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Insomnia and mortality: a meta-analysis

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Summary

The purpose of this review was to evaluate the strength of evidence for a relationship between risk of mortality and frequent and ongoing insomnia using a meta-analytic strategy.

Seventeen studies, including a total of 36,938,981 individuals followed up for a mean of 11.6 years, reporting the investigation of the association between mortality and frequent (≥3 nights/week), ongoing (≥1 month) insomnia were identified.

There was no difference in the odds of mortality for those individuals with symptoms of insomnia when compared to those without symptoms (OR= 1.06, 95%CI=0.61-1.84, *p*=.84). This finding was echoed in the assessment of the rate of mortality in those with and without symptoms of insomnia using the outcomes of multivariate models, with the most complete adjustment for potential confounders, as reported by the individual studies included in this meta-analysis (HR= 1.07, 95%CI=.96-.1.19, *p*=.22). Additional analyses revealed a tendency for an increased risk of mortality associated with hypnotic use.

The current evidence reinforces the use of cognitive therapy, within a CBTi framework, as a frontline non-pharmacological treatment for insomnia to reassure patients their longevity will not be impacted as a consequence of suffering from insomnia.

Keywords: Insomnia, mortality, sleep disturbance, death
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Introduction

As the most common sleep disorder, insomnia affects the lives of 10-30% of the population (1) which at a conservative estimate equates to around 2.5 million individuals living in Australia alone and 770 million world wide. Insomnia is characterized by a subjective report of difficulty falling asleep, maintaining sleep or nonrestorative sleep coupled with daytime impairment (2). The impact of the disorder on the quality of the lives of sufferers is widespread across both psychological and physiological functioning. Impaired daytime functioning including fatigue, problems with cognitive performance, complaints of depressed mood and feelings of anxiety, difficulty maintaining social relationships and ill health are all hallmark characteristics of the disorder (2, 3). Growing empirical evidence, including meta-analytic, suggests that insomnia is strongly associated with significant medical morbidity including depression (4, 5), dementia (6) and cardio-metabolic outcomes including hypertension (7-9), and diabetes (10, 11), and inflammatory processes (12), however it remains unclear whether the risk of mortality is increased for those suffering from insomnia.

Various theoretical models propose an increased risk of mortality attributed to insomnia either from a psychological or physiological standpoint. It is well established that insomnia is an independent risk factor for the development of various psychological disorders, namely depression and anxiety (13-15). Although the mechanisms by which insomnia precedes the development of psychological disorders is unknown (16), the comorbidity of these disorders is proposed to increase risk of mortality in those with insomnia. This is presumably due to the elevated rates of self-harm and suicide characteristic of these psychological disorders (17).

Findings from physiological studies also suggest a proposed mechanism for increased risk of mortality in insomnia. Several studies have demonstrated that activation of the

hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (sympathetic division), including increased 24h metabolic rate, increased heart rate and impaired heart rate variability, is increased in those suffering insomnia (18-21). This physiological over activation has been inconsistently associated with hypertension, diabetes and ultimately increased mortality (22, 23).

However empirical support for the notion that mortality risk is increased in insomnia has been inconsistent. Despite some support from small-scale longitudinal and prospective cohort studies (24, 25), longitudinal research conducted with large samples (*N*>300k) of diverse age ranges have reported no association or even a negative association between risk of mortality and insomnia (26, 27). For instance, Chien and colleagues (24) and Vgontzas et al. (25) both found mortality risk was significantly increased for those suffering insomnia in their prospective cohort and longitudinal studies with ~14-year follow up. Contrary to these findings, Gapstur and colleagues (26) reported no support for the association between insomnia frequency and fatal prostate cancer at 28 years of follow up in their large prospective cohort study of U.S. adults. Kripke et al. (27) sampled over 1.1 million individuals and found a *reduced* mortality rate for those individuals complaining of insomnia symptoms on 6-year follow up. Given this disparity, firm conclusions regarding mortality risk and its association with insomnia have not been able to be drawn.

The body of literature exploring the association between mortality and insomnia has numerous flaws which likely contribute to the inconsistent findings including small numbers of deaths, lack of measurement or statistical control for factors confounding the relationship between mortality and insomnia, such as lifestyle factors (i.e. smoking, obesity) and medication use particularly hypnotics (28), loss to follow up and typically small effect sizes. More importantly, the majority of studies focus on assessing the relationship between mortality and sleep duration, rather than insomnia per se. Although objective short sleep

duration is characteristic of some types of insomnia (29), it is certainly not the case types of insomnia associated with misperception of objective sleep duration and quality. In our earlier work (30), we found that 57% of individuals diagnosed with insomnia had an objective sleep duration of more than 6hrs (total sample $N = 91$). Likewise, Vgontzas and colleagues (25) reported objective sleep duration longer than 6 hours in 40% of their sample of 55 individuals diagnosed with insomnia. Furthermore, most studies also do not account for the frequency (nights/week of insomnia symptoms) or severity of insomnia. Given these major shortcomings, any conclusions, which may be drawn about the association between insomnia and increased risk of mortality, are limited. The question of whether insomnia is associated with an increased risk for death remains unanswered.

The importance of understanding whether insomnia is associated with an increased risk for death should not be underestimated and has significant implications for public health and the treatment of insomnia. Non-pharmacological interventions are considered best practice for the treatment of ongoing insomnia. The gold-standard treatment, Cognitive Behaviour Therapy (CBTi), produces robust and durable therapeutic improvements, extending well beyond the period of therapy, which are typically superior to pharmacological preparations without the known side effects and issues of tolerance and dependence (31-33). Given CBTi aims to modify poor sleep habits, regulate sleep/wake schedules, correct faulty beliefs and attitudes about sleep, and develop adaptive coping skills (34), the incorporation of education around the relationship between insomnia and risk for death is likely to hold significant therapeutic weight. If indeed there is an increased mortality risk for those suffering from insomnia, successful treatment, preferably with Cognitive Behaviour Therapy (CBTi), may also reduce morality risk. On the other hand, if there is no increased mortality risk associated with insomnia, this would form a valuable and therapeutic aspect of cognitive therapy. A core cognitive feature of insomnia is amplification of the consequences of

insomnia with many sufferers subscribing to the underlying belief that insomnia is detrimental to health (34). To the authors' knowledge, the extent to which this belief extends to increased risk of mortality per se remains to be empirically investigated. Nevertheless the anecdotal clinical experience of the authors' is that this belief is expressed by many patients, particularly older adults with comorbid medical conditions. The incorporation of the psychoeducation around the lack of increased mortality risk in insomnia would be very therapeutic in a cognitive context to reduce anxiety about insomnia and thereby potentially boost the efficacy of treatment. In that case although it would not reduce mortality risk, many therapeutic benefits occur with successful treatment of insomnia with CBTi such as reduced fatigue, depressive, anxiety, and stress symptoms, and generally improved quality of life (35, 36).

