

ORIGINAL ARTICLE

The heritability of insomnia: A meta-analysis of twin studies

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Abstract

Twin studies of insomnia exhibit heterogeneity in estimates of heritability. This heterogeneity is likely because of sex differences, age of the sample, the reporter and the definition of insomnia. The aim of the present study was to systematically search the literature for twin studies investigating insomnia disorder and insomnia symptoms and to meta-analyse the estimates of heritability derived from these studies to generate an overall estimate of heritability. We further examined whether heritability was moderated by sex, age, reporter and insomnia symptom. A systematic literature search of five online databases was completed on 24 January 2020. Two authors independently screened 5644 abstracts, and 160 complete papers for the inclusion criteria of twin studies from the general population reporting heritability statistics on insomnia or insomnia symptoms, written in English, reporting data from independent studies. We ultimately included 12 papers in the meta-analysis. The meta-analysis focussed on twin intra-class correlations for monozygotic and dizygotic twins. Based on these intra-class correlations, the meta-analytic estimate of heritability was estimated at 40%. Moderator analyses showed stronger heritability in females than males; and for parent-reported insomnia symptoms compared with self-reported insomnia symptoms. There were no other significant moderator effects, although this is likely because of the small number of studies that were comparable across levels of the moderators. Our meta-analysis provides a robust estimate of the heritability of insomnia, which can inform future research aiming to uncover molecular genetic factors involved in insomnia vulnerability.

KEYWORDS

behavioural genetics, environment, genes, inheritance patterns, sleep, sleep initiation and maintenance disorders

Abbreviations: A, additive genetic influence; C, shared environmental influence; CI, 95% confidence interval; CSHQ, Child Sleep Habits Questionnaire; D, non-additive genetic influences; DSM-III-R, diagnostic and statistical manual of mental disorders, 3rd edition revised; DSM-IV-TR, diagnostic and statistical manual of mental disorders, 4th edition text revision; DSM-V, diagnostic and statistical manual of mental disorders, 5th edition revised; DZ, dizygotic twins; E, non-shared environmental influence; ESzdz, Fisher's Z-score of the DZ twin correlation; ESzmm, Fisher's Z-score of the MZ twin correlation; F, females; F, F-statistic used in analysis of variance; GxE, gene-environment interaction; H², heritability; I², heterogeneity statistic; ISI, Insomnia Severity Index; ISQ, Insomnia Symptoms Questionnaire; JPSQ, Johns & Palmer Sleep Questionnaire; JSPS, Jenkins sleep problem scale; M, males; MZ, monozygotic twins; rDZ, dizygotic twin correlation; rMZ, monozygotic twin correlation; SE, standard error; T, t-test statistic.

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1 | INTRODUCTION

Insomnia is a complex disorder exhibiting diverse symptomology and a multifaceted aetiology. Diagnostic classifications for insomnia disorder acknowledge this complexity, and include difficulty initiating sleep, difficulty maintaining sleep, and/or awakening earlier than desired.^{1,2} These symptoms are accompanied by difficulties in other areas of daytime functioning, and occur at least three times a week for at least

3 months.² Prevalence of insomnia in the general population ranges from approximately 10% for those meeting diagnostic criteria for insomnia disorder, to approximately 30% for those experiencing occasional symptoms.³ Whilst the International Classification of Sleep Disorders (ICSD 3)² diagnostic criteria for insomnia disorder have moved away from sub-typing based on symptomology, it is worth noting that not all individuals experience the same manifestation of insomnia. A study focussing on >3500 individuals with insomnia disorder from a Norwegian population based cohort⁴ showed that most individuals exhibit one symptom of insomnia in isolation: approximately 30% experienced difficulty maintaining sleep, ~17% difficulty initiating sleep, and ~11% awakening earlier than desired. The remaining 41% experienced a combination of symptoms.⁵ Moreover, insomnia subtypes have recently been found in a data-driven way in >2000 individuals with probable insomnia.⁶ Subtypes could be distinguished based on their multivariate profiles of many traits, including personality, emotion, reward sensitivity, stress reactivity and trauma history. The multivariate profile differences between subtypes were extensive, but could roughly be summarised as: "...highly distressed; moderately distressed but reward sensitive (ie, with intact responses to pleasurable emotions); moderately distressed and reward insensitive; slightly distressed with high reactivity (to their environment and life events); and slightly distressed with low reactivity".⁶ It is possible that the different manifestations of insomnia stem from distinct aetiology.

Insomnia vulnerability involves both genetic and environmental influences. This has been confirmed by numerous studies utilising a variety of study designs, including quantitative genetic designs (family and twin studies), and molecular genetic designs (candidate gene studies⁷ and genome-wide association studies [GWAS], eg, References 8-12). Family studies note a familial patterning of insomnia, estimating that around a third of patients with insomnia have a first-degree relative with the disorder,^{13,14} with mothers as the most commonly afflicted relative. This pattern could be reflective of the fact that there is generally a female preponderance to insomnia,¹⁵ but it could also suggest a role for maternal DNA, or that mothers with insomnia influence the environment in ways conducive to insomnia. Numerous twin studies have concurred that insomnia stems from a combination of genetic and environmental factors, although heritability estimates exhibit substantial heterogeneity varying between 14%¹⁶ and 79%¹⁷ in child and adolescent populations, and between 22%¹⁸ and 57%¹⁹ in adults. This heterogeneity may be explained by sex, age of the population under study, reporter (ie, whether the symptoms are self-reported, reported by a parent or clinician), or the specific insomnia symptom present. It is possible that the aetiology of the different manifestations of insomnia is distinct. For example, getting to sleep may be predicted by a distinct set of genes that control the transition from wakefulness to sleep, whereas staying asleep may be controlled by different mechanisms. Likewise, early morning awakening may be related to distinct genetic and environmental factors.

