Insomnia disorder subtypes derived from life history and traits of affect and personality

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Summary

Background Insomnia disorder is the second most prevalent mental disorder, and it is a primary risk factor for depression. Inconsistent clinical and biomarker findings in patients with insomnia disorder suggest that heterogeneity exists and that subtypes of this disease remain unrecognised. Previous top-down proposed subtypes in nosologies have had insufficient validity. In this large-scale study, we aimed to reveal robust subtypes of insomnia disorder by use of data-driven analyses on a multidimensional set of biologically based traits.

Methods In this series of studies, we recruited participants from the Netherlands Sleep Registry, a database of volunteers aged 18 years or older, who we followed up online to survey traits, sleep, life events, and health history with 34 selected questionnaires of which participants completed at least one. We identified insomnia disorder subtypes by use of latent class analyses. We evaluated the value of our identified subtypes of insomnia disorder by use of a second, non-overlapping cohort who were recruited through a newsletter that was emailed to a new sample of Netherlands Sleep Registry participants, and by assessment of within-subject stability over several years of follow-up. We extensively tested the clinical validity of these subtypes for the development of sleep complaints, comorbidities (including depression), and response to benzodiazepines; in two subtypes of insomnia disorder, we also assessed the clinical relevance of these subtypes by use of an electroencephalogram biomarker and the effectiveness of cognitive behavioural therapy. To facilitate implementation, we subsequently constructed a concise subtype questionnaire and we validated this questionnaire in the second, non-overlapping cohort.

Findings 4322 Netherlands Sleep Registry participants completed at least one of the selected questionnaires, a demographic questionnaire, and an assessment of their Insomnia Severity Index (ISI) between March 2, 2010, and Oct 28, 2016. 2224 (51%) participants had probable insomnia disorder, defined as an ISI score of at least 10, and 2098 (49%) participants with a lower ISI score served as a control group. With a latent class analysis of the questionnaire responses of 2224 participants, we identified five novel insomnia disorder subtypes: 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. In a second, non-overlapping replication sample of 251 new participants who were assessed between June 12, 2017, and Nov 26, 2017, five subtypes were also identified to be optimal. In both the development sample and replication sample, each participant was classified as having only one subtype with high posterior probability (0·91–1·00). In 215 of the original sample of 2224 participants with insomnia who were reassessed 4·8 (SD 1·6) years later (between April 13, 2017, and June 21, 2017), the probability of maintaining their original subtype was 0·87, indicating a high stability of the classification. We found differences between the identified subtypes in developmental trajectories, response to treatment, the presence of an electroencephalogram biomarker, and the risk of depression that was up to five times different between groups, which indicated a clinical relevance of these subtypes.

Interpretation High-dimensional data-driven subtyping of people with insomnia has addressed an unmet need to reduce the heterogeneity of insomnia disorder. Subtyping facilitates identification of the underlying causes of insomnia, development of personalised treatments, and selection of patients with the highest risk of depression for inclusion in trials regarding prevention of depression.

Funding European Research Council and Netherlands Organization for Scientific Research.

Lancet Psychiatry 2019

Published Online
January 7, 2019
http://dx.doi.org/10.1016/S2215-0366(18)30464-4

See Online/Comment
http://dx.doi.org/10.1016/S2215-0366(18)30513-3

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Introduction

Insomnia is a common health problem; a third of the population report sleep complaints and about 10% of the population meet the diagnostic criteria for insomnia disorder,[1,2] making it the second most prevalent mental disorder.[3] Despite the high prevalence and considerable heritability of insomnia[4] and the identification of genes that confer an associated risk of insomnia,[5,6] it has been difficult to characterise insomnia consistently with respect to cognition,[7] mood,[8] family history,[9] history of life events,[10]

Research in context

Evidence before this study

Clinical and biomarker findings on insomnia disorder show inconsistencies across patients and studies, and this heterogeneity is suggested to be caused by unrecognised subtypes. Subtypes of insomnia disorder have previously been proposed top-down. It was presumed that these subtypes would differ with respect to stable sleep-related characteristics. Unfortunately, such subtypes had insufficient reliability and validity, so heterogeneity still prevails. No previous study investigated whether subtypes can be revealed using a high-dimensional data-driven approach, including biologically based traits that could more indirectly be related to insomnia. We searched PubMed for work published before Feb 19, 2018, with the search terms "insomnia AND data-driven AND subtype", which revealed only two papers. One of these papers was a study report that included insomnia as a dimension to subtype 203 patients with major depressive disorder. The other paper was our theoretical systematic review on variables of relevance in a high-dimensional data-driven approach to find subtypes of insomnia.

Added value of this study

To our knowledge, our study represents the first identification of five novel and robust subtypes of insomnia disorder and the first demonstration of the usefulness of these subtypes in reducing clinical and biomarker heterogeneity. We used a high-dimensional data-driven analysis of 34 biologically based traits that were assessed by questionnaires in a large sample (4322 participants) among which 2224 participants had probable insomnia disorder. We also developed and validated a more concise Insomnia Type Questionnaire with the most discriminating 200 of the original 523 questions, representing 17 of the original 26 characteristics, to reliably assess subtypes in an independent sample. After a follow up of 4·8 (range 0·5–7·0) years, there was a probability of 0·87 that participants would maintain their original subtype, which was in sharp contrast to the low stability of previous subtypes that were suggested in top-down studies (eg, a third of participants maintained their subtype for 4 months). In derived and independent samples, we validated the clinical relevance of our identified subtypes by identification of subtype differences in developmental trajectories of sleep complaints, health risks, response to pharmacological and non-pharmacological treatments, and a neurophysiological biomarker.

Implications of all the available evidence

Marked subtype differences in the risk of depression in people with insomnia could enable selection of high-risk individuals for preventive interventions by use of the Insomnia Type Questionnaire that we developed, which includes automated scoring. By reducing previously unrecognised heterogeneity, subtyping will facilitate identification of biomarkers, elucidation of the mechanisms of insomnia, and development of personalised treatments for insomnia disorder. Subtyping is reliable and can be accomplished in large populations by use of the internet.

personality,[11] polysomnography,[12] sleep microstructure,[13] and brain imaging.[14] Such inconsistencies suggest unrecognised subtypes of insomnia disorder and stall progress in our understanding of its underlying mechanisms, with which we could improve interventions. Subtypes of insomnia disorder that were previously proposed top-down[15–18] predominantly focused on sleep-related characteristics (such as sleep-onset insomnia), had low reliability,[15,16] and were discarded from major nosologies.[17,18]

See Online for appendix

However, we suspected that clearer subtypes of insomnia disorder might emerge if they were developed bottom-up and data-driven, with a multidimensional set of stable, biologically based non-sleep characteristics that are relevant to insomnia.[19] Such a wider perspective on discriminating characteristics has been shown to be important in other disorders. For example, subtyping attention deficit hyperactivity disorder according to temperament trait dimensions explained more of its heterogeneity than previous nosological criteria.[20] It is conceivable that insomnia disorder could similarly represent a heterogeneous group of patients in whom different underlying mechanisms are reflected in biologically based traits that lead to indistinguishable sleep complaints. Finding insomnia disorder subtypes would then require inclusion of traits that might only indirectly relate to sleep but can be highly relevant to insomnia, such as hyperarousal, personality, and mood traits.[5,6,19]

For the **Netherlands Sleep Registry** see www.slaapregister.nl

The biological basis of traits related to insomnia (appendix pp 20–28)[19] makes it conceivable that several specific combinations of traits can be unfavourable for sleep regulation. Our previous genome-wide association studies[5,6] indicated that insomnia disorder is genetically more closely related to attributes associated with mood, personality, and wellbeing than to sleep-related phenotypes. We therefore aimed to investigate whether insomnia disorder presents as different subtypes that are reflected in a multivariate pattern of stable characteristics, such as life history, trait positive and negative affect, and personality.

