The interaction between polygenic risk and environmental influences: A direct test of the 3P model of insomnia in adolescents

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Background: Stress is a universal phenomenon and one of the most common precipitants of insomnia. However, not everyone develops insomnia after experiencing a stressful life event. This study aims to test aspects of Spielman's '3P model of insomnia' (during adolescence) by exploring the extent to which: (a) insomnia symptoms are predicted by polygenic scores (PGS); (b) life events predict insomnia symptoms; (c) the interaction between PGS and life events contribute to the prediction of insomnia symptoms; (d) gene–environment interaction effects remain after controlling for sex. **Methods:** The sample comprised 4,629 twins aged 16 from the Twin Early Development Study who reported on their insomnia symptoms and life events. PGS for insomnia were calculated. In order to test the main hypothesis of this study (a significant interaction between PGS and negative life events), we fitted a series of mixed effect regressions. **Results:** The best fit was provided by the model including sex, PGS for insomnia, negative life events, and their interactions (AIC = 26,158.7). Our results show that the association between insomnia symptoms and negative life events is stronger for those with a higher genetic risk for insomnia. **Conclusions:** This work sheds light on the complex relationship between genetic and environmental factors implicated for insomnia. This study has tested for the first time the interaction between genetic predisposition (PGS) for insomnia and environmental stressors (negative life events) in adolescents. This work represents a direct test of components of Spielman's 3P model for insomnia which is supported by our results. **Keywords:** Genetics; GxE; insomnia; life events; polygenic score; sleep.

Introduction

Insomnia is the most prevalent sleep disorder and is among the most common complaints in clinical practice (Morin et al., 2015). Insomnia is characterized by both nocturnal and diurnal symptoms. These symptoms include difficulties initiating or maintaining sleep and impairments of daytime functioning (Morin et al., 2015; Ohayon, 2002). The prevalence of insomnia varies widely depending on the criterion used to define insomnia. For example, one review found that it ranges from 6% (when diagnosed according to the DSM-IV) to around one-third of the population (when considering those with at least one symptom of insomnia) (Ohayon, 2002). Insomnia is related to psychiatric disorders such as depression, anxiety, attention deficit hyperactivity disorder (ADHD), schizophrenia, and bipolar disorder among others (Alvaro, Roberts, & Harris, 2013; Gregory, Agnew-Blais, Matthews, Moffitt, & Arseneault, 2017; Lewis et al., 2019; Madrid-Valero et al., 2020; Robertson, Cheung, & Fan, 2019). Insomnia and poor sleep quality are also included as diagnostic criteria for some of these disorders (American Psychiatric Association, 2013). Despite the importance of insomnia at all stages of the lifespan, insomnia during

adolescence is underrecognized, underdiagnosed, and undertreated even though it is a highly prevalent condition (de Zambotti, Goldstone, Colrain, & Baker, 2018).

In order to reduce the impact of insomnia, it is of interest to understand the etiology of this disorder. An understanding of its etiology will enable us to identify who may be at risk of insomnia, and who may benefit from preventative interventions. Twin studies have shown that insomnia is substantially influenced by genetic factors, accounting for between 39% and 40% of the variability in general population samples (Barclay, Kocevska, Bramer, Van Someren, & Gehrman, 2021; Madrid-Valero, Rubio-Aparicio, Gregory, Sánchez-Meca, & Ordoñana, 2021). This has also been found in genome-wide association studies (GWAS), although the SNP-based heritability estimate is lower than twin heritability (Watanabe et al., 2022).

