Title: Shared genetic architecture underlying sleep and weight in children

Running title: Shared genetics of sleep and weight in children

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Abstract

Meta-analyses suggest shorter sleep as a risk factor for obesity in children. The prevailing hypothesis is that shorter sleep causes obesity by impacting homeostatic processes. Sleep duration and adiposity are both heritable, and the association may reflect shared genetic aetiology. We examined the association between a body mass index (BMI) genetic risk score (GRS) and objectively-measured total sleep time (TST) in a cohort of Norwegian children (enrolled at age 4 in 2007-2008) using cross-sectional data at age 6. The analytical sample included 452 6-year old children with complete genotype and phenotype data. The outcome was actigraphic total sleep time (TST) measured at age 6 years. Genetic risk of obesity was inferred using a 32-single nucleotide polymorphism (SNP) weighted GRS of BMI. Covariates were BMI-Standard deviation scores (SDS) (which takes into account age and sex) and, in a sensitivity analysis socioeconomic status. Analyses consisted of Pearson's correlations and linear regressions. In our sample, 54% of participants were male; mean (SD) TST, age and BMI were 9.6 (0.8) hours, 6.0 (0.2) years and 15.3 (1.2) kg/m^2, respectively. BMI and TST were not correlated, r=-0.003, p=0.946. However, the BMI GRS was associated with TST after adjusting for BMI-SDS, standardised ß=-0.11; 95% confidence interval (CI)=-0.22, -0.01. To our knowledge, this is the first study to establish a relationship between genetic risk of obesity and objective sleep duration in children. Findings suggest some shared genetic aetiology underlying these traits. Future research could identify the common biological pathways through which common genes predispose to both shorter sleep and increased risk of obesity.

Keywords: total sleep time, body mass index, genetic risk score, objective measurements.

Main text

Introduction

Meta-analyses have established that shorter sleep duration is robustly associated with increased obesity risk in children [1–4]. Some studies find that boys are more susceptible to sleep loss and thus, at greater risk of becoming obese [5]. The prevailing hypothesis is that shorter sleep causes homeostatic changes that may causally increase obesity risk. For example, evidence suggests that short sleep can lead to alterations in the 'hunger hormones', leptin (which promotes satiety) and ghrelin and that these changes lie on the causal pathway between sleep duration and obesity [6–8]. In one of the first studies to show this, participants were subjected to two days of sleep restriction and two days of sleep extension, during which calorie intake and exercise were under systematic control [8]. Findings indicated that leptin levels decreased by 18%, whilst hunger, ghrelin and appetite increased by 24%, 28% and 23%, respectively [8]. Recent research has also started to examine the reverse relationship, as well as a bidirectional relationship between sleep and weight, such that baseline BMI might also predict prospective changes in sleep duration, yet this has only been found in South Asian children, to date [9]. An alternative hypothesis is that sleep and weight are associated because they share some of their common genetic aetiology. Twin and family studies report high heritability for body mass index (50%-90%) [10–12], and moderate heritability for self-reported sleep duration (30%-50%) [11,13,14] in both adults and children One of these twin studies found no evidence of shared underlying genetic components between BMI and sleep duration [14].

Another method for examining shared genetic aetiology underlying sleep and adiposity is to establish if common genetic variants that predispose to higher BMI, predispose also to shorter sleep duration. Genetic risk scores (GRS) are now widely used to aggregate genome-wide markers to infer individuals' genetic predisposition to a trait of interest, as well as to highlight potential shared genetic aetiology between two traits [15]. Genome-wide meta-analyses have identified 97 common genetic variants that are robustly associated with BMI in adults and children, and in the aggregate explain approximately 3% of the variation.

Two studies to date have examined the relationship between a genetic risk score for obesity (comprising 69 single nucleotide polymorphisms identified through a genome-wide meta-analysis of BMI) and self-reported sleep duration in approximately 120,000 adults from the UK Biobank, who were between 40 and 69 years of age at baseline [16,17].They found no association between the genetic risk score and sleep duration, but this does not necessarily

mean that BMI and sleep duration do not share underlying genetic influences in children, via perhaps, previously understudied biological pathways. This is also important because research suggests that the relationship between sleep duration and BMI weakens with age [18,19]. Further, although individuals' genomes remain unchanged throughout the life course, differing levels of gene expression have been linked to specific disease states and cellular responses and these processes can be age-related [20].

No previous studies have investigated the association between genetic risk of obesity and sleep duration in children, and no studies with children or adults have used objectively measured sleep duration. This is a considerable advantage, as self-reported sleep duration may be prone to misreporting and bias [21]. However, actigraphy has been validated against polysomnography [22–25], which is the gold standard measurement. The study reported here examined, for the first time, the association between a BMI GRS and actigraphy-measured sleep duration in a community sample of Norwegian children. We hypothesised that higher genetic risk of obesity might be associated with shorter sleep duration in children, unlike in adults, consistent with a common genetic architecture underlying both sleep and weight in children.

