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RESEARCH ARTICLE

Schizophrenia liability shares common molecular genetic risk factors with sleep duration and nightmares in childhood [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Sleep abnormalities are common in schizophrenia, often appearing before psychosis onset; however, the mechanisms behind this are uncertain. We investigated whether genetic risk for schizophrenia is associated with sleep phenotypes.
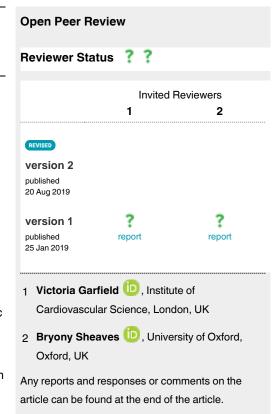
Methods: We used data from 6,058 children and 2,302 mothers from the Avon Longitudinal Study of Parents and Children (ALSPAC). We examined associations between a polygenic risk score for schizophrenia and sleep duration in both children and mothers, and nightmares in children, along with genetic covariances between these traits.

Results: Polygenic risk for schizophrenia was associated with increased risk of nightmares (OR=1.07, 95% CI: 1.01, 1.14, p=0.02) in children, and also with less sleep (β=-44.52, 95% CI: −88.98, −0.07; p=0.05). We observed a similar relationship with sleep duration in mothers, although evidence was much weaker (p=0.38). Finally, we found evidence of genetic covariance between schizophrenia risk and reduced sleep duration in children and mothers, and between schizophrenia risk and nightmares in children.

Conclusions: These molecular genetic results support recent findings from twin analysis that show genetic overlap between sleep disturbances and psychotic-like experiences. They also show, to our knowledge for the first time, a genetic correlation between schizophrenia liability and risk of nightmares in childhood.

Keywords

polygenic risk, genetic correlation, schizophrenia, sleep, childhood, ALSPAC

Open Peer Review

Reviewer Status ? ?

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	1	**2**
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version 1 published 25 Jan 2019	? report	? report

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the Avon Longitudinal

Study of Parents and Children (ALSPAC) gateway.

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Author roles: Reed ZE: Formal Analysis, Investigation, Writing – Original Draft Preparation; **Jones HJ**: Formal Analysis, Methodology, Writing – Review & Editing; **Hemani G**: Methodology, Writing – Review & Editing; **Zammit S**: Conceptualization, Supervision, Writing – Review & Editing; **Davis OSP**: Conceptualization, Supervision, Writing – Review & Editing

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Introduction

Sleep disturbance is very common in psychotic disorders such as schizophrenia. For example, a meta-analysis of observational studies showed that sleep efficiency and total sleep time are diminished in schizophrenia, whilst sleep latency is increased, independent of medications[1]. These findings are supported by polysomnography studies[2]. Similarly, sleep dysfunction is more common in individuals at ultra-high-risk for psychosis[3], and is associated with higher risk of incident psychotic experiences[4], paranoid thinking[5] and hallucinatory experiences[6] in population-based cohort studies.

A recent report from the Twins Early Development Study (TEDS) demonstrated that psychotic-like experiences and sleep disturbances in adolescence share genetic influences[7]. Using data from 4,800 pairs of twins, they found a mean genetic correlation of 0.54 between self-reported paranoia, hallucinations and cognitive disorganisation, and self-reported sleep quality and insomnia. Bivariate heritability analyses showed that shared genetic influences accounted for on average 65% of the phenotypic correlation between phenotypes. This genetic relationship could be explained in several ways. For example, genetic variants could independently influence sleep and psychotic-like experiences, both sleep and psychotic-like experiences could be affected by a shared genetically influenced process, or there could be a causal relationship between sleep and psychotic-like experiences. We aimed to build on these analyses by using a polygenic risk score derived from the largest genome-wide association study (GWAS) of schizophrenia to date[8] to investigate the genetic relationship between schizophrenia liability, sleep duration and childhood nightmares through two complimentary approaches.

First, we examined whether genetic risk for schizophrenia is associated with sleep dysfunction during childhood and adulthood in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC). We did this by combining information from the Psychiatric Genomics Consortium (PGC) GWAS into a polygenic risk score that indexes cumulative genetic risk for schizophrenia. The PGC report a variance explained in schizophrenia by the polygenic risk score at a p-value threshold of 0.05 of 7%[8]. This approach has previously shown that genetic risk for schizophrenia is associated with phenotypes such as cognitive deficits[9,10], anxiety and negative symptoms[11] during childhood and adolescence.

Second, we assessed the genetic covariance between schizophrenia and sleep measures in childhood and adulthood using polygenic risk score data to estimate the average genome-wide relationship between these phenotypes.

Methods

Cohort description

ALSPAC is a prospective birth cohort study which initially recruited 14,541 pregnant women living in the Bristol area in the UK, with an expected delivery date from 1st April 1991 to the 31st December 1992[12]. A total of 14, 676 foetuses were included in the initial ALSPAC sample, with 14,062 live births and, of these, 13,988 were alive after 1 year. At 7 years of age further recruitment occurred, resulting in a total sample size for analyses of 15,458, with 14,755 live births and 14,701 alive at 1 year. Data has been collected on mothers and their offspring via questionnaires, clinic visits and other forms of information. The ALSPAC sample is generally representative of the UK population of the same age, although, like many other cohorts, there is over-representation of more affluent groups (6.22% with low household income, as indicated by free school meals, in ALSPAC compared to 12.49% in the National Pupil Database) and under-representation of non-White minority ethnic groups (96.09% White ethnicity in ALSPAC compared to 86.50% in the National Pupil Database)[12]. However, to avoid false positive results from population stratification, our analyses included only those with European ancestry. We also excluded those without both the genetic and the phenotypic data required, leaving between 5,121 and 6,058 children and 2,302 mothers in each analysis. Table 1 summarises the number of individuals with data available for each of

Table 1. Number of genotyped participants with each outcome measure.

Age	Outcome measure	N[1]	Percentage female
Children			
4 years 9 months	Sleep duration	6058	48.6%
5 years 9 months	Sleep duration	5641	48.9%
6 years 9 months	Sleep duration	5534	48.9%
9 years 7 months	Sleep duration	5735	49.4%
11 years 8 months	Sleep duration	5170	50.2%
12 years	Nightmares	5121	51.1%
Mothers			
Average age of 40 years 9 months	Sleep duration	2302	100%

[1]The number of participants with both phenotype and genotype data available

the outcome measures. Including all the time points examined for sleep duration, there were a total of 28,138 data points.

