Van Hees et al., 2015). The following sleep variables were estimated from actigraphy: sleep duration, sleep onset latency, and wake after sleep onset. Sleep duration is the total time asleep during the night (TST, hr), indicating the time between sleep onset and wake time minus the time scored as wake. Sleep onset latency is the time (SOL, min) between bedtime reported in the sleep diary and sleep onset as estimated by the actigraph. Wake after sleep onset (WASO, min) is the duration of wake during the sleep period. The same sleep variables were also derived from self-reported sleep diaries. Sleep measures were represented as an average across all days the accelerometer was worn. Nights were excluded if the wear time was under 6 hr or if sleep duration was estimated to be less than 4 hr.

Statistical analyses

We used linear mixed model to study associations of PRS-I and PRS-SD with repeatedly measured mother-reported sleep problems and multiple linear regression models for individual time points and actigraphy outcomes. Standardized PRS-I and PRS-SD computed at different *p*-value thresholds were used as independent predictor variables, and repeatedly measured mother-reported sleep problems or actigraphic sleep as outcome variables. Models were adjusted for age at sleep

assessment, sex, and first four genetic principal components (to account for residual stratification within the sample). For sensitivity analyses, we additionally adjusted the primary models for maternal affective symptoms at child's age 3 years assessed with the Brief Symptom Inventory (De Beurs, 2004). We also analyzed associations of PRS-I and PRS-SD with self-reported sleep diary outcomes at the time of actigraphy assessment. Finally, to assess the specificity of the findings we also analyzed whether parasomnia items of the CBCL were associated with PRS-I or PRS-SD. Because both predictor and outcome variables were inherently correlated, we adjusted the statistical significance thresholds for multiple comparisons for the effective number of tests (Meff) correction (Brainstorm et al., 2018; Nyholt, 2004), without the assumption of independence of tests. Based on correlation matrices between 14 PRS scores on the one hand, and sleep outcomes on the other hand, we estimated a total of 11 independent tests for linear mixed models ($p < .0045$), and 76 independent tests for multiple regression models with individual time points of sleep problem assessment ($p < .00065$).

Results

Our sample consisted of 2,458 children, of which 51% were girls. Sleep problems were reported by mothers at 4 time points from 1.5 ($n = 2{,}099$), 3 ($n = 2{,}026$), 6 ($n = 2{,}111$), and 10–15 years ($n = 1{,}018$) of age and with actigraphy ($n = 975$) at 10–15 years of age. Summary statistics for all sleep parameters are presented in Table 1. Actigraphy estimates indicated that between ages 10 and 15, children slept 7.6 ± 0.8 hr a night and were awake for an average of 22.3 ± 3.6 min during the sleep period. Figure 1 presents effect estimates for the associations of PRS-I and PRS-SD with mother-reported and actigraphic sleep traits for each individual time point.

Associations between PRS-I and sleep outcomes

A higher PRS-I was associated with more mother-reported sleep problems across childhood and adolescence (Table 2). Longitudinal associations remained statistically significant after multiple testing correction at several pTs ($B_{\text{PRS-I} < 0.001} = .09$, 95% CI: 0.05; 0.14, $B_{\text{PRS-I} < 0.01} = .09$, 95% CI: 0.04; 0.14, $B_{\text{PRS-I} < 0.1} = .07$, 95% CI: 0.02; 0.12), and effects were consistent across all time points and pTs (see Figure 1 and Table 2). These associations only slightly attenuated after adjustment for maternal affective symptoms ($B_{\text{PRS-I} < 0.001} = .08$, 95% CI: 0.03; 0.13, $B_{\text{PRS-I} < 0.01} = .07$, 95% CI: 0.02; 0.12, $B_{\text{PRS-I} < 0.1} = .04$, 95% CI: −0.01; 0.09). Most of the associations observed at individual time points, however, did not survive correction for multiple testing with the exception of the association of PRS-I at pT < 0.001 with mother-reported sleep problems at age 6 years ($B_{\text{PRS-I} < 0.001} = .15$, 95% CI: 0.08; 0.21, p-value < .00002). Highest explained variance for sleep problems at 1.5 years was $R^2 = .0040$ with PRS-I at p-value threshold at .02245 and for sleep problems at 6 years $R^2 = .009$ with PRS-I at p-value threshold of .00105. A summary of the variance by PRS-I at all predefined Pt is given in Table S1a. PRS-I was weakly associated with parasomnia symptoms between 1.5 and 6 years, but these associations did not survive multiple testing correction (Table S3), and was not related to actigraphically estimated sleep (TST: $B_{\text{PRS-I} < 5e08} = -.01$, 95% CI: −0.06; 0.03; WASO: $B_{\text{PRS-I} < 5e08} = .18$, 95% CI: −0.03; 0.40; SOL: $B_{\text{PRS-I} < 5e08} = .0001$, 95% CI: −0.04; 0.04). Table S2 shows the associations of PRS-I with self-reported sleep diary outcomes at the time of actigraphy assessment. These analyses also show no associations with PRS-I.