The purpose of this review was to evaluate the strength of evidence for a relationship between risk of mortality and frequent (≥3 nights/week) and ongoing (≥1 month) insomnia. Data from studies investigating the association between mortality and insomnia was gathered and a meta-analytic strategy used to provide a quantitative summary of data on this topic. Meta-analysis of similar and methodologically sound studies is considered to provide a high level of evidence (37) and potentially a more precise estimate of the underlying 'true effect' than any individual study alone (38).

Method

Design

A quantitative summary of data from studies investigating the association between symptoms of insomnia and the risk of mortality is provided using a meta-analytic strategy.

Literature search and inclusion criteria

Electronic databases, including MEDLINE, Web of Science, OvidSP, PsycInfo, PubMED, and online journals (e.g. SLEEP, Archives of General Psychiatry, Circulation etc.) were used to identify and retrieve research articles exploring the relationship between insomnia and the risk of mortality. Relevant publications were located in all journals using an advanced search with the search terms *insomnia* [Title/Abstract] AND *mortality* [Text word]. The search was also expanded by manually identifying relevant publications from the reference lists of retrieved literature.

Publications were included in this review if they met the following criteria: 1) published in a peer-reviewed journal in English, 2) utilized an adult sample (18 years and over), 3) included at least one measure of insomnia symptoms (either subjective) and mortality (all cause or specific), 4) symptoms of insomnia must be frequent (reported on at least 3 nights per week) and ongoing(reported for at least one month), and 5) authors provided appropriate statistics from which mortality risk can be assessed (i.e. number of deaths/survival in insomnia and no-insomnia groups, or hazard ratios and accompanying 95% confidence intervals). The literature search was conducted from April to May, 2017.

Statistical analyses

Data extraction and quality assessment

Insomnia symptoms were assessed primarily using subjective reports consistent with the diagnostic criteria for insomnia (2, 3) and included at least one of the following; difficulty falling asleep, staying asleep, or waking up too early in the morning with or without accompanying impairments to daytime functioning. These symptoms were required to be frequent (≥3 nights/week) and ongoing (≥1 month) and were either self-reported by the study participants, clinical sleep specialist or psychiatrist. The date and cause of mortality was confirmed via death certificates sourced from national death registries.

The quality of the included studies was assessed across five different domains proposed to be sources of potential bias (39). The domains assessed included study participation (i.e. recruited sample is representative of the population of interest), study attrition, satisfactory measurement of the outcome variable, measurement of confounding variables and adequate statistical analyses. Hayden and colleagues (39) propose a sixth domain of potential bias, adequate measurement of the prognostic factor, however given stringent criteria for the assessment of insomnia are included in the inclusion criteria, the included studies were not assessed on this domain. The ratings for included studies are presented in Table 1. The retrieved studies were reviewed for eligibility independently by the authors (NL and LL) in an un-blinded and standardised manner in accordance with the selection criteria. Instances of disagreement between the reviewers were resolved by consensus. The same approach was used when assessing the quality of the included studies.

Meta-analyses

All analyses were conducted using *Comprehensive Meta-analysis*, version 3.0 (40). *Comprehensive Meta-analysis* is a leading meta-analysis program that has capacity to use a range of different data formats, including the use of reported effect sizes (i.e. hazard ratio) or to calculate effect sizes from commonly reported statistics such as death and survival data. The software provides standard meta-analysis methods including the reporting of the forest plot and accompanying statistics. The tool also supports additional analyses including subgroup, moderator, and publication bias analyses.

Un-adjusted analyses

To assess the risk of mortality associated with insomnia independent of any other factors that might affect risk, odds ratios (OR) and associated 95% confidence intervals for all-cause mortality were calculated for each study from the extracted death and survival data for the insomnia and no insomnia groups.

Adjusted analyses

The aim of these analyses was to assess the risk of mortality associated with insomnia above other factors that potentially confound this association. The included studies used different outcome measures to assess the association between insomnia and mortality when accounting for confounding variables. Some studies reported relative risk while the majority reported hazard ratio. The present meta-analysis used hazard ratio (HR) as the main outcome measure. The HR of the multivariate models with the most complete adjustment for potential confounders from each included study were used for these analyses. The confounding variables included in the models is shown for the individual studies in Table 1.

Additional analyses were also undertaken to examine whether mortality risk differed according to shared characteristics of the included studies and potential moderating factors (i.e. characteristics of the study population and design, as well as confounding factors such lifestyle factors, including excessive alcohol consumption, smoking, obesity, and hypnotic use).

The unadjusted and adjusted analyses obtained pooled OR/HR estimates using inverse variance weights in random-effects models. OR/HR for insomnia symptoms and mortality outcomes were pooled for studies with similar, good sleeper, reference categories.

Interpretation of main outcome measures

To assist in the interpretation of the outcomes of this meta-analyses, it is relevant to provide a brief guide to the interpretation of odds ratios (outcome of unadjusted analyses) and hazard ratios (outcome of adjusted analyses).

Odds Ratio (OR) represents the odds than an outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of that exposure, whereas Hazard Ratio (HR) refers to the instantaneous risk. In the context of this meta-analysis, OR indicates the odds, or likelihood, of mortality in those with symptoms of

insomnia compared to those with no symptoms. Unlike OR, HR is not a cumulative estimate. HR reflects the estimated risk of mortality for those with symptoms of insomnia, relative to those with no symptoms, at any given point of time. The interpretation of OR and HR is similar, keeping in mind the distinction of time periods. Increased odds of mortality, and a faster rate of death, for those with symptoms of insomnia relative to those without, is indicated by an OR and HR greater than 1, respectively. OR and HR less than one indicates a protective effect with a decreased likelihood of mortality, and slower rate of death, for those with symptoms of insomnia compared to those with no symptoms, respectively. It is important to note these ratios are comparisons between two groups and give no indication of how quickly death occurs in either group.

Heterogeneity and publication biases

The *Q*-statistic (also referred to as Cochrane's *Q*) provided an indication of the variability of the effect sizes (41). When significant, the *Q*-statistic indicates the variability in study effect size is greater than expected by chance. It is important to note the *Q*-statistic is vulnerable to bias from sample size, therefore it is often interpreted in conjunction with the I^2 statistic which quantifies the degree of heterogeneity. In the current analyses, I^2 is reported for instances when the *Q*-statistic is significant.

Funnel plots of the effect size relative to standard error were used to assess possible publication bias. Funnel plots which appear symmetrical upon visual inspection suggest no bias is present.