Further details of ALSPAC can be found through the searchable data dictionary. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local Research Ethics Committees. Written informed consent was obtained from participants or parents of participants, for children. Children were invited to give assent where appropriate. Study members have the right to withdraw their consent for elements of the study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available on the study website (http://www.bristol.ac.uk/alspac/researchers/research-ethics/).

Phenotypic measures

Sleep duration. Information about sleep duration in children was obtained from parent-completed questionnaire data collected at the ages of 4, 5, 6, 9 and 11 years. Sleep duration was calculated as the difference between reported time that the child went to sleep and time they awoke on weekdays.

Sleep duration in the mothers was assessed through questionnaire data collected when they were on average 40.78 years old (SD=4.52). Participants were asked how many hours and minutes they slept for on work days on average in the last year.

Nightmares. The presence of nightmares was assessed through semi-structured interviews with participants at around the age of 12 and a half years[4,13]. Briefly, children were asked questions about nightmares, night terrors and sleepwalking since their 12th birthday, such as *"Since your 12th birthday have you had any dreams that woke you up? Were they frightening?"*. Positive responses were followed by further questions to distinguish between nightmares and night terrors. These were then rated as present, suspected or absent. In this study we use data on nightmares only as this was associated with psychotic experiences in a previous study[13], and we wanted to examine whether this extended to genetic risk for schizophrenia.

Covariates. We used the child's sex and age as covariates in the analyses of children's sleep outcomes. We included mother's age as a covariate in the analyses of mother's sleep duration.

Genetic data

Genetic data for children and mothers was collected in the form of blood samples during clinic visits. Genotyping for children was conducted using the Illumina HumanHap 550quad chip and data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. ALSPAC mothers were genotyped using the Illumina human660W-quad array at Centre National de Génotypage (CNG) and genotypes were called with Illumina GenomeStudio.

Quality control measures were conducted, and SNPs were excluded based on missingness, Hardy-Weinberg equilibrium P value and minor allele frequency. Samples were excluded based on gender mismatches, indeterminate X chromosome, minimal or excessive heterozygosity, disproportionate missingness, insufficient sample replication and evidence of population stratification. A total of 9,115 children and 500,527 SNPs passed the filters and data was imputed with a phased version of the 1000genomes reference panel from the Impute2 reference data repository. 9,048 mothers and 526,688 SNPs passed the filters and data was imputed using Impute V2.2.2 against the reference panel (all polymorphic SNPs excluding singletons), using all 2186 reference haplotypes (including non-Europeans). After these procedures, removing participants with cryptic relatedness >5% and those who had withdrawn consent, there were 8,252 children and 8,252 mothers with genotype data available.

Polygenic risk score construction

We constructed polygenic risk scores using Plink version 1.9[14] for each individual using summary statistics from the PGC schizophrenia GWAS[8]. SNPs with an imputation quality score greater than 0.9 and which were available in ALSPAC were clumped for linkage disequilibrium (LD), using an R^2 of 0.25. We generated weighted polygenic risk scores by summing the number of risk alleles present for each SNP (0, 1 or 2) weighted by the logarithm of its discovery sample odds ratio (OR). For estimating covariance (see below) we constructed twelve polygenic risk scores based on different thresholds of the schizophrenia GWAS p-values (1×10^{-7} to 0.5). The score constructed with a p-value threshold (pT) of 0.05 captured the most variance in genetic liability for schizophrenia in the PGC sub-datasets[8], so we used this as our primary exposure, with the remainder reported in Extended data Table 1 and Extended data Figure 1[15]. Polygenic risk scores were z-standardised, so effect sizes are given per standard deviation (SD) increase in polygenic risk score.

Statistical analysis

Association between polygenic risk score and sleep phenotypes. We conducted statistical analyses in R version 3.2.2[16] and Stata version 14.2[17]. First, we investigated the association between the polygenic risk score for schizophrenia liability and sleep duration in childhood, by combining all time points into one stacked dataset. We used a linear mixed-effects model, with age nested within family ID as a random effect and covariates age, age[2] and sex. We tested for an association between the polygenic risk score for schizophrenia liability and nightmares using an ordinal model with sex as a covariate. We tested the association between the polygenic risk score for schizophrenia liability and sleep duration in mothers using a linear model with age as a covariate. To estimate the variance explained by the schizophrenia polygenic risk score at pT 0.05 for each outcome we obtained r-squared values from models without covariates; an adjusted r-squared was obtained from the linear model, a pseudo r-squared was obtained from the ordinal model and a marginal r-squared (the proportion of variance explained by the fixed factors) was obtained for the linear mixed-effects model.

Estimating genetic covariance between schizophrenia liability and sleep phenotypes in childhood and adulthood. Because individual level data were available for the sleep phenotypes

and summary data were available for the schizophrenia phenotype, we used the Additive Variance Explained and Number of Genetic Effects Method of Estimation (AVENGEME)[18] to estimate the genetic covariance between schizophrenia liability and sleep duration and schizophrenia liability and nightmares in children, and between schizophrenia liability and sleep duration in mothers. To estimate a genetic model AVENGEME used the T-scores from results of the association between a series of polygenic risk scores at different discovery sample thresholds and the outcomes, sample sizes from the training and test samples, the number of variants used to create the scores, the p-value thresholds used to create the scores and the population prevalence of schizophrenia (we used 0.04) and case/control sampling fractions for the PGC data (0.43). Using this information, the approach is able to estimate the variance explained by genetic effects in the training sample, the variance explained by the polygenic risk score in the outcomes in ALSPAC, the genetic covariance between the training and target samples and the proportion of null SNPs with no effect on the trait in the training sample.

Results
Association between polygenic risk of schizophrenia and sleep phenotypes

Sleep duration in children. We found that a 1SD increase in the schizophrenia polygenic risk score was associated with a decrease in sleep duration of 44.52 seconds (95% CI: −88.98, −0.07; p=0.05) (Table 2). This was consistent across other polygenic risk score thresholds (pT 0.01–0.5) (Extended data, Table 1 and Extended data, Figure 1[15]). Examining sleep duration at different ages indicates that the effect size increases after age 5 (Extended data, Table 2[15]), although there was little evidence of an interaction between polygenic risk and age when an interaction term was added to the mixed-effects model (p=0.23).