Methods

Study design and participants

We used data provided by participants from the Netherlands Sleep Registry (NSR), an online platform and linked database that extensively surveys sleep, personality and affect traits, life events, and health conditions.[19] NSR volunteers are recruited via media, advertisements, and flyers that are distributed at health-care institutions and conventions. Recruitment communications for the NSR stress the need for volunteers who cover the spectrum of those who sleep well to those who sleep poorly. As a

result, participants in the NSR database represent a uniform distribution with respect to the severity of insomnia: 38% of participants have insomnia, 29% of participants have subclinical insomnia, and 33% of participants have clinical insomnia.[21] The only inclusion criterion was an age of 18 years or older. Participants completed a variable number of randomly selected questionnaires (of 34 questionnaires) at their convenience, resulting in a varying number and set of completed questionnaires between participants. Those with an insomnia severity index (ISI) score of at least 10 were included as cases with probable insomnia disorder; participants with an ISI score of less than 10 were included as controls. Among the participants with probable insomnia disorder, we invited a randomly drawn subset by email to participate in a longitudinal follow up. Additionally, new NSR participants were recruited by newsletter for validation in a second, non-overlapping cohort. The Medical Ethical Committee of the Academic Medical Centre of Amsterdam and the Central Committee on Research Involving Human Subjects approved of implicit informed consent.

Model development

Characteristics that were relevant to insomnia were first identified by a systematic review[19] and an assessment of genetic correlations.[5,6] Sufficient data were available for 34 characteristics, each representing a questionnaire sum score, that covered features of life history, fatigue and arousal, personality, mood, and happiness, among others (appendix p 29). To prevent multicollinearity, we selected only the characteristics that had the lowest median correlation with each of the other characteristics, preserving 26 characteristics for analyses. The preserved characteristics and observed score ranges are shown in the appendix (p 32).

To identify subtypes among the patients with insomnia disorder, we chose a model-based unsupervised clustering technique—latent class analysis—because this approach can handle missing data, include variables that are measured on different scales, and classify new patients (appendix p 2). To determine the most probable number of subtypes, we increased the number of classes stepwise, and we selected the model that minimised the Bayesian information criterion. Any participant who completed even only one characteristic questionnaire is of value to estimate the latent class model, because even one observation carries information on the observed range of that characteristic. However, a profile of several characteristics is required to subtype an individual, and the availability of only a few characteristics is insufficient to identify the subtype profile to which an individual belongs. Therefore, we evaluated the quality of the model on a subsample of 1046 individuals who completed at least ten and up to 26 questionnaires, each representing independent characteristics (appendix p 16). Details on model estimation, evaluation, and assumptions are shown in the appendix (p 2).

For multivariate visualisation of subtypes, we standardised each individual characteristic score to the corresponding distribution of scores in the control group. The values of positive characteristics (such as wellbeing) were reverse coded and renamed (eg, reduced wellbeing), such that higher values would uniformly indicate higher general distress. To quantify the effect sizes of group differences, we computed Cohen's d, often labelled small (0·2), medium (0·5), and large (0·8).[22]

To facilitate implementation, we used a regression with least absolute shrinkage and selection (lasso) regularisation to select a subset of characteristics that still accurately predicted class membership, from which we developed the Insomnia Type Questionnaire (ITQ; appendix pp 4, 37).

Model validation

We recruited a new, non-overlapping validation sample of people with probable insomnia disorder (with an ISI score[21] of at least 10) through the NSR. With this sample, we validated the robustness of the number of classes by use of a latent class analysis and again selected the model that minimised the Bayesian information criterion. Moreover, we verified the use of the ITQ in subdividing these patients into subtypes. Details on regularisation and ITQ construction are shown in the appendix (p 4).

Finally, to validate the trait-like stability of subtype classification, we assessed the consistency of subtype membership over a maximum of 7 years by use of a latent transition analysis (appendix p 5) in a proportion of the original participants.

Clinical validation

After the subtypes of insomnia disorder were found and validated, we extensively investigated clinical relevance of these subtypes for the developmental trajectories of sleep complaints, current comorbidities, risk of depression, and response to benzodiazepine intake. We also investigated the clinical relevance of two subtypes for an electroencephalogram biomarker and the effectiveness of cognitive behavioural therapy (CBT) for insomnia (appendix p 16).

To assess clinical relevance in NSR participants, we first used χ^2 tests to evaluate differences in the developmental trajectories of sleep complaints across the lifespan between the subtypes, and we used Fisher's exact tests for differences in comorbid sleep-disorders, lifetime and current risk of depression, and other comorbidities.

Second, a subsample of NSR participants with insomnia disorder used five-point bipolar Likert-type scales to rate whether difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and fatigue were worsened or improved after incidental benzodiazepine use the preceding night, relative to their usual severity. Ratings by subtype were compared with *F* tests and *t* tests.

Third, in a separate sample, we investigated the subtype-dependent effects of 4 weeks of online CBT for insomnia

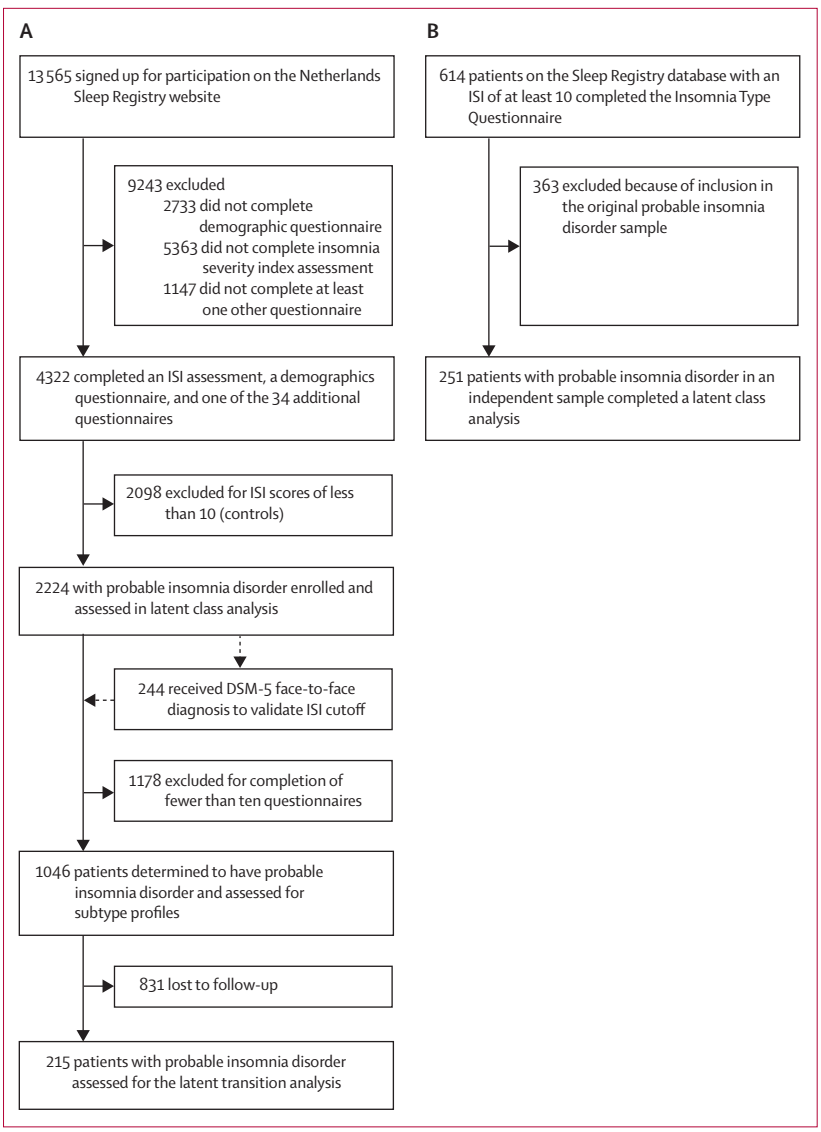


Figure 1: **Trial profile of the main cohort (A) and of a non-overlapping cohort used to validate the subtypes (B)**

on the ISI score of people diagnosed with insomnia disorder.[17,18] ITQ-based subtyping identified sufficient participants of subtype 2 and subtype 4. We used mixed effect models to compare treatment effects in this sample.