Whilst there are a handful of reviews of the genetics of insomnia,^{7,20,21} to our knowledge there has been no systematic evaluation of its heritability. The aim of this study is to systematically review studies investigating the heritability of insomnia or insomnia-

related phenotypes and to perform a meta-analysis of these studies to generate a robust estimate of the genetic contribution to individual differences in insomnia. Additionally, this study aims to determine whether the heritability of insomnia is moderated by sex, age, reporter and insomnia symptom.

2 | MATERIALS AND METHODS

2.1 | The twin design

In quantitative behavioural genetics, the classical twin design relies on knowledge of the relative differences in genetic and environmental correlations between monozygotic (MZ) and dizygotic (DZ) twins, which enables us to parse variance in a phenotype into relative proportions of additive genetic (where genes at a locus "add up" to influence behaviour; A), shared environmental (C) and non-shared environmental (E) influences. MZ twins share on average 100% of their segregating genes, whilst DZ twins share around 50% of their segregating genes. Thus, additive genetic influences can be assumed to play a role in a phenotype if the MZ twin correlation (r_{MZ}) is greater than the DZ twin correlation (r_{DZ}). It is also possible to partition variance into non-additive *interactive* genetic influences (D), which are indicated when the r_{MZ} correlation is greater than double the r_{DZ} correlation. The shared environment is estimated to be equal between both MZ and DZ twins and is typically attributed to family or social environments that are shared within a family that account for their similarity, and thus are equated at 1 for both MZ and DZ twins. Non-shared environmental influences on the other hand account for unique experiences of twins within a family which contribute to their differences. Thus, non-shared environmental influences are equated at 0 between pairs of both MZ and DZ twins. Using these correlations we can calculate a measure of heritability, denoted h^2 , using Falconer's formula as follows: $A = 2(r_{MZ} - r_{DZ})$. The proportion of shared environmental influences contributing to a phenotype is calculated as: $C = r_{MZ} - A$. Finally, non-shared environmental influences on a phenotype are the only factors that account for differences between identical twins, hence: $E = 1 - r_{MZ}$.

2.2 | Literature search

The following databases were searched from inception to identify relevant articles: Embase.com (1971-), Medline ALL via Ovid (1946-), Web of Science Core Collection (1975-), Cochrane CENTRAL Register of Trials via Wiley (1992-) and Google Scholar. The searches were designed by an experienced information specialist (WMB).²² The initial search was conducted on 20 February 2019, which was later updated to search for additional items on 24 January 2020, with the search strategies outlined in the Supplementary material (Data S1). Search results were limited to English language only but no further limitations were applied.

2.3 | Study selection procedure

The following criteria were used to select studies:

2.3.1 | Inclusion criteria

A primary research study that:

1. Investigated broadly defined insomnia phenotypes (excluding sleep quality, which is the focus of other meta-analyses^{23,24}), including specific symptoms of difficulties getting to sleep, staying asleep, early morning awakening, non-refreshing sleep (relevant to earlier diagnostic criteria²⁵), assessed with questionnaires (parent- or self-reported) or clinician rating;
2. Is a general population sample;
3. Is a behavioural genetic study utilising one of the following designs: classical twin study, twin/sibling study;
4. Reports descriptive information about sample (n, male/female ratio);
5. Reports statistics necessary for effect size calculations (intra-class correlation coefficients; variance components);
6. Reported on independent samples, or different data from overlapping samples;
7. Is published in English.

2.3.2 | Exclusion criteria

A study that:

1. Did not measure insomnia, but rather reported other sleep parameters such as sleep duration or quality, “sleep problems” that were ill defined, or used a composite “sleep problem” score that included parasomnias, nightmares, bedtime resistance and so forth;
2. Included a population with psychiatric or medical disorder;
3. Included only monozygotic twins;
4. Reported no heritability estimates or twin correlations;
5. Was a review;
6. Was a meta-analysis.

The first two authors independently screened titles and abstracts of the references yielded from the final search for concordance with the inclusion criteria. The full-texts of the papers meeting our inclusion criteria were then read by the first two authors to further assess eligibility, with 77.5% concordance between the authors. Differences in decision between the two authors who read the papers were resolved by further discussion. Reference sections of those included were then assessed.

