

Clinical implications of the causal relationship between insomnia and depression: how individually tailored treatment of sleeping difficulties could prevent the onset of depression

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Abstract Major depression commonly co-occurs with symptoms of insomnia. However, the underlying psychobiological mechanisms which can explain this relationship are still not well understood. Hyperarousal and negative emotionality have been proposed to be possible mediating factors. Several studies have suggested that insomnia could be a predictor of depression. A recent meta-analysis conducted by our group showed that people with insomnia have a two-fold risk to develop depression, compared to people with no sleep difficulties. Thus, early diagnosis and treatment of insomnia could, at least partially, prevent the development of future depression, by identifying people at risk for depression and deliver personalized intervention protocols to improve individual outcome. Modifications of existing treatment modules are needed, as adding sleep protocols to the treatment of depression and affective regulation protocols to the treatment of insomnia, enhance the accessibility for the treatment of insomnia, and develop sleep education protocols in early periods of life.

Keywords Depression · Insomnia · Clinical predictor · Cognitive behaviour therapy for insomnia · First level interventions · Prevention

Depression

Major depression is a heterogeneous disorder with a variable course which is associated with high levels of disability, impairment in quality of life, and increased mortality rates. It adversely affects physical health, cognitive performance, and social relationships.

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition [1], the diagnosis of major depression requires the presence (for a period of 2 weeks) of at least five out of a list of nine symptoms that include, for example, sadness, loss of interest in usual activities, lowered appetite, fatigue, insomnia symptoms, and suicidal ideas. Depression is the leading cause of disability in both women and men in United States and worldwide and one of the ten leading disorders for global disease burden [2]. In Europe it has been estimated that around 13% of the population have a major depressive episode at some time of their lives [3]. It comprises 6% of the total disease burden and almost 1/3 of all neuropsychiatric diseases and the costs of depression correspond to 1% of the total economy of Europe [4]. Beside the high prevalence, depression has also a recurrent aspect, i.e. a person who suffered from depression once is vulnerable to relapses. Despite of the high impact of depression in the general population, consensus reports underline that individuals with depression are being underdiagnosed and undertreated [5]. The increase in the prescription of antidepressants registered over the past 20 years is mostly dependent on increased long-term prescribing, but not on early recognition of depression [6]. The clear necessity of deepening the knowledge about the treatment of depression in order to

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reduce its impact on modern society requires a further effort in the recognition of clinical early predictors of depression and the development of alternative treatments.

Depression and insomnia

Major depression commonly co-occurs with symptoms of insomnia [7, 8]. The International Classification of Sleep Disorders (2nd edition [9]) defines insomnia as a difficulty in initiating/maintaining sleep or non-restorative sleep accompanied by decreased daytime functioning, such as fatigue/malaise, daytime sleepiness, mood disturbance/irritability, motivation/energy/initiative reduction, and attention/concentration/memory impairment, persisting for a period of at least 4 weeks. The relationship between depression and insomnia has been observed for a long time. Already at the beginning of the 20th century, Kraepelin [10] described the close link between the two conditions. Nevertheless, the conceptualization of this relationship has radically changed during the last decade. Insomnia has been traditionally viewed in the field of psychiatry as a symptom of psychopathology, especially depression (overview see [11, 12]). More recently, insomnia has been re-considered as a primary disorder if it is present without the co-existence of other clinically relevant psychiatric or medical diseases, and as a secondary disorder if otherwise. Considering the link to depression, however, chronic insomnia can also exist years before the first onset of a depressive episode. Consequently, it has been suggested that “comorbid” insomnia may be a more appropriate term than “secondary” insomnia [13–15]. Insomnia and depression are conceptualized now as two independent diagnostic entities with different clinical courses and characteristics which share some psychobiological characteristics, as for example hyperarousal [12]. The next edition of DSM, DSM-V, will probably abandon the primary/secondary concept and instead introduce “insomnia disorder” as the main diagnostic category for insomnia, allowing specification whether or not it is co-morbid with another mental or medical disorder [16].