Finally, as a preliminary illustration of the potential of subtyping in finding clinically relevant biomarkers and clues to differential underlying brain mechanisms, we subtyped volunteers of an independent study on electroencephalogram event-related potentials (ERPs). Among participating patients diagnosed with insomnia disorder,[17,18] only those with insomnia disorder subtypes 2 and 4 were sufficiently represented (defined as more than ten participants per group) for reliable ERP averages. The ERP results of these participants were compared with those of controls without sleep complaints. In a so-called auditory oddball task, volunteers listen to repeated standard tones and occasional tones of a deviating pitch. Electroencephalograms are simultaneously recorded, which allows for an evaluation of trait-like brain responses that reflect information-processing aspects such as adaptation and attention. Artifact-free ERPs at the Pz location of the 10-20 system of electrodes that were referenced to both mastoids were averaged over 170 standard tones and 30 deviating tones. We used cluster-based random permutation tests to evaluate the significance of group differences across the ERP curve, covering early sensory responses, a mid-latency indicator of adaptation, attention, and salience (determined by the P300 potential amplitude), and a late indicator of emotional relevance (determined by the late positive potential amplitude).[23]

Statistical analysis

Latent class analysis and latent transition analysis were done with Latent GOLD version 5.0. Other analyses used the R (version 3.2.4) packages effsize, leaps, glmnet, and stabs, SPSS (version 23.0), and MLwiN version 2.02. The analysis scheme and corresponding subsamples are shown in the appendix (p 16).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

All questionnaires (appendix p 29) were completed online between March 2, 2010, and Nov 26, 2017. Face-to-face interviews in a subsample of 244 participants were conducted between Jan 9, 2012, and Sept 30, 2016, at the Netherlands Institute for Neuroscience (Amsterdam, The Netherlands). Data collected between March 2, 2010, and Oct 28, 2016, in participants of the Netherlands Sleep Registry (NSR) were used (figure 1). Of the 13 565 people who signed up for the NSR, 4322 participants completed at least one of the 34 included questionnaires, in addition to a demographics questionnaire and an assessment of their ISI. 2224 (51%) participants fulfilled the criterion of an ISI score[21] of at least 10 for probable insomnia disorder in community samples and were included in the latent class analysis. 2098 (49%) participants had an ISI score of less than 10 and served as controls. The validity of the ISI cut-off was confirmed in a subsample of 244 (11%) of the participants, who were also diagnosed in a face-to-face interview with DSM-5 criteria.[17] 195 (80%) of these participants were diagnosed with insomnia disorder with these criteria, of whom 185 (76%) had an ISI of at least 10 (sensitivity 94·9%); of the 49 (20%) participants without this diagnosis, 41 (17%) had an ISI of less than 10 (specificity 83·7%). In absence of face-to-face

	Control	Insomnia disorder subtype (n=1046)				
		1 (highly distressed)	2 (moderately distressed, reward sensitive)	3 (moderately distressed, reward insensitive)	4 (slightly distressed, high reactive)	5 (slightly distressed, low reactive)
Demographics						
Number (% with subtype)	2098	200 (19%)	323 (31%)	153 (15%)	209 (20%)	161 (15%)
Number of women (% with subtype)	1558	164 (20%)	271 (33%)	100 (12%)	176 (22%)	106 (13%)
Number of men (% with subtype)	540	36 (16%)	52 (23%)	53 (23%)	33 (14%)	55 (24%)
Age, years	47·2 (15·8)*†‡	49·5 (12·5)†‡	48·9 (14·3)*†‡	53·9 (13·9)§	54·0 (12·1)§¶	56·6 (12·5)§¶
Insomnia characteristics						
Insomnia severity index score	4·0 (2·9)*†‡§¶	17·8 (4·9)*†‡§	15·8 (4·1)¶	16·5 (4·6)‡¶	15·0 (3·9)¶	14·8 (3·7)*¶
Difficulty initiating sleep, mean score	0·5 (0·6)*†‡§¶	2·0 (1·4)	1·8 (1·3)	1·9 (1·4)	1·6 (1·4)	1·7 (1·3)
Difficulty maintaining sleep, mean score	0·6 (0·8)*†‡§¶	2·8 (1·3)	2·6 (1·2)	2·8 (1·3)	2·8 (1·3)	2·7 (1·2)
Early morning awakening, mean score	0·5 (0·7)*†‡§¶	2·3 (1·4)	2·1 (1·3)	2·1 (1·4)	2·1 (1·3)	2·1 (1·3)
Dissatisfied with sleep, mean score	1·0 (0·8)*†‡§¶	3·1 (0·8)	3·0 (0·8)	3·0 (0·7)	2·9 (0·8)	2·9 (0·7)
Interference with daily functioning, mean score	0·6 (0·7)*†‡§¶	2·9 (0·9) *†‡§	2·4 (0·9)‡¶	2·6 (1·0)†‡¶	2·2 (1·1)*¶	2·0 (1·0)*§¶
Noticeable impaired quality of life, mean score	0·5 (0·7)*†‡§¶	2·1(1·0)*†‡§	1·7 (0·9)¶	1·8 (1·1)‡¶	1·6 (1·0)¶	1·5 (0·9)*¶
Worried about sleep, mean score	0·3 (0·6)*†‡§¶	2·5 (1·0)†‡§	2·2 (0·9)†‡¶	2·3 (1·0)†‡	1·8 (1·0)*§¶	1·8 (0·9)*§¶
Sleep duration	7 h 24 min (59 min)*†‡§¶	6 h 8 min (1 h 57 min)	6h 7 min (1 h 19 min)	5 h 58 min (1 h 34 min)	5 h 47 min (1 h 23 min)	5 h 51 min (1 h 16 min)
Co-occurring sleep disorders						
Restless leg syndrome	94 (7·1%)*†§¶	32 (19·8%)	51 (19·1%)	22 (16·4%)	32 (17·4%)	14 (10·8%)
Periodic leg movement disorder	13 (1·0%)†§¶	15 (9·3%)	11 (4·1%)	4 (3·0%)	10 (5·4%)	3 (2·3%)
Obstructive sleep apnoea syndrome	128 (9·6%)*†§¶	39 (24·1%)	54 (20·2%)	32 (23·9%)	33 (17·9%)	19 (14·6%)
Narcolepsy	1 (0·1%)	2 (1·2%)	0	0	2 (1·1%)	0
Parasomnia						
Recurrent nightmares	67 (5·0%)*†§¶	42 (25·9%)*†‡§	43 (16·1%)†‡¶	17 (12·7%)¶	12 (6·5%)§¶	8 (6·2%)§¶
Night terror	7 (0·5%)	3 (1·9%)	2 (0·7%)	3 (2·2%)	1 (0·5%)	0
Sleepwalking	2 (0·2%)	1 (0·6%)	0	1 (0·7%)	1 (0·5%)	0
Sleep-related hallucinations	25 (1·9%)¶	16 (9·9%)	10 (3·7%)	3 (2·2%)	5 (2·7%)	3 (2·3%)
Sleep-related dissociative episodes	1 (0·1%)	2 (1·2%)	1 (0·4%)	0	1 (0·5%)	0
Eating or drinking during sleep	0¶	3 (1·9%)	1 (0·4%)	2 (1·5%)	2 (1·1%)	0
Confusional arousals	16 (1·2%)†§¶	30 (18·5%)*†‡§	13 (4·9%)‡¶	2 (1·5%)¶	7 (3·8%)¶	0§¶
Sleep-related leg cramps	96 (7·2%)¶	25 (15·4%)	26 (9·7%)	17 (12·7%)	23 (12·5%)	13 (10·0%)
Sleep paralysis	18 (1·4%)	7 (4·3%)	8 (3·0%)	5 (3·7%)	5 (2·7%)	2 (1·5%)
Rapid eye movement phase sleep behaviour	7 (0·5%)	6 (3·7%)	3 (1·1%)	3 (2·2%)	0	1 (0·8%)
Sleep-related bruxism	68 (5·1%)	12 (7·4%)	24 (9·0%)	6 (4·5%)	8 (4·3%)	8 (6·2%)
Sleep-related groaning or catathrenia	158 (11·9%)§¶	43 (26·5%)	53 (19·9%)	24 (17·9%)	28 (15·2%)	11 (8·5%)
Exploding head syndrome	35 (2·6%)†§¶	17 (10·5%)	16 (6·0%)	6 (4·5%)	13 (7·1%)	8 (6·2%)
Sleep related enuresis	1 (0·1%)	0	0	0	0	0

(Table 1 continues on next page)