Results

Selection of studies

Figure 1 shows the flow of the literature search process. Four hundred and thirty eight publications were identified. Of these, 105 investigated the relationship between insomnia and

mortality. Eighty-eight papers were excluded (reasons for exclusion are listed in Figure 1). A total of 17 studies met inclusion criteria and were entered into the meta-analysis.

<Insert Figure 1 about here>

Characteristics of included studies

The characteristics of the included studies are summarised in Table 1. A total of 36,938,981 subjects were included in the meta-analysis, of whom 366,024 (approximately 10%) were suffering from insomnia. Eight of the 17 studies included the presence of daytime impairments in their definition of insomnia. Sample sizes ranged from ~150 to >35,000,000. Follow up periods varied from 2.2 years to 28 years, with a mean follow up of 11.6 (*SD*=2.3). The included studies were conducted in eight countries across the world including the United States (*N*=7), Europe (*N*=3), and Asia (*N*=7). Most of the included papers assessed insomnia as self-reported according to the diagnostic criteria (DSM-IV or ICSD-IV). Of these studies, four required self-reported symptoms to be confirmed by a sleep physician or psychiatrist (42-45). Most of the studies used definitions including difficulty initiating and/or maintaining sleep, and/or waking too early (46-52), while others were broad in their definition, such as presence of a complaint of insomnia (24-27).

The quality of the included studies varied. Collectively, the majority of studies (82%) measured the outcome variable satisfactorily with many (47%) also having measured confounding variables adequately. Unfortunately, only a few studies accounted adequately for study participation (29%) and statistical analyses (29%) with none of the included studies describing or accounting well for attrition.

Insomnia and mortality risk

Unadjusted analysis

The weighted rate of mortality among those suffering from insomnia was 1.8% relative to 3.5% for those without insomnia. The unadjusted analysis was conducted using OR

and associated 95% confidence intervals calculated for each study from extracted death and survival data. There was no difference in the odds of mortality for those individuals with symptoms of insomnia when compared to those without symptoms (OR= 1.06, 95%CI=0.61-1.84). Heterogeneity between the studies was high and significant (Q=2680.91, I^2=99.52, p<.001). The results of the meta-analysis are further summarised in Table 2 below.

It is possible the former odds of mortality is merely a reproduction of the results of one individual study (43), which accounts for 96% of the total sample size of the analysis. Therefore the analysis has been replicated with the exclusion of this study. As a result, the odds of mortality for those individuals with symptoms of insomnia increased marginally relative to those without symptoms (OR= 1.16, 95%CI=0.81-1.67). The heterogeneity between studies remained high and significant (Q=439.65, I^2=97.27, p<.001).

<Insert Table 2 about here>

Adjusted analysis

This analysis was conducted using the HR reported in the individual studies for the multivariate models with the most complete adjustment for potential confounders. These results are consistent with the unadjusted analysis, revealing the rate of mortality was comparable for those with symptoms insomnia when compared to those without symptoms (HR= 1.07, 95%CI=.96-.1.19). Heterogeneity between the studies was high and significant (Q=156.31, I^2=88.48, p<.001), with I^2 suggesting at least 88% of the variance is generated from real differences between studies at the study level. The results of the meta-analysis are further summarised in Table 3 below. Given the heterogeneity observed additional analyses were conducted to explore potential differences between studies and moderating factors which may explain this heterogeneity.

<Insert Table 3 about here>

Additional moderator and subgroup analyses

Additional analyses were conducted to investigate potential differences between studies by grouping studies according to shared characteristics including composition of the sample (i.e. age, sex, country of cohort [European, non-European], cohort type [community-based, patient sample]), and methodological considerations (i.e. sample size, length of follow up, presence of daytime impairments included in the definition of insomnia, account for confounding variables including at least one lifestyle factor [e.g. excessive alcohol consumption, smoking, obesity] and use of hypnotic medications). The fixed effects analyses reveal those studies with female, community-based samples show a tendency to report a reduced rate of mortality when compared to studies with male, patient-based samples (Table 4). Studies with a shorter duration of follow up, and somewhat larger sample size also tended to report a decreased rate of mortality. The reported rate of mortality is lower in those studies that did not include the presence of daytime impairments in their definition of insomnia and focused solely on nocturnal symptoms. Studies that statistically accounted for a minimum of at least one lifestyle factor and those that controlled for the use of hypnotic medications reported a consistent and reduced rate of mortality.

<Insert Table 4 about here>

Publication bias

Funnel plots of the effect size and standard error were performed for both the unadjusted and adjusted analyses to investigate possible publication bias. The funnel plot for the unadjusted analyses appeared symmetrical upon visual inspection indicating the absence of publication bias. However, the funnel plot of the adjusted analyses tended to show a higher concentration of studies on the right side of the mean. This indicates that smaller studies (which appear towards the bottom) with larger than average effects are more likely to be published. Therefore, there is concern that studies that fall to the left side of the mean may exist but are missing from the analysis. The Duval and Tweedie's (53) 'Trim and Fill' method allows the determination of where the missing studies are likely to fall within the plot

and the re-computation of the combined effect after adding them to the analysis. The 'Trim and Fill' method initially locates the unbiased effect through the iterative trimming of the asymmetric studies from the right-hand side of the funnel plot. The method then fills the plot by re-inserting the trimmed studies on the right-hand side as well as the imputed studies on the left-side of the mean. Using this method 5 studies have been deemed as missing and have therefore been imputed into the plot shown in Figure 2. Under the random effect model the observed HR was 1.07 (.96-1.19). Using the 'Trim and Fill" method the adjusted HR is decreased to 0.98 (.88-1.09).

<Insert Figure 2 about here>

Discussion

The present study is the first to use a meta-analytic strategy to summarise data from published studies investigating the relationship between mortality and frequent (≥3 nights/week), ongoing (≥1 month) insomnia and in doing so evaluate the strength of evidence for an association between the two. These results provide support for the lack of an association between increased risk of mortality and insomnia. The meta-analysis of 17 studies, including a total of 36,938,981 individuals followed up for a mean of 11.6 years, revealed the risk of mortality did not differ significantly for those with symptoms of insomnia when compared to those without symptoms. This finding was echoed in the assessment of the rate of mortality in those with and without symptoms of insomnia using the outcomes of multivariate models, with the most complete adjustment for potential confounders, as reported by the individual studies included in this meta-analysis.