Causal relationship between depression and insomnia: possible psychobiological mechanisms

The psychobiological mechanisms that underline the relationship between depression and insomnia are still not well understood. Neurobiological and sleep EEG studies indicate that high levels of arousal could explain the close link between the two conditions and represent a possible mediating factor. Another possible mechanism involved is altered emotionality. Koffel and Watson [17] evaluated the relationship between nighttime and daytime symptoms of insomnia and depression. Nighttime symptoms were defined as poor sleep quality,

long sleep latency, and minutes awake at night; daytime symptoms were conceptualized as fatigue and sleepiness. This relationship was tested in three different samples: 349 college students, 213 older adults, and 266 psychiatric outpatients. Both nighttime and daytime symptoms of insomnia were found to be significantly related to depression. Moreover, daytime symptoms were associated with a higher negative emotionality and a lower positive emotionality in all three samples. Based on these results, it can be assumed that heightened negative emotionality and diminished positive emotionality explain the psychological mechanism which mediates the relationship between insomnia and depression [18]. That is, insomnia may lead to depression by altering emotional responses. Consistently, altered emotional responses to visual stimuli have been reported in people with insomnia as compared to good sleepers [19]. It may be speculated that initially primary insomnia is a condition strictly connected to hyperarousal (e.g. [20]), which if it gets chronic impairs also the emotional system leading to the increased risk to develop depression.

Insomnia as a clinical early predictor of depression: results from a meta-analytic study

The link between depression and insomnia is very close; up to 80% patients with depression have sleep complaints consistent with insomnia [8]. The high percentage suggests that the two conditions are not just randomly associated. Several authors have proposed that insomnia could be a predictor of depression instead of being just a symptom of affective disorders.

Ford and Kamerow [21] were the first to note that a causal relationship between insomnia and depression exists based on data from a longitudinal epidemiological study. Since then more than 40 studies have been published evaluating the predictor question (overview see [18, 22]). A recent study from our group aimed at evaluating the causal link between insomnia and depression by performing a meta-analysis of longitudinal epidemiological studies [23]. Considering all relevant longitudinal studies published from 1980 to 2010, 46 studies were identified which evaluated simultaneously insomnia complaints and depressed psychopathology. Within these, 25 studies were excluded as they did not satisfy the following criteria: 1) insomnia predicting follow-up depression and not the other way round; 2) definition of sleep complaints consistent with the DSM-IV definition of insomnia; 3) depression assessed basing on the DSM-IV definition or through standardized questionnaires; 4) participants with significant depression at baseline excluded from the study; 5) follow-up conducted at least after 12-months from the baseline; 6) effect size reported and/or computable.

The 21 studies selected for meta-analytic computations had a mean sample size at follow-up of 3200 participants with a mean age of 46 years ($sd=22.4$). The mean percentage of women in the studies was of 55% ($sd=4.5$), excluding one study in which all participants were males [24]. On average, the follow-up assessment was conducted after 71 months ($sd=96.0$). Descriptive characteristics of the included studies are reported in Table 1.

Incidence of depression at follow-up in people with insomniac symptoms was in percentage 13.1%, while it was 4.0% in people without sleep difficulties. Considering that an incidence rate of 9.9% has been reported for depression in the general population [44], it is interesting to notice that: a) the incidence is high in patients with insomnia and b) the incidence is extremely reduced in a group without any experience of sleep difficulties.

The logarithms of the odds ratios and their confidence intervals (CI) were used for meta-analytic calculations. Considering all the 21 studies selected together, the heterogeneity index was statistically significant (Q-value = 124.7; $df(Q) = 20$; $p < 0.001$; and $I^2 = 84.0$). By performing sensitivity analysis, it was found that the majority of heterogeneity between studies was explained by those studies which reported standardized residuals of $>+3$ or

<-3 [21, 26, 32, 37]. Excluding these outliers from the analysis, the heterogeneity test was not longer significant (Q-value = 20.1; $df(Q) = 16$; $p = 0.2$; and $I^2 = 20.3$). The summarized odd ratios determined by applying the “fixed-effects meta-analytic model” was of 2.1 (CI: 1.9–2.4; see Fig. 1).