Nightmares in children. We found evidence of increased risk of nightmares in those with greater polygenic risk (OR=1.07; 95% CI: 1.01, 1.14; p=0.02) (Table 2). We found a similar pattern for other polygenic risk score thresholds (0.05–0.5) (Extended data, Table 4 and Extended data Figure 2[15]). We found no evidence that the proportional odds assumption was violated (p=0.89).

Adjusting for the mothers' polygenic risk score in the analyses for sleep duration and nightmares in children had minimal effect (Extended data Tables 3 and 5[15]), indicating that the association is not confounded by the mother's psychopathology.

Sleep duration in mothers. The effect size of the association between schizophrenia polygenic risk score and sleep duration in mothers was similar to that seen in children, although evidence in support of this association was extremely weak (β=-57.90 seconds; 95% CI: −186.57, 70.76; p=0.38) (Table 2), most likely because the smaller sample size in the mothers' cohort led to lower power and less precise estimates. The results in mothers for other polygenic risk score thresholds can be seen in Extended data Table 6 and Extended data Figure 3[15], where scores calculated at more stringent p-value thresholds showed small positive associations (1×10^{-7} to 0.01) compared with small negative associations for pT 0.5 to 0.01.

Genetic overlap between sleep phenotypes and schizophrenia risk

In the ALSPAC children, our AVENGEME analyses indicate a positive covariance between nightmares and genetic liability for schizophrenia (covariance= 0.07, 95% CI: 0.05, 0.10). We found a negative covariance between sleep duration and genetic liability for schizophrenia in children (covariance= −0.008, 95% CI: −0.20, −0.003) and between sleep duration and genetic liability for schizophrenia in mothers (covariance= −0.04, 95% CI: −0.07, −0.01) (see Extended data Table 7[15] for full results).

Discussion

We investigated whether genetic risk for schizophrenia is associated with sleep outcomes during childhood and adulthood. Our results demonstrate, for the first time with molecular genetic data, that greater polygenic risk for schizophrenia is associated with shorter sleep duration, and we report a new association between greater polygenic risk of schizophrenia and increased risk of nightmares in early life.

These results build on previous twin study findings of shared genetic effects between schizophrenia and disrupted sleep[7] by showing that the association extends to collections of known and measured DNA variants identified through recent well-powered GWAS studies.

The effect size of schizophrenia genetic risk on sleep duration in childhood in this study is small, equating to only a few minutes of sleep difference between individuals scoring three standard deviations above, compared to individuals scoring three standard deviations below the mean for polygenic risk. This is likely to reflect both measurement error in the parent-reported outcome measures, measurement error in the estimation of the

Table 2. Associations between schizophrenia polygenic risk (pT 0.05) and sleep outcomes.

Sleep phenotype (units)	Beta or OR	95% CI	R-squared[1]	P-value
Sleep duration in children (seconds)	-44.52	-88.98, -0.07	0.0002	0.05
Nightmares in children (ordinal, OR)	1.08	1.01, 1.14	0.001	0.02
Sleep duration in mothers (seconds)	-57.90	-186.59, 70.76	0.00004	0.34

[1]The r-squared values were a marginal r-squared (the proportion of variance explained by the fixed effects) for sleep duration in children, Nagelkerke's pseudo r-squared for nightmares and the adjusted r-squared for sleep duration in mothers.

effect sizes of the individual DNA variants that make up the polygenic score, and the fact that the pool of variants for the polygenic score is itself an incomplete set of human genomic variation, where many of the variants are imperfect proxies for true causal variants. Because of this, it seems likely that this small effect size is indicative of the stronger polygenic association reported by twin studies. Similarly, although we have reported results for sleep duration, we have no direct measure of sleep quality, so the marginally lower duration of sleep may index greater disruption in sleep architecture that could have important effects on psychopathology. The R^2 value for sleep duration indicates that the schizophrenia polygenic risk score explains 0.02% of the variation in sleep. To put this into context, the PGC article reports that 7% of the variation in schizophrenia is explained by the polygenic risk score[8]. In cross-disorder analyses, the schizophrenia polygenic risk score explains smaller amounts of variation ranging from 0.08% for autism spectrum disorder to 2.3% for bipolar disorder[19], with similarly low variance explained for cognition (<1%)[10]. Therefore, whilst we find a small amount of variation explained in sleep duration, this is on a similar scale to other cross-disorder analyses.

We were, however, able to combine measures of sleep duration from several different ages, which is likely to have reduced error that was not shared across measurement occasions. In addition, the data we used were from a population-based sample that is less likely to be subject to some of the biases associated with ascertainment of clinical samples.

Whilst these findings provide evidence of some underlying shared genetic mechanism between sleep phenotypes and schizophrenia, they do not allow us to determine the reason behind these associations. They could be due to pleiotropy, the phenotypes lying on a causal pathway, population stratification (although this is less likely due to restriction to those with a European ancestry) or a third unknown variable that causes both outcomes, where the PGC schizophrenia GWAS may have an ascertainment bias based on recruitment of those who had experienced this third variable.

Recent studies indicate that there may be a causal relationship. For example, a trial of cognitive-behavioural therapy for insomnia in people with psychosis reported a decrease in persecutory delusions, hallucinations, anxiety and depression[20], suggesting a causal effect of sleep dysfunction on psychopathology post-onset of psychosis. However, another study reported more mixed results with psychosis symptoms[21], and effects of sleep disturbance on incidence of psychosis might differ from those on illness severity. Randomised control trials that examine the impact of sleep interventions on psychosis incidence are not feasible given the incidence rate of psychotic disorders. Our results seem to mostly suggest the direction described in the first study, where disturbed sleep may result in increased risk for schizophrenia as our study finds associations with disturbed sleep in childhood and adolescence prior to any disorder and the association is with schizophrenia risk. However, it is possible that the reverse direction could be true if schizophrenia risk results in sub-clinical symptoms that cause disturbed

sleep. There could also be a bi-directional causal association present or no causal association at all. Future well-powered analyses using techniques such as Mendelian randomisation will be useful for examining whether relationships are causal and the direction of causality.

Conclusion

Our results use molecular data to support and extend the findings from twin studies of an overlap of genetic influences on sleep phenotypes and schizophrenia. We have presented novel findings with our use of polygenic risk scores that specifically relate to liability for schizophrenia risk, as opposed to psychotic experiences. In addition, we found a novel relationship of shared genetic influences between schizophrenia and nightmares in children.