Methods

Sample

We analysed data from the second wave (age 6) of the Trondheim Early Secure Study (TESS), comprised of Norwegian children born in Trondheim in 2003 and 2004. Detailed recruitment procedure and sample characteristics are described elsewhere [26]. Because the main aim of TESS was to capture mental health, participants were screened with the parent-reported Strengths and Difficulties Questionnaire (SDQ) (emotional and behavioural problems) for 4- to 16-year-olds [27]. To oversample for mental health problems and thus increase variability and statistical power, children were divided into four strata based on these scores (0-4, 5-8, 9-11, 12-40). The probability of being selected increased with increased SDQ scores (37%, 48%, 70% and 89% from the respective strata). The sampling was accounted for in the statistical analyses (see below). Ethical approval for TESS was granted by the Regional Committee for Medical and Health Research Ethics, Mid-Norway and written informed consent was obtained. Participants were included who had genotype data, as well as BMI, actigraphy-measured total sleep time (TST). Thus, we had a total of 452 children for this analysis, the majority (>95%) of whom were of White ethnicity (Table 1).

Measures

TST was measured with the ActiGraphTM GT3X accelerometer (Manufacturing Technology Incorporated, Fort Walton Beach, FL, USA). Participants wore the actigraphs on their hip for 7 consecutive days, including whilst asleep and were instructed to remove them only whilst showering or bathing. TST was converted from raw data by employing Sadeh's algorithm [28], once time in bed and out of bed was manually set by examining each night, using ActiLife software. Sadeh's algorithm automatically differentiates prolonged sitting from sleep. In addition to actigraphy, a questionnaire was supplied asking whether participants had been ill and more or less active than usual during the seven days of measurement. Actigraphy has been shown to be valid and reliable for measuring TST, when compared to polysomnography (PSG), which, as mentioned earlier, is the gold standard method.

Researchers measured body weight (kg) and height (m) of the children using digital scales (Heightronic digital stadiometer: QuickMedical, Model 235A and Tanita BC420MA). BMI was converted to age- and sex-adjusted standard deviation scores (SDS) derived using British reference data [29] as previous TESS papers have used these, rather than Norwegian reference data [30]. Weight status (healthy weight, overweight and obese) was determined using the BMI IOTF cut-offs for children. Sleep duration categorization of <9 and ≥9 hours was used as per the latest recommendations from the American Academy of Sleep Medicine (AASM) [31].

Genotyping and genetic risk score (GRS)

DNA was extracted and stored from a 2-milliletre saliva sample taken from TESS participants at the second data collection wave (age 6), using the Oragene DNA saliva kit (DNA Genotek). To generate a Custom Oligo Assay Pool, genetic loci of interest were sent to Illumina. Genotyping was performed at the Norwegian University of Science and Technology's Genomics Core Facility, with the GoldenGate Genotyping Universal-32 assays (Illumina). The arrays were subsequently scanned using an Illumina HiScan and processed in GenomeStudio.

A 32-SNP BMI GRS (see Table 2) was constructed using external weights from the Genetic Investigation of Anthropometric Traits Consortium (GIANT) [32]. The BMI GRS was standardised to have a mean=0 and SD=1. These SNPs were the ones that had been discovered through GWAS when TESS participants were genotyped. This GRS was also recently used in another TESS publication [30].

Statistical analyses

We obtained either means and SDs for continuous measures, or frequency and %s for categorical measures to describe our sample (Table 1). We examined the phenotypic association between BMI and TST, as well as BMI-SDS and TST, using Pearson's correlations. Assumptions for Pearson's correlations and linear regressions were checked, including level of measurement (all measures used were continuous), linearity and outlier influence. We also checked for homoscedasticity of residuals with both a diagnostic plot and the Breusch-Pagan test. The former showed that there could be some cause for concern, but the test had a p-value =0.483 indicating that the variance of the residuals was not likely to be heterogenous. Multicollinearity was checked with the variance inflation factor (VIF) and all values (in our multivariable Model 2 as detailed below) were 1, indicating no cause for concern. Outlier influence was checked using Cook's distance and with a cut-off of 4/n (4/452) all of the d values were very close to 0. Our scatter plot of the BMI GRS and objective total sleep time showed that, in line with the weak Pearson's correlation coefficient (r=-0.09, p=0.047) the linear relationship between these variables was weak. Thus, we performed additional analyses including separate quadratic (GRS_{BMI}^2) and cubic (GRS_{BMI}^3) terms in our models and we saw no evidence of non-linear relationships between the BMI GRS and TST (all beta coefficients for the linear relationship remained similar enough to not affect interpretation, and p-values for the quadratic and cubic terms were >0.05).