A moderate heritability for insomnia means that there is also substantial environmental influence. Investigation of environmental factors, in combination with knowledge of underlying genetic factors, will increase our predictive ability to identify individuals at risk for insomnia. There are multiple risk factors for insomnia such as increased age, female sex, and genetic factors (Madrid-Valero, Martinez-Selva, Ribeiro Do Couto, Sanchez-Romera, &

Ordonana, 2017; Morin et al., 2015). However, adult literature also shows numerous social determinants of insomnia-related phenotypes. For example, sleep disturbances are more common in individuals who are unemployed, on low income, or with low educational attainment (Ford & Kamerow, 1989; Grandner et al., 2010; Ohayon, 2002). Of note, the most frequently reported precipitating factors for insomnia are stressful life events related to health, family relationships, work, or school, and which are perceived as negative events (Bastien, Vallières, & Morin, 2004; Ellis et al., 2021). The literature regarding how genes and environments interact is scarce. In twin modeling, it has been shown that genetic factors that may influence sleep quality may be shared with those that influence exposure to stressful life events, reflecting gene–environment correlation (Barclay, Eley, Rijsdijk, & Gregory, 2011).

The possibility of gene–environment interaction (GxE) aligns with Spielman's '3P model of insomnia' (Spielman, Caruso, & Glovinsky, 1987). The model suggests that insomnia manifests when a predisposing factor (e.g. a genetic factor) is triggered by a precipitating factor (such as an environmental stressor). A recent study in support of this idea has demonstrated that those with high sleep reactivity (a tendency toward cognitive or physiological hyperarousal at night or in response to stress) have a stronger relationship between weekly stressful life events and insomnia (Walker et al., 2022). This reinforces the idea that a predisposing factor could exacerbate the effects of a precipitating factor.

Stress is a universal phenomenon and one of the most common precipitants of insomnia (Morin, 2022). However, not everyone develops insomnia following a stressful life event (Morin, 2022). Therefore, making use of PGS, this study aims to test the diathesis-stress model, where stressful life events may activate a vulnerability, transforming the potential for insomnia into actual symptoms. This study explores the extent to which: (a) insomnia symptoms are predicted by the PGS derived from a reference GWAS; (b) life events predict insomnia symptoms; (c) the interaction between PGS and life events contribute to the prediction of insomnia symptoms; and (d) GxE effects remain after controlling for sex since there are large differences between men and women when it comes to the prevalence of insomnia (Zhang & Wing, 2006).

Method
Participants

The sample comprised 10,346 twins from the Twins Early Development Study (TEDS). TEDS is a community-based, longitudinal study of twins born in England and Wales between 1994 and 1996 (Haworth, Davis, & Plomin, 2013; Rimfeld et al., 2019). This sample is reasonably representative of the general population (Kovas, Haworth, Dale, &

Plomin, 2007). Zygosity was assessed using either DNA testing or a questionnaire, which has shown an accuracy of over 95% (Price et al., 2000). Ethical approval for TEDS was provided by the King's College London ethics committee (ref: PNM/09/10-104). Written informed consent was obtained prior to each wave of data collection from parents and from twins themselves from age 16 onward.

This work focuses on data collected at age 16. In this wave, 19,874 families were contacted and invited to participate and 47.3% of these families provided data. Differences between participating and nonparticipating families have been reported elsewhere (Zavos et al., 2016). Analyses here focused on a study within this wave of data collection called LEAP-1, which includes participants who provided data about insomnia ($N = 7,908$), life events ($N = 10,136$), and had PGS for insomnia ($N = 10,346$). Of the LEAP-1 participants, 4,634 participants had data for all three variables. The sample comprised both MZ (25%) and DZ (75%) twins and was 54% female. Five participants were excluded due to medical reasons which affected their participation in the study.

Measures

Insomnia was assessed using the Insomnia Severity Index questionnaire (ISI; Bastien, Vallières, & Morin, 2001). This questionnaire is composed of seven items enquiring about symptoms of insomnia over the previous month. Scores vary from 0 to 28 where a higher score represents greater insomnia symptoms (Bastien et al., 2001). Psychometric properties of this questionnaire have shown to be adequate (Morin, Belleville, Bélanger, & Ivers, 2011). Cronbach's alpha in this sample was .89.