Associations between PRS-SD and sleep outcomes

Adolescents with a higher polygenic propensity for longer reported sleep duration had longer actigraphy-estimated sleep duration ($B_{\text{PRS-SD} < 0.1} = .05$, 95% CI: 0.01; 0.10), but also more wake after sleep onset ($B_{\text{PRS-SD} < 0.1} = .33$, 95% CI: 0.11; 0.55). This can translated into on average 3 min more sleep, at the cost of 1% more wake (average of 0.3 min). These associations, however, did not survive correction for multiple testing. Highest explained variance for actigraphic sleep duration was observed with PRS-SD at a p-value threshold of .0004 ($R^2 = .0075$), and for wake after sleep onset with PRS-SD at p-value threshold of .0460 ($R^2 = .010$). A summary of the variance explained by PRS-SD at all predefined Pt is given in Table S1b. Using more inclusive p-value thresholds (pT < 0.05, pT < 0.1 and pT < 0.5), higher PRS-SD was also associated with less mother-reported sleep problems in adolescence ($B_{\text{PRS-SD} < 0.1} = -.23$, 95% CI: −0.39; −0.06), and a similar trend was observed in longitudinal models (Table 2: $B_{\text{PRS-SD} < 0.1} = -.10$, 95% CI: −0.10; 0.0001). These associations also did not survive correction for multiple comparisons and should be interpreted with caution. Table S2 shows the associations of PRS-SD with self-reported sleep diary outcomes at the time of actigraphy assessment. Higher PRS-SD from more inclusive p-value thresholds ($p < .1$) was associated with longer sleep diary-reported TST, but analyses did not survive correction for multiple testing. PRS-SD was not associated with diary-reported WASO. PRS-SD was also not associated with parasomnia symptoms between 1.5 and 6 years of age.

Discussion

Our study showed that PRSs based on GWASs of sleep in adults are predictive of sleep already in early childhood, and these associations extend into adolescence. The genetic predisposition to insomnia was specifically related to sleep problems (including insomnia-like symptoms such as frequent awakenings or difficulty initiating sleep) reported by the mother, but not to actigraphic sleep parameters.