2.4 | Data extraction

The following data was extracted from each study independently by the first and second author using standardised coding sheets: date,

authors, title, country, registry name, total sample size, subgroup sample sizes (males, females, MZ, DZ), study type (classical twin study, twin/sibling study), sample age (categorised into distinct developmental periods of middle to late childhood, 8-12 years; adolescence, 13-17 years; adulthood, 18+ years), reporter (self-reported, parent-reported, clinician reported), measure of insomnia, insomnia symptom (any insomnia symptom, difficulty initiating sleep, difficulty staying asleep/nocturnal awakening, early morning awakening, non-restorative sleep), twin intraclass correlations (rMZ and rDZ), sampling variances for MZ and DZ, and variance components (A, C, D and E). Table 1 provides an overview of the included studies.

2.5 | Statistical analysis

Statistical analyses were run in R (version 3.5.1) using the “Metafor” package²⁶ using a random-effects model for heritability analyses, and a mixed-effects multi-level model to examine the influence of any moderators. Several of the studies provided more than one effect size such as separate estimates for males and females; for different measures of insomnia; and for different age groups. In these instances, the effect sizes were associated with a study identification number, and this was used to categorise the effect sizes at the level of the sample/study. This approach has been used previously,²⁷ and accounts for the possibility of there being greater similarity between phenotypes from overlapping samples. This has been suggested to increase power and utilise the maximum information in our data.²⁷ In papers that reported multiple effects on the same sample and same phenotypes at different time points we report the statistics derived from the data with the largest sample size.

Commonly reported effect size estimates in behavioural genetic research are raw MZ and DZ correlations, as well as the resulting proportions of variance attributed to A, C and E estimated from these correlations. Multiple studies only presented their best fitting model (dropping non-significant parameters) and reported only the variance decomposition based on this best fitting model. This model choice and preference is sensitive to sample size, thereby possibly presenting a biased estimate (often an overestimation) of genetic influences on sleep.²⁸ We therefore decided to meta-analyse the rMZ and rDZ correlations rather than the standardised variance components. Thus, we performed multi-level meta-analysis utilising rMZ and rDZ correlations which were most consistently reported in the papers (ie, 23 effect sizes of standardised variance components were reported for insomnia symptoms compared with 40 rMZ and rDZ twin correlations).

We transformed the raw rMZ and rDZ correlations into Fisher's Z scores (denoted $ES_{z_{mz}}$ and $ES_{z_{dz}}$) which are assumed to be normally distributed—an assumption which is required to accurately derive estimates of mean effect sizes, and to ensure statistical tests are unbiased.²⁹ We meta-analysed $ES_{z_{mz}}$ and $ES_{z_{dz}}$ separately using a method that takes into account the potential dependency between effect sizes reported within papers, as suggested previously.²⁷ Meta-analysed $ES_{z_{mz}}$ and $ES_{z_{dz}}$ were then transformed back to rMZ and rDZ to aid interpretation, and estimates of h^2 were calculated using

TABLE 1 Characteristics of twin studies

Author (year)	Country	nMZ	nDZ	Age, years (SD)	Sex	Measure of insomnia	Reporter	rMZ	rDZ
Barclay et al (2015) ¹⁶	United States	739	672	8.3 (mode)	M/F	DSM-III-R criteria for clinically significant insomnia	Clinician	0.33	0.1
Cox et al (2020) ^{32a}	United States	157	85	40.7 (13.8)	F	Womens health initiative insomnia rating scale	Self	0.44	0.22
Drake et al (2011) ³⁴	United States	242	276	22.5 (2.8)	F	DSM-IV-TR insomnia criteria	Self	0.55	0.3
					F	Difficulties falling asleep	Self	0.19	-0.03
					F	Difficulty staying asleep	Self	0.24	0.09
					F	Non-refreshing sleep	Self	0.33	0.22
		135	219	22.5 (2.8)	M	DSM-IV-TR insomnia criteria	Self	0.48	0.03
					M	Difficulties falling asleep	Self	0.19	0.36
					M	Difficulty staying asleep	Self	0.35	0.11
M	Non-refreshing sleep	Self	0.35	0.17					
Gregory et al (2006) ¹⁷	United Kingdom	100	199	8.5 (range 8.16-8.92)	M/F	CSHQ: difficulty initiating sleep	Parent	0.81	0.29
						CSHQ: night waking	Parent	0.56	0.42
						CHSQ: difficulty initiating sleep	Self	0.23	0.03
						CSHQ: night waking	Self	0.34	0.05
Gregory et al (2016) ⁵¹	United Kingdom	187	324	20.3 (1.76)	M/F	ISQ	Self	0.34	0.22
Heath et al (1990) ³¹	Australia	1227	748	18-88 (range)	F	JPSQ: initial insomnia	Self	0.33	0.14
						JPSQ: disturbed sleep (no. night time awakenings)	Self	0.35	0.1
						JPSQ: anxious insomnia	Self	0.38	0.28
						JPSQ: depressed insomnia	Self	0.33	0.22
		565	352	18-88 (range)	M	JPSQ: initial insomnia	Self	0.31	0.15
						JPSQ: disturbed sleep (no. night time awakenings)	Self	0.3	0
						JPSQ: anxious insomnia	Self	0.28	0.12
JPSQ: depressed insomnia	Self	0.31	0.21						
Hublin et al (2011) ⁵³	Finland	926	1969	43.9 (7.8)	F	Insomnia symptoms (7 item questionnaire)	Self	0.42	0.21
						Difficulty in initiating sleep	Self	0.44	0.25
						Nocturnal awakenings	Self	0.45	0.24
						Early morning awakening	Self	0.33	0.15
		628	1295		M	Insomnia symptoms (7 item questionnaire)	Self	0.4	0.11
						Difficulty in initiating sleep	Self	0.38	0.15
						Nocturnal awakenings	Self	0.45	0.22
Early morning awakening	Self	0.37	0.04						
Hur et al (2012) ⁶⁵	United Kingdom	893	884	50 (13.2)	F	Frequency of trouble sleeping in past year	Self	0.27	0.15
Lind et al (2015) ¹⁸	United States	503	346	29.3 (7.7) and 35.1 (7.5)	F	Composite score of past month insomnia symptoms	Self	0.23	0.18
		703	485	35.5 (9.1) and 37 (9.1)	M	Composite score of past month insomnia symptoms	Self	0.28	0.09
McCarren et al (1994) ³⁵	United States	1200	1605	33-51 (range)	M	JSPS: insomnia composite score	Self	0.29	0.15