Negative life events were assessed using a reduced version of the Coddington Life Event Scale (CLES) (Coddington, 1972). This scale is composed of the 20 items most relevant to adolescents. This version has been previously used (Shakoor et al., 2016; Wootton, Davis, Mottershaw, Wang, & Haworth, 2017). Participants self-reported whether they had experienced any of the events in the past 6 months. Additionally, if the event had occurred, participants also informed whether they found the experience: 'Very unpleasant', 'Moderately unpleasant', 'Neither unpleasant nor pleasant', 'Moderately pleasant', or 'Very pleasant'. In this study, we focused on negative life events (those rated as 'very unpleasant' or moderately unpleasant'). This variable was calculated by summing 'Moderately unpleasant' (1) and 'Very unpleasant' (2) responses. The responses 'No' and 'Neither unpleasant nor pleasant' were coded as 0. All questions are available elsewhere (supplementary table 4; Peel et al., 2023).

Polygenic scores (PGS). PGS for individuals are the sum of the number of trait-associated allelic genetic variants weighted by their association effect size based on summary statistics. In this study, we used summary statistics from the GWA study by Jansen et al. (2019) which used a sample of more than 1.3 million participants (cases and controls for insomnia, see Jansen et al. (2019) supplementary tables 1 and 2 for a full description). The SNP-based heritability was estimated at 7% – which is the upper limit of the predictive value of this PGS for insomnia using this GWAS. PGS were calculated using LDpred which re-weights the variant effect sizes using a prior on their effect size (based on the heritability and assumed fraction of causal markers that influence the trait), adjusting for the linkage disequilibrium in the sample (Vilhjálmsson et al., 2015). Details about genotyping can be found elsewhere (https://www.teds.ac.uk/datadictionary/studies/dna.htm). The TEDS genotypic sample was composed of data from both the Affymetrix and OEE platforms, which were combined, and quality control procedures were applied (these methods are described in detail in S1 methods, supplementary methods, Selzam et al. (2018)). The initial sample comprised 11,869 samples. From this initial sample, 1,523 samples were

removed due to possible non-European ancestry, heterozygosity anomalies, and genotype call rate <0.98. PGS were statistically adjusted for the first 10 principal components, chip, and plate using the regression method, and were z-standardized (mean = 0, SD = 1) to avoid potential effects due to population stratification and genotyping. Three thresholds for PGS were available (p = .01, p = .3 and p = 1), which represent an assumption on the fraction of genetic markers that are causally influencing the trait. For example, p = 1 represents the assumption that all genetic variants contribute to trait development. Analyses were performed using the p = 1 threshold since it was the threshold with the highest predictive value (p = .001 and r^2 = .002) for insomnia symptoms. The p = .01 threshold was not significantly associated with symptoms of insomnia.

Statistical analyses

This study was preregistered on the Centre for Open Science Website (https://osf.io/qsd2a). In order to test the main hypothesis of this study, we fitted a series of mixed effect regressions to control for the relatedness of the sample (i.e. including family as a random effect). The analyses were performed using the lme4 package in R (Bates, Machler, Bolker, & Walker, 2015). First, we fitted the full model (life events, insomnia PGS, and the interaction terms) including sex as a covariate. The interactions between the moderator and predictors (i.e. insomnia PGS × sex and life events × sex) were also included as is standard practice in gene-by-environment interaction (GxE) studies (Keller, 2014). Then, reduced nested models were compared in order to check whether one or more parameters could be dropped without a decrease in model fitting. The fit of the models was compared using the Akaike information criterion (AIC). We also reported the p-value for the comparison among models. However, the use of p-values using mixed models is discouraged (and intentionally not reported by lme4) and the method to obtain these values has certain limitations (Luke, 2017). As recommended, we are not focusing exclusively on p-values when using mixed regression models (Luke, 2017). Negative life events and symptoms of insomnia showed positive skewness, within an acceptable range (1.71 and 1.39 for symptoms of insomnia and negative life events respectively). All continuous variables were mean-centered in the regression models in order to avoid possible multicollinearity.