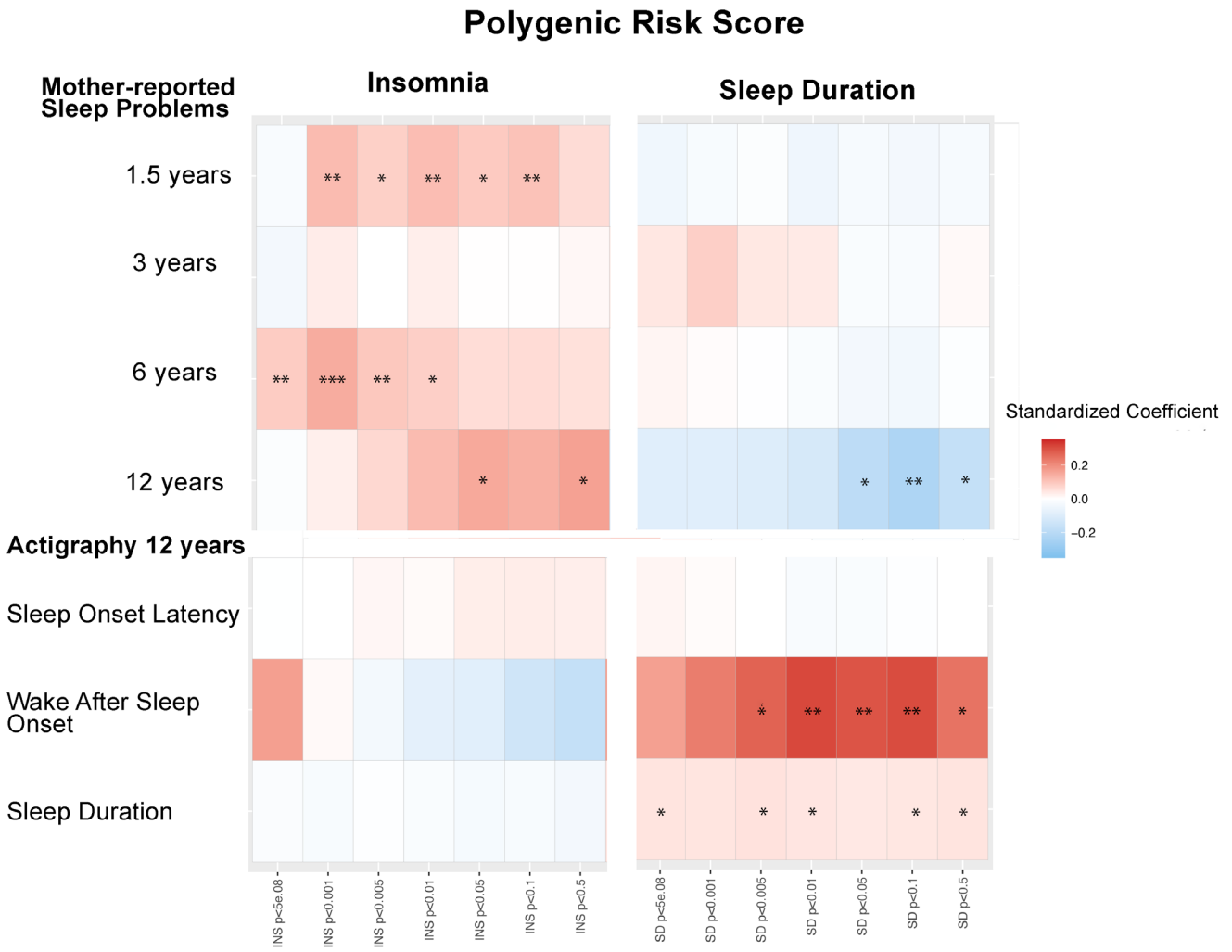

Figure 1 Associations between polygenic risk scores for insomnia and sleep duration and sleep traits across childhood and adolescence. Associations of PRS-I and PRS-SD with mother-reported sleep problems at 1.5, 3, 6, and 10–15 years and with actigraphy measures at 10–15 years (mean 12.6). Effect sizes were estimated using linear regression models with sleep traits at each time point as outcomes, adjusted for age at sleep measurement, sex, and genetic principal components. Statistical significance: *<.05, **<.01, and ***<.00065 (multiple testing-corrected *p*-value).

Conversely, the genetic predisposition for longer reported sleep duration was related to slightly longer actigraphically estimated sleep duration, but at the cost of 1% more wake during the night. Despite considerable genetic overlap between insomnia and self-reported sleep duration (r_g between −.48 and −.52) (Dashti et al., 2019; Jansen et al., 2019), we show that the PRSs for each trait have distinctive associations with congruent sleep traits already in childhood. Importantly, we show that genetic risk for insomnia is observable on a behavioral level (i.e. sleep problems) already in childhood.

Though this is the first study providing direct evidence that genetic susceptibility for poor sleep is reflected in sleep problems already in early childhood, previous studies already provided support for this hypothesis. Notably, a recent cross-sectional study also showed PRS-I to be associated with difficulty initiating and maintaining sleep in 9- to 10-year-olds (Ma et al., 2021). Twin studies have also shown that the heritability of sleep duration is highest during childhood (up to 18 years) (Kocevska et al., 2021), and the heritability of parent-reported insomnia symptoms is higher as compared to self-reported, possibly reflecting shared-method bias (Barclay et al., 2021). A recent polygenic risk study also showed that PRS for morningness (as identified in adults) is associated with earlier sleep onset across early childhood, whereas eveningness was associated with later sleep onset, as well as poorer actigraphically measured sleep efficiency (Morales-Muñoz et al., 2021). These findings corroborate those of our study and demonstrate that genetic propensity for sleep phenotypes measured in adulthood is related to sleep patterns and problems already in childhood. The studies also illustrate how findings from GWAS can be utilized to create PRS that are successfully validated in independent populations (Ronald, 2020), and in our case, a pediatric population with up to 15 years of follow-up.

