A systematic review protocol examining the biological, physiological, and psychological factors that contribute to the development of insomnia

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Introduction

Insomnia is a sleep disorder that affects an individual's ability to sleep. Symptoms include trouble falling asleep, waking up in the middle of the night, and their overall sleep quality diminishing as a whole [1]. The aim of this review is to summarise the causes and triggers of insomnia, as well as possible prevention and treatment. The importance and overall goal of this review are to consider the different factors that can affect insomnia and to summarise research on the relationships between insomnia and these factors. Research questions considered in this review included genetic factors and the relationship of insomnia with mental health and physical health. The three key relationships examined and the focal points of the data extraction are biological, psychological, and physiological factors that pertain to insomnia. Data extraction consisted of retrieving information on the biological, psychological, and physiological factors, participant count, demographic and selection method, and study design. Data was then synthesised, with key themes being identified.

Summary of search results

A total of 51 research papers were found through searches done via Google Scholar. From these, 43 were screened after eight duplicates were removed. After the removal of ten irrelevant studies, 33 were assessed for eligibility. Out of these, 18 were excluded of which 10 had limited access, four had wrong study designs, two had wrong publication years, one had a wrong route of administration, and another had the wrong setting. Thus, in the end, the resulting 15 studies were eligible and were taken to the next stage for in-depth analysis.

Study characteristics

Of the fifteen studies in this systematic review, there are four cross-sectional, five observational, three longitudinal, one historical, one cohort, and one using mixed methods. Excluding the millions of subjects that two worldwide studies researched, a total of 474,309 participants have been included in this literature review. Of the two worldwide studies that studied the general population, one was of the cohort design and the other a cross-sectional study. The remaining three cross-sectional studies consisted of population sizes of 39 to 2379. The five observational studies had participant numbers ranging from 13 to 453 379. There were 80 to 9875 in each of the three longitudinal studies. The historical study and the mixed methods study had 545 and 383 participants, respectively. Six of the studies were from the USA, two from the Netherlands, and one each from Canada, Saudi Arabia, Iran, Australia, Norway, Spain, and the UK. Many instruments were used to evaluate insomnia, anxiety, depression, nocturnal rumination, chronic pain, etc.

Study Characteristics and Data Extraction (see appendix for raw data tables)

Author (s)	Design	Country	Partici-pants	Demographic	Selection method	Factors of insomnia
Drake et al. (2017) [2]	Observational	USA	n = 35	Adults with indication of developing a sleep disorder in the future; half of them with familial risk of insomnia and half without it	Recruited from participants of previous study	Subjects with familial risk for insomnia exhibit an insufficient production of cortisol in response to stress, leading to outcomes such as PTSD and Depression However, they do not exhibit any abnormalities in their nervous system responses
Abd El-Kader et al. (2020) [3]	Longitudinal	Saudi Arabia	n = 80	Chronic primary insomnia subjects aged 35-56 years	Insomnia patients enrolled in study and excluded ones with history of drugs, alcohol, mental disorders, and those who exercise regularly	Insomnia is correlated with immune system activity, psychological well being, and physical activities. Physical activities can reduce the severity of insomnia.
Fernandez-Mendoza et al. (2013) [4]	Cross-Sectional	USA	n = 1741	Men and women from Central Pennsylvania	Randomly selected. Divided into two categories. The first for participants who get 6 hours of sleep or more while the second consisted of participants with less than 6 hours of sleep	Insomniatic patients perform poorly compared to the well-rested population in neuropsychological tasks such as processing speed, attention, visual memory, and verbal fluency.
Hysing et al. (2013) [5]	Longitudinal	Norway	n = 9875	Adolescents aged 16-19	All secondary students in spring 2012 were invited to participate	Younger subjects are in a smaller risk of Insomnia. Among these subjects, however, girls are at a greater risk.
Lin et al. (2021) [6]	Cross-sectional	Iran	n = 1791	College students across three campuses with mean age of 27.2 years	Insomnia patients enrolled in study and excluded ones with history of drugs, alcohol, mental disorders, and those who exercise regularly	Factors such as physical activities in evenings and excessive screen time are correlated with insomnia. Furthermore, anxiety and depression are common predictors of insomnia.

Lindsay et al. (2022) [7]	Cross-sectional	Canada	n = 2379	University students aged 17-22 years	First year students with age range chosen via survey and excluding self-reported non-cisgender individuals	Having increased cognitive arousal during bedtime and mentality characteristics such as perfectionism and low self-esteem are significant contributors to insomnia.
Morin et al. (2004) [8]	Cohort	USA	General population	General population	A poll given to the general population	Use of therapy, proper sleep hygiene and cognitive behavioural therapy has proven to have impacts on insomnia.
O'Hagan et al. (2017) [9]	Cross-Sectional	Australia	n = 39	Participants with non-specific LBP ranging from 18-79 years of age	Recruited from primary care centres and from the Sydney community through advertising.	Insomnia during a given night leads to an increased amount of lBP in the following day. Furthermore, slow-wave sleeps result in a poor sleep quality. Treatments such as hypnoses drugs are effective yet not suggested for patients with psychiatric disorders.
	Cohort		n = 344	Patients of primary care centres of the Sydney and Newcastle areas ranging from 18-75 years old	Included patients had LBP, new onset insomnia (mild to moderate), and had sufficient understanding of the English language.	
Renom-Guiteras et al. (2014) [10]	Observational	Spain	n = 61	Patients admitted to palliative care unit	Patients in PCU in a university hospital for more than 2 nights	Common reported causes of insomnia are pain and dyspnea. Dyspnea and nocturnal rumination are correlated with insomnia, as rumination has been associated with increased emotional distress, which by itself is a factor leading to insomnia.
Van Someren et al. (2019) [11]	Cross-sectional	Netherlands	n = 1.1 million	Participants worldwide who are within the category of 14 to 17 years, 18-25 years, and older than 65 years	Establishment of a model stating how insomnia results from insufficient overnight adaptation to stress	Identified cell types and tissues are involved in shaping the brain such that it is vulnerable to insomnia. Genes such as MEIS, RLS and PLMS are involved with insomnia, and some of these genes are also correlated with other physical disorders such as restless leg syndrome.

Vargas et al. (2019) [12]	Historical	USA	n = 545	Patients with both MDD and insomnia	Patients who met DSM-IV criteria.	Insomnia patients are at great risk of depression. Both Insomnia and depression are associated with high physiological and cognitive sensitivity.
Varkevisser et al. (2005) [13]	Observational	Netherlands	n = 13	Individuals diagnosed with chronic insomnia, age range 31-54	Individuals referred to the Westeinde Hospital were chosen	Hyperarousal is not a significant underlying factor for Insomnia. Rather, other factors such as psychiatric disorders are more directly related.
Espie et al. (2019) [14]	Observational	USA	n = 1711	Patients with self-reported insomnia	Patients were recruited and delivered DCBT via web and mobile channels plus treatment	Patients reported improvements in their quality of sleep, better functional health and psychological well-being.
Kalmbach et al. (2018) [15]	Longitudinal	USA	n = 2316	Individuals with no history of mental disorders or insomnia were selected	Insomnia patients enrolled in study via survey with no severe mental illness	Factors such as emotional stress play a significant role in sleep reactivity. A decrease or increase in sleep reactivity is also correlated genetically.
Lane et al. (2019) [16]	Observational	UK	n = 453379	Identified 57 loci for self-reported insomnia cases in the UK, including registries aged 40-69 and living <25 miles from the study centre	Genes from the UK's biobank were compared within each study	There are shared genetic architectures between patients of insomnia and those with physical disorders. Patients who exercise have seen improvement in their sleep quality.

Synthesis of findings

Subjects with a familial risk for insomnia exhibit a "blunted cortisol response to stress" which is the insufficient production of cortisol when responding to stress. This can lead to a disruption in physiological homeostasis, leading to adverse outcomes like sleep disturbance, depression, etc [2]. Insomnia is prevalent in 13.6-23.8% of adolescents. Younger subjects spent more time in bed and were less likely to develop insomnia than older subjects. Girls are significantly more likely to develop insomnia and have greater sleep onset latency [5]. In palliative care patients, insomnia was connected to dyspnoea. Higher scores on the Hospital Anxiety and Depression Scale were associated with a patient's belief that they suffered from insomnia. Nocturnal rumination, the persistence of emotionally and physically distressing thoughts, has been shown to have a direct link to insomnia [10].

Insomniatic patients perform poorly compared to the well-rested population in neuropsychological behaviours, with biological, educational, and mental factors considered. These tasks include processing speed, attention, visual memory, and verbal fluency [4]. One factor of insomnia is the sleep cycle, specifically phase 1 and 3. Shorter periods of phase 3 sleep and/or extended periods of phase 1 sleep amplify the risk of insomnia. There is an association between pain, insomnia, and disability. Insomnia in a given night leads to increased pain in the day following. Those with lower back pain or disability experience more N1 sleep and are more vulnerable to insomnia. Hypnosis drugs are unsuitable for patients with psychiatric disorders [9]. Insomnia creates a risk for depression. Insomnia and depression are associated with high physiological sensitivity. Insomniacs react to negative events with more stress than non-insomniacs do. As a result, they lean toward poorer coping strategies than good sleepers would [12].

The use of Genome-Wide Association Studies (GWAS) gives clues about the involvement of biological functional pathways, tissues, and cell types in patients with insomnia. Results illustrate that the identified cell types and tissues may be involved in shaping the brain's circuitry such that it makes individuals vulnerable to insomnia. As well, the MEIS gene, which is usually implicated with physical disorders such as restless leg syndrome is involved to some degree in insomnia patients. However, the most involved genes are RLS and PLMS genes. This suggests that there are common genetic architectures between individuals with Insomnia and other physical disorders [11]. Other than physical disorders, psychiatric disorders share a bi-directional link with insomnia, hence psychiatric disorders could be a major contributor to insomnia [16]. In order to cure insomnia, Digital Cognitive behavioural therapy has impacted the quality of sleep among patients with insomnia, resulting in better functional health and psychological well-being amongst patients [14].

Genetically inherited sleep reactivity can contribute to insomnia in the future [15]. The degree of these activities can predict insomnia in the future. Medical disorders such as heart disease can lead to insomnia [8]. Moreover, the cardiac rate was raised and vagal tone was lowered among patients with insomnia, and they also experienced an increase in Saliva Cortisol [13]. Stress is also a major predictor of insomnia. Individuals who are dealing with anxiety are at great risk of insomnia. Stress and anxiety are often mischaracterized with hyperarousal during sleep, although this factor is inconsistent when associated with insomnia [13]. Digital Cognitive Therapy and proper sleep hygiene proved to have significant improvements for those who are diagnosed with insomnia [14]. It is also known that insomnia and immune system activity are proportionally correlated. The severity of insomnia is reduced with physical activities such as exercises [3]. However, investigations illustrate that being more active in the evenings contributes to daytime sleepiness, and the inability to sleep at night, thus leading to insomnia. Other physical causes of insomnia are correlated to excessive screen time and social media use [6]. Furthermore, overall psychological well-being diminishes with insomnia. Within University students, it is seen that perfectionism and low self-esteem are significant predictors of insomnia. Arousal during bedtime also puts an individual at risk of insomnia [7].

Discussion

Quality of sleep plays a crucial role in the condition of an individual's health, lifestyle, mental status, and habits. Certain groups such as girls, those with disabilities or genetically inherited health conditions, and night owls are significantly more susceptible to insomnia due to biological, physiological, and psychological factors. One universal solution to insomnia does not yet exist. This review process concurs that insomnia affects a large fraction of the population in a negative manner and implies a need for prevention and treatment. This document outlines contributors to the development of insomnia and associated trends in insomniacs' behaviours. While this review meets its purpose of identifying factors and correlations to the sleep disorder, material to reference in findings was limited. Reliable sources with relevant information to analyse were difficult to locate. Many search results consisted of other review protocols. That being said, there are steps to be taken in future research to eliminate this limitation. Other search engines could be browsed for a wider variety of results. Alternatively, our initial query can be modified to better target desired documentation. In comparison to the original protocol, this review process provides the proof and analysis to support previously made claims and answer the question, "What biological, physiological, and psychological factors contribute to the development of insomnia?". While the original document provides a general answer as to what contributes to insomnia, this review provides examples and makes in-depth conclusions based on findings. The intention following the completion of this process is to inform the general population on how insomnia develops and to provide more cause-to-research treatment.

Appendix

Individual raw data tables for each team member

J.M.

Author (s)	Design	Country	Partici-pants	Demographic	Selection method	Biological	Physiological	Psychological
Drake et al. (2017) [2]	Observational	United States	n = 35	Adults with indication of developing a sleep disorder in the future; half of them with familial risk of insomnia and half without	Recruited from participants of previous study	No significant biological factors relating to insomnia	Subjects with familial risk for insomnia exhibit "blunted cortisol response to stress"; insufficient production of cortisol in response to stress necessitates reliance on other systems, disrupting "physiological homeostasis"; leads to adverse outcomes (e.g. PTSD, depression, sleep disturbance, schizophrenia, substance abuse, etc.)	Subjects with familial risk for insomnia do not exhibit abnormalities in autonomic nervous system response
Hysing et al. (2013) [5]	Longitudinal	Norway	n = 9875	Adolescents aged 16-19	All secondary students in spring 2012 were invited to participate	younger subjects had longer time in bed, larger sleep need, more sleep deficiency, less insomnia than older subjects; time in bed increased with age for girls and decreased with age for boys	girls are significantly more likely to have/develop insomnia; depending on criteria used, prevalence of insomnia ranges from 13.6% to 23.8% of adolescent subjects; sleep onset latency was longer for girls than boys; girls have lower sleep efficiency than boys	No significant biological factors relating to insomnia
Renom-Guit eras et al. (2014) [10]	Observational	Spain	n = 61	Patients admitted to palliative care unit	Patients in PCU in a university hospital for	results of multiple instruments shows high frequency of insomnia in palliative care	Insomnia was correlated with dyspnoea, nocturnal rumination, higher performance status and inversely correlated with daytime sleepiness	Higher Hospital Anxiety and Depression Scale score and presence of anxiety were associated with patient belief of insomnia; nocturnal

				more than 2 nights	patients; pain and dyspnoea were most reported causes of sleep disturbance			rumination showed significant association with insomnia, rumination has been associated with increased emotional distress and physical health problems

C.I.

Author (s)	Design	Country	Partici-pants	Demographic	Selection method	Biological	Physiological	Psychological
O'Hagan et al. (2017) [9]	Cross-Sectional	Australia	n = 39	Participants with non-specific LBP ranging from 18-79 years of age	Recruited from primary car centres and from the Sydney community through advertising.	Insomnia during a given night leads to an increased amount of LBP in the day following. Those with greater levels of disability experience lighter sleep	Shorter periods of SWS result in poor sleep quality. Those with greater levels of disability or LBP are most impacted by N1 sleep.	While hypnosis drugs prove to be more effective than placebo in treating insomnia and LBP, they are not deemed safe for patients with psychiatric disorders
	Cohort		n = 344	Patients of primary care centres of the Sydney and Newcastle areas ranging from 18-75 years old	Included patients who had LBP, new onset insomnia (mild to moderate), and had sufficient understanding of the English language.			
Fernandez-Mendoza et al. (2013) [4]	Cross-Sectional	United States	n = 1741	Men and women from Central Pennsylvania	Randomly selected. Divided into two categories. The first for participants who get 6 hours of sleep or more while the second consisted of participants with less than 6 hours of sleep.	Insomniatic patients perform poorly compared to the well-rested population in neuropsychological tasks such as processing speed, attention, visual memory, and verbal fluency (biological, educational, and mental factors taken into account)		
Vargas et al. (2019) [12]	Historical	United States	n = 545	Patients with both MDD and insomnia	Patients who met DSM-IV criteria.	Patients with insomnia are at high risk for depression	Both insomnia and depression are associated with high physiological and	Those with insomnia consider negative events as more stressful than those without insomnia. As a

						cognitive sensitivity, specifically shown through stress responses and through A-typical behaviour	result, they lean toward poorer coping strategies than good sleepers would

J.L.

Author (s)	Design	Country	Partici-pants	Demographic	Selection method	Biological	Physiological	Psychological
Kalmbach et al. (2018) [15]	Longitudinal	United States	n = 2316	Individuals with no history of mental disorders or insomnia were selected	Insomnia patients enrolled in study via survey with no severe mental illness	Sleep reactivity can be genetically inherited, and can predict insomnia in the future. High or low sleep reactivity can predict the likelihood of getting insomnia in the future	Individuals who experience stressful events in their lives tend to trigger insomnia. Stress is mischaracterized as hyperarousal during sleep. Hyperarousal is suggested to be an inconsistent factor when associated with insomnia	Emotional factors have an impact on insomnia and sleep reactivity, and show that there is correlation between depression and insomnia
Morin et al. (2004) [8]	Cohort	United States	General Population	General Population	A poll given to the general population	Can be a result of certain medical disorders (ex. chronic pain, various heart diseases, Alzheimer's)	Using therapy and proper sleep hygiene can help insomnia. Cognitive behavioural therapy, (Educational, behavioural, and cognitive components) proved to have great improvement for those diagnosed with insomnia	Insomnia can be caused by certain psychological disorders (Anxiety, depression, bipolar disorder) as well as drug use
Varkevisser et al. (2005) [13]	Observational	Netherlands	n = 13	Individuals diagnosed with chronic insomnia, age range 31-54	Individuals referred to the Westeinde Hospital were chosen	Cardiac rate raised and vagal tone lowered with insomnia patients, but not by a large margin. Increase of saliva cortisol	Hyperarousal showed to not be a huge underlying factor for insomnia patients	Individuals with insomnia tend to worry about sleep. Anxiety and arousal are factors that contribute to insomnia

H.E.

Author (s)	Design	Country	Partici-pants	Demographic	Selection method	Biological	Physiological	Psychological
Espie et al. (2019) [14]	Observational	United States	n = 1711	Patients with self-reported insomnia	Patients were recruited and delivered DCBT via web and mobile channels plus treatment	Patients reported improvement in sleep-related quality of life. Other outcomes comprised cognitive failures	Patients experienced better functional health after the therapy, with a global health scale range of 10-50	DCBT improved psychological well-being amongst patients
Van Someren et al. (2019) [11]	Cross-sectional	Netherlands	n = 1.1 million	Participants worldwide who are within the category of 14 to 17 years, 18-25 years, and older than 65 years	Establishment of a model stating how insomnia results from insufficient overnight adaptation to stress	Genome Wide Association Studies revealed clues about the involvement of functional pathways, tissues and cell types in patients with insomnia. The identified cell types and tissues may be involved in shaping the brain circuitry in such a way that makes people vulnerable to insomnia	The MEIS gene has been implicated with physical disorders such as restless leg syndrome and is to some degree involved during insomnia. However, most cases see involvement of the RLS and PLMS genes	It is important to identify risk factors that contribute to insomnia. Some of these factors include bad night of sleep
Lane et al. (2019) [16]	Observational	United Kingdom	n = 453379	Identified 57 loci for self-reported insomnia cases in the UK, including registries aged 40-69 and living <25 miles from the study centre	Genes from the UK's biobank were compared within each study	From participants of European ancestry, 29% report cases of insomnia, with higher prevalence of females to males. There are shared genetic architectures between individuals with insomnia and behavioural traits, as well as physical disorders such as restless leg syndrome	Patients who exercise often have seen improvements in their sleep quality. Genetic evidence illustrates that insomnia is linked to some physiological disorders as some of these disorders do contain similar genetic architectures	Patients with psychiatric disorders are linked with insomnia since there is a strong bi-directional link between these disorders and insomnia

A.K.

Author (s)	Design	Country	Participants	Demographic	Selection method	Biological	Physiological	Psychological
Abd El-Kader et al. (2020) [3]	Longitudinal	Saudi Arabia	n = 80	Chronic primary insomnia subjects aged 35-56 years	Insomnia patients enrolled in study and excluded ones with history of drugs, alcohol, mental disorders, and those who exercise regularly	Insomnia and immune system activity are proportionally correlated	Severity of insomnia is reduced with physical exercise	Overall psychological well-being diminishes with insomnia
Lin et al. (2021) [6]	Cross-sectional	Iran	n = 1791	College students across three campuses with mean age of 27.2 years	Insomnia patients enrolled in study and excluded ones with history of drugs, alcohol, mental disorders, and those who exercise regularly	Being more active in evenings causes daytime sleepiness and inability to sleep at night, thus leading to insomnia	Excessive screen time and social media use in evening time relate to mediated effects of insomnia	Anxiety and depression are directly linked to sleep loss and insomnia
Lindsay et al. (2022) [7]	Cross-sectional	Canada	n = 2379	University students aged 17-22 years	First year students with age range chosen via survey and excluding self-reported non-cisgender individuals	No significant biological factors relating to insomnia	Having increased cognitive arousal at bedtime predisposes insomnia	Perfectionism, low self-esteem and external locus of control are significant predictors of insomnia

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