Results

Descriptive statistics are displayed in Table 1. Females reported higher levels of insomnia symptoms than males ($\overline{X}$ = 4.25 vs. $\overline{X}$ = 3.28; p < .05). Regarding negative life events males and females reported a similar score – albeit significant differences were found due to the large sample size ($\overline{X}$ = 0.89 vs. $\overline{X}$ = 0.81, p = .009), similar values were also found for PGS for insomnia ($\overline{X}$ = 0.01 vs. $\overline{X}$ = 0, p = .769). A substantial proportion of the sample (N = 761; 16.4%) reported a score of more than eight points which has been previously suggested as a cutoff to detect individuals at risk of insomnia (Morin et al., 2011). Regarding negative life events, scores ranged from 0 to 5 and 21.8% of the sample (N = 1,011) reported a score ≥2.

The full model and reduced models are presented in Table 2. Overall, the best fit (as indicated by the lowest AIC) was provided by the full model (AIC = 26,158.7) (Table 2). This model shows that

Table 1 Descriptive statistics

	Male	Female	Total
Total, N (%)	2,125 (46)	2,504 (54)	4,629 (100)
Age (SD)	16.15 (0.68)	16.14 (0.68)	16.15 (0.68)
Mean ISI (SD)	3.28 (3.9)	4.25(4.5)	3.81 (4.2)
Mean negative life events (SD)	0.81 (1.0)	0.89 (1.1)	0.85 (1.1)
Mean PGS insomnia (SD)	0 (1.0)	0.01 (1.0)	0 (1.0)

Higher scores represent more symptoms of insomnia, negative life events, or a higher genetic predisposition. ISI, Insomnia Severity Index; PGS, polygenic scores.

an increase in negative life events is associated with an increase in insomnia symptoms, and this increase is more pronounced for those with higher genetic vulnerability for insomnia. For example, we found differences in ISI scores (depending on the genetic vulnerability for insomnia [i.e. PGS for insomnia]) of around 0.5 points for participants reporting 2 negative life events and differences of 1 ISI point or higher for those reporting 4 or more negative life events. All models are compared against the full model (model I) except model III which is compared with model II to provide information about the interaction term without covariates. For the sake of clarity, comparisons of reduced models are here presented first. First of all, reduced models removing PGS of insomnia (Model V; AIC = 26,161.8; p = .028) and negative life events (model VI; AIC = 26,383.0; p = <.001) showed a lower fit, and fitted significantly worse, as compared to the full model. Second, the interaction between PGS for insomnia and negative life events was a significant predictor of symptoms of insomnia. Models removing the interaction but retaining sex (model IV; AIC = 26,160.0; p = .071, compared with model I) and excluding sex (model III; AIC = 26,226.3; p = .039, compared with model II) showed a poorer fit. Note that the p-value for the comparison between model I and model IV is slightly above .05 but the AIC value is lower for model I (AIC = 26,158.7), and hence, this is focused on as our model of best fit. Furthermore, the model including the interaction term (model I) explained 0.10% more of the variance as compared to the model without the interaction term (model IV). Sex was a significant predictor of insomnia symptoms since dropping this variable resulted in a significant worse fit (AIC = 26,224.1; p < .001) (Table 2). We performed a sensitivity analysis using the p = .3 threshold and the same pattern of results was found as compared to the p = 1 threshold. Figure 1 clearly shows the effect of the interaction between PGS for insomnia and negative life events. Results are displayed in this figure for high genetic predisposition (+1SD in PGS for insomnia), medium genetic predisposition (mean value), and low genetic predisposition (−1SD in PGS for insomnia). In this figure, differences in around

one point in insomnia symptoms (ISI) are found, depending on the genetic predisposition group for those with high levels of negative life events. There are no differences between ISI scores based on genetic predisposition groups for those reporting low levels of negative life events.

Discussion

This study has tested for the first time the interaction between genetic predisposition (PGS) and environmental stressors (negative life events) for insomnia symptoms in adolescents. This work represents a direct test of key components of the 3P model of insomnia (Spielman et al., 1987). Results from this study support this model. Here, we find that negative life events may have a bigger impact on insomnia symptoms in those with a higher as compared to lower genetic predisposition for insomnia. Conversely, the intensity of the precipitating factor (environmental stress) may need to be higher for those with a lower genetic risk for insomnia (predisposing/protecting factor) in order to trigger the disorder.