The current meta-analytic findings authenticate the outcomes of recent large-scale longitudinal research, which report no association between mortality and insomnia (26, 27, 46). However, these findings are contrary to some of the literature reviews on this topic. This discrepancy is unsurprising given the majority of studies included in many literature reviews

assess the relationship between mortality and sleep duration, not insomnia (27). Although objective short sleep duration is associated with a host of adverse health outcomes and an increased risk of mortality (29), short sleep is not equivalent to insomnia (25, 30). Objectively short sleep duration is typically not observed among those suffering the more prevalent types of insomnia, which are characterised by the misperception of sleep duration and quality. Furthermore, short sleep duration can be self-imposed and be present in individuals without symptoms of sleep disturbance (54, 55). Therefore it is inappropriate to extend the association of increased mortality observed in those with objective short sleep duration to insomnia. It is recommended future work report objective sleep duration to facilitate an understanding of the role sleep duration plays in the association between insomnia and mortality.

Additional analyses were conducted to examine whether mortality risk differed according to characteristics of the study population and design, and confounding factors including excessive alcohol consumption, smoking, obesity, and hypnotic use. These analyses suggest a tendency for a reduced rate of mortality among community-dwelling females when compared to male patients. Studies with a shorter duration to follow-up and larger sample sizes, reported a diminished rate of mortality among those reporting symptoms of insomnia relative to those who did not.

Of particular interest are the implications for the association between mortality and insomnia when considering the criteria used to define insomnia and the influence of hypnotic use. The studies that included the presence of daytime impairments in their definition of insomnia reported a 56% chance of those with insomnia dying before those without, where a 50% chance would indicate that there is no difference in the rate of death between those with and without insomnia. In contrast, those studies that focused their definition of insomnia on nocturnal symptoms alone reported a 49% probability, or very little difference, of those with insomnia dying before those without symptoms. Although it was not statistically significant,

it is plausible an increased mortality when daytime symptoms are present may be attributed to the relationships between daytime symptoms of depressed mood, anxiety, fatigue and ill health, and quality of life with mortality risk. It may also be that daytime symptoms index a more severe or vulnerable type of insomnia which may confer greater health risk. To the authors' knowledge, this assessment is unique to the present study and needs to be replicated.

Hypnotic use also influences the rate of mortality between those with symptoms of insomnia and those without. The chance of those with symptoms of insomnia dying before those without was 49% among the studies that controlled for the use of hypnotic preparations. This chance was increased by 6% among studies that failed to account for hypnotic use. The increased rate of mortality associated with hypnotic use has also been reported by others. Kripke and colleagues (27) reported prescription sleeping pill use was significantly associated with mortality after control for insomnia in their large sample of over 1.1 million adults. Likewise Chen and colleagues (56) found consistent, increased mortality risk among those who use hypnotics frequently, even after controlling for insomnia. Therefore, when hypnotic medications are not controlled is it likely that the insomnia group have a much higher usage rate of these medications and it is the medications which are associated with increasing mortality risk not insomnia. Unfortunately the interpretation for the implications of potential risk of increased mortality risk associated with acute versus chronic hypnotic use is limited due to the considerable variability in the duration of hypnotic use among the studies included in this meta-analysis.

The current findings have significant implications for the treatment of insomnia. At present, the evidences does not support an increased risk of mortality from insomnia symptoms, even among those suffering from daytime impairments. This reinforces the strength of cognitive therapy for reassuring patients of no impact on their longevity as a consequence of their insomnia and altering the commonly held underlying belief that

insomnia is detrimental to their health, a core cognitive feature of insomnia (34). As previously mentioned the extent to which this belief extends to increased risk of mortality remains to be empirically tested, but anecdotal evidence of many clinicians supports the expression of this sentiment by many patients. This knowledge and reassurance may help reduce their anxiety related to this matter and in doing so break the cycle of insomnia. The focus should therefore be on improvement of sleep efficiency, daytime symptoms and overall quality of life as addressed by CBTi.

Limitations and directions for future research

These analyses should be interpreted with some degree of caution given several limitations. The current review identified only 17 studies that examined the relationship between mortality and frequent, ongoing insomnia. These studies typically had short follow up durations (mean=11.6yrs, *SD*=2.3, range=2.2-28yrs) and few deaths. Firm conclusions about the relationship between mortality and insomnia cannot be established until more research with longer follow up periods are conducted and published. Many of the studies included in this review differed with respect to their definition of insomnia. Although most assessed the presence of insomnia as self-reported according to the diagnostic criteria (DSM-IV or ICSD-IV), several studies were very broad in their definition with less than half acknowledging and including the presence of daytime impairments in addition to nocturnal symptoms. Ideally insomnia should be assessed in accordance with diagnostic criteria rather than merely as the presence of a complaint of 'insomnia' or difficulties initiating or maintaining sleep. Furthermore, several studies assessed self-reported sleep quality using a single survey item which requires the individual to provide a retrospective recall of their sleep. It is recommended that prospective self-reported sleep be assessed using sleep diaries which provide more accurate information regarding sleep quality than a single survey item that requires a retrospective recall of sleep (57). Sleep diaries provide the gold-standard

assessment of subjective sleep and should be implemented in the context of large prospective cohort studies to collect better quality data relating to subjective sleep (57). It is also noteworthy that studies which assessed insomnia symptoms based on self-report did not assess the cognitive status of the participants. Cognitive status may impact self-reported insomnia symptoms and constitutes a medical morbidity. All of the included studies controlled for the influence of comorbid physical conditions, however a number of potentially confounding variables, such as use of hypnotic preparations (58), severity of insomnia, presence of comorbid psychiatric disorders (e.g. depression, anxiety), and lifestyle factors (e.g. excessive alcohol consumption, smoking) known to increase the risk of mortality were either not measured or statistically controlled in some of the studies included in this review. It is recommended that future research evaluate the risk of mortality and insomnia independently from other related variables.

Conclusions

The association between mortality and frequent, ongoing insomnia was not supported in the current quantitative summary of the literature. This meta-analysis revealed the risk of mortality did not differ significant for those with symptoms of insomnia when compared to those without symptoms. The lack of an association between mortality and insomnia was also observed when using the most complete adjustment for potential confounders, as reported by the individuals studies included in this meta-analysis. The current evidence reinforces the use of cognitive therapy, within a CBTi framework, as a frontline non-pharmacological treatment for insomnia to reassure patients their longevity will not be impacted as a consequence of suffering from insomnia. It is recommended treatment should focus on improvement of sleep efficiency, daytime symptoms and overall quality of life as addressed by CBTi.

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Practice points

1) There is insufficient evidence to support an association between mortality and frequent (≥3 nights/week), ongoing (≥1 month) insomnia.
2) The current findings emphasise the use of cognitive therapy, within a CBTi framework, as a frontline non-pharmacological treatment for insomnia to reassure patients their longevity will not be impacted as a consequence of suffering from insomnia. Treatment should focus on improvement of sleep efficiency, daytime symptoms and overall quality of life as addressed by CBTi.