Table 2 Associations between polygenic risk scores for insomnia and sleep duration and sleep outcomes across childhood

	Outcomes											
	Mother report			Actigraphy[b]								
	Sleep problems between 1.5, 3, 6, and 10 years[a]			TST, hr			SOL, min			WASO, min		
Predictors	*B*	95% CI	*p*	*B*	95% CI	*p*	*B*	95% CI	*p*	*B*	95% CI	*p*
Polygenic risk score for insomnia (PRS-I)												
$p < 5e08$	.002	−0.04; 0.05	.919	−.01	−0.05; 0.03	.576	.0001	−0.04; 0.04	.997	.18	−0.03; 0.39	.096
$p < .001$	**.09**	**0.05; 0.14**	**.0001**	−.02	−0.06; 0.02	.353	.001	−0.04; 0.05	.941	.02	−0.19; 0.24	.839
$p < .005$	.07	0.02; 0.11	.005	−.01	−0.05; 0.03	.632	.01	−0.03; 0.05	.645	−.05	−0.27; 0.16	.624
$p < .01$	**.09**	**0.04; 0.14**	**.0002**	−.01	−0.06; 0.02	.414	.01	−0.04; 0.05	.756	−.09	−0.31; 0.13	.429
$p < .05$	.04	0.02; 0.11	.006	−.03	−0.08; 0.01	.171	.03	−0.02; 0.07	.225	−.09	−0.32; 0.12	.384
$p < .1$	**.07**	**0.02; 0.12**	**.004**	−.03	−0.07; 0.02	.253	.03	−0.02; 0.07	.213	−.15	−0.37; 0.07	.173
$p < .5$	.06	0.01; 0.11	.011	−.03	−0.08; 0.01	.151	.03	−0.01; 0.08	.167	−.16	−0.38; 0.06	.159
Polygenic risk score for sleep duration (PRS-SD)												
$p < 5e08$	.004	−0.04; 0.05	.861	.05	0.001; 0.09	.044	.02	−0.04; 0.05	.462	.16	−0.05; 0.38	.151
$p < .001$	.01	−0.04; 0.06	.709	.04	−0.01; 0.08	.091	−.002	−0.05; 0.04	.907	.19	−0.03; 0.40	.085
$p < .005$	−.005	−0.05; 0.04	.842	.05	0.004; 0.09	.034	−.003	−0.05; 0.04	.864	.25	0.04; 0.47	.019
$p < .01$	−.02	−0.07; 0.03	.441	.05	0.003; 0.09	.036	−.02	−0.06; 0.03	.453	.32	0.11; 0.54	.003
$p < .05$	−.04	−0.09; 0.01	.109	.04	−0.00; 0.09	.056	.02	−0.03; 0.06	.462	.31	0.09; 0.53	.005
$p < .1$	−.05	−0.10; 0.0001	.051	.05	0.002; 0.09	.042	−.002	−0.04; 0.04	.907	.33	0.11; 0.55	.003
$p < .5$	−.02	−0.07; 0.03	.390	.05	0.01; 0.10	.019	−.003	−0.05; 0.04	.864	.28	0.05; 0.50	.015

All models are adjusted for sex, genetic principal components, and age at sleep assessment.
[a]Estimates based on linear mixed model with random effect for child's age. Adjusted *p*-value considered significant $p < .0045$ are indicated with bold.
[b]Estimates based on individual multiple linear regression models. Adjusted *p*-value considered significant $p < .00065$ are indicated with bold.