	Control	Insomnia disorder subtype (n=1046)				
		1 (highly distressed)	2 (moderately distressed, reward sensitive)	3 (moderately distressed, reward insensitive)	4 (slightly distressed, high reactive)	5 (slightly distressed, low reactive)
(Continued from previous page)						
Comorbidities in main ICD-10 disease categories						
Infectious	11 (0·8%)	5 (3·1%)	2 (0·7%)	0	7 (3·8%)	1 (0·8%)
Neoplasms	13 (1·0%)§	3 (1·9%)	14 (5·2%)	3 (2·2%)	2 (1·1%)	3 (2·3%)
Blood-related	11 (0·8%)	4 (2·5%)	3 (1·1%)	5 (3·7%)	6 (3·3%)	1 (0·8%)
Endocrine	71 (5·3%)*†§¶	30 (18·5%)	36 (13·5%)	18 (13·4%)	26 (14·1%)	10 (7·7%)
Nervous system	14 (1·1%)†‡	4 (2·5%)	0*†‡	4 (3·0%)§	8 (4·3%)§	6 (4·6%)§
Eye	172 (12·9%)	25 (15·4%)	46 (17·2%)	25 (18·7%)	24 (13·0%)	17 (13·1%)
Ear	85 (6·4%)	18 (11·1%)	25 (9·4%)	11 (8·2%)	19 (10·3%)	11 (8·5%)
Circulatory system	64 (4·8%)§¶	20 (12·3%)	26 (9·7%)	11 (8·2%)	13 (7·1%)	11 (8·5%)
Respiratory system	81 (6·1%)	8 (4·9%)	22 (8·2%)	16 (11·9%)	20 (10·9%)	17 (13·1%)
Digestive system	29 (2·2%)§¶	14 (8·6%)	17 (6·4%)	8 (6·0%)	5 (2·7%)	3 (2·3%)
Skin	114 (8·6%)	25 (15·4%)	36 (13·5%)	21 (15·7%)	23 (12·5%)	13 (10·0%)
Musculoskeletal system	177 (13·3%)*†§¶	47 (29·0%)	67 (25·1%)	30 (22·4%)	41 (22·3%)	26 (20·0%)
Genitourinary system	71 (5·3%)*†§¶	20 (12·3%)	32 (12·0%)	19 (14·2%)	22 (12·0%)	11 (8·5%)
Pregnancy	5 (0·4%)	1 (0·6%)	1 (0·4%)	1 (0·7%)	0	0
Perinatal originating conditions	2 (0·2%)	1 (0·6%)	1 (0·4%)	1 (0·7%)	0	0
Congenital malformations	6 (0·5%)	2 (1·2%)	5 (1·9%)	0	1 (0·5%)	0
Symptoms not elsewhere classified	83 (6·2%)*†§¶	49 (30·2%)‡§	51 (19·1%)‡¶	33 (24·6%)‡	38 (20·7%)‡	12 (9·2%)*†§¶
Consequences of external causes	123 (9·2%)*†§¶	36 (22·2%)	46 (17·2%)	32 (23·9%)	34 (18·5%)	17 (13·1%)
Comorbidities in ICD-10 subcategories of mental and behavioural disorders (categories F00–F99, except F70–F79)						
Organic	5 (0·4%)	3 (1·9%)	3 (1·1%)	1 (0·7%)	0	0
Substance-related	1 (0·1%)*¶	3 (1·9%)	3 (1·1%)	4 (3·0%)	0	0
Schizophrenia	3 (0·2%)	3 (1·9%)	0	0	1 (0·5%)	0
Mood	38 (2·9%)*§¶	59 (36·4%)*†‡§	16 (6·0%)*†¶	25 (18·7%)†‡§¶	1 (0·5%)*§¶	3 (2·3%)*¶
Anxiety	39 (2·9%)*§¶	59 (36·4%)*†‡§	33 (12·4%)†‡¶	14 (10·4%)†‡¶	6 (3·3%)*§¶	1 (0·8%)*§¶
Physiological or physical	0*†§¶	10 (6·2%)	7 (2·6%)	4 (3·0%)	3 (1·6%)	0
Personality	7 (0·5%)*§¶	26 (16·0%)*†‡§	6 (2·2%)¶	6 (4·5%)¶	1 (0·5%)¶	0¶
Developmental	2 (0·2%)	1 (0·6%)	3 (1·1%)	1 (0·7%)	0	0
Childhood onset	6 (0·5%)§¶	17 (10·5%)*†‡§	11 (4·1%)‡¶	3 (2·2%)¶	2 (1·1%)¶	0§¶
Lifetime depression, anxiety, and bipolar disorder						
Lifetime depression	155 (11·6%)*§¶	88 (54·3%)*†‡§	72 (27·0%)†‡¶	46 (34·3%)†‡¶	15 (8·2%)*§¶	17 (13·1%)*§¶
Lifetime anxiety	69 (5·2%)*‡§¶	60 (37·0%)*†‡§	47 (17·6%)†‡¶	20 (14·9%)†‡¶	12 (6·5%)*§¶	1 (0·8%)*§¶
Lifetime bipolar	10 (0·8%)¶	8 (4·9%)*‡§	2 (0·7%)¶	0¶	2 (1·1%)	0¶

Data are n (%) or mean (SD). Data about sleep disorders and other comorbidities are from 1333 participants in the control group, 162 participants with insomnia disorder subtype 1, 267 participants with insomnia disorder subtype 2, 134 participants with insomnia disorder subtype 3, 184 participants with insomnia disorder subtype 4, and 130 participants with insomnia disorder subtype 5 who completed online structured interview modules. Sleep duration was obtained from the Pittsburgh Quality of Sleep Index. Description of the ICD-10 disease categories is available online Restless leg syndrome was with the four diagnostic criteria defined by the International Restless Leg Syndrome Study Group. Estimates of periodic leg movement disorder, obstructive sleep apnoea syndrome, and narcolepsy were made without the polysomnographic assessment required for diagnosis. Obstructive sleep apnoea syndrome was assessed with the Berlin Questionnaire. *p<0·05 versus insomnia disorder subtype 3 after Bonferroni correction. †p<0·05 versus insomnia disorder subtype 4 after Bonferroni correction. ‡p<0·05 versus insomnia disorder subtype 5 after Bonferroni correction. §p<0·05 versus insomnia disorder subtype 2 after Bonferroni correction. ¶p<0·05 versus insomnia disorder subtype 1 after Bonferroni correction.

Table 1: **Demographics, insomnia characteristics, and sample prevalence estimates of current sleep disorders, main ICD-10 disorder categories, the ICD-10 mental disorder subcategories, as well as lifetime depression, for controls and each of the insomnia disorder subtypes**

For the **WHO International Classification of Diseases version 10** see http://www.who.int/classifications/icd/icdonlineversions/en/

diagnosis of the other participants, our definition of insomnia disorder, for brevity, should be read as probable insomnia disorder, as suggested by the severity of insomnia symptoms. On April 13, 2017, a newsletter was sent among registered NSR users who opted-in for communications, to collect follow-up data, which were collected between April 13, 2017, and June 21, 2017. Of the 1046 participants who were originally assessed for at least ten characteristics (ie, with at least ten questionnaires), 831 (79%) participants were lost to follow-up and 215 (21%) participants were assessed in the follow-up latent transition analysis.

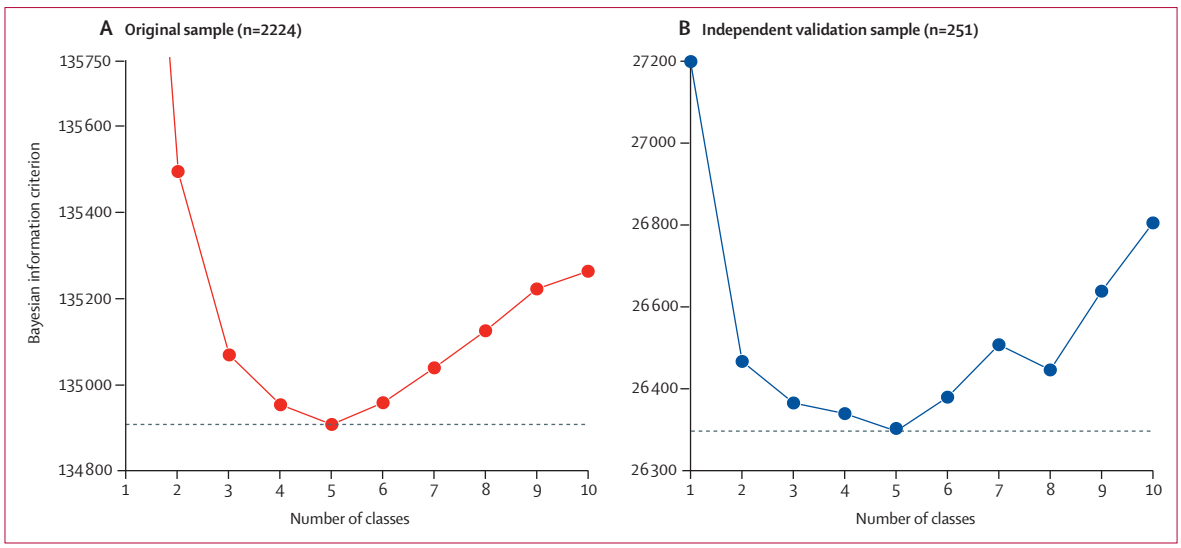


Figure 2: **Goodness of fit of the BIC**

BIC for 1-10 latent class models in the original sample (A) and the independent validation sample (B). The BIC indicates the goodness of fit of a model and penalises model complexity. For models within a given sample, lower BIC values indicate a better fit. In both samples, the BIC is minimised at five classes. BIC=Bayesian information criterion.