Research agenda

1) More studies investigating the relationship between mortality and frequent (≥3 nights/week), ongoing (≥1 month) insomnia, with long follow up periods, are required.
2) Ideally, future research should evaluate the risk of mortality and insomnia independently from other related variables, such as use of hypnotic preparations and presence of comorbid psychiatric disorders (e.g. depression, anxiety), and lifestyle factors (e.g. excessive alcohol consumption, smoking).

3) Sleep diaries provide the gold-standard assessment of subjective sleep and should be implemented in the context of large prospective cohort studies to collect better quality data relating to subjective sleep.

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Table 1 Characteristics of the included studies

Study	Population description	Cohort size (%male)	Mean (*SD*) age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[x]
					Insomnia	Mortality				
Bertisch, Pollock (49)	Multicentre, community dwelling in the U.S.C	4994 (46.5)	M=64.0 (11.1)	Median=11.6 (IQ=10.2-12.4)	Self-reported – At least one of the following on 16-30 nights per month "Have trouble falling asleep", "wake up during the night and have difficulty getting back to sleep", "wake up too early in the morning and unable to get back to sleep" or "take sleeping pills or other medication to help you sleep"	Deaths were identified through review of medical records	1163	Age, sex, ethnicity, smoking status, AHI, antidepressant use, BMI, hypertension, total cholesterol and HDL, blood pressure, diabetes	All cause and deaths related to cardiovascular disease.	Participation + Attrition - Outcome measure + Confounders + Statistical analysis ±
Chen, Su (56)[#]	Community dwelling in Shih-Pai area of Taipei, Taiwan.	4064 (55.8)	M=73.8 (5.7)	M=7.0 (2.1)	Self-reported-Pittsburgh Sleep Quality Index responses used to diagnose insomnia as per DSM-VI criteria	National death registry of the Department of Health, Taiwan	1004	Age, sex, education, living and marital status, BMI, smoking status, alcohol consumption, pain snoring, depression, excessive sleepiness, poor sleep, acute and chronic insomnia, hypnotic use, total sleep time, presence of major systemic illness	All cause and deaths related to neoplasm, cardiovascular and pulmonary disease	Participation ± Attrition ± Outcome measure + Confounders + Statistical analysis ±
Chien, Chen (24)	Community dwelling in Chin-Shan township Taipei, Taiwan.	3430 (49.7)	≥35	Median=15.9 (IQ= 13.1- 16.9)	Self-reported – "How frequent is your insomnia?" with 4 response alternatives including no insomnia, occasional insomnia (2-3 times/month), frequent insomnia (2-3	Deaths were identified from official death certificates and further verified by house-to-house visits	901	Age, sex, BMI, smoking status, alcohol consumption, marital status, education level, regular exercise, family history of coronary heart disease, baseline hypertension, diabetes	All cause and cardiovascular mortality.	Participation ± Attrition ± Outcome measure + Confounders

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Study	Population description	Cohort size (%male)	Mean (*SD*) age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[X]
					Insomnia	Mortality				
					times/week), nearly every day, referring to the past one year.			cholesterol, HDL, triglyceride, glucose, and uric acid level.		+ Statistical analysis ±
Choi, Song (45)[#]	Patients at Center for Sleep and Chronobiology at Seoul National University Hospital.	1344 (51.5)	47.0 (14.4	M=11.8 (SD not reported)	Difficulty initiating or maintaining sleep for ≥ 3 months; certified psychiatrists' confirmation of insomnia symptoms based on the DSM-IV criteria; maintenance of an AHI < 5 and PLM< 15; and no sign of any other sleep disorder, such as narcolepsy or RBD, based on PSG.	Death records from Statistics of Korea, the national bureau of statistics.	110	Age, sex, sleep efficiency	All cause	Participation + Attrition - Outcome measure + Confounders ± Statistical analysis +
Choi, Song (42)[#]	Patients at Center for Sleep and Chronobiology at Seoul National University Hospital.	4225 (70.8)	48.6 (14.1	M=10.5 (4.1)	Difficulty initiating or maintaining sleep for ≥ 3 months; certified psychiatrists' confirmation of insomnia symptoms based on the DSM-IV criteria; maintenance of an AHI < 5 and PLMI < 15; and no sign of any other sleep disorder, such as narcolepsy or RBD, based on PSG.	Death records from Statistics of Korea, the national bureau of statistics.	354	Age, sex, BMI, hypertension, diabetes.	All cause and cardiovascular mortality.	Participation + Attrition - Outcome measure + Confounders ± Statistical analysis ±
Gamaldo, Beydoun (43)[#]	Patients >60yrs selected from U.S. Nation-wide Inpatient	35, 258, 031 (44)	47.9 (0.02)[^]	10	Defined by clinical sleep specialist documented using International	As documented in patient file	Not reported	Age, sex, race, median household income, insurance status, admission day	All cause	Participation ± Attrition -

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Study	Population description	Cohort size (%male)	Mean (*SD*) age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[x]
					Insomnia	Mortality				
	database (2002-2012)				Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes			(weekend/weekday, bed size, ownership of hospital, location/teaching status and region of hospital		Outcome measure **±** Confounders **-** Statistical analysis **±**
Gapstur, Diver (26)	Large prospective cohort study of U.S. adults recruited for The Cancer Prevention Study - II	305,057 (100)	53.3 (7.9)	28	Self-reported - "On the average, how many times per month do you have insomnia?" Frequency of insomnia was classified as never; infrequent or 1, 2, 3–9, and ≥10 nights/month; or missing if left blank	Deaths were identified and verified by 1) obtaining death certificates and 2) linkage to the National Death Index	4974	Age, race, education, BMI, smoking status, history of prostate cancer, painful/frequent urination	Prostate cancer	Participation **+** Attrition **-** Outcome measure **+** Confounders **±** Statistical analysis **±**
Kabat, Xue (50)	General population recruited via 40 clinical centres throught he US.	158,203 (0.0)	63.3 (7.2)	Median=17.8	Self-reported – Women's Health Initiative Insomnia Rating Score. Individuals are asked to indicate how many times per week they have had trouble falling asleep, waking up during the night, waking earlier than planned, trouble getting back to sleep, and rate the overall restfulness of sleep over a 4 week period.	Death certificates, medical records, autopsy reports, and via the National Death Index	30,400	Age, smoking status, pack-years of smoking, alcohol intake, hormone therapy, BMI, red meat intake, physical activity, marital status, depression, history of diabetes, cancer, and cardiovascular disease, systolic blood pressure, health status, education level, ethnicity, study participation, sleep duration (hrs) and insomnia adjusted for use of sleep aids.	All cause mortality, and deaths related to cardiovascular disease, cancer and other causes.	Participation **±** Attrition **-** Outcome measure **+** Confounders **+** Statistical analysis **+**