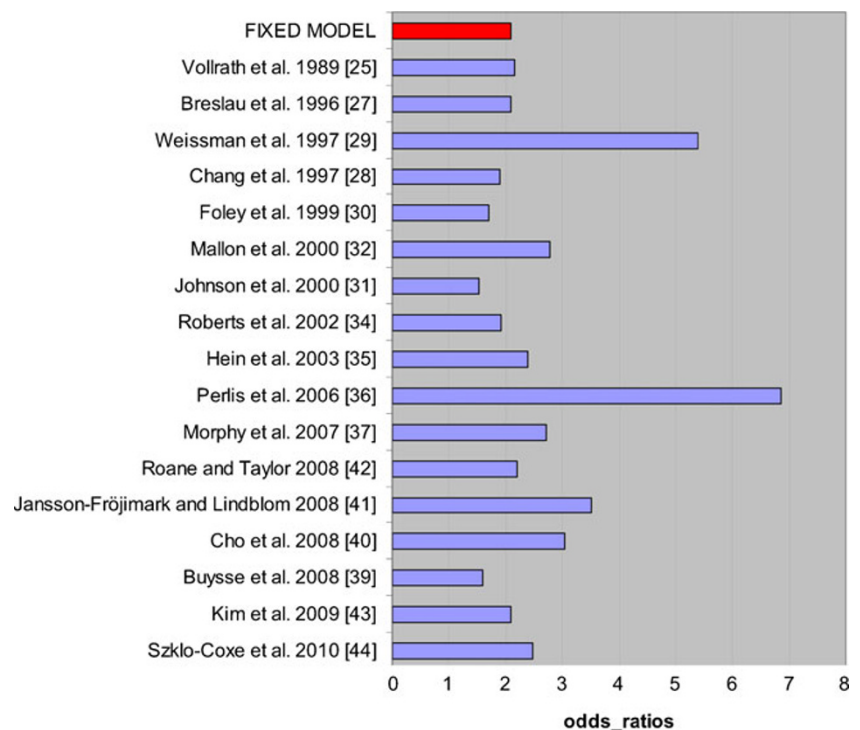
Classifying the studies according to age, we considered three groups: working-age group, elderly group (>60), and a children and adolescent group. The same meta-analytic calculations were applied to each one of these three age-groups. Studies with mixed-age participants (i.e. studies recruiting participants aged 18 years or older) were not considered for age-groups calculations. The elderly group was heterogeneous (Q-value = 8.8; $df(Q) = 5$; $p = 0.1$; and $I^2 = 43.1$), however this heterogeneity was explained by studies which considered clinical samples and not the general population as the other studies [26, 34, 35]. Once we excluded data from these studies, we found non-heterogeneity between studies in all three age-groups. The summarizing odds ratios for these three age-groups were respectively: 2.1 (CI: 1.7–2.6) for the working-age group; 1.9 (CI: 1.6–2.3) for the elderly group; and 2.0 (CI: 1.5–2.7) for the children and adolescents group.