The 2224 participants with probable insomnia disorder had a mean age of 51·1 (SD 13·7) years and 1726 (78%) participants with probable insomnia disorder were female (table 1). 2098 control participants (with an ISI<10) had a mean age of 47·2 (15·8) years, and 1558 (74%) control participants were female.

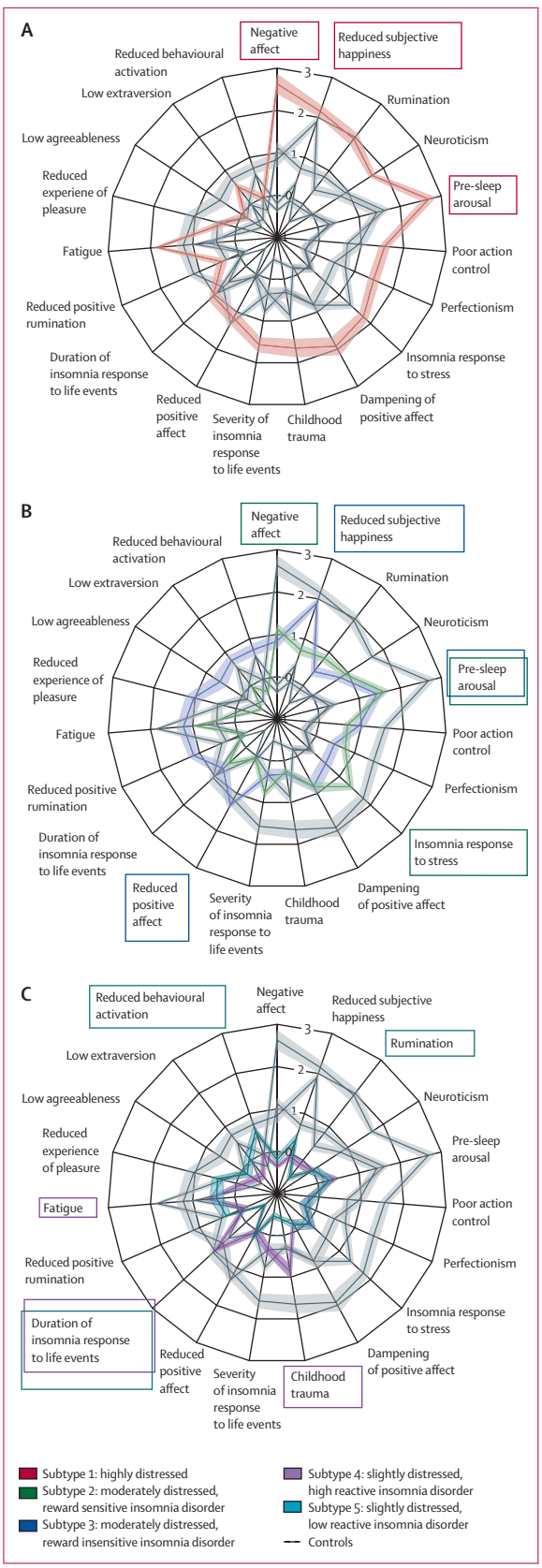
With a minimal Bayesian information criterion, we found that a five-class model was optimal among the 2224 participants whose responses were used to estimate the model. To interpret the estimated model, we used this model to subtype the 1046 (47%) participants who completed at least ten and up to 26 questionnaires (figure 2; appendix p 34). Most participants were uniquely assigned to only one of the five subtypes, as indicated by high posterior probabilities (0·91–0·99) and a low misclassification estimate (13%; appendix p 35). The demographics, insomnia characteristics, and comorbidities of the 1046 people with insomnia who completed at least ten questionnaires are shown in table 1.

Their multivariate profiles of the group means of characteristics (life history and affect and personality traits) for each subtype, ranked clockwise according to subtype-explained variance (from 41% variance in negative affect to 15% variance in behavioural activation), are shown in figure 3, and all 26 characteristics are shown in the appendix (p 19). The diameter of the profiles represents the overall level of burdensome characteristics—ie, high for one subtype, moderate for two subtypes, and slight for two subtypes. The profiles also discriminate between subtypes by their multivariate fingerprint shape.

Among the 1046 people with insomnia who completed at least ten questionnaires, 200 (19%) participants were classified in subtype 1, which indicated high general distress (figure 3). The three characteristics that deviated most markedly from control group participants concerned high pre-sleep arousal (Cohen's d=2·55) and negative affect (d=2·31) and reduced subjective happiness (d=2·15; p<0·0001 for all three). Most other characteristics differed by more than 1 standard deviation, except for reduced positive rumination (d=0·41; p<0·0001) and reduced experience of pleasure (d=0·31; p=0·0016), which were within 0·5 standard deviations of the control group results. Subtype 1 can be termed highly distressed insomnia disorder.

323 (31%) participants were classified in subtype 2 and 153 (15%) participants were classified in subtype 3; both showed moderate general distress but could be distinguished by their profile (figure 3). For subtype 2, pre-sleep arousal (d=1·57), insomnia response to stress (d=1·38), and negative affect (d=1·12) deviated most markedly from control participants (p<0·0001 for all three). Relative to the overall moderate general distress, the high arousal and response to stress of subtype 2 appears like the disorder that is conventionally referred to as psychophysiological insomnia. Subtype 2 participants did not show particularly low positive affect (d=0·06; p=0·3), positive rumination (d=–0·13; p=0·06), or experience of pleasure (d=–0·36; p<0·0001); all of these findings were within 0·5 standard deviations of the results of control participants, and even appeared more favourable regarding positive rumination and experience of pleasure. Subtype 2 can be termed moderately distressed, reward-sensitive insomnia disorder.

By contrast, subtype 3 is primarily characterised by reduced positivity. Specifically, reduced subjective happiness (d=1·89), positive affect (d=1·34), positive rumination (d=1·18), and experience of pleasure (d=1·00)



all deviated from the findings in control participants by more than 1 standard deviation (p<0·0001 for all four). Positive rumination and experience of pleasure were more reduced in subtype 3 than in any other subtype. Subtype 3 also differed markedly from controls (d=1·42; p<0·0001), but not from subtype 2 (d=0·17; p=0·12), regarding pre-sleep arousal. Subtype 3 can be termed moderately distressed, reward-insensitive insomnia disorder. The characteristics that distinguish between the similarly distressed subtypes 2 and 3 most are more strongly reduced positive affect (d=1·55) and more strongly reduced positive rumination (d=1·55) in subtype 3 relative to subtype 2 (both p<0·0001).

209 (20%) participants were classified in subtype 4, and 161 (15%) participants were classified in subtype 5; participants in both subtypes showed low general distress but can be distinguished by their profiles (figure 3). Participants in subtype 4 showed a longer duration of insomnia response to life events (d=0·94) and more frequent childhood trauma (d=0·82) and fatigue (d=0·60) relative to controls (from which they differed by >0·5 of a standard deviation; p<0·0001 for all three). Subtype 4 can be termed slightly distressed, high reactive insomnia disorder because of the long-lasting insomnia response after a life event.