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Study	Population description	Cohort size (%male)	Mean (*SD*) age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[X]
					Insomnia	Mortality				
Kanno, Yoshihisa (44)[#]	Patients admitted for heart failure, Fukushima Medical University, Japan.	1011 (60.4)	67.4 (14.7	M=2.19 (SD not reported)	Insomnia was defined by several physicians as (1) usual use of hypnotics ("Do you take hypnotics more than 3 times per week") or (2) presence of insomnia in addition to impairment of daytime function, based on ICSD-II criteria.	Dates of all deaths were obtained from the medical records or the cardiologists at the patients' referring hospital.	151	Age, sex, New York Heart Association functional class III or IV, BMI, systolic blood pressure, heart rate, preserved LVEF, B-type natriuretic peptide, sodium, albumin, presence of hypertension, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease, anemia, RAAS inhibitors, β-blockers, diuretics, inotropics and device therapy.	Cardiac deaths	Participation ± Attrition - Outcome measure + Confounders - Statistical analysis ±
Kripke, Garfinke (27)	Diverse selection of American adults	1116936 (480841)	57.4 (10.(	6	Self-report – "On the average, how many times per month do you have insomnia?"	Death certificates	77, 639	Sleep duration, demographic risk factors, habits, health, medication use for sleep	All cause and heart disease, cerebrovascular accidents, breast cancer, colon cancer, other cancers, accidents, suicide, homicide.	Participation ± Attrition - Outcome measure + Confounders + Statistical analysis +
Lallukka, Podlipskyte (46)	Finnish, Norwegian and Lithuanian men and women	Finnish cohort=6605 (1347) Norwegian cohort=6236 (2387)	Finnish cohort=4(60 Norwegia cohort=4(45	Finnish cohort=12.7 (1.3) Norwegian cohort=14.1 (1.2)	Self-report - (i) difficulties initiating sleep; (ii) nocturnal awakenings (sleep maintenance problems); and (iii) waking up too early. The reference time was the previous 4	Statistics Finland and Norwegian Cause of Death Registry and from the Lithuanian Regional Mortality	Finnish cohort=213 Norwegian cohort=160 Lithuanian cohort=158	Age, martial status, education, smoking, alcohol, physical inactivity, obesity, diabetes, cardiovascular diseases, depression, shift work, sleep	All cause	Participation ± Attrition - Outcome measure + Confounders

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Study	Population description	Cohort size (%male)	Mean (*SD*) age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[x]
					Insomnia	Mortality				
		Lithuanian cohort=1602 (600)	Lithuania cohort=3 74	Lithuanian cohort=6.0 (2.7)	weeks. Suffering from insomnia symptoms 15 nights or more often during the previous 4 weeks was classified as having frequent insomnia. Others were classified as having occasional insomnia.	Register		duration, and self-rated health		± Statistical analysis ±
Laugsand, Strand (47)	Population based health survey, Norway.	54279 (45.9)	44.6 (13.2	11.3 (2.9)	Self-report – difficulty initiating sleep ("Have you had difficulties falling asleep in the last month?"), difficulty maintaining sleep ("During the last month, have you woken up too early and not been able to get back to sleep") or non-restorative sleep ("How often do you suffer from poor sleep?").	National cause of death registry.	408	Age, sex, marital status, education, shift work, systolic blood pressure, total cholesterol, diabetes mellitus, BMI, physical activity, smoking, alcohol, previous acute myocardial infarction, depression, anxiety.	Heart failure	Participation + Attrition - Outcome measure ± Confounders ± Statistical analysis ±
Lee, Auyeung (48)	Older community dwelling adults living in Hong Kong.	3427 (50.9)	74.0 (4.7)	5.14 (0.2)	Self-report – Difficulty falling sleep, difficulty getting back to sleep after waking up at night, waking up too early or having trouble staying sleep, and non-restorative sleep. Insomnia defined as answering "16 to 30 nights per month" to any of these questions.	Death registry kept by the Department of Health under the Hong Kong Specialist Administration Region government.	297	Age, medical conditions, smoking, use of sleep medications, insomnia, self-reported sleep apnea, daily napping, overweight, and frailty status	All cause	Participation ± Attrition - Outcome measure + Confounders + Statistical analysis ±

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Study	Population description	Cohort size (%male)	Mean (*SI* age in years*	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[x]
					Insomnia	Mortality				
Parthasarathy, Vasquez (51)[#]	Community-based living in Tuscon, Arizona.	1409 (45.1)	47.0 (14.(	20	Insomnia defined according to ISCD criteria including persistent symptoms of trouble falling asleep, staying asleep, or waking up too early in the morning – accompanied by at least one symptom of impaired daytime functioning.	Death certificates from the National Death Index.	318	Age, sex, BMI, smoking, pack-years of smoking, regular physical exercise and hypnotic use.	All cause, heart disease, cancer, and chronic obstructive pulmonary disease	Participation **±** Attrition **-** Outcome measure **+** Confounders **+** Statistical analysis **+**
Sivertsen, Pallesen (59)[#]	Adults living in the Hordaland Country, Western Norway aged 40-45 yrs	6236 (38.1)	42.6 (1.5)	13-15	Self-reported – Karolinska Sleep Questionnaire. Insomnia defined as meeting the DSM-IV criteria. Subjects were categorized as having insomnia if they reported problems with sleep onset, sleep maintenance, or early morning awakening (or a combination) "several times a week" or " always" over the past three months, in addition to reporting daytime tiredness/sleepiness mostly/several days per week.	Norwegian Cause of Death Registry	160	Age, sex, education, health behaviours, body mass index, somatic diagnoses, somatic symptoms, musculoskeletal pain, mental disorders, obstructive sleep apnea, sleep medication use, and sleep duration.	All cause	Participation **±** Attrition **-** Outcome measure **+** Confounders **+** Statistical analysis **+**
Vgontzas, Liao (25)	Adults residing in two counties of Central	1741 (42.6)	48.6 (13.4	Male= 13.9 (3.5)	Self-reported - The presence of "insomnia" was defined by a com-	Deaths were identified by matching social	248	Age, race, education, BMI, smoking status, alcohol use,	All cause	Participation **±** Attrition