The positive associations of PRS-SD and actigraphically estimated longer sleep are in line with a previous cross-sectional study reporting that PRS-SD was associated with longer parent-reported sleep duration in children and adolescents (Dashti et al., 2019). In adolescents, the genetic predisposition for longer self-reported sleep was not only reflected in longer sleep but also in more wake after sleep onset. Genetic variants associated with longer self-reported sleep may be associated with more objectively measured wake after sleep onset because actigraphy assesses movement; thus, longer sleep duration is typically associated with longer time in bed and subsequently with more arousals that may or may not be subjectively experienced as wakefulness. The effect sizes, though small, show that genetically determined longer sleep comes at the price of increased wakefulness during the sleep period.

Dashti et al. (2019) also showed that the PRS for longer sleep duration is associated with other cardio-metabolic health indices, but also with the development of insomnia (Dashti et al., 2019). Our analyses at more lenient p-value thresholds ($pT < 0.05$, 0.1, and 0.5) showed that a stronger genetic propensity for longer sleep (higher PRS-SD) was associated with less mother-reported sleep problems at age 10–14 years, but not yet so earlier in childhood. PRSs including genetic variants that do not reach genome-wide significance may better chart the polygenic nature of a trait, for example sleep duration (Marees et al., 2018). This approach can also lead to the inclusion of more variants that overlap with other sleep characteristics, for example genes determining both sleep duration and insomnia (Dashti et al., 2019; Jansen et al., 2019). Indeed, genetic correlation between self-reported sleep duration and insomnia is estimated between −0.48 (Jansen et al., 2019) and −0.52 (Dashti et al., 2019); thus, genes responsible for these traits are partially overlapping. Therefore, genetic variants that contribute small effects for the interindividual variability in reported sleep duration in adults may also contribute to poor sleep (i.e. insomnia symptoms) emerging in adolescence. It could be speculated that mothers report more sleep problems for adolescents who are genetically predisposed to shorter sleep. Alternatively, these effects could be explained by an underlying characteristic which shows high correlations with sleep duration and insomnia both on a phenotypic and genetic level [e.g. psychiatric (O'Connell et al., 2021), neurologic (Brainstorm et al., 2018), or metabolic disorders (Mei et al., 2020)].

Vice versa, the PRS-I was not associated with actigraphic sleep parameters, which could be due to lack of power, but could also indicate that the polygenic risk for insomnia specifically predicts perceived (subjective) sleep, in particular insomnia-like symptoms, and not with sleep duration. This indicates that genetic variants associated with insomnia are specifically associated with subjective sleep problems and their effects can be observed already at 1.5 years of age. On a broader note, these results demonstrate that subjective experience of sleep and objective sleep are at least partly genetically independent and also point toward a limited applicability of actigraphy in the context of insomnia disorder. Another polygenic risk study (Koshmanova et al., 2022), however, strongly supports the idea that polygenic propensity for insomnia is associated with objective indicators of suboptimal sleep quality, that is less deep sleep (slow-wave sleep) as measured with polysomnography. The genetic propensity for insomnia is thus persistent, and insomnia may be lifelong trait, unlikely to be learned later in life. This highlights the importance of early detection and intervention for sleep problems in childhood. However, given that our models explain <1% of the variance, the development and lifetime course of insomnia are likely multifactorial and should likely be treated as such from an early age. Remission rates of adult insomnia remain below 40% with the current preferred treatment and only marginally increase by adding pharmaceuticals (Morin et al., 2020; Seyffert et al., 2016); thus, our findings also open up an intriguing new view on how to combat insomnia. Possibly, chronic insomnia may be prevented by targeting sleep of children with a high PRS-I.

Importantly, by showing that genes predisposing adults to insomnia play a role in poor sleep from toddlerhood to adolescence we provide indirect evidence for a persistency of the 'poor sleeper' phenotype across the lifetime. This opens the opportunity to design and conduct further research on genetically informed early detection and prevention of sleep problems. This is particularly important as sleep problems can be persistent from childhood to adulthood, and early sleep intervention programs have been shown to also benefit school and behavioral outcomes (Siva Kumar, Rajan, Pasupathy, Chidambaram, & Baskar, 2021). Finally, as treating insomnia in adulthood results in improvement in depressive symptoms (Ho, Chan, Lo, & Leung, 2020; Leerssen et al., 2020), supporting optimal sleep early in childhood may also offer an opportunity to prevent affective disorders before they develop. If our study is replicated, intervention programs that target sleep could be performed in subpopulations that are genetically vulnerable to poor sleep (e.g. children of parents with insomnia disorder), potentially benefiting physical and mental health from childhood and extending into adult years.