Linear regression analyses were used to investigate the association between the BMI GRS and TST, whereby we first ran a crude univariable model (Model 1=GRS_{BMI} only), followed by a model with additional adjustment for BMI-SDS (Model 2= GRS_{BMI} + BMI-SDS). We also performed exploratory analyses to understand the potential interaction between the BMI GRS and sex in relation to TST, but as this interaction was not significant (*p*=0.151) in a regression model that included the BMI GRS and the BMI GRS*sex term, we did not include this in any further analyses. As a sensitivity analysis (Model 3), we also adjusted for socioeconomic status (SES – measured in TESS as 0=professionals/skilled labour, n=583 and 1=unskilled labour, n=192) to check whether the BMI GRS was associated with SES. Analyses were performed in Stata, v.14 and because the sample was screen-stratified, probability weights where the number of children in the stratum were divided by the number of participants in the same stratum were calculated to arrive at corrected population estimates. A 5% level of significance was adopted and our main hypothesis was 2-sided. Results are expressed as standardised beta coefficients and represent SD differences in TST per 1-SD increase in the BMI GRS.

Results

Sample characteristics and Pearson's correlations

Mean sleep duration in our sample was 9.6 hours (SD=0.8, minimum= 6.3, maximum= 12.4). As there was only one obese participant, we merged the overweight and obese categories (Table 1). The mean age was 6.0 years (SD=0.2) and our sample was 54% male. We observed no phenotypic correlation between BMI and TST, r= -0.003, p=0.946, or between BMI-SDS and TST, r=-0.001, p=0.980.

Association between the BMI GRS and BMI, and variance explained by the BMI GRS
The BMI GRS was associated with BMI, ß= 0.17; 95% CI= 0.03, 0.31. The BMI GRS explained 1.8% of the variance in BMI and 1.5% of the variance in BMI-SDS.

Associations between the BMI GRS and TST

In our data, the BMI GRS explained 1.1% of the variance in TST. In the crude linear regression, the BMI GRS was associated with shorter TST by 0.11 SDs (ß=-0.11; 95%CI=-0.21, -0.01). In Model 2, when adjusting for BMI-SDS (which takes into account age and sex), the BMI GRS remained associated with TST (ß=-0.11; 95%CI=-0.22, -0.01). Our final model (Model 3) was a sensitivity analysis additionally adjusting for SES and showed consistent results with no attenuation of the association between GRS_{BMI} and TST (ß =-0.11; 95%CI=-0.21, -0.01).

Discussion
To our knowledge, this was the first study to examine the association between measured genetic risk of obesity, and objectively measured sleep duration in children. We found that higher genetic risk of obesity was associated with a 5-minute decrease in objectively-measured TST independently of age, sex and BMI, in this sample of 6-year-old children. Our 32-SNP BMI GRS accounted for 1.1% of the variance in TST in our sample, which is reasonably comparable the variance explained in BMI (1.7%). These results suggest that shared genetic aetiology may exist between BMI and total sleep time, as measured by waist actigraphy. Our genetic findings support the cross-sectional observational literature on BMI and sleep duration in children (Liu et al., 2012) and highlight one important potential pathway via which this association may operate.

The phenotypic correlation between BMI and TST in our data was very small and not significant, although it was in the same direction as the association between the BMI GRS and TST. One possible explanation for the discrepancy between phenotypic and genetic results could be that because Trondheim is not a particularly obesogenic environment, the children in our sample are able to maintain their BMI within a healthy range, irrespective of

their genetic risk of obesity. This is reflected in our sample characteristics which clearly shows that 84.5% of the sample are within the normal weight range. In line with this, a recent study in adults found that living in an obesogenic environment, particularly in highly deprived areas, can exacerbate the genetic risk of obesity [34] and thus, increase an individual's odds of becoming overweight or obese. However, this has not yet been investigated in children. Also, interestingly, a recent analysis of TESS showed that although most children in the sample have a BMI within the healthy range, genetic risk did in fact predict increased BMI over time [30].

Although the biological mechanisms that might be shared by BMI and sleep duration remain largely unknown, we consider a specific pathway that could, at least partially, underlie this shared aetiology. Our 32-SNP GRS included an intron (rs9939609) in the fat-mass and obesity-associated (FTO) gene, as well as a variant in the melanocortin receptor-4 (MC4R) gene. FTO and MC4R are both highly expressed in the hypothalamus [35], which contains the ventrolateral preoptic nucleus (VLPO), a modest cluster of neurons that are activated by sleep-promoting neurotransmitters. However, this is only one example of a relevant pathway and future research could perform downstream analysis to explore whether any robustly-associated BMI genetic variants are on the causal pathway for sleep duration.