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Study	Population description	Cohort size (%male)	Mean (*SD* age in years[*]	Years of follow up	Measurements		Number of deaths	Comorbidities and confounders considered	Types of mortality examined	Study quality ratings[x]
					Insomnia	Mortality				
	Pennsylvania (Dauphin and Lebanon)			Female=10.3 (1.2)	plaint of insomnia with a duration of at least 1 year	security numbers with 2 death record services: the U.S. Social Security Death Index and the Pennsylvania State Bureau of Healthy Information and Policy Vital Records Section		depression, sleep disordered breathing, hypertension, diabetes.		- Outcome measure + Confounders ± Statistical analysis ±
Wang, Ho (52)[#]	Hemodialysis patients, National Taiwan University Hospital	151 (49.0)	64.6 (13.9	>3 (mean not reported)	Self-reported – Athens Insomnia Scale based on ICD-10 criteria for insomnia.	Not reported	46	Age, sex, education, albumin, alkaline phosphatase and glucose.	All cause	Participation ± Attrition - Outcome measure - Confounders ± Statistical analysis ±

AHI=Apnea Hyponea Index; BMI=Body Mass Index; DSM-VI=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HDL=High-Density Lipoprotein; ICD=International Classification of Diseases; ICSD=International Classification of Sleep Disorders; IQ=Interquartile Range; LVEF=Left Ventricular Ejection Function; RAAS=Reserved Angiotensin Aldosterone System

[#] Studies that included the presence of daytime impairments in their definition of insomnia.

[*] For instances where the authors have not provided mean age, age range is stated.

[^] Weighted mean age +/- standard error

[x] Quality ratings are based on the scale developed by Hayden et al. (2006) and scored across the following domains study participation, study attrition; outcome measurement, confounding measurement, and analysis.. + indicates good quality, ± indicates neutral quality, and – indicates poor quality

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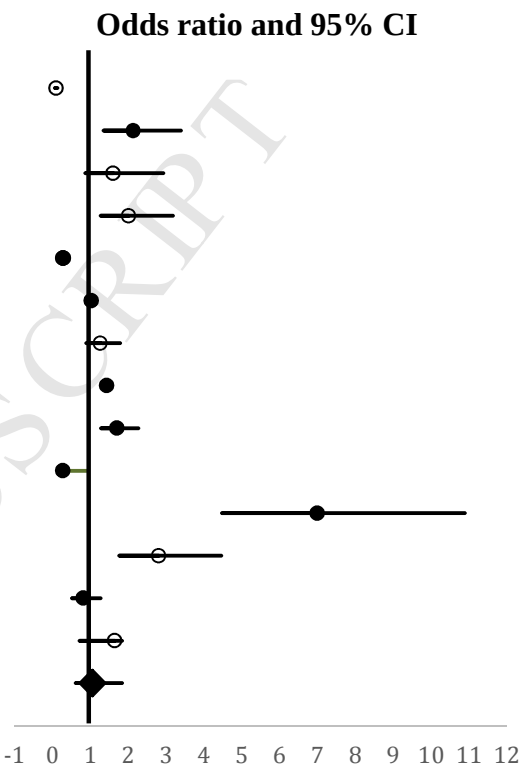
Table 2
Forest plot for mortality risk in insomnia using outcomes calculated from extracted death and survival data

Study	Odds Ratio (95% CI)	Weight, %
Chen et al. 2013(56)	.09 (.06-.13)	7.2%
Chien et al. 2010(22)	2.13 (1.35-3.39)	7.1%
Choi et al. 2017(45)	1.60 (.87-2.93)	6.8%
Choi et al. 2017(36)	2.01 (1.27-3.18)	7.1%
Gamaldo et al. 2016(43)	.28 (.27-.29)	7.5%
Gapstur et al. 2014(26)	1.02 (.94-1.12)	7.4%
Kanno et al. 2016(44)	1.26 (.89-1.79)	7.2%
Kripke et al. 2002(27)	1.43 (1.36-1.52)	7.5%
Lallukka et al. 2016(46)	1.70 (1.28-2.27)	7.3%
Laugsand et al. 2014(47)	.91 (.14-.27)	7.3%
Lee et al. 2014(48)	6.99 (4.48-10.89)	7.1%
Sivertsen et al. 2014(59)	2.80 (1.76-4.46)	7.1%
Vgontzas et al. 2010(25)	.81 (.52-1.27)	7.1 %
Wang et al. 2017 (52)	1.64 (.71-1.84)	6.4%
Total	**1.06 (.61-1.84)**	
Test for overall effect: Z= 0.20 (p=.84)		



Note: Open markers in forest plot denote studies that included the presence of daytime impairments in their definition of insomnia

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Table 3
Forest plot for mortality risk in insomnia using hazard ratios from multivariate models with the most complete adjustment for potential confounders

Study	Hazard Ratio (95% CI)	Weight, %
Bertisch et al 2018(49)	0.99 (.77-1.27)	8.5%
Chen et al. 2013(56)	0.64 (.43-.96)	4.9%
Choi et al. 2017(45)	.89 (.48-1.65)	2.5%
Choi et al. 2017(42)	8.11 (1.03-63.72)	0.3%
Kabat et al. 2018(50)	1.11 (1.07-1.15)	15.2%
Kanno et al. 2016 (38)	1.90 (1.33-2.71)	5.7%
Kripke et al.* 2002(27)		
- Male	.94 (.91-.97)	15.2%
- Female	.86 (83-.89)	15.2%
Lallukka et al.* 2016(46)		
- Male (Finland)	1.20 (.52-2.77)	2.1%
- Female (Finland)	.67 (.34-1.32)	2.3%
- Male (Lithuania)	1.06 (.43-2.59)	1.3%
- Female (Lithuania)	1.04 (.55-1.98)	0.9%
- Male (Norway)	1.85 (.91-3.76)	2.0%
- Female (Norway)	1.61 (.54-4.81)	1.5%
Laugsand et al. 2014(47)	1.27 (.94-1.70)	7.1%
Lee et al. 2014(48)	0.90 (.56-1.44)	3.9%
Parthasarathy et al. 2015(51)	1.18 (.91-1.54)	8.0%
Sivertsen et al. 2014(59)	3.34 (1.67-6.87)	2.1%
Wang et al. 2017(52)	1.30 (.57-2.98)	1.5%
Total	**1.07 (.96-1.19)**	
Test for overall effect: Z= 1.23 (p=.22)		

Note: Open markers in forest plot denote studies that included the presence of daytime impairments in their definition of insomnia.*– HR reported separately for men and women in these studies. Lallukka and colleagues report HR separately for men and women in their three samples of adults from Finland, Norway and Lithuania

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Table 4 – Subgroup and moderator analyses

