The effects of sleep duration on health: a systematic review of systematic reviews and meta-analyses

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Abstract

In health promotion and health policy, sleep is starting to appear on the agenda as an important determinant of health. However, up until now no comprehensive overview has been provided of all the important health consequences of sleep duration. The objective of this study was to clarify the effects of sleep duration on various health outcomes, and provide possible explanations of the underlying mechanisms. PubMed, Embase/Medline, Scopus and Psycinfo databases were searched for eligible publications. Studies with sleep duration as exposure and health outcomes including cancer, cardiovascular disease, mental health, and metabolic syndrome, obesity & diabetes were selected. Twenty-three publications were identified, all of which were systematic reviews, meta-analyses or a combination of both. Findings suggest that short sleep duration is strongly and consistently associated with an increased risk of cardiovascular disease, mental health disorders, obesity, metabolic syndrome and diabetes. Long sleep duration is associated with increased risk of certain types of cancer, cardiovascular disease(s), obesity, metabolic syndrome and diabetes. However, disparities in study designs and the difficulty in establishing causality preclude any definitive conclusions. Nevertheless, the results are important in guiding the assessment of current evidence and defining what research is lacking. Further research should investigate the underlying mechanisms in order to establish causality with more certainty, using prospective study designs with a large sample size.

Keywords: sleep duration, cancer, cardiovascular disease, mental health, obesity, metabolic syndrome, immunity, diabetes.

The effects of sleep on health:

A comprehensive overview of systematic reviews and meta-analyses

1. Introduction

On average, we spend a third of our lives asleep. Sleeping is a primitive behavior intrinsic to life, essential for growth and proper functioning. In our increasingly modern, fast-paced world, sleep curtailment is becoming more common due to busy lifestyles, our 24-hour society, social media use, blue light exposure, and social norms. In many industrialized societies, these factors are contributing to a trend towards fewer hours of sleep per night (Gallicchio & Kalesan, 2009). People general prefer spending more time on leisure activities and working longer hours instead of getting enough sleep. However, there is also evidence suggesting that in some countries, like Australia, Finland, Sweden, the United States and the United Kingdom, the average sleep duration is increasing (Bin, Marshall, & Glozier, 2013).

Simultaneously, the occurrence of non-communicable diseases is also on the rise, and they are now the leading cause of death worldwide, causing more deaths than all other causes combined (World Health Organization, 2014). Many epidemics like obesity, diabetes, cancer and cardiovascular disease (CVD) are becoming more prominent public health problems. Up until recently, the main determinants of health used in epidemiology of non-communicable diseases and in health policy were exercise, smoking, alcohol, diet and relaxation. Not much attention has been paid to the effects that sleep duration may have on health. However, due to increased media interest and accumulating evidence that sleep may also contribute significantly to various aspects of our health, more research is being done to elucidate the potential consequences of inadequate and excessive sleep on health.

Specifically, this accumulating evidence suggests that short sleep duration puts people at a higher risk of various negative health outcomes, like cardiovascular disease, type II diabetes, hypertension and obesity. However, many of the data is merely suggestive and causality is hard to determine. Conversely, people with longer sleep duration are also indicated to have a higher risk of similar negative health outcomes. The body of research examining these associations between short and long sleep and mortality and morbidity is still limited, and there is a general lack of knowledge about the underlying mechanisms (Cappuccio, D'Elia, Strazzullo, & Miller, 2010).

While many studies have attempted to investigate the relationships between sleep and health, no literature review could be found that provided a comprehensive overview of all the important potential effects of short and long sleep duration on health. This paper aims to systematically review and

synthesize all the available epidemiological evidence available on the association between sleep duration and health outcomes. The answer to the research question "what are the effects of sleep duration on various aspects of our health, and what are the underlying mechanisms?" will provide the means with which to answer relevant questions that are emerging in society regarding sleep. It can also be used as an input for public health policy, and to identify areas where research is lacking.