Our study has multiple strengths including the prospective design with repeated measures of mother-reported sleep over a follow-up of up to 15 years, the availability of genotype data in a large group of children, as well as, in a subsample, actigraphic measures of sleep. Since polygenic risk

is determined at conception, the reported associations should be independent of confounding and thus provide indirect evidence for genetically determined persistence of individual differences in sleep from childhood to adulthood.

A limitation of the findings is that in spite of their overall congruency, the significance of most of the individual time-point analyses did not survive correction for multiple testing; thus, chance could explain some of the findings. However, longitudinal models showed a consistency of the observed effects between PRS-I and sleep problems across childhood and early adolescence and were robust to correction for multiple testing and adjustment for maternal psychopathology. In addition, given that both PRSs and sleep outcomes have inherently large proportion of shared variance (repeated measures), the multiple testing correction applied may still be too stringent and potentially remove some true effects. Given the low explained variance of our models, however, the clinical or ecological implications of our findings may be limited. This could be related to the nature of the sample (pediatric), to the measures used (mother report), but could also be related to the low explained variance in the GWAS (2.6% for insomnia (Dashti et al., 2019; Jansen et al., 2019) and 0.7% for sleep duration). There are also some methodological limitations that deserve mention. First, mother-reported sleep may be influenced by maternal perceptions and expectations. Although we have included a more objective assessment of sleep, future studies should aim to also include self-reports and reports of the father, or other care givers. Second, the actigraphy data collection was performed only in a subsample, which limits the ability for direct comparisons of the reported finding (e.g. associations of polygenic propensity for insomnia with mother-reported sleep problems vs. with actigraphic sleep). Third, the C + T calculated PRSs need to be further evaluated in other pediatric cohorts. Moreover, the PRSs cannot be generalized to other ethnic groups due to differences in allele frequencies, LD patterns, and effect sizes of common SNPs across different ethnic populations.

In conclusion, our study shows that genetic predisposition to insomnia, as determined in adults, is reflected in poor sleep already in toddlerhood and persists to adolescence. Specifically, we showed that polygenic risk for insomnia is observable on a phenotypic level already in toddlerhood (e.g. more mother-reported sleep problems). We moreover showed that effects of genetic vulnerability to insomnia differ from effects of an increased genetic liability for longer sleep duration. Genetic liability for a longer sleep duration is associated with longer actigraphic sleep duration, but may also lead to more wake during the night. Our results highlight the importance of considering qualitative, quantitative, objective, and subjective sleep characteristics from early age onwards. The manifestation of genetic liability in sleep phenotypes early in life offers potential targets for early risk estimation, detection, prevention, and intervention, with possible long-term benefits.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. (a) Amount of variance explained (R^2) explained by the PRS-I for each PRS threshold. (b) Amount of variance explained (R^2) explained by the PRS-SD for each PRS threshold.

Table S2. Associations between polygenic risk scores for insomnia and sleep duration and sleep diary measures.

Table S3. Longitudinal associations between polygenic risk scores for insomnia and sleep duration and parasomnia items from the Child Behavior Checklist.

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Dr. Kocevska conceptualized and designed the study, ran the analyses, and drafted the manuscript. Prof. Dr. van Someren obtained the funding, conceptualized the design of the study, supervised the work, and co-drafted and critically reviewed the manuscript for important intellectual content. Dr Trajanoska, Dr. Mulder, and Dr. Koopman-Verhoeff helped with the acquisition, analysis, or interpretation of data and critically reviewed the manuscript. Dr. Tiemeier and Dr. Luik supervised the work and provided critical revision of the manuscript for important intellectual content. All the authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Key points

- Our study shows that the genetic variants associated with insomnia and sleep duration identified in adults affect sleep patterns already in childhood.
- The genetic susceptibility for insomnia affects sleep already from 1.5 years of age and continues to do so during childhood and (pre-)adolescence development.
- At the age of 10–15 years, the genetic propensity for longer sleep duration comes at the cost of more wake after sleep onset.
- Genetic liability for the 'poor sleeper' phenotype is observable early in childhood and likely persists into later life.

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