Table 1 Study descriptive characteristics

Authors and Publ Year	N (bsl)	N (fu)	m_age	age_group	fu (months)	OR (95%CI)
Ford and Kamerow [21], 1989	10.534	7.954	45.79	Mixed (>18 years)	12	39.8 [19.8–80.0]
Vollrath et al. [25], 1989	591	457	21.0	Working	84	2.2 [1.2–4.0]
Brabbins et al. [26], 1993	1.070	701	69.8	Elderly	36	1.4 [1.1–1.8]
Breslau et al. [27], 1996	1.007	979	26.1	Working	42	2.1 [1.1–4.0]
Chang et al. [24], 1997	1.053	941	26.0	Working	408	1.9 [1.2–3.2]
Weissman et al. [28], 1997	18.571	7.113	48.2	Mixed (>18 years)	12	5.4 [2.6–11.3]
Foley et al. [29], 1999	9.282	6.899	80.1	Elderly	36	1.7 [1.3–2.2]
Johnson et al. [30], 2000	823	717	6.0	Child and ado	60	1.5 [0.4–6.5]
Mallon et al. [31], 2000	1.870	1.244	55.0	Working	144	2.8 [1.6–4.9]
Roberts et al. [32], 2000	2.730	2.370	64.9	Mixed (>18 years)	12	4.9 [3.1–7.6]
Roberts et al. [33], 2002	4.175	3.136	15.0	Child and ado	12	1.9 [1.3–1.9]
Hein et al. [34], 2003	775	664	60.0	Elderly	60	2.4 [1.3–4.5]
Perlis et al. [35], 2006	247	147	72.0	Elderly	12	6.9 [1.3–36.1]
Morphy et al. [36], 2007	2.363	1.589	50.0	Mixed (>18 years)	12	2.7 [1.4–5.4]
Neckelmann et al. [37], 2007	74.977	25.130	54.1	Mixed (>18 years)	132	1.1 [0.8–1.6]
Buyse et al. [38], 2008	591	278	19.5	Working	240	1.6 [1.1–2.1]
Cho et al. [39], 2008	351	329	69.0	Elderly	24	3.1 [1.1–8.8]
Jansson-Fröjmark and Lindblom [40], 2008	1.812	1.489	42.0	Working	12	3.5 [2.1–5.8]
Roane and Taylor [41], 2008	4.494	3.582	16.0	Child and ado	78	2.2 [1.3–3.6]
Kim et al. [42], 2009	1.204	909	72.2	Elderly	24	2.1 [1.5–3.0]
Szklo-Coxe et al. [43], 2010	1.533	555	53.6	Working	44	2.5 [0.8–7.5]

Publ Year publication year; bsl baseline; fu follow-up; m_age mean age; OR odds ratios; CI confidence interval; mixed mixed-age group; working working-age group; elderly elderly group; child and ado children and adolescents

Fig. 1 Odds ratios relative to each single study and summarizing odds ratio after exclusion of the outliers



Insomnia as a clinical early predictor of depression: what we still need to know

Results from this meta-analytic study show that people with insomnia have a two-fold risk to develop depression, compared to people with no insomniac sleep difficulties. In spite of the high variability in study populations, study designs, and measures, the pooled estimates were high and remained high also after exclusion of the outliers. The 21 studies included in the meta-analysis had large sample sizes and considered a large amount of time between baseline and follow-up which allow to consider long-term relationships between depression and insomnia.

The main limitation of the meta-analysis is that intervening variables were not taken into account in many of the studies considered, for example anxiety disorders, drug or alcohol abuse or socio-economic situation. Moreover, the definition of insomnia given in the DSM-IV includes three criteria: a sleep difficulty criterion (difficulty in initiating/maintaining sleep or non-restorative sleep); a duration criterion (a period of at least 4 weeks); and a daytime impairment criterion (decreased daytime functioning, such as fatigue/malaise, daytime sleepiness, mood disturbance/irritability, motivation/energy/initiative reduction, and attention/concentration/memory impairment). However, the studies included in the meta-analysis often failed to consider the duration and the daytime impairment criteria. More specifically, eight of the 21 studies based their diagnosis only on the presence of problems in

initiating and maintaining sleep, thus considering only insomnia symptoms, but not insomnia as a disorder. It could be possible that insomnia as a disorder has an even higher impact on the development/incidence of depression than sleep difficulties alone. In addition, studies on children and/or adolescents are only few up to now: in our meta-analysis only three studies evaluated these populations. As insomnia is a clinical predictor of depression, studying the clinical link in younger samples could help in developing early-detection or prevention programs which could reduce the risk for onset of depression in adults.