TABLE 1 (Continued)

Author (year)	Country	nMZ	nDZ	Age, years (SD)	Sex	Measure of insomnia	Reporter	rMZ	rDZ
						JSPS: wake tired/worn out	Self	0.25	0.12
						JSPS: trouble falling asleep	Self	0.26	0.12
						JSPS: trouble staying asleep	Self	0.3	0.09
Taylor et al (2015) ³³	United Kingdom	1722	4091	16	M/F	ISI	Self	0.42	0.2
Watson et al (2006) ^{19a}	United States	521	414	32 (range 18-90)	M/F	How often do you have trouble falling asleep or staying asleep?	Self	0.47	0.15

Note: Age = mean unless otherwise stated (mode or range in years as presented in the original papers \pm SD where reported).

Abbreviations: CSHQ: Child Sleep Habits Questionnaire; DSM-III-R, diagnostic and statistical manual of mental disorders, 3rd edition revised; DSM-IV-TR, diagnostic and statistical manual of mental disorders, 4th edition text revision; F, females; ISI, Insomnia Severity Index; ISQ, Insomnia Symptoms Questionnaire; JPSQ, Johns & Palmer Sleep Questionnaire; JSPS, Jenkins Sleep Problem Scale; M, males; nDZ, number of dizygotic twins from complete twin pair; nMZ, number of monozygotic twins from complete twin pairs; rDZ, dizygotic twin intraclass correlation; rMZ, monozygotic twin intraclass correlation; SD, standard deviation.

^aOverlapping samples.

Falconer's formulae.³⁰ Moderator effects were examined in separate models to determine the difference in heritability estimates as a function of sex, age, reporter or symptom of insomnia.

3 | RESULTS

3.1 | Search results

Our final search yielded 8575 hits, after which 5644 remained once duplicates were removed. A further 5484 publications were excluded after the first two authors independently screened the titles and abstracts for concordance with the inclusion criteria. The full-texts of the remaining 160 were independently read by the first two authors to assess eligibility. Differences in decision between the two authors who read the papers were resolved by further discussion ($n = 36$) after which a further 148 were excluded. Reference sections of those included were assessed, and no additional papers were identified. Reasons for exclusion are outlined in the PRISMA Flowchart (Figure 1).

3.2 | Description of included studies

A total of 12 papers were included in the meta-analysis (see Table 1 for summary of studies). Of these, 11 reported on independent studies (two papers were included from the University of Washington Twin Registry). Five studies reported results from the United States, four from the United Kingdom, one from Australia and one from Finland. The total sample size of the independent studies was 47 794 individuals, including 10 291 MZ twin pairs and 13 606 DZ twin pairs. The earliest publication date was 1990³¹ whilst the most recent publication was in 2020.³² Every study used a different method to assess insomnia. The study with the smallest sample included 242 twin pairs³² whilst the study with the largest sample included 5813 pairs.³³

Five studies reported on both males and females together, four studies provided MZ and DZ correlations separately for males and females, one study included only males, and two studies included only females. Nine of the studies examined the heritability of insomnia in adulthood (ranging from 18 to 90 years), two examined middle to late childhood (8-12 years) and one in adolescence (13-16 years).