Life events and PGS for insomnia are both significant predictors of insomnia symptoms. Our results confirm the robust association between negative life events and insomnia symptoms, those who report stressful life events report higher scores for insomnia symptoms (Ellis et al., 2021; Short et al., 2022). Furthermore, our study has also revealed that PGS calculated in adults (Jansen et al., 2019) is a significant predictor of insomnia in adolescence – although, the proportion of the variance explained by PGS of insomnia is still small. PGS has its predictive limit value in heritability (Choi, Mak, & O'reilly, 2020). In a previous study, using a twin design, we confirmed that insomnia is substantially influenced by genetic factors in this sample (41%) (Madrid-Valero et al., 2020). However, there is still a gap between estimates from twin studies and SNP-based heritability which has been estimated at 7%–8% (Jansen et al., 2019; Watanabe et al., 2022). Sex was also a significant predictor of insomnia symptoms, but similar mean PGS values were found for men and women. This chimes well with the previous literature: women usually report higher levels of insomnia (Zhang & Wing, 2006), but the magnitude of genetic and environmental influences on insomnia symptoms seems to be similar for both sexes (Madrid-Valero, Rubio-Aparicio, et al., 2021). This has also been confirmed at a molecular level (Jansen et al., 2019).

Table 2 Models predicting insomnia symptoms

Model (model for comparison)	Estimate	SE	df	t-Value	Standardized estimate	AIC	R^2	Model comparison (p-Value)
I						**26,158.7**	**.064**	
Negative life events	1.025	0.076	4,612	13.477	0.255			
PGS insomnia	0.085	0.082	4,573	1.040	0.020			
Negative life events*PGS insomnia	0.104	0.058	4,621	1.806	0.026			
Sex	−0.926	0.120	4,589	−7.715	−0.109			
Sex*Negative life events	−0.397	0.115	4,514	−3.454	−0.064			
Sex*PGS insomnia	0.119	0.120	4,556	0.992	0.019			
II (I)						26,224.1	.050	<.001
Negative life events	0.873	0.058	4,413	14.96	0.217			
PGS insomnia	0.144	0.062	4,197	2.343	0.034			
Negative life events*PGS insomnia	0.119	0.057	4,617	2.056	0.030			
III (II)						26,226.3	.049	.039
Negative life events	0.878	0.058	4,420	15.066	0.218			
PGS insomnia	0.143	0.062	4,200	2.313	0.034			
IV (I)						26,160.0	.063	.071
Negative life events	1.034	0.076	4,612	13.621	0.257			
PGS insomnia	0.087	0.082	4,574	1.066	0.021			
Sex	−0.093	0.120	4,589	−7.746	−0.110			
Sex*Negative life events	−0.406	0.115	4,516	−3.540	−0.066			
Sex*PGS insomnia	0.111	0.120	4,553	0.923	0.017			
V (I)						26,161.8	.063	.028
Negative life events	1.038	0.076	4,613	13.684	0.258			
Sex	−0.931	0.120	4,588	−7.754	−0.110			
Negative life events*Sex	−0.407	0.115	4,513	−3.545	−0.066			
VI (I)						26,383.0	.016	<.001
PGS insomnia	0.145	0.084	4,585	1.731	0.034			
Sex	−1.006	0.123	4,577	−8.187	−0.118			
PGS insomnia*Sex	0.064	0.123	4,536	0.519	0.010			