2. Methods

2.1 Search strategy and article selection

A search of the literature up to January 12th, 2017 was performed by a literature specialist and the primary author using the databases of Embase/Medline, PubMed, Psycinfo and Scopus, using the following search terms and their synonyms: "sleep duration", "sleep deprivation", "health", "mental health", 'mortality', 'morbidity', 'diseases', 'depression', 'anxiety', 'suicide', 'cognition', 'cancer', 'metabolism', 'metabolic disorder', 'diabetes', 'obesity', 'hormone regulation', 'immunity', 'cardiovascular disease', 'blood pressure'. These terms were searched for in the titles or as most important keyword. There were no language restrictions. A filter was placed to only search for systematic reviews or meta-analyses. The full electronic search for the Embase/Medline database is presented in Appendix A.

The primary author reviewed all identified studies by screening the title and abstracts, and selected studies if they met the following inclusion criteria: (1) published after 2000; (2) a systematic review and/or meta-analysis of studies; (3) adult population (18+) was examined; (4) the exposure of interest was sleep duration; (5) the outcome of interest was cardiovascular disease, cancer, mental disorders, metabolic syndrome, obesity or diabetes, as these were the most prominent in the initial literature; (6) the studies clearly identified what they considered short, long or average sleeping hours; (7) the populations studied consisted of healthy individuals with no diagnosed sleep conditions or other comorbid diseases at the time of measurement or during the follow-up period, such as a mood disorder, hypertension, or other potential risk factors for the studied health outcomes. Studies were excluded if they investigated non-human species, or the effects of total sleep deprivation, sleep apnea, insomnia or sleep-disordered breathing, and if they researched circadian disruption/misalignment or effects of napping, as the effect of these may interfere with the outcomes of interest. Additionally, if a review was already included in another high-quality systematic review or meta-analysis, it was excluded from the

current study in order to avoid using the same results or study populations twice. No gender restrictions were applied. The criteria were approved by a secondary supervisor.

2.2 Quality assessment and data extraction

The quality of the selected studies was assessed using the Quality Assessment of Systematic Reviews and Meta-Analyses checklist from the National Institutes of Health (National Institutes of Health, 2014). This is a validated checklist used to identify possible weaknesses or biases in study design or search strategy. Each item was labeled with a (+) or (-), depending on whether the study in question met the criteria or not. A cut-off score was not used, as all criteria are essential for a high-quality review. The items were as follows: (1) Is the review based on a focused question that is adequately formulated and described? (2) Were eligibility criteria for included and excluded studies predefined and specified? (3) Did the literature search strategy use a comprehensive, systematic approach? (4) Were titles, abstracts and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias? (5) Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity? (6) Were the included studies listed along with important characteristics and results of each study? (7) Was publication bias assessed? and (8) Was heterogeneity assessed (for meta-analyses only). If a study did not meet all of the checklist criteria, it was excluded from the review.

Of the selected studies, the full texts were retrieved and the data was extracted. The following data was extracted from the full-texts: (1) Author's name & year of publication; (2) study type (systematic review/meta-analysis) and study-designs of included studies; (3) number of studies included; (4) the outcome(s) analyzed; (5) findings; (6) possible biases. A summary of these data can be found in tables 1-4.

2.3 Data-analysis

The PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were adhered to for all stages of the design, analysis and reporting of this review (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009). These guidelines include a checklist with criteria for the title, abstract, introduction, methods, results, discussion and funding, to ensure internal validity of the review. The checklist can be found in appendix B. The results were categorized by outcome and each outcome was analyzed separately and in comparison to other outcomes. Possible mechanisms

underlying the associations found were explained using evidence included in the systematic review/meta-analysis and additional sources where necessary.

3. Results

3.1 Literature search

A total of 1141 studies were identified (figure 1). Of these, 961 studies were excluded because they did not have the desired exposures or outcomes of interest. A further 64 were excluded because they did not meet the quality requirements. Of the remaining 116, 70 were included in another, more recent systematic review or meta-analysis, and were therefore also excluded. Twenty-three were excluded because the study population was below 18 year of age. This left 23 eligible studies for inclusion in this systematic review. Seven of these were systematic reviews, six were meta-analyses, and ten were a combination of meta-analyses and systematic reviews.