Data availability

Underlying data

The ALSPAC data management plan (http://www.bristol.ac.uk/alspac/researchers/data-access/documents/alspac-data-management-plan.pdf) describes in detail the policy regarding data sharing, which is through a system of managed open access. The steps below highlight how to apply for access to the data included in this paper and all other ALSPAC data. The datasets used in this analysis are linked to ALSPAC project number B2172; please quote this project number during your application.

1. Please read the ALSPAC access policy (PDF, 627 kB) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.

2. You may also find it useful to browse the fully searchable ALSPAC research proposals database, which lists all research projects that have been approved since April 2011.

3. Please submit your research proposal for consideration by the ALSPAC Executive Committee. You will receive a response within 10 working days to advise you whether your proposal has been approved.

If you have any questions about accessing data, please email alspac-data@bristol.ac.uk.

Extended data

Extended data Tables 1–7 and Figures 1–3 are available via the Open Science Framework: Schizophrenia liability shares common molecular genetic risk factors with sleep duration and nightmares in childhood. DOI: http://www.doi.org/10.17605/OSF.IO/HPZ5Y[15].

Supplementary Table 1. Associations between standardised schizophrenia polygenic risk score and sleep duration in children in ALSPAC.

Supplementary Table 2. Results from linear regressions for sleep duration and polygenic risk score for schizophrenia at each of five time points in childhood in ALSPAC.

Supplementary Table 3. Associations between standardised schizophrenia polygenic risk score and nightmares in children in ALSPAC.

Supplementary Table 4. Associations between standardised schizophrenia polygenic risk score and sleep duration in children in ALSPAC, whilst adjusting for mother's polygenic risk at the same threshold.

Supplementary Table 5. Associations between standardised schizophrenia polygenic risk score and nightmares in children in ALSPAC, whilst adjusting for mother's schizophrenia polygenic risk score at the same threshold.

Supplementary Table 6. Associations between schizophrenia polygenic risk score and sleep duration in mothers in ALSPAC.

Supplementary Table 7. Results from estimating a polygenic model using AVENGEME, with T-scores from the observational associations and the same 12 thresholds used for the polygenic risk score construction.

Supplementary Figure 1. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and sleep duration in children in ALSPAC.

Supplementary Figure 2. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and nightmares in children in ALSPAC.

Supplementary Figure 3. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and sleep duration in mothers in ALSPAC.

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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PubMed Abstract | **Publisher Full Text** | **Free Full Text**

Open Peer Review

Current Peer Review Status: ?   ?

Version 1

Reviewer Report 30 April 2019

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? **Bryony Sheaves** (iD)

Department of Psychiatry, University of Oxford, Oxford, UK

Thank you for the opportunity to review this manuscript which seeks to address whether molecular genetic risk for schizophrenia is associated with both sleep duration and nightmares in the ALSPAC sample. Sleep disruption is common in samples with psychosis, so examining a potential genetic association is a sensible line of inquiry. The manuscript is well written. The below points are for consideration, and primarily relate to contextualising the research among the wider sleep and psychosis literature.

Introduction:
- It is currently unclear why i) sleep duration and ii) nightmares specifically have been chosen as markers of sleep dysfunction. Introducing the reader to literature on what is already known about sleep dysfunction in clinical samples with psychosis is important to help readers understand the clinical presentation under investigation and choice of measures.

Methods:
- What is the rationale for the choice of covariates?

- The sleep duration data uses only weekday sleep which may be confounded by chronotype. Those who are 'evening types' may be more prone to longer sleep duration at the weekend to 'catch up' on lost hours of sleep during the week (social jet lag), but this would be missed by the current measurement method for sleep duration. Was there a rationale for using only weekday sleep? If the choice was driven by the data available then this should be acknowledged as a limitation.

Results:
- I think the phrasing for the result of 'sleep duration in mothers' may be unintentionally misleading. Whilst the effect size may be similar, the confidence intervals are wide, suggesting the effect size is imprecisely estimated (as the authors acknowledge). At the moment the manuscript reads as if increasing the sample size would improve the evidence in support of the association. It wouldn't necessarily, but it would allow estimation of the effect with greater precision.

Discussion:

- There is little discussion about the result linking nightmares and schizophrenia. It would be helpful to discuss the size of the effect, and contextualise the result within relevant existing literature linking nightmares with psychosis.

- A study which may help address whether the results are due to pleiotropy is an experimental study by Reeve *et al.* (2018[1]) which manipulated sleep duration and assessed the impact on psychotic like experience.

- Given evidence that there are differing levels of heritability for individual psychotic experiences, is the research limited by the fact that it has assessed risk for schizophrenia as a whole?

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical psychologist specialising in the understanding and treatment of sleep disruption for patients with psychosis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Aug 2019
Zoe Reed, University of Bristol, Bristol, UK

Introduction:
- It is currently unclear why i) sleep duration and ii) nightmares specifically have been chosen as markers of sleep dysfunction. Introducing the reader to literature on what is already known about sleep dysfunction in clinical samples with psychosis is important to help readers understand the clinical presentation under investigation and choice of measures.

Response: The sleep duration phenotype was selected due to repeated measures of this over time, which gave us greater power to detect an effect. It was therefore the most accurate measure we had available in ALSPAC for sleep quality. We selected the nightmare phenotype due to recent research within ALSPAC suggesting an association between nightmares and psychotic experiences (Fisher *et al.*, 2014). Sleep duration and nightmares have both been found to be associated with schizophrenia in previous studies. We have added the following text to the introduction (paragraph 1):

"Sleep disturbance includes a range of phenotypes, such as decreased sleep duration, which is associated with schizophrenia [26] and nightmares which is associated with psychotic experiences and patients with early psychosis [4, 13, 25]."

Methods:
- What is the rationale for the choice of covariates?

Response: We have included just age and sex as covariates as other covariates would fall, temporally, between the polygenic score and the sleep outcomes and may act as mediators so adjusting for these could lead to misleading results. We have added the following text to the covariates section in the methods to clarify this:

"We did not control for covariates beyond age and sex within the analyses as these would fall temporally between the independent variables (polygenic scores) and outcome (sleep) and could therefore act as mediators. Adjusting for these potential mediators could lead to misleading results."