Higher scores represent more symptoms of insomnia, negative life events, or a higher genetic predisposition. Continuous variables were mean-centered. Model in bold represents the model with the lowest AIC value and which is selected as our model of best fit. R^2 expressed as a proportion.
AIC, Akaike information criterion; ISI, Insomnia Severity Index; PGS, polygenic scores; SE, standard error.
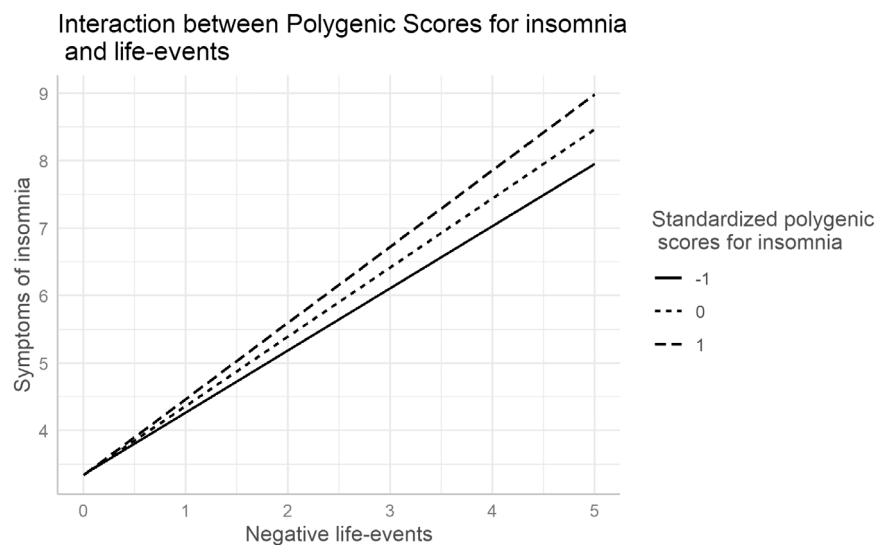
Figure 1 Regression model for the interaction between standardized polygenic scores for insomnia and life events. Three groups for polygenic scores are presented: (1) high genetic predisposition (+1*SD*); (2) medium genetic predisposition (mean value); and (3) low genetic predisposition (−1*SD*)

This work also sheds light on the complex relationship between genetic and environmental factors implicated in insomnia during a critical period of the lifespan. As stated by Morin in a recent editorial, it is of interest to elucidate the mechanisms underlying the vulnerability to insomnia (Morin, 2022). This study advances our knowledge about the etiology of insomnia by showing that genetic vulnerability acts as a threshold (with ample interindividual variation) that could be exceeded in the event of environmental stressors such as negative life events. Genetic predisposition for insomnia could be related to a wide variety of biological and psychological factors such as hyperarousal (Riemann et al., 2010; Schneider, Denis, Buysse, Kovas, & Gregory, 2019), neurotransmitters implicated in sleep–wake regulation (Morin et al., 2015), and a tendency toward worry or excessively ruminative (Clancy, Prestwich, Caperon, Tsipa, & O'connor, 2020) and also dysfunctional beliefs about sleep (Schneider, Kovas, & Gregory, 2019). Furthermore, our results also converge with the study by Walker et al. (2022), which demonstrated a stronger relationship between greater stressful life events and greater insomnia symptoms for those with high 'sleep reactivity' (predisposition to experience insomnia following acute stressors). Interestingly, PGS for insomnia symptoms became nonsignificant once we added negative life events and the interaction between negative life events and PGS for insomnia. This reinforces the idea that genetic influences cannot be understood without taking environmental influences into account – genetic influences need the environment to be expressed (at least in the context of insomnia). Insomnia is a complex disorder that is influenced by multiple factors, both genetic and environmental, and there is a complex interrelationship among them.

Results from this study have implications for both clinical and research practice. First, we have shown that PGS scores could be a useful tool to identify people at risk of suffering from insomnia during adolescence. These findings could eventually pave the way to more accurate and tailored prevention programs. Furthermore, we have also shown that this genetic predisposition interacts with environmental stressors (i.e. negative life events) so in the future, it might be fruitful for preventive programs to focus on participants with a high genetic predisposition and especially following negative life events. A high heritability is often misunderstood as genetic determinism. As we previously demonstrated, these conceptions could potentially influence treatment outcomes since patients might interpret this information as suggesting that certain treatments are not valuable (Madrid-Valero et al., 2021). In fact, efforts should be aimed at supporting participants at high risk of experiencing insomnia. The role of protective factors such as coping skills, social support, and resilience should be further investigated and tested (especially) among people at high risk. Finally, sleep reactivity can also be reduced by using cognitive behavioral therapies (Chan et al., 2021).