Briefly, we acknowledge that our study has certain limitations. Firstly, our findings may only be applicable to children of White/European descent. Secondly, our BMI GRS was constructed using only 32 GWAS SNPs, which does not cover the whole spectrum of more recent BMI genome-wide SNPs [35]. However, this GRS was significantly related to BMI in our sample and has previously been shown to be associated with prospective BMI in TESS [30]. Thirdly, we did not perform power calculations for our analyses, yet our sample size was predetermined and thus, not amenable to change. The realised power of our analyses is communicated through the widths of the 95% confidence intervals. Fourthly, due to pleiotropy, one or more of the BMI SNPs may be associated with other traits [36]. Related to this point, is the possibility that these SNPs might affect sleep duration via another indirect pathway, such as for example, appetite [37].

Our study also possesses important strengths. We analysed objective total sleep time, measured by actigraphy, which is less prone to error than self-reported sleep duration [38,39]. BMI was researcher-measured, rather than parent-reported. Finally, when we adjusted for SES we saw no evidence that this confounded the relationship between the BMI GRS and TST in our sample.

In conclusion, this study found a novel association between a BMI GRS and sleep duration in children. Our findings highlight the existence of potentially important shared genetic underpinnings between these two highly complex phenotypes. Future studies should investigate this association in larger samples, with other sleep phenotypes, in distinct age groups (including older adults), and with prospective data.

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Table 1. *Sample characteristics in TESS, at age 6*

	Mean (SD)/N (%)
Age (years)	6.0 (0.2)
BMI (kg/m^2)	15.3 (1.2)
BMI-SDS	-0.2 (0.8)
Sex *Boys* *Girls*	 246 (54.4%) 206 (45.6%)
Weight status *Underweight* *Normal weight* *Overweight/obese*	 52 (11.5%) 382 (84.5%) 18 (4.0%)
Total sleep time (hours)	9.6 (0.8)

Note. BMI= body mass index, BMI-SDS=Body Mass Index Standard Deviation Score.

Table 2. *SNPs included in the BMI GRS*

Chr	Nearest Gene	rs	Alleles	BMI-Increasing Allele	Frequency of BMI-Increasing Allele	GWAS Effect-Size for BMI
1	NEGR1	rs2568958	A/G	A	60%	0.13
	TNNI3K	rs1514177	C/G	G	43%	0.07
	PTBP2	rs11165643	C/T	T	63%	0.06
	SEC16B	rs10913469	C/T	C	21%	0.21
2	TMEM18	rs7567570	C/T	C	82%	0.31
	ADCY3, RBJ	rs10182181	A/G	G	51%	0.14
	FANCL	rs887912	A/G	A	29%	0.10
3	CADM2	rs7640855	A/G	A	20%	0.10
	ETV5	rs7647305	C/T	C	79%	0.12
4	SLC39A8	rs13107325	C/T	T	8%	0.19
5	FLJ35779	rs2112347	G/T	T	65%	0.10
	ZNF608	rs6864049	A/G	G	55%	0.07
6	TFAP2B	rs2206277	A/G	A	18%	0.13
9	LRRN6C	rs1412235	C/G	C	31%	0.11
	LMX1B	rs867559	A/G	G	21%	0.24
11	STK33, RPL27A	rs4929949	C/T	C	52%	0.06
	BDNF	rs6265	A/G	G	52%	0.18
	MTCH2	rs10838738	A/G	G	34%	0.05
12	BCDIN3, FAIM2	rs7138803	A/G	A	36%	0.12
13	MTIF3	rs1475219	C/T	C	20%	0.09
14	PRKD1	rs11847697	C/T	T	3%	0.17
	NRXN3	rs10150332	C/T	C	23%	0.13
15	MAP2K5	rs2241423	A/G	G	78%	0.13
16	GPRC5B	rs12446554	G/T	G	87%	0.17
	SH2B1	rs4788102	A/G	A	39%	0.15
	FTO	rs9939609	A/T	A	36%	0.38
18	MC4R	rs921971	C/T	C	28%	0.21
19	KCTD15	rs29941	C/T	C	67%	0.06
	ZC3H4, TMEM160	rs3810291	A/G	A	68%	0.09

Note. BMI=body mass index, Chr=chromosome, GWAS=genome-wide association studies. Alleles are reported from the forward strand. The nearest gene is reported for the locus identified in the BMI GWAS by the GIANT consortium (Speliotes et al., 2010). GWAS effect

sizes are the per-allele change in BMI estimated in meta-analysis of BMI GWAS by the GIANT consortium.