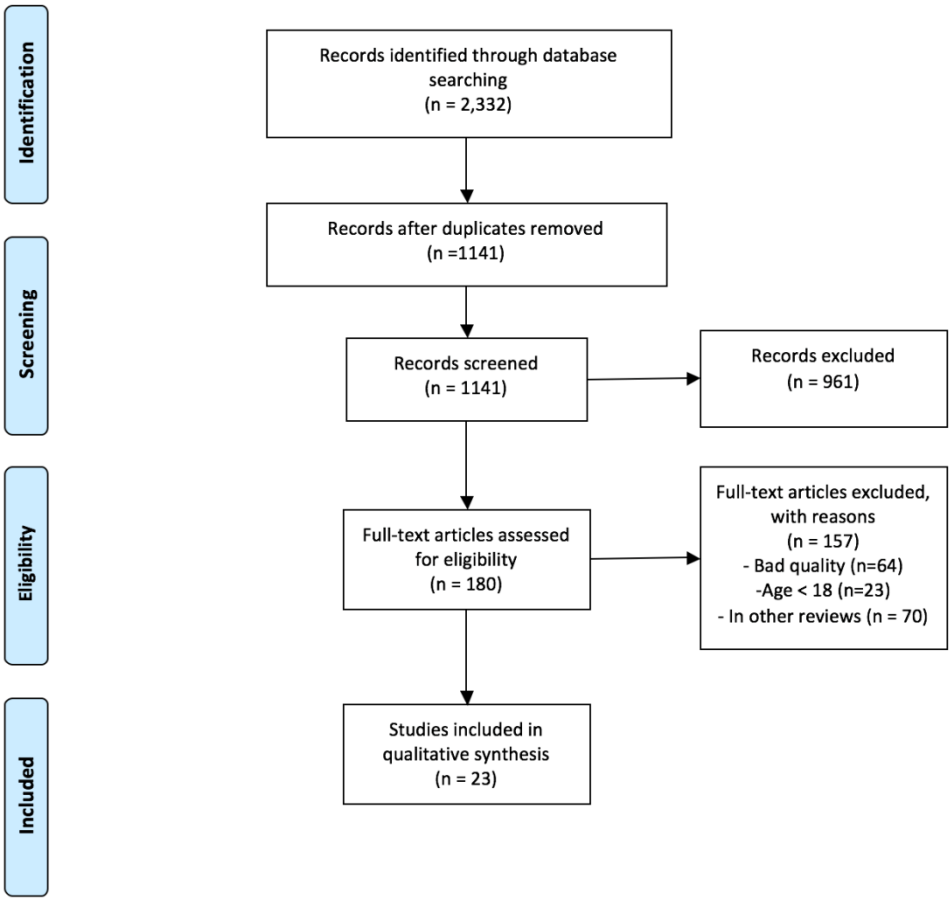

Figure 1. Literature search for systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

3.2. Sleep duration as a risk factor for cancer

Table 1 shows the results of the data extraction from the six included reviews about cancer risk. Two of these were meta-analyses, one was a systematic review and three were meta-analyses with a systematic review. All the meta-analyses used prospective study designs. Some systematic reviews also included cross-sectional designs, but the results mentioned here were primarily based on prospective studies, as cross-sectional or case-control studies limit causal inference. The study designs of each study can be found in tables 1-7.

The meta-analysis of prospective studies by Ma, Yao, Lin, Chen, and Yu (2016) defined short sleep as ≤6 or ≤5 hours per night and long sleep as ≥9 or ≥10 hours per night. Their results suggest that long sleep duration is associated with a moderately increased risk of cancer mortality (RR = 1.11), compared to the reference group who sleep 7-9 hours a night. Short sleep duration was not significantly associated with increased cancer mortality (RR=1.05). The effect of long sleep duration on cancer mortality was strongest in women, the Asian population, in studies with shorter follow-up durations, and in studies with long sleep defined as ≥10 hours per night. Another review of prospective studies showed similar results, with the effect of long sleep duration being a RR of cancer mortality of 1.21 (Gallicchio & Kalesan, 2009). The results were similar for males and females. The included studies took into account comorbidities, socio-economic status or factors, and lifestyle factors, and have shown that these factors do not explain (all of) the associations between sleep duration and mortality.

The systematic review and meta-analysis of prospective studies by Zhao et al. (2013) investigated the effects of sleep duration on the risk of developing cancer. Short sleep was defined as ≤5 or ≤6 hours per night, and long sleep as ≥9 hours. The reference group slept 7-8 hours per night. Their results suggest that neither short nor long sleep duration is significantly associated with increased cancer risk, with a hazard risk of 1.06 and 0.91, respectively. However, using subgroup analysis they found that among the Asian