By contrast, participants classified in subtype 5 scored about 0·5 of a standard deviation lower than control participants on both the duration (d=–0·64) and severity (d=–0·51) of insomnia response to life events, on childhood trauma (d=–0·41), and on rumination (d=–0·55; p<0·0001 for all three). However, relative to the overall low level of distress in participants classified in subtype 5, they scored higher than control participants on reduced behavioural activation (d=0·59), reduced experience of pleasure (d=0·46), and fatigue (d=0·43; p<0·0001 for all three). Subtype 5 can be termed slightly distressed, low reactive insomnia disorder. The characteristics that discriminate the similarly distressed subtypes 4 and 5 most are duration (d=1·68) and severity (d=1·04) of insomnia response to life events, and childhood trauma (d=1·11; p<0·0001 for all three), which are less frequent in participants with subtype 5. Further details of these classifications are shown in the appendix (p 36).

Figure 3: **Multivariate profile plots of the subtypes of insomnia**
Data are scaled subtype group means (95% CIs), in which *Z* scores have been standardised to the mean and standard deviation of controls for each characteristic, with the subtype-explained variance, ranked clockwise from the top. (A) Highly distressed subtype (subtype 1). (B) Moderately distressed subtypes (subtype 2, which was reward sensitive, and subtype 3, which was reward insensitive). (C) Low distress subtypes (subtype 4, which was high reactive, and subtype 5, which was low reactive). Positive characteristics (eg, positive rumination) were reverse-coded and renamed (eg, reduced positive rumination), such that higher values uniformly indicate higher general distress for all characteristics throughout the plot. Coloured boxes indicate the three characteristics that differentiate each subtype most from control participants.

Lasso regularisation selected the 19 most discriminating characteristics for the ITQ (appendix pp 4, 14). The selection correctly classified 904 (86%) of 1046 original participants, with high posterior probabilities (0·90–0·97).

Use of the ITQ to classify 251 new participants also resulted in high posterior probabilities (0·92–1·00) and low misclassification (10%). The robustness of a specific five-class solution was verified in this non-overlapping cohort. Again, as compared with latent class analysis models with more or fewer subtypes, a five-class solution was optimal, as indicated by the lowest Bayesian information criterion (figure 2) and excellent posterior probabilities (0·99–1·00) and misclassification (4·5%).

215 (21%) of 1046 participants who were reassessed 4·8 (SD 1·6) years later maintained their subtype at a probability of 0·87, indicating a high stability of these subtypes (table 2). Participants who were originally classified as highly or moderately distressed subtypes had high probabilities (0·86–0·89) of maintaining their subtype after an average of 4·8 years. The consistency of subtypes between baseline and follow-up was more modest for those who were first classified in subtypes 4 (0·67) or 5 (0·44). However, participants who were originally classified in subtype 4 or 5 and switched subtype almost exclusively switched to the other slightly distressed subtype: those classified as subtype 4 had a probability of 0·94 that they would maintain a slightly distressed subtype (4 or 5) and those classified as subtype 5 had a probability of 0·81 that they would maintain a slightly distressed subtype (4 or 5).

Although the current severity of the three key insomnia complaints of difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening did not differ between subtypes (table 1), their developmental onset differed markedly. Most notably, half of the participants classified in subtypes 1 and 2 reported difficulty initiating sleep by their teenage years but, in participants classified in subtypes 4 and 5, half of the participants reported difficulty initiating sleep only by age 40 years (figure 4; appendix p 8). Subtypes 1 and 2 thus both represent more participants with insomnia disorder that might conventionally be labelled idiopathic insomnia.

The proportion of participants with comorbid sleep disorders (table 1) did not differ across subtypes, except for recurrent nightmares and confusional arousals, which were both highest in subtype 1 and lowest in subtype 5. The proportions of participants classified within each subtype who reported diseases in the main ICD-10 categories, including mental and behavioural disorders. are also shown in table 1. Two main categories were differentially represented between subtypes: diseases of the nervous system were most frequent in participants classified in subtype 5 and least frequent in participants classified in subtype 2, and symptoms not elsewhere classified were most frequent in participants classified in subtype 1 and least frequent in participants classified in subtype 5. Four mental and behavioural disorder subcategories (mood, anxiety, personality, and childhood onset) were differentially represented across subtypes, mostly driven by a high prevalence of these disorders in participants classified in subtype 1.

	Subtype 1 at follow-up	Subtype 2 at follow-up	Subtype 3 at follow-up	Subtype 4 at follow-up	Subtype 5 at follow-up
Subtype 1 at baseline	0·87	0·12	0	0	0
Subtype 2 at baseline	0	0·86	0	0·14	0
Subtype 3 at baseline	0	0·01	0·89	0·10	0
Subtype 4 at baseline	0	0·01	0·05	0·67	0·27
Subtype 5 at baseline	0	0·09	0·09	0·37	0·44

Table 2: **Probability of participants maintaining their insomnia disorder subtype between baseline and 4·8 (SD 1·6) years later, based on their responses to the Insomnia Type Questionnaire.**

The prevalence of current and lifetime depression differed markedly across subtypes (both $\chi^2(4)>110$; both $p<0·0001$; table 1) and were most frequent in participants classified in subtype 1, who also reported the greatest frequency of recurrent nightmares, in accordance with previously reported associations of insomnia, nightmares and depression.[24] Notably, current depression was three times less prevalent in participants classified in subtype 2 (16 [6%] of 267 participants) than in participants classified in subtype 3 (25 [19%] of 134 participants), despite their similar indications of general distress (figure 3). There was up to a five times difference between subtypes in the lifetime risk of depression (table 1).

Incidental benzodiazepine intake affected difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and fatigue differently across the five subtypes ($F(16,406)=1·75$; $p=0·04$). The most notable differences with benzodiazepine intake were reported in difficulty maintaining sleep, which improved most in participants classified in subtypes 2 and 4 but not in subtype 3 (figure 4; appendix p 9).

CBT for insomnia affected the ISI scores of patients differently between subtypes 2 and 4 (appendix pp 9, 10). Compared with control group patients who were awaiting CBT, this treatment ameliorated difficulty initiating sleep significantly more in subtype 2 (mean change in score –0·8 [SD 1·9]; $p=0·0003$) than in subtype 4, where it was ineffective (0·1, [SD 1·5]; $p=0·69$). This disparity in response to CBT was also reflected in the total ISI score (–5·5, SD 7·8; $p<0·0001$; *vs* –3·1, SD 7·3; $p=0·003$ in type 4). Notably, the underrepresentation of subtypes 1, 3, and 5 in this sample illustrates how commonly differing selection criteria can strongly affect the subtype distribution of the study. We found that strict criteria on mood symptoms impeded inclusion of participants in subtypes 1 and 3 from participation in this study, whereas a low prevalence and age exclusion criteria impeded inclusion of participants of subtype 5.

Compared with control group participants without sleep complaints, the ERP to standard tones exclusively showed a stronger positive deflection during a wide late