- The sleep duration data uses only weekday sleep which may be confounded by chronotype. Those who are 'evening types' may be more prone to longer sleep duration at the weekend to 'catch up' on lost hours of sleep during the week (social jet lag), but this would be missed by the current measurement method for sleep duration. Was there a rationale for using only weekday sleep? If the choice was driven by the data available then this should be acknowledged as a limitation.

Response: Thank you for highlighting this. In children the measure is week day sleep and in mothers the measure is work day sleep. We acknowledge that both of these measures have limitations, for example, as you point out, chronotype could be an issue with weekday sleep. However, as this measure is used in children, this is likely to be less of an issue than in adults, and we hoped to capture routine sleep, hence why we have not used sleep on weekends (which was also available), which may vary more than weekday sleep. For the mothers, the limitation is slightly different, in that it only applies to those that work but it was the only measure available and again probably better than non-work days for capturing routine sleep. We have added the following text to the discussion (paragraphs 5 and 6):

"Small effect sizes may also reflect measurement error and quality of the parent-reported outcome measures. Self-reported sleep duration is subjective and therefore there will be some measurement error introduced when reporting average sleep duration, so the effect sizes we report here may underestimate the true correlations. This measurement error would also impact the

parent-reported measures of sleep in their children, though we opted to use child's sleep duration on weekdays only and not on weekends to capture routine sleep patterns.

Although we combined measures of sleep duration from several different ages, which is likely to have reduced error that was not shared across measurement occasions, sleep duration in the mothers is reported at a single time point and is unlikely to be consistent throughout the life course. The question for mother's sleep duration also asks specifically about sleep on work days which may result in a bias if individuals who do not work did not answer this question. However, using data from another question asking, "Have you had any jobs or regular voluntary work in the past year?", we found that of those who responded "yes" to this question, 98.64% responded to the question about sleep on work days. Of those who responded "no" to this question, 94.65% responded to the question about sleep on work days. These are quite similar response rates and although the latter is slightly smaller, we believe that this impact is negligible. More reliable measures of sleep duration are not currently available in the ALSPAC cohort, however, future studies comparing self-report measures to objective measures (such as accelerometer-derived sleep estimates 22) may help to estimate the potential biases in our results. Similarly, although we have reported results for sleep duration, we have no direct measure of sleep quality, so the marginally lower effect size for duration of sleep may index greater disruption in sleep architecture that could have important effects on psychopathology."

Results:
- I think the phrasing for the result of 'sleep duration in mothers' may be unintentionally misleading. Whilst the effect size may be similar, the confidence intervals are wide, suggesting the effect size is imprecisely estimated (as the authors acknowledge). At the moment the manuscript reads as if increasing the sample size would improve the evidence in support of the association. It wouldn't necessarily, but it would allow estimation of the effect with greater precision.

Response: Thank you for highlighting this. We have edited the sleep duration in mothers results paragraph to avoid misleading the reader:

"The estimated effect size of the association between schizophrenia polygenic risk score and sleep duration in mothers was similar to that seen in children, although confidence intervals are wide, so evidence in support of this association was weak (β=-49.97 seconds; 95% CI: –150.48, 50.55; p=0.33) (Table 2). The smaller sample size in the mothers' cohort has most likely led to lower power and therefore less precise estimates. An increased sample size would allow for estimation of this effect with greater precision."

Discussion:
- There is little discussion about the result linking nightmares and schizophrenia. It would be helpful to discuss the size of the effect, and contextualise the result within relevant existing literature linking nightmares with psychosis.

Response: We have added the following text to the second paragraph of the discussion to add some more context to the nightmares and schizophrenia relationship:

"In addition, finding a small to moderate association between greater polygenic risk of schizophrenia and increased risk of nightmares supports previous phenotypic observations between nightmares and psychotic experiences suggesting the presence of nightmares may be an

early risk indicator for psychosis [4, 13, 25] and suggesting that this relationship could be partly genetically mediated."

- A study which may help address whether the results are due to pleiotropy is an experimental study by Reeve *et al.* (2018[1]) which manipulated sleep duration and assessed the impact on psychotic like experience.

Response: We thank the reviewer for suggesting this study and we have added a reference to this, as indicated in the text below. This evidence of a causal association supports the idea that the genetic correlation may be due to a causal pathway rather than direct pleiotropy.

"For example, the findings could be due to horizontal pleiotropy, whereby genetic variants associated with schizophrenia are also independently associated with sleep phenotypes. The findings could also be due to causality, where either liability to schizophrenia causes disruption to sleep, or sleep disruption causes schizophrenia and so variants associated with sleep phenotypes are captured by the schizophrenia GWAS, which seems to be supported by experimental evidence [23]. It is also possible that the polygenic risk score for schizophrenia may capture a shared risk factor for both schizophrenia and sleep disruption, e.g. urbanicity, and so the results represent the effect of this unknown shared risk factor on both phenotypes. Finally, associations may also be induced by population stratification where spurious results arise due to differences in genetic backgrounds between the discovery and target samples (although this is less likely due to restriction to those with a European ancestry). However, we also acknowledge that given that the effects detected in the current study are small, investigating underlying mechanisms between sleep factors and schizophrenia would be difficult. Objective sleep measures and more complete knowledge of the genetic variants related to sleep and schizophrenia would likely increase power to explore mechanisms."

- Given evidence that there are differing levels of heritability for individual psychotic experiences, is the research limited by the fact that it has assessed risk for schizophrenia as a whole?

Response: This is an interesting point to consider and we have added the following text to indicate this limitation (paragraph 7 of discussion):

"As schizophrenia is highly heritable, better-powered GWAS will inevitably identify further variants and more accurately estimate genetic effect sizes, resulting in polygenic scores that account for a greater proportion of the variance. In addition, in our study we were unable to assess individual domains of schizophrenia, for example hallucinations, delusions or negative symptoms, as there are currently no available well powered GWAS for these outcomes. Future studies that reduce measurement error through objective measurements of sleep and more comprehensive polygenic risk scores that, for example, index specific symptom domains as well as disorder, will likely estimate more accurate and larger effect sizes than those we report here. As such, it is probably unwise to rule out clinical relevance on the basis of current effect size estimates."

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 February 2019

?   **Victoria Garfield** (iD)

MRC Unit of Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, London, UK

This study used data from the well-known ALSPAC cohort to investigate whether there is shared genetic aetiology between sleep duration and nightmares, and schizophrenia liability, as sleep disturbances are common in schizophrenia. The authors used data from both mothers and children and implemented well-established methods for genetic analyses. Overall, this study is interesting, clearly written and well-conducted, but there are some important concerns that need to be addressed before indexing.