	Effect size, *n*	HR (95% CI)	QBetween	*p*
Age			1.16	.282
- < 65	16	.97 (.95-.99)		
- ≥ 65	3	1.10 (.87-1.39)		
Sex			13.90	<.001
- Male	4	.94 (.91-.97)		
- Female	4	.86 (.83-.89)		
Country			1.58	.209
- European	13	.97 (.95-.99)		
- Non-European	6	1.11 (.90-1.37)		
Cohort type			11.32	.001
- Community	15	.97 (.95-.99)		
- Patient	4	1.59 (1.19-2.11)		
Study size			3.61	.057
- < 5,000	14	1.10 (.97-1.24)		
- ≥ 5,000	5	.97 (.95-.99)		
Length of follow up			99.81	<.001
- <10 years	8	.91 (.88-.93)		
- ≥ 10 years	11	1.11 (1.07-1.15)		
Daytime impairments			8.59	.003
- Yes	7	1.25 (1.05-1.48)		
- No	12	.97 (.95-.99)		
Lifestyle factors			9.70	.002
- Controlled	16	.97 (.95-.99)		
- Uncontrolled	3	1.54 (1.15-2.05)		
Hypnotic use			9.21	.002
- Controlled	7	.97 (.95-.99)		
- Uncontrolled	12	1.21 (1.05-1.39)		

*<.05

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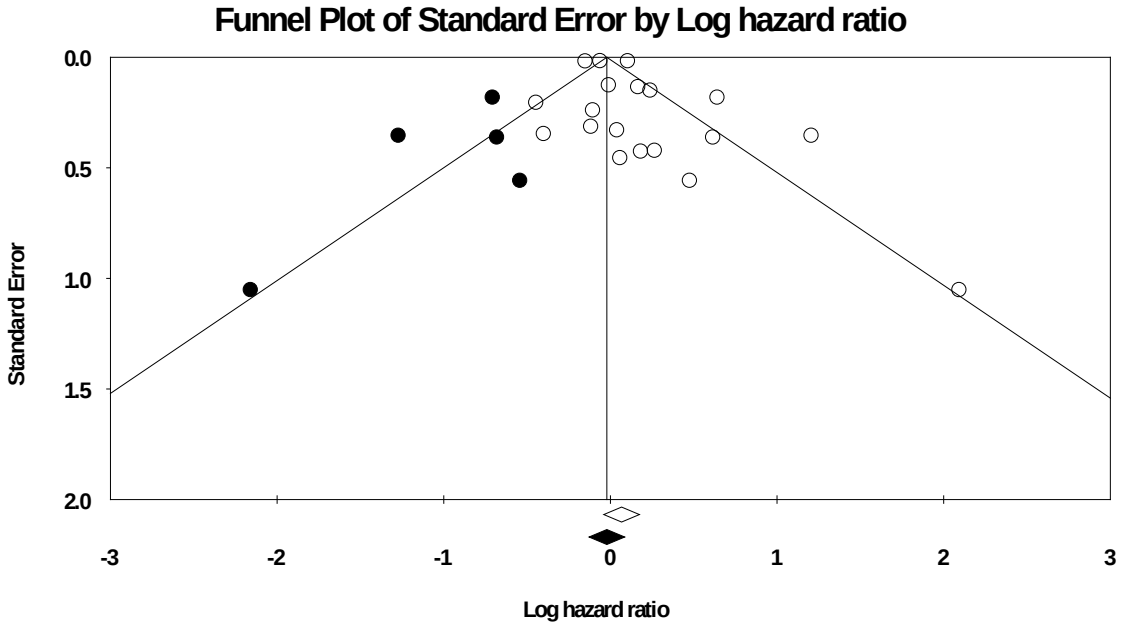

Figure 2 – Funnel plot of meta-analysis using hazard ratios from multivariate models with the most complete adjustment for potential confounders

Note the observed studies are shown by the open shapes and the studies imputed using the 'Trim and Fill' method are shown in the closed shapes

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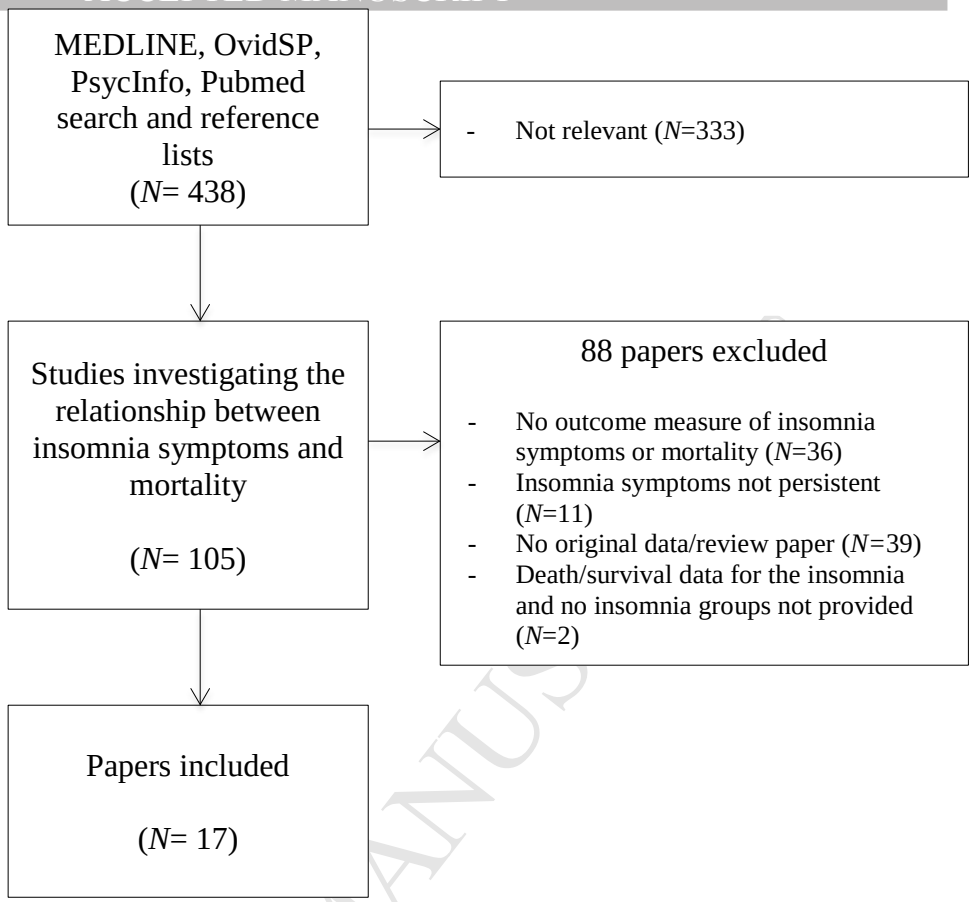

Figure 1 – Flow of literature through the search process

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