3.3 | Meta-analysis results

The 12 papers provided 40 MZ and 40 DZ correlations to be included in the meta-analysis. Some studies meeting inclusion criteria reported multiple correlations, totalling 52 MZ and 52 DZ correlations, but only one set was included from each study where there were correlations reported from the same sample at different ages in separate publications. Figure 2 displays the forest plots of the correlations included in the meta-analysis. MZ correlations ranged between 0.19³⁴ and 0.81.¹⁷ DZ correlations ranged between -0.03 ³⁴ and 0.42.¹⁷ Standardised broad-sense heritability estimates (where available) ranged from 0% for self-reported difficulty initiating sleep³⁴ to 79% for parent-reported difficulty initiating sleep.¹⁷ There was little contribution of the shared environment, which ranged from 0%^{17,19,35} to 27%.³⁴ Non-shared environmental influences contributed between 21% for parent-reported difficulty initiating sleep¹⁷ to 83% of variability in self-reported difficulty initiating sleep.¹⁷

A multi-level meta-analysis was performed in order to explore the heterogeneity between studies and to take into account the dependency between multiple effect sizes derived from each individual study (in cases where there were reports separately for males and females, different reporters, or different symptoms of insomnia reported). This yielded an overall MZ correlation of 0.36 (Fisher's Z-score $rMZ = 0.38$, $SE = 0.03$, $t = 12.58$, $P < .001$, 95% CI = 0.32-0.44) and an overall DZ correlation of 0.16 (Fisher's Z-score $rDZ = 0.16$, $SE = 0.01$, $t = 11.67$, $P < .001$, 95% CI = 0.13-0.19). Heterogeneity was relatively high for correlations in both monozygotic ($I^2 = 89\%$)

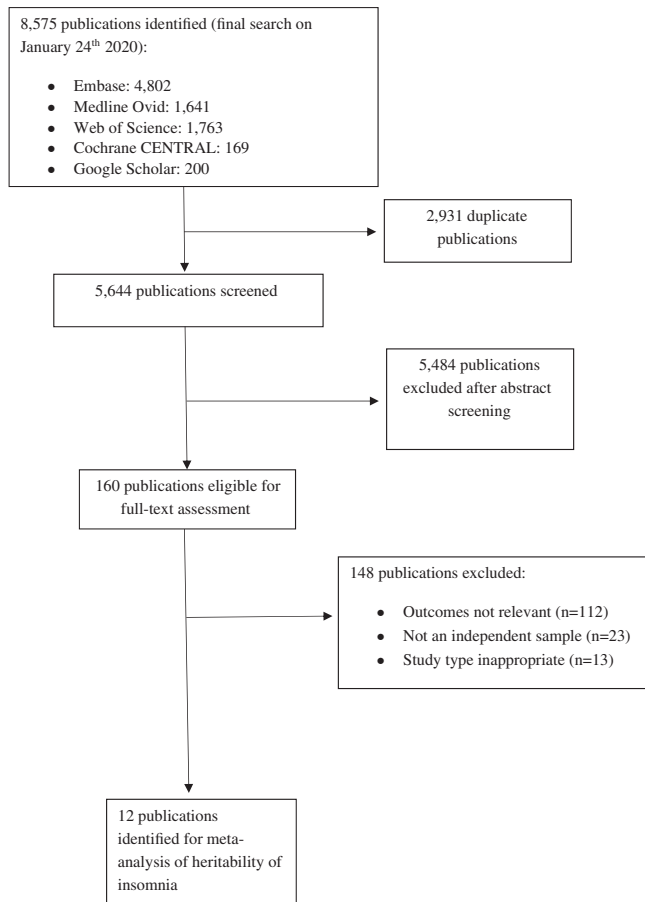


FIGURE 1 PRISMA flowchart of systematic reviewing and study inclusion/exclusion

and dizygotic ($I^2 = 82\%$) twins. Using Falconer's formula to determine the estimate of heritability based on the MZ and DZ correlations derived from the meta-analysis yielded an overall heritability estimate of 40%. This indicates that 40% of differences between individuals in

insomnia symptoms is because of differences in their genetic make-up.

Moderator analyses were then performed to determine whether sex, age, reporter or insomnia symptom moderated the MZ and DZ correlations in the meta-analysis (see Table 2). There was no effect of sex on the MZ correlations ($F(1, 30) = 0.93, P = .34$), however, there was a sex difference for the DZ correlations ($F(1, 30) = 4.63, P = .04$). Hence, DZ correlations in these studies significantly differed for males and females ($r_{DZ} = 0.17$ and 0.15 , respectively), leading to a higher heritability estimate for females compared with males. There was no effect of age on the MZ correlations ($F(2, 37) = 1.94, P = .16$) nor DZ correlations ($F(2, 37) = 0.22, P = .80$), although it is likely there was not enough variability in our categorical age variable to determine moderator effects.

Eleven of the studies utilised self-report data, one utilised clinician ratings,^{16,31} and one reported both parent-reported data as well as self-reported data from children.¹⁷ Moderator analyses showed a significant effect of reporter on the MZ correlations ($F(2, 37) = 16.40, P < .001$) and DZ correlations ($F(2, 37) = 5.10, P < .01$). MZ and DZ correlations were significantly larger for parent-reported insomnia than self-reported and clinician rated data. Additionally, DZ correlations for insomnia symptoms that were reported by clinician were significantly smaller than DZ correlations for self-reported insomnia symptoms. Finally, moderator analyses showed no significant differences in the MZ correlations as a function of insomnia symptom ($F(4, 35) = 0.31, P = .87$), nor the DZ correlations ($F(4, 35) = 0.25, P = .91$).