Strengths and limitations

This study has several advantages such as the use of a large sample and a powerful design. Furthermore, this study represents a direct test of a theory-driven research question. However, it also has some limitations and conclusions from this work should be considered in light of them. First, we focused on symptoms of insomnia rather than the diagnosis. However, this approach allows us to generalize our results to the general population and reflects that notion that symptoms of insomnia are on a

continuum. Second, our research focus was on adolescents, yet no previous PRS of insomnia has focused on this developmental stage, meaning that we had to focus on a PRS derived from an adult sample. Nonetheless, in the context of this research we demonstrated that an adult sample-derived PRS can be applied to an adolescent population too. While focusing on PRS it is also noteworthy that while the PRS for insomnia captures the main genetic effects on insomnia, it does not necessarily imply vulnerability to stress. There could be meaningful differences between mechanisms underlying insomnia and stress vulnerability. Further research is needed in order to identify the specific pathways of underlying these complex relationships (e.g. hypothalamic–pituitary–adrenal axis functioning). Third, the proportion of variance explained by PGS is still limited due to methodological and sample size issues. Fourth, it was not possible to perform a sensitivity analysis using summary statistics from the most recent GWAS of insomnia (Watanabe et al., 2022) as these data were not available at the time of analyses. Of note, we acknowledge that this more recent GWAS found a very similar SNP-based heritability as compared to the GWAS of focus in these analyses (Jansen et al., 2019). Finally, statistical power is reduced when it comes to interaction effects. We used a large sample and our statistical power to detect small effect sizes (0.1%) was around 80% (calculated using the R package 'InteractionPowerR'). Nevertheless, future studies should attempt to replicate our results using even larger sample sizes, in different populations and using the most up-to-date GWAS information.

Conclusions

This study investigated for the first time the interaction between polygenic risk and environmental influences on insomnia. Our results show that there is a significant interaction between both variables which supports the 3P model of insomnia. This is clear evidence of the diathesis-stress model for insomnia. In other words, the amount of 'stress' needed to trigger insomnia is different based on the genetic vulnerability. Notwithstanding the above caveats, further research is needed to extend these results to other samples (e.g. adult samples) and use different conceptualizations of environmental risk for insomnia.

Ethical standards

Ethical approval for TEDS was provided by the King's College London ethics committee (ref: PNM/09/10-104). Written informed consent was obtained prior to each wave of data collection from parents and from twins themselves from age 16 onward.

Disclosures

A.G. is an advisor for a project initially sponsored by Johnson's Baby. She is a consultant for Perrigo (2021+). She receives royalties for two books Nodding Off (Bloomsbury Sigma, 2018) and The Sleepy Pebble (Flying Eye, 2019). She receives royalties for gift product The Gift of Sleep (Lawrence King Publishers, 2023). She is a regular contributor to BBC Focus magazine and has contributed to other outlets (such as The Conversation, The Guardian and Balance Magazine). She occasionally receives sample products related to sleep (e.g. blue light-blocking glasses) and has given a paid talk to a business. She is a specialist subject editor at JCPP (sleep) for which she receives a small honorarium. She has contributed a paid article to Neurodiem. She was previously a director at Sleep Universal Limited (2022). N.B. is Director of Sleep Universal Limited (though this work is in no way connected to the present manuscript). J.J.M-V. has no conflicts of interest.

Author contributions

JJMV, NLB, and AMG contributed to the study conception and design. Analyses were performed by JJMV and supervised by NLB and AMG. The first draft of the manuscript was written by JJMV under the supervision of AMG. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Data availability statement

Under restrictions. JJM-V had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Key points

- Insomnia is the most common sleep disorder and is linked to almost every psychiatric disorder.
- Not everyone develops insomnia after experiencing a stressful life event.
- Negative life events have a greater impact on insomnia symptoms in those with a higher as compared to lower genetic risk for insomnia.
- The intensity of the precipitating factor (environmental stress) may need to be greater in those with a lower genetic risk (predisposing/protecting factor) as compared to a higher genetic risk in order to trigger insomnia.

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