Major points:
1. I am not sure about the GWAS data that has been used for creating the schizophrenia polygenic risk scores, although I am aware that this is the best that is available. In particular, I am unsure of how valid it is here to weight child polygenic risk scores by effects from a (case-control) GWAS in adults, particularly for a disorder like schizophrenia, which is also much more likely to be diagnosed in adulthood. Could the authors comment on this and in their response, detail whether this was given any consideration and whether they think this is important? If they believe it not to be as important or have affected any of the results, I think an explanation should be provided.

2. There is no real acknowledgement in the Discussion section on the potential limitations of having used subjective sleep data for both mothers and children. Regarding the data in mothers, I know that all that was available was one timepoint, but it is important to acknowledge and briefly discuss that self-reported sleep data may be prone to error and some bias. There are plenty of studies to cite which show that the agreement between subjective and objective sleep duration data in adults is, at best, modest. Furthermore, the sleep data in mothers was only available when they were aged around 40 years, which is also important to acknowledge, as sleep duration changes throughout the life course and for example, mothers who have young children are less likely to have 'normal' sleep patterns compared to mothers who have older children or no children. Also, the question on sleep duration only assessed weekday sleep, which is another important thing to acknowledge and discuss. However, my understanding was that during this data sweep (~40 years) mothers were asked about both weekday and weekend sleep and that a weighted average was then taken. I also thought that there were sleep and genetic data available on up to ~7000 ALSPAC mothers at this age, so 2,302 seems much smaller. Could the authors please comment on this, as well as the above points on self-reported sleep?

In relation to the child sleep data, it is also crucial to acknowledge that parent-reported data can be problematic (it was very quickly glossed over in the Discussion) and may also not agree with data collected via objective methods, such as actigraphy. This is because parents may misreport bedtimes and time they woke up, particularly if their child does not follow the most conventional bedtime, for example. Another important thing to consider here is that the question only asked about bedtime and time they awoke on *weekdays* and we know that as children get older their bedtimes change and they are more likely to go to bed at a different time during the weekend and potentially, wake up at different times.

In general, it is important to acknowledge that if subjective and objective sleep measures correlate poorly

then results could be different if objective measures were analysed.

Introduction:
1. Could the authors provide the age range or mean age of the twins in the previous TEDS study?

Methods:
1. Page 4: sleep duration section – it says that mothers were asked about how long they 'slept for on **work** days', should this be 'week' days?

2. Page 4: Covariates – what is the justification for the (quite narrow) choice of covariates? I think this needs to be included, as there could be other important covariates to consider.

3. Page 4: PRs construction – please could the authors include a reference or very brief reason for the clumping threshold of 0.25, as well as what your window for inclusion was (in kb)?

Results:
1. I cannot see a table with any sample characteristics anywhere – could the authors please include a table with at the very least, mean (SD) sleep durations for children at each age, mean (SD) sleep duration for mothers, %males or females (for children), mean (SD) age? One important reason for including the mean sleep durations for children and mothers is to see whether they were similar to the recommended averages for their ages, in line with guidelines for sleep for both children and adults.

2. I think it's slightly unclear exactly how the main PRS results were obtained in children – in the supplementary file there are results presented by age, but the main results presented in Table 2 in the main text are unclear in terms of the sample used in these analyses. Presumably, there were some children who were present at 4 years of age but then lost to follow-up? I think that this could be clearer in terms of who was included in which analyses.

3. Is it correct to say that adjusting for the mother's PRS and finding very little effect of this on the results in children shows that the 'association is not confounded by the mother's *psychopathology*', given that the term psychopathology is broad and does not only encompass schizophrenia? The mother's PRS was only a schizophrenia PRS, so would adjusting for this not simply ensure that the results in children were not affected by the mother's genetic risk of schizophrenia or similar?

Discussion:
1. Page 6: the authors say that we still do not know the exact mechanisms behind the associations that they found between schizophrenia and sleep measures. However, wouldn't these be extremely difficult to determine for such small effects?

2. Page 6: Could the authors give an example of what sort of 'third variable' they are referring to when they say that the PGC GWAS may have ascertainment bias?

3. It might be of interest in future to also perform a similar study with fathers/other adult males, as effects could be different.

4. Also, only sleep duration was examined and other sleep phenotypes may have different associations with a schizophrenia PRS. There are large-scale GWAS of other sleep phenotypes

available too.

5. The authors have briefly acknowledged that the effect sizes they observed are small. They are, indeed, very small and a couple of the results have very wide 95% confidence intervals. In light of these very small effect sizes, could the authors comment, in the Discussion section, on the potential clinical meaning of these?

Supplementary file:
1. Could the authors please include the R^2 values in each table for each PRS at every threshold? I think it would be informative for the reader to see how the R^2 varied throughout the different models.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: I collaborated very closely with Dr Gibran Hemani a few years ago on a research project. Here is some extra information about the project: Title: 'Genome-wide Association Study of Sleep duration' Dates: late 2014 to early 2016. I can confirm that this did not influence my review of Reed et al. and I believe that I reviewed the manuscript as best I could, influenced only by what was in the article and my scientific expertise.

Reviewer Expertise: Genetic epidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Aug 2019
Zoe Reed, University of Bristol, Bristol, UK

Major points:

1. I am not sure about the GWAS data that has been used for creating the schizophrenia polygenic

risk scores, although I am aware that this is the best that is available. In particular, I am unsure of how valid it is here to weight child polygenic risk scores by effects from a (case-control) GWAS in adults, particularly for a disorder like schizophrenia, which is also much more likely to be diagnosed in adulthood. Could the authors comment on this and in their response, detail whether this was given any consideration and whether they think this is important? If they believe it not to be as important or have affected any of the results, I think an explanation should be provided.