4 | DISCUSSION

4.1 | Summary of main findings

The present analyses provide an overall meta-analytic heritability estimate of insomnia and insomnia phenotypes of 40%. This estimate is

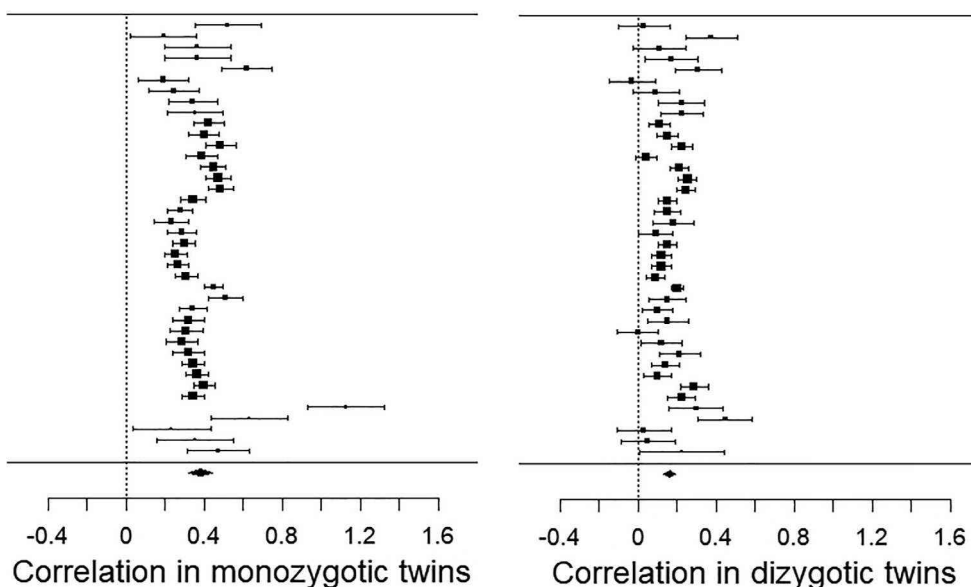


FIGURE 2 Forest plots of the monozygotic and dizygotic twin pair correlations from 40 effects with standard error bars

TABLE 2 Results from moderator analyses

Moderator	Categories	k	MZ			DZ			H ²
			Fishers rMZ	95% CI	rMZ	Fishers rDZ	95% CI	rDZ	
Sex	Male	5	0.33	0.27–0.39	0.32	0.17	0.12–0.21	0.17 ^a	0.30
	Female	6	0.35	0.29–0.41	0.34	0.15	0.11–0.19	0.15	0.37
Age	Middle to late Childhood	2	0.5	0.35–0.64	0.46	0.18	0.09–0.27	0.18	0.57
	Adolescence	1	0.45	0.22–0.68	0.42	0.20	0.04–0.36	0.20	0.45
	Adult	9	0.35	0.29–0.41	0.34	0.16	0.13–0.19	0.16	0.36
Reporter	Parent ^a	1	0.9	0.71–1.10	0.72	0.37	0.23–0.51	0.35 ^a	0.72
	Self-report	11	0.36	0.30–0.41	0.35	0.16	0.13–0.18	0.16	0.37
	Clinical Assessment	1	0.34	0.16–0.53	0.33	0.10	–0.06–0.26	0.10	0.46
Insomnia Symptom	Any insomnia symptom	11	0.39	0.32–0.47	0.37	0.17	0.13–0.22	0.17	0.41
	Difficulty initiating sleep	5	0.36	0.26–0.47	0.35	0.17	0.10–0.23	0.17	0.35
	Difficulty staying asleep/nocturnal awakenings	5	0.38	0.28–0.48	0.36	0.15	0.09–0.21	0.15	0.43
	Early morning awakenings	2	0.33	0.20–0.47	0.32	0.14	0.05–0.23	0.14	0.36
	Non-restorative sleep	1	0.31	0.08–0.54	0.30	0.12	–0.05–0.29	0.12	0.36

Abbreviations: H²: heritability estimate calculated as 2(rMZ–rDZ); k = number of studies that were included in the moderator analysis; rDZ = dizygotic twin intraclass correlation; rMZ = monozygotic twin intraclass correlation; 95% CI: 95% confidence interval.

^aSignificant difference between levels of the moderator, $P < .05$.

derived from 40 effect sizes from 12 papers from general population samples of children, adolescents and adults, spanning an age range of 8 to 90 years. Our meta-analytic approach took into account the varying sample sizes of the included studies and in total draws on data from 47 794 twins. Moderator analyses showed that the heritability of insomnia may be higher in females compared with males. Additionally, in a paediatric population, moderator analyses showed significantly higher heritability of insomnia for parent-reported compared with self-reported insomnia symptoms, although this point should be interpreted cautiously given that the moderator analysis was based on only one study including parent reported data and one study including clinician rated data.