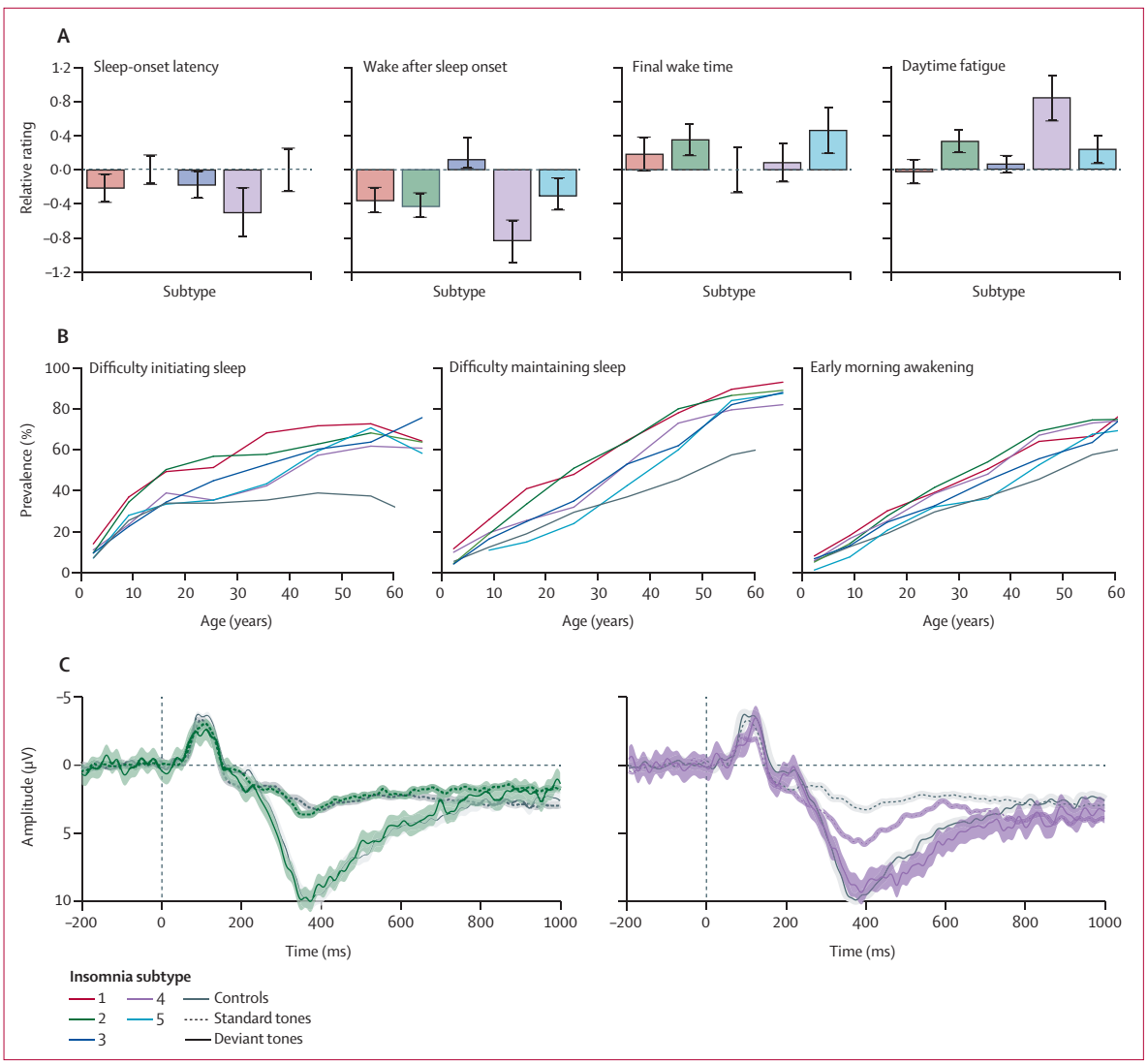


Figure 4: **Clinical relevance of insomnia disorder subtypes**
(A) The effect of incidental benzodiazepine use the preceding night on sleep and daytime fatigue (n=112). (B) Percentage of participants with insomnia subtypes (n=796) and control participants (n=1024) who reported any difficulty initiating or maintaining sleep or early morning awakening. (C) Auditory event-related potentials for standard tones and deviant tones that were recorded during an auditory oddball task for participants with insomnia disorder subtypes 2 (n=16) and 4 (n=13) and control group participants (n=31).

period of information processing up to at least 1000 ms after the tone was played in participants classified in subtype 4, and this finding was significantly different from controls at 273–348 ms (p=0·038), 361–493 ms (p=0·014), and 724–1000 ms (p=0·004; figure 4). ERPs of subtype 2, by contrast, were indistinguishable from those of control group participants. These findings indicate hyperreactive late processing specifically in subtype 4, who appeared to experience even standard tones as more salient (as indicated by the P300 potential amplitude) and emotionally relevant (as indicated by the late positive potential amplitude), in agreement with their questionnaire-based label of being highly reactive.[23]

Discussion

In our study, we identified five insomnia disorder subtypes that were differentiated by biologically based traits and life history. The subtypes that we identified were a highly distressed type that was characterised by distress across all domains; two moderately distressed types, one of which was reward sensitive and the other of which was reward insensitive; and two slightly distressed subtypes, one of which showed high reactivity to life events and the other of which showed low reactivity. Subtyping was stable over time, clinically relevant, and biologically meaningful, as indicated by enhanced salience and emotion signalling in the brain of participants classified as type 4. Subtyping is feasible

with a concise set of questions that we have made available (appendix p 37), including automated scoring.

The subtypes were not primarily distinguished by existing clinical demarcations such as difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening, nor by comorbid sleep disorders. Rather, subtypes emerged as specific, multivariate profiles of stable characteristics that were not directly related to sleep but were relevant to insomnia.[19] High or low scores on single variables were not unique to our insomnia subtypes, but the fingerprints of specific combinations of score levels on these characteristics are unique to the subtypes. Ancillary analyses (appendix p 10) showed that none of the five subtypes resembled subtypes that can be found with bottom-up subtyping of people without insomnia.

The stability of subtypes over several years that we found was notable. Most participants were identically classified 4·8 (SD 1·6) years after their initial subtyping (at a probability of 0·87), which compares favourably to previous clinical subtyping that showed poor reliability[15] and instability over even a brief period (33% over 4 months).[14] To our knowledge, our insomnia disorder subtypes are the first to fulfil the primary requirement of stability that is necessary to find differential trajectories for, biomarkers of, and treatment responses in insomnia disorder.

Clinically, our identified subtypes provide precision targets to improve cognitive, emotional, and behavioural interventions. For example, because a meditation intervention lowers pre-sleep arousal,[25] this treatment could particularly be recommended for people with insomnia disorder of subtypes 1, 2, and 3, which are characterised by high pre-sleep arousal. Interventions that aim to improve positive affect and happiness[26] could be evaluated for people with insomnia subtypes 3 and 5, who showed a disproportional reduced positive affect or experience of pleasure. Finally, sleep problems related to childhood adversity, which was most prevalent among participants with subtypes 1 and 4, could require trauma therapy rather than CBT for insomnia only.[27]

The clinical relevance of subtyping reaches beyond insomnia. Possibly related to a strong genetic overlap,[5] insomnia is a primary risk factor for depression.[8] The Global Consortium for Depression Prevention stated that the best chance to combat the global burden of depression is to identify people who run the highest risk and to provide them with preventive interventions.[28] Supported by the strong differences in current comorbid and lifetime depression, our subtyping approach could enable us to identify people with insomnia disorder who are most at risk for developing depression, and to prioritise their inclusion in preventive trials. Participants with subtype 1 insomnia scored highly on several symptoms of depression and showed the highest risk of lifetime depression. However, near half of participants classified in subtype 1 had never experienced depression. This finding is of considerable clinical interest for at least two reasons. First, people with subtype 1 insomnia disorder might have subclinical depression, and people with this subtype are most suitable to select for intervention programmes that aim to prevent depression. Use of our ITQ could facilitate such selection. Second, there could be an unknown factor that makes the unaffected half of our participants with subtype 1 resilient to depression despite a high risk.

For **Insomnia Type Questionnaire scoring** see https://tfblanken.shinyapps.io/itqapp/

We illustrated how differentiation between subtypes 2 and 4 could propel the identification of biomarkers that would otherwise remain hidden by heterogeneity. ERPs deviated from the values in controls in participants with subtype 4 insomnia but not subtype 2 insomnia. The high amplitude late positive potential of the ERP in subtype 4 could relate to polymorphisms in the β1-receptor gene and response to beta-blockers, thus providing an example of a drug-targetable biomarker.[23] More specifically C/C homozygotes for the G1165C polymorphism in the β1-adrenergic receptor showed a larger late positive potential amplitude than G/C heterozygotes and G/G homozygotes. Moreover, our ERP finding supports consistency of labelling subtype 4 as reactive across psychometric traits and neurophysiology, thus meeting an important goal of the Research Domain Criteria.[29]

Finally, we constructed and validated our ITQ, including automated analysis, to facilitate subtyping in future studies on insomnia. This subtyping can be done online and will accelerate insight into underlying causes and biomarkers of insomnia disorder and the development of better, more personalised treatments.

Some limitations should be mentioned. First, although five subtypes were found to be optimal in both the original sample and the second, non-overlapping validation cohort, we cannot exclude the existence of other subtypes—for example, among people who do not volunteer for online assessment—because the NSR did not sample randomly from the general population. We deliberately did not exclusively sample from sleep clinics because, unfortunately, insomnia often goes unnoticed in general practice.[16] Sleep centre-based studies overrepresent complex insomnia in people who are more affected, but the NSR reaches a more diverse population of people with insomnia disorder. A possible disadvantage of case-control comparisons from the NSR could be that the control group might have been biased to include more people with a special interest in sleep or helping science. Therefore, replication of our study in a strict population-based sample will be useful.