Response: Thank you for raising this point; we agree that we should justify this. Our primary aim here was specifically to look at whether genetic liability to develop schizophrenia in adulthood is related to sleep in childhood, so we used the best available genetic predictors of adult schizophrenia. But we strongly agree with the general point that the relationship between DNA variants and outcomes can be different at different ages (some of us have previously published on this e.g. Haworth and Davis, 2014), so if we were particularly interested in liability to childhood schizophrenia then weightings from an adult GWAS might not be appropriate. We have added clarification on why we constructed polygenic risk scores in children to the discussion (paragraph 1 of discussion):

"In this study we used summary statistics from a schizophrenia GWAS of an adult, clinical sample to construct polygenic risk scores in children and adults in the aim of understanding how schizophrenia genetic liability manifests in childhood. Our results demonstrate, for the first time with molecular genetic data, that greater polygenic risk for schizophrenia is associated with shorter sleep duration in both childhood and adulthood, and we report a new association between greater polygenic risk of schizophrenia and increased risk of nightmares in early life."

Haworth CMA and Davis OSP (2014) From observational to dynamic genetics. Front. Genet. 5:6. doi: 10.3389/fgene.2014.00006

2. There is no real acknowledgement in the Discussion section on the potential limitations of having used subjective sleep data for both mothers and children. Regarding the data in mothers, I know that all that was available was one timepoint, but it is important to acknowledge and briefly discuss that self-reported sleep data may be prone to error and some bias. There are plenty of studies to cite which show that the agreement between subjective and objective sleep duration data in adults is, at best, modest. Furthermore, the sleep data in mothers was only available when they were aged around 40 years, which is also important to acknowledge, as sleep duration changes throughout the life course and for example, mothers who have young children are less likely to have 'normal' sleep patterns compared to mothers who have older children or no children. Also, the question on sleep duration only assessed weekday sleep, which is another important thing to acknowledge and discuss. However, my understanding was that during this data sweep (~40 years) mothers were asked about both weekday and weekend sleep and that a weighted average was then taken. I also thought that there were sleep and genetic data available on up to ~7000 ALSPAC mothers at this age, so 2,302 seems much smaller. Could the authors please comment on this, as well as the above points on self-reported sleep?

In relation to the child sleep data, it is also crucial to acknowledge that parent-reported data can be problematic (it was very quickly glossed over in the Discussion) and may also not agree with data collected via objective methods, such as actigraphy. This is because parents may misreport bedtimes and time they woke up, particularly if their child does not follow the most conventional bedtime, for example. Another important thing to consider here is that the question only asked about bedtime and time they awoke on *weekdays* and we know that as children get older their

bedtimes change and they are more likely to go to bed at a different time during the weekend and potentially, wake up at different times.

In general, it is important to acknowledge that if subjective and objective sleep measures correlate poorly then results could be different if objective measures were analysed.

Response: Thank you for highlighting these potential limitations. In response, we have added the following text to the discussion (paragraphs 5 and 6 of discussion):

"Small effect sizes may also reflect measurement error and quality of the parent-reported outcome measures. Self-reported sleep duration is subjective and therefore there will be some measurement error introduced when reporting average sleep duration, so the effect sizes we report here may underestimate the true correlations. This measurement error would also impact the parent-reported measures of sleep in their children, though we opted to use child's sleep duration on weekdays only and not on weekends to capture routine sleep patterns.

Although we combined measures of sleep duration from several different ages, which is likely to have reduced error that was not shared across measurement occasions, sleep duration in the mothers is reported at a single time point and is unlikely to be consistent throughout the life course. The question for mother's sleep duration also asks specifically about sleep on work days which may result in a bias if individuals who do not work did not answer this question. However, using data from another question asking, "Have you had any jobs or regular voluntary work in the past year?", we found that of those who responded "yes" to this question, 98.64% responded to the question about sleep on work days. Of those who responded "no" to this question, 94.65% responded to the question about sleep on work days. These are quite similar response rates and although the latter is slightly smaller, we believe that this impact is negligible. More reliable measures of sleep duration are not currently available in the ALSPAC cohort, however, future studies comparing self-report measures to objective measures (such as accelerometer-derived sleep estimates [22]) may help to estimate the potential biases in our results. Similarly, although we have reported results for sleep duration, we have no direct measure of sleep quality, so the marginally lower effect size for duration of sleep may index greater disruption in sleep architecture that could have important effects on psychopathology."

In addition, we thank you for highlighting the sample size differences in the ALSPAC mothers analysis sample. This was due to an error in a script which resulted in more mothers being removed from the analyses than intended. Therefore, we have rerun all analyses with the correct sample size (n = 4,906) and have updated the results to reflect this. We do not observe any major differences in the results and conclusions for these analyses. However, we note that the sample size is still smaller than 7,000 individuals due to the number of individuals who have both phenotypic and genetic data.

Introduction:

1. Could the authors provide the age range or mean age of the twins in the previous TEDS study?

Response: The age range or mean age are not specifically provided in the TEDS paper, but data was collected when all children were around age 16 years. We have added this to the introduction in the relevant section (paragraph 2 of the introduction):

"A recent report from the Twins Early Development Study (TEDS) demonstrated that psychotic-like experiences and sleep disturbances in adolescence, around the age of 16 years, share genetic influences[7]."

Methods:

1. Page 4: sleep duration section – it says that mothers were asked about how long they 'slept for on **work** days', should this be 'week' days?

Response: This is correctly labelled as work days. I have added this potential limitation to the discussion (see above), as this may result in individuals that do not work not responding. However, we have checked this using another question, in the same questionnaire, asking "Have you had any jobs or regular voluntary work in the past year?". We found that of those who responded "yes" to this question, 98.64% responded to the question about sleep on work days. Of those who respnded "no" to this question, 94.65% responded to the question about sleep on work days. These are quite similar response rates and although the latter is slightly smaller we believe that this impact is negligible. We have added these percentages in the following text to the discussion (paragraph 6):

"The question for mother's sleep duration also asks specifically about sleep on work days which may result in a bias if individuals who do not work did not answer this question. However, using data from another question asking, "Have you had any jobs or regular voluntary work in the past year?", we found that of those who responded "yes" to this question, 98.64% responded to the question about sleep on work days. Of those who responded "no" to this question, 94.65% responded to the question about sleep on work days. These are quite similar response rates and although the latter is slightly smaller, we believe that this impact is negligible."

2. Page 4: Covariates – what is the justification for the (quite narrow) choice of covariates? I think this needs to be included, as there could be other important covariates to consider.

Response: We have included just age and sex as covariates as other covariates would fall, temporally, between the polygenic score and the sleep outcomes and may act as mediators so adjusting for these could lead to misleading results. We have added the following text to the covariates section in the methods to clarify this:

"We did not control for covariates beyond age and sex within the analyses as these would fall temporally between the independent variables (polygenic scores) and outcome (sleep) and could therefore act as mediators. Adjusting for these potential mediators could lead to misleading results."