4.2 | Interpretation of findings

The heritability of insomnia at 40% is similar to that for sleep quality and duration,^{23,24} as well as anxiety, depression and neuroticism, arguably the three traits that are most closely related to insomnia.⁸ Meta-analytic and large-scale studies provide heritability estimates of 32% for anxiety disorder,³⁶ 38% for major depression,^{37,38} and 39% for neuroticism.³⁹ There was considerable heterogeneity in the heritability estimates derived from the individual studies included in our meta-analysis, ranging from 14% to 79%, with our estimate of 40% lying between the two. Whilst our analysis focussed exclusively on twin studies, family studies of insomnia concur that there is familial aggregation of insomnia. Family studies in the insomnia field report a variety of statistics, making it difficult to calculate a robust estimate, but studies show that between 35% and 73% of patients with

insomnia-type phenotypes also have a relative with sleep disturbances/insomnia.^{13,14,40} Using a similar metric, other family studies yield a relative risk of having insomnia of 1.8 to 4.42 in those with positive biological family history.^{41–43} Finally, other family studies have showed that around 29% to 37% of variability in stress-related sleep disturbance, and 48% to 61% for current and lifetime insomnia disorder, is accounted for by familial factors.^{42,44,45} Thus, different study designs converge on the finding of a heritable component of insomnia, but that vast heterogeneity exists.

Our analysis examined several potential moderators to identify explanations for such heterogeneity. Our analysis included seven studies that examined sex differences in heritability of insomnia. Our moderator analyses indicated that DZ correlations were moderated by sex, leading to a higher heritability estimate for females (37%) compared with males (30%)*. Research highlights a female preponderance of poor sleep and insomnia across the lifespan,^{15,46,47} and our analysis suggests that this may be because of greater influence of heritable factors. Although GWAS have previously reported some sex difference in risk genes,^{8,9,11,12} it is worth noting that, to our knowledge, only one twin study of insomnia has investigated qualitative sex differences—that is, whether the same genes are influential for insomnia for males and females, finding no evidence of such differences.¹⁸ Future research should aim to examine the extent of genetic correlation between the sexes.

Whilst we observed no effect of age on heritability, it is possible that this is because of the small number of studies included in infant ($n = 0$), child ($n = 2$), and adolescent ($n = 1$) populations, limiting our power to examine potential age differences. Whilst there were three papers that examined young adulthood (18–30 years), and four that

examined middle adulthood (31–51 years), two papers examined the full range of ages from 18 to 90 years. We decided against a further break down of adult ages in our moderator analysis because of the unclear and arbitrary delineation of age groups. Our search indicates that infant, child and adolescent populations are under-represented in the field examining insomnia. Many paediatric populations examine more broadly defined “sleep problems” or “sleep disturbances” which inevitably did not meet our inclusion criteria. Hence, we included no studies of populations younger than 8 years. Paediatric insomnia often stems from the need for the caregiver to be present for sleep onset, and the difficulty in breaking this behavioural association.⁴⁸ The childhood insomnia studies that we did include intriguingly showed that parent-reported insomnia symptoms appear more heritable than when the same symptoms are reported by the children themselves (although it should be remembered that this is based on one study only). A possible explanation for this finding could be that parents are more likely to report greater similarity for MZ compared with DZ twins, and have less knowledge of the sleep behaviour of their children, accounting for the disparity between theirs and their child's own reports. Thus, the child-reported estimates may be a more accurate reflection of the heritability of insomnia in childhood populations.

Our moderator analyses did not show differences in heritability among different insomnia symptoms (although the small number of studies included in each category of the moderator analysis may not have been powered to detect such differences). Examination of the individual studies that parsed the data into variance components show a range of broad sense heritability estimates between 28% and 57% for any insomnia symptom ($n = 8$); 0% to 79% for difficulty initiating sleep ($n = 3$); 25% to 42% for difficulty staying asleep ($n = 3$); 34% to 35% for early morning awakening ($n = 1$); and 26% for awakening tired/worn out ($n = 1$). That is not to say that there may be different genes accounting for the different manifestations of insomnia. Future behavioural genetic research should investigate the extent of genetic overlap between insomnia symptoms. It is possible that different mechanisms account for difficulties getting to sleep compared with awakening earlier than desired, given that different brain areas and neurotransmitter systems may be involved in sleep onset, maintenance and offset. There may be a role for genes controlling circadian regulation in difficulties with sleep timing, whereas nocturnal awakenings may be in part accounted for by genes controlling the regulation of, and transitions between, slow-wave sleep and rapid eye movement sleep. That said, studies aiming to elucidate which genes are involved in normal sleep regulation have yet to yield robust and consistent genes across studies and populations.

Insomnia, being a complex trait, is highly polygenic, that is, the vulnerability involves a complex combination of many small genetic influences. Whilst recent GWAS show little consistency in genes involved, they converge on the finding that genetic influences on insomnia may be shared with those contributing to psychiatric and metabolic traits.^{8–12,49} This is mirrored by twin studies which have showed substantial genetic overlap between insomnia and anxiety, depression,^{50,51} pain and somatic symptoms⁵² and obesity.¹⁹

It is likely that genetic factors interact to influence insomnia vulnerability. Whilst the majority of studies included in this meta-analysis only examined additive genetic effects, one of the studies found evidence of non-additive genetic effects.⁵³ Furthermore, 68% of the MZ correlations reported in this meta-analysis were more than twice the magnitude of the corresponding DZ correlations, a pattern which is indicative of genetic interactions.