Clinical implications: how treating sleeping difficulties could prevent the onset of depression

The close link between depression and insomnia, and the causal role that symptoms of insomnia have in the development of a depressive disorder necessitate not only further research in order to understand the underlying psychobiological mechanisms, but also argue for the development of innovative clinical updates. Some recent studies showed that adding cognitive-behaviour therapy for insomnia (CBT-I) is efficacious in patients with both symptoms of insomnia and depression and guarantees a better treatment outcome in this population than standard antidepressive treatment alone [45, 46]. The strategies included in the CBT-I are summarized in Table 2.

Table 2 Strategies included in the cognitive behaviour treatment for insomnia (CBT-I)

CBT-I strategy	Description
Stimulus control strategy	<i>Behavioural strategy.</i> A set of instructions directed to associate the stimulus “bed” with the behaviour “sleep” and to reinforce a regular sleep–wake schedule: 1) go to bed only when tired; 2) use the bed to sleep only (no TV; no food; etc.); 3) plan pre-bed routines to do every night before going to bed; 4) get out of bed when unable to sleep; 5) arise at the same time every morning; 6) no napping
Sleep restriction	<i>Behavioural strategy.</i> A method which aims at making the patient staying in bed only for the time she or he sleeps. It consists in reducing the time spent in bed to the mean time generally slept by the patient. The amount of time allowed to sleep planned with the therapist should be respected also during weekends
Sleep hygiene education	<i>Behavioural and educational strategy.</i> General health instructions about factors that might influence sleep (e.g. sport, light, temperature; etc.)
Relaxation	<i>Behavioural and cognitive strategy.</i> A set of methods aiming at reducing somatic or cognitive hyperarousal (e.g. progressive muscle relaxation; autogenic training; imagery training; meditation)
Cognitive reconstructing	<i>Cognitive strategy.</i> A strategy directed to reduce the impact of dysfunctional beliefs and attitudes about sleep
Cognitive control	<i>Cognitive strategy.</i> The patient is instructed to sit comfortably in an armchair and write down a list of worries and a list of what to do the next day. The rationale of this strategy is to prevent emotionally loaded intrusive thoughts during the sleep-onset period, as all worries have been “already” processed before going to bed
Paradoxical intention	<i>Cognitive strategy.</i> Strategy aimed at reducing the anticipatory anxiety at the time to fall asleep. Patients are instructed to stay quietly in bed with the eyes closed and to try to keep awake as long as they can. This takes away the responsibility to try to fall asleep, which in turn lead to fall asleep quicker

Applying protocols directed to reduce sleep difficulties and related cognitive and emotional aspects to the routine of psychological therapy of depression seems to lead to better outcomes and to diminish the risk for recurrent depression. On the other hand, adding protocols directed to ameliorate affective regulation in people with insomnia could prevent the risk for developing depression. Consistently, some preliminary research has been conducted using the Pennebaker writing intervention to treat people with insomnia (e.g. [47, 48]). This intervention consists of the instruction to write down thoughts, worries and emotions. It is supposed that writing about emotional experiences is a method to facilitate emotional processes. Harvey and Farrel [48] found in 44 poor sleepers that those who underwent a 3-nights Pennebaker writing intervention reported shorter sleep-onset latencies compared to a no-writing group. Mooney, Espie and Broomfield [47] found that a Pennebaker writing group reported significantly reduced pre-sleep arousal compared to a control group. However, they did not find an effect of the intervention on sleep-onset latencies. Further research in this area is needed to determine the clinical relevance of this type of intervention.