3. Page 4: PRs construction – please could the authors include a reference or very brief reason for the clumping threshold of 0.25, as well as what your window for inclusion was (in kb)?

Response: We have used an R^2 clumping threshold of 0.25 in line with previous literature (e.g. St Pourcain *et al.*, 2018), but we agree there is no general consensus. We used a 500kb window for inclusion, and we have clarified this in the polygenic risk score construction section of the methods.

Pourcain BS, Robinson EB, Anttila V, Sullivan BB, Maller J, Golding J, *et al.* ASD and

schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. Mol. Psychiatry. Nature Publishing Group; 2018;23:263–70.

Results:

1. I cannot see a table with any sample characteristics anywhere – could the authors please include a table with at the very least, mean (SD) sleep durations for children at each age, mean (SD) sleep duration for mothers, %males or females (for children), mean (SD) age? One important reason for including the mean sleep durations for children and mothers is to see whether they were similar to the recommended averages for their ages, in line with guidelines for sleep for both children and adults.

Response: We agree, and we have added these sample characteristics to table 1.

2. I think it's slightly unclear exactly how the main PRS results were obtained in children – in the supplementary file there are results presented by age, but the main results presented in Table 2 in the main text are unclear in terms of the sample used in these analyses. Presumably, there were some children who were present at 4 years of age but then lost to follow-up? I think that this could be clearer in terms of who was included in which analyses.

Response: For the main results in children for sleep duration we combined all time points into one stacked dataset and used a linear mixed-effects model with age nested within family ID as a random effect. This resulted in 28,138 data points included in that model. This information is included in the text of the methods section. We have also added this information to the table 2 legend to clarify this.

3. Is it correct to say that adjusting for the mother's PRS and finding very little effect of this on the results in children shows that the 'association is not confounded by the mother's *psychopathology*', given that the term psychopathology is broad and does not only encompass schizophrenia? The mother's PRS was only a schizophrenia PRS, so would adjusting for this not simply ensure that the results in children were not affected by the mother's genetic risk of schizophrenia or similar?

Response: Yes, this is correct, thank you for highlighting that. We have changed this to genetic liability to schizophrenia.

Discussion:

1. Page 6: the authors say that we still do not know the exact mechanisms behind the associations that they found between schizophrenia and sleep measures. However, wouldn't these be extremely difficult to determine for such small effects?

Response: We have added the following text to the discussion (paragraph 8) to reflect this:

"However, we also acknowledge that given that the effects detected in the current study are small, investigating underlying mechanisms between sleep factors and schizophrenia would be difficult. Objective sleep measures and more complete knowledge of the genetic variants related to sleep and schizophrenia would likely increase power to explore mechanisms."

2. Page 6: Could the authors give an example of what sort of 'third variable' they are referring to when they say that the PGC GWAS may have ascertainment bias?

Response: We have rephrased this in the paper to clarfy what we mean by this. To clarify, we mean that the polygenic risk score manifests as a shared risk factor for both schizophrenia and disordered sleep. This risk factor would be unknown, however this could be something like urbanicity which could increase risk of developing schizophrenia and disordered sleep. We have changed the text to the following in the discussion (paragraph 8 of discussion):

"For example, the findings could be due to horizontal pleiotropy, whereby genetic variants associated with schizophrenia are also independently associated with sleep phenotypes. The findings could also be due to causality, where either liability to schizophrenia causes disruption to sleep, or sleep disruption causes schizophrenia and so variants associated with sleep phenotypes are captured by the schizophrenia GWAS, which seems to be supported by experimental evidence [23]. It is also possible that the polygenic risk score for schizophrenia may capture a shared risk factor for both schizophrenia and sleep disruption, e.g. urbanicity, and so the results represent the effect of this unknown shared risk factor on both phenotypes. Finally, associations may also be induced by population stratification where spurious results arise due to differences in genetic backgrounds between the discovery and target samples (although this is less likely due to restriction to those with a European ancestry)."

3. It might be of interest in future to also perform a similar study with fathers/other adult males, as effects could be different.

Response: We have added the following text to the discussion (paragraph 9 of discussion):

"It would also be interesting to see whether the same relationship between polygenic risk for schizophrenia and sleep duration is observed in adult males, as were only able to examine this in adult females here."

4. Also, only sleep duration was examined and other sleep phenotypes may have different associations with a schizophrenia PRS. There are large-scale GWAS of other sleep phenotypes available too.

Response: We agree that it would be interesting to look at a range of sleep phenotypes, however, the sleep measures investigated were the best measures available in ALSPAC. Whilst it would be interesting to incorporate sleep GWAS data into this study to look at whether genetic risk for sleep duration increases risk of schizophrenia, we do not have a measure of diagnosis of schizophrenia within ALSPAC.

5. The authors have briefly acknowledged that the effect sizes they observed are small. They are, indeed, very small and a couple of the results have very wide 95% confidence intervals. In light of these very small effect sizes, could the authors comment, in the Discussion section, on the potential clinical meaning of these?

Response: We have added the following text to the discussion (paragraph 3 of the discussion), where we discuss the small effect size:

"Although the effect sizes we report imply limited clinical relevance, the aforementioned limitations

on our measurement of both sleep and genetic risk for schizophrenia provide a practical upper bound for the effect size we could have found. As schizophrenia is highly heritable, better-powered GWAS will inevitably identify further variants and more accurately estimate genetic effect sizes, resulting in polygenic scores that account for a greater proportion of the variance. In addition, in our study we were unable to assess individual domains of schizophrenia, for example hallucinations, delusions or negative symptoms, as there are currently no available well powered GWAS for these outcomes. Future studies that reduce measurement error through objective measurements of sleep and more comprehensive polygenic risk scores that, for example, index specific symptom domains as well as disorder, will likely estimate more accurate and larger effect sizes than those we report here. As such, it is probably unwise to rule out clinical relevance on the basis of current effect size estimates."

Supplementary file:
1. Could the authors please include the R^2 values in each table for each PRS at every threshold? I think it would be informative for the reader to see how the R^2 varied throughout the different models.

Response: These have been added for all tables for the different thresholds for sleep duration in children and mothers and for nightmares.

Competing Interests: No competing interests were disclosed.