Of course, the other side of the coin is the role of the environment. Whilst family studies have limited ability to tease apart familial effects because of genetics or the shared environment, twin studies can partition the variance into these components. All but one of the studies included in this meta-analysis found no role of the shared environment in predicting insomnia, with the remaining (and largest) source of variance being the non-shared environment. This is echoed throughout the behavioural genetic literature for many psychological and behavioural phenotypes in adult populations.⁵⁴ On the contrary, in 8 year old twins, Gregory and colleagues estimated that a quarter of the variability in parent-reported night waking was because of environmental influences shared between family members.¹⁷ The relative lack of shared environmental influence in adulthood compared with childhood is a common finding across the behavioural genetic field, and its lack of importance in insomnia is likely because of the small number of behavioural genetic studies of insomnia in children.

The importance of the non-shared environment is perhaps no surprise given that many individuals often report a significant environmental “trigger” of their sleep disturbance (such as stressful life events). Spielman's 3P model of insomnia highlights the role of predisposing, precipitating and perpetuating factors in its genesis and maintenance.⁵⁵ Spielman's 3P model acknowledges that genetic and environmental factors may interact to bring about an episode of insomnia: genetic predisposition alone is not sufficient to disturb sleep, but genetic vulnerability coupled with an environmental trigger is the recipe for the onset of insomnia. If this is the case, the heritability derived from twin and family studies is conservative as such designs are unable to parse variance into that accounted for by gene-environment interaction (GxE) and such effects would inflate the non-shared environmental component. Molecular genetic research has found support for the role of GxE in insomnia. For example, several studies have showed that environmental stress moderates the association between a variant of the serotonin transporter gene and likelihood of experiencing poor sleep or insomnia.^{56–58}

4.3 | Limitations and suggestions for future research

There are several limitations of our approach that must be considered when interpreting our heritability estimate. First, we only included papers that explicitly measured “insomnia” or “insomnia symptoms”, and excluded papers with less clearly defined “sleep problems”, the latter of which may have included symptoms akin to insomnia. There were 15 papers that met all other inclusion criteria that measured more broadly defined “sleep problems” or “sleep disturbances” that

we decided to exclude because they included insomnia-related phenotypes among a constellation of other sleep phenotypes, and it was not possible to tease apart symptoms purely related to insomnia. For example, four papers used the child behaviour checklist (CBCL)⁵⁹ which combines items including “overtired”; “sleeps less than most kids”; “sleeps more than most kids during day and/or night”; and “trouble sleeping”. Similarly, three papers used the Child Sleep Habits Questionnaire (CSHQ),⁶⁰ which combines items relating to multiple sleep disturbances, including insomnia, but also encompassing bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night wakings, parasomnia, sleep-disordered breathing, and daytime sleepiness. The analyses presented by the study authors did not tease apart those items purely relating to insomnia. Second, heritability is a population statistic derived from population variance,⁶¹ so may only be generalizable to the populations under study. The studies included in this meta-analysis were all from developed countries, including the United States, United Kingdom, Europe and Australia, so our estimate of heritability may not be generalizable to other populations. This highlights the necessity of further quantitative and molecular genetic research in other countries and populations worldwide. Third, some may argue that twin studies are not representative of the general non-twin population. Whilst twin studies are a stronger method for teasing apart heritability, family studies may be considered more representative. As pointed out above, family studies reporting on familial aggregation of insomnia (n = 9) appear consistent with our estimates. Encouragingly, estimates from twins appear consistent with non-twins in a number of psychiatric traits, including sleep difficulties.⁶² Fourth, whilst the studies included report on the general population in most cases, it is inevitable that these will include cases of individuals with psychiatric disorder. Whilst the samples are not exclusively in psychiatric populations, given the high comorbidity between insomnia and numerous psychiatric traits,^{63,64} it is likely that the data will capture some patient populations despite our strict inclusion/exclusion criteria. Finally, there may have been measurement error in the assessment of insomnia. The vast heterogeneity in heritability derived from each study may be accounted for by measurement error within those studies. Measurement error is subsumed within the non-shared environmental component of variance, and hence will reduce the heritability estimate. Every study used a different measure to assess insomnia and so we could not examine measure of insomnia as a moderator. Whilst the aim of our moderator analyses was to separate heritability across insomnia symptoms and to examine reporter effects, the measure of insomnia may have also moderated the heritability estimate, and some measures may be a truer reflection of the manifestation of insomnia than others. Future research should refine and harmonise measures of insomnia (aligned to diagnostic criteria) to aid comparability between studies.

5 | CONCLUSIONS

Insomnia exhibits a strong genetic component. Our meta-analysis of twin studies yielded a heritability estimate of 40% which is likely

moderated by sex and reporter. The remaining variance in adult populations is accounted for by the non-shared environment, and there is likelihood that gene–environment interactions are also at play. The shared environment may be important in childhood populations, although most behavioural genetic research in paediatric populations examines more broadly defined “sleep problems”. Future research should examine the extent of genetic overlap between insomnia symptoms and work towards a consistent measure of insomnia across quantitative and molecular genetic studies of insomnia.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE

* Note that these estimates are smaller than the overall heritability estimate of 40% as the moderator analyses are based on a smaller number of studies.

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SUPPORTING INFORMATION

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

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