Second, we defined probable insomnia disorder by an ISI cutoff score of 10. Although this cutoff has been validated several times[5,21] and the ISI has been validated for web-based assessment,[30] it could be asked whether the cutoff can indicate insomnia of sufficient severity to warrant independent clinical attention and thus a separate DSM-5 diagnosis. A randomised trial[31] in patients with major depressive disorder used the same ISI cutoff of 10

to define comorbid insomnia; this study found that clinical attention to insomnia of this severity was highly valuable because treatment reduced insomnia and depression. This finding adds to the clinical validity of the ISI cutoff. The traditional approach to treat only the other morbidity, with the expectation that insomnia will resolve, is not regarded as the most appropriate approach;[17] treatment of both conditions simultaneously might improve the outcomes for both conditions.[32] In support of this hypothesis, a meta-analysis[33] that included 17 studies that used ISI scores supported treatment of insomnia in conjunction with comorbid psychiatric and medical conditions.

Finally, traits that we have not assessed could discriminate yet other subtypes. Although we cannot exclude this possibility, it should be noted that we included an unprecedentedly large number of stable characteristics. Moreover, subtypes were defined by several characteristics, suggesting at least some robustness for unobserved characteristics. Within these limitations, the identification of subtypes enables important possibilities for pursuing subtype-specific risks, biomarkers, or treatment responses.

In summary, we found that insomnia disorder can be classified into robust subtypes that can be discriminated by multivariate profiles of traits of affect and personality and life history. Subtyping was highly consistent after 4·8 years of follow up, results could be replicated in a second, non-overlapping cohort, and the subtypes could reliably be assessed with the ITQ. Insomnia subtyping paves the way for studies that aim to prevent depression, resolve inconsistencies in and reduce heterogeneity of insomnia, and reveal differential causes of and develop better tailored personalised treatment for insomnia disorder.

Contributors

TFB was the lead investigator, collected data, analysed and interpreted the data, and drafted the paper. JSB, JR, KD, DS, and RW collected data and ran the laboratory studies. DB supervised data analyses and interpretation and critically reviewed the manuscript. JKV supervised the latent class analyses. CP, JR, and YW analysed the data that were obtained in the laboratory studies. EJWVS was chief investigator, devised the study, supervised data collection, analysis, and interpretation, and critically reviewed the manuscript. All authors commented upon and approved the final manuscript.

Declaration of interests

All authors declare no competing interests.

Acknowledgments

The Netherlands Organization for Scientific Research (The Hague; VICI innovation grant no. 453–07–001) and the European Research Council (no. ERC-ADG-2014–671084 INSOMNIA) supported this work.

References

1 Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder. *Nat Rev Dis Primers* 2015; **1:** 15026.
2 Chung KF, Yeung WF, Ho FYY, Yung KP, Yu YM, Kwok CW. Cross-cultural and comparative epidemiology of insomnia: the diagnostic and statistical manual (DSM), international classification of diseases (ICD) and international classification of sleep disorders (ICSD). *Sleep Med* 2015; **16:** 477–82.
3 Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21:** 655–79.
4 Lind MJ, Aggen SH, Kirkpatrick RM, Kendler KS, Amstadter AB. A longitudinal twin study of insomnia symptoms in adults. *Sleep* 2015; **38:** 1423–30.
5 Hammerschlag AR, Stringer S, de Leeuw CA, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nat Genet* 2017; **49:** 1584–92.
6 Jansen PR, Watanabe K, Stringer S, et al. Genome-wide analysis of insomnia (n=1 331 010) identifies novel loci and functional pathways. *bioRxiv* 2018; 214973.
7 Fortier-Brochu É, Beaulieu-Bonneau S, Ivers H, Morin CM. Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Med Rev* 2012; **16:** 83–94.
8 Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011; **135:** 10–19.
9 Beaulieu-Bonneau S, LeBlanc M, Merette C, Dauvilliers Y, Morin CM. Family history of insomnia in a population-based sample. *Sleep* 2007; **30:** 1739–45.
10 Sinha SS. Trauma-induced insomnia: a novel model for trauma and sleep research. *Sleep Med Rev* 2016; **25:** 74–83.
11 van de Laar M, Verbeek I, Pevernagie D, Aldenkamp A, Overeem S. The role of personality traits in insomnia. *Sleep Med Rev* 2010; **14:** 61–68.
12 Baglioni C, Regen W, Teghen A, et al. Sleep changes in the disorder of insomnia: a meta-analysis of polysomnographic studies. *Sleep Med Rev* 2014; **18:** 195–213.
13 Feige B, Baglioni C, Spiegelhalder K, Hirscher V, Nissen C, Riemann D. The microstructure of sleep in primary insomnia: an overview and extension. *Int J Psychophysiol* 2013; **89:** 171–80.
14 Van Someren EJW, Van Der Werf YD, Ramautar JR, et al. Imaging causes and consequences of insomnia and sleep complaints. In: Nofzinger E, Maquet P, Thorpy MJ, eds. Neuroimaging of sleep and sleep disorders. Cambridge, UK: Cambridge University Press, 2013, pp 187–96.
15 Edinger JD, Wyatt JK, Stepanski EJ, et al. Testing the reliability and validity of DSM-IV-TR and ICSD-2 insomnia diagnoses: results of a multitrait-multimethod analysis. *Arch Gen Psychiatry* 2011; **68:** 992–1002.
16 Hohagen F, Käppler C, Schramm E, Riemann D, Weyerer S, Berger M. Sleep onset insomnia, sleep maintaining insomnia and insomnia with early morning awakening—temporal stability of subtypes in a longitudinal study on general practice attenders. *Sleep* 1994; **17:** 551–54.
17 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5), 5th edn. Washington, DC: American Psychiatric Press, 2013.
18 Diagnostic Classification Steering Committee. International classification of sleep disorders, 3rd edn. Rochester, MN: American Academy of Sleep Medicine, 2014.
19 Benjamins JS, Migliorati F, Dekker K, et al. Insomnia heterogeneity: characteristics to consider for data-driven multivariate subtyping. *Sleep Med Rev* 2017; **36:** 71–81.
20 Karalunas SL, Fair D, Musser ED, Aykes K, Iyer SP, Nigg JT. Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: toward biologically based nosologic criteria. *JAMA Psychiatry* 2014; **71:** 1015–24.
21 Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011; **34:** 601–08.
22 Cohen J. Statistical power analysis for the behavioral sciences. New York, NY: Routledge Academic, 1988.
23 de Rover M, Brown SB, Boot N, et al. Beta receptor-mediated modulation of the late positive potential in humans. *Psychopharmacology (Berl)* 2012; **219:** 971–79.
24 Sandman N, Valli K, Kronholm E, Revonsuo A, Laatikainen T, Paunio T. Nightmares: risk factors among the Finnish general adult population. *Sleep* 2015; **38:** 507–14.
25 Ong JC, Shapiro SL, Manber R. Combining mindfulness meditation with cognitive-behavior therapy for insomnia: a treatment-development study. *Behav Ther* 2008; **39:** 171–82.
26 Seligman ME, Steen TA, Park N, Peterson C. Positive psychology progress: empirical validation of interventions. *Am Psychol* 2005; **60:** 410–21.

27 Bader K, Schäfer V, Schenkel M, Nissen L, Schwander J. Adverse childhood experiences associated with sleep in primary insomnia. *J Sleep Res* 2007; **16:** 285–96.

28 Cuijpers P, Beekman AT, Reynolds CF. Preventing depression: a global priority. *JAMA* 2012; **307:** 1033–34.

29 Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Soc* 2010; **167:** 748–51.

30 Thorndike FP, Ritterband LM, Saylor DK, Magee JC, Gonder-Frederick LA, Morin CM. Validation of the insomnia severity index as a web-based measure. *Behav Sleep Med* 2011; **9:** 216–23.

31 Blom K, Jernelöv S, Rück C, Lindefors N, Kaldo V. Three-year follow-up comparing cognitive behavioral therapy for depression to cognitive behavioral therapy for insomnia, for patients with both diagnoses. *Sleep* 2017; 40.

32 Roth T. Comorbid insomnia: current directions and future challenges. *Am J Manag Care* 2009; **15** (suppl)**:** S6–13.

33 Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: a meta-analysis. *JAMA Intern Med* 2015; **175:** 1461–72.