With respect to possible prevention programs, based on the results presented above, it seems reasonable that treating sleep difficulties at an early stage can prevent affective sequelae. Evidence-based treatments for insomnia include hypnotic drugs, benzodiazepine (BZ) and benzodiazepine receptor agonists (BZRA), and cognitive behavioural treatment for insomnia (CBT-I) (overview see [49]). However, with respect to hypnotic drugs, guidelines suggest to restrict prescriptions to limited periods of times, i.e. 3 to 4 weeks due to the risks

inherent in these drugs, mainly tolerance and dependence. On the other hand, CBT-I has been found to be efficacious both at short- and long-term, but is available only to a tiny minority of afflicted individuals, as it is still mainly limited to academic environments and often used only in research contexts.

As emphasized before, there is a necessity to systematically address insomnia and to spread the possibility to access to psychological treatment of insomnia in the general population. One approach suggested consists in the “stepped care model” (e.g. [50]). This model offers a generic approach to care management by delivering low intensity treatments to a wide number of individuals. In case of treatment failure, individuals can step forward to next levels that are characterized by more specialized programs and deliverers. The first level would work as prevention program for individuals at risk, while the superior levels would correspond to CBT-I delivered by a psychologist.

At the first level, one possible method is to deliver CBT-I in primary care through structured protocols delivered by unspecialized professionals. Espie et al. [50] have found that trained and supervised nurses can successfully deliver CBT-I in primary care routine of general medicine practice. CBT-I was organized in a structured protocol divided in five sessions comprising: (a) sleep information; (b) sleep hygiene and relaxation; (c) sleep scheduling; (d) cognitive approaches; (e) developing a strong and natural sleep pattern.

Another possible first level alternative to spread the CBT-I protocols in primary care and reach a large number of individuals is the use of the internet. Internet-based treatment has the potential to reach a large number of

people [51]. Studies which applied cognitive-behaviour therapy to internet protocols for treating psychiatric disorders showed that these are effective in reducing psychological symptoms (e.g. [52]). Only three studies investigated the efficacy of CBT-I delivered through internet [51, 53, 54]. These studies indicate a significant improvement in the treatment groups in total sleep time, sleep onset latency, nocturnal awakenings, time awake at night, sleep efficiency, sleep quality and insomnia severity. Moreover, effects on cognitive variables, for example on dysfunctional beliefs about sleep and pre-sleep mental activity, and on daytime consequences were found. All the three studies available up to date [51, 53, 54] found that online CBT-I is efficacious. An internet-based CBT-I program may be an effective tool to reach people that are not willing to go to a psychotherapist.

As insomnia is a clinical predictor of depression, interventions in early periods of life could lead to significant benefits for the individual and improve public health outcomes. However, studies on children and adolescents are still too few and the issue needs further investigation. Chronic insomnia affects up to 25% of children [55]. However, only few studies investigated treatment efficacy in this population. Improving preventive parents' education for children in the earliest years of life and developing school programs for children could have a huge impact on insomnia prevalence and incidence. In fact, according to the transdiagnostic model of insomnia (e.g. [56]), insomnia is not only a clinical predictor for depression, but for psychopathology in general. It could be possible that the treatment of insomnia is a generally effective preventive strategy for mental health. This effect could be even stronger in children and adolescents because the future development of psychiatric disorders in adult age might be prevented.

Conclusions and outlook

Compared to people with no sleep difficulties, people with insomnia have a two-fold risk to develop depression. Insomnia and depression are nowadays conceptualized as two independent diagnostic entities with different clinical courses and characteristics which, however, share some psychobiological aspects, as for example hyperarousal. One possible mechanism involved in the etiology of both insomnia and depression is altered emotionality. It could be possible that insomnia, being a condition strictly connected to hyperarousal, is associated with an alteration in the emotional system, which, in turn, leads to the increased risk for depression. This theoretical assumption has important clinical implications. Modifications of existing clinical treatment modules are needed in order to add sleep protocols to the treatment of depression and protocols for affective regulation to the treatment of insomnia. Moreover,

there is a need to enhance the accessibility for the treatment of insomnia in the general population, either through the “stepped care” approach or through internet programs. Finally, sleep education protocols in early periods of life could lead to significant benefits for the individual and improve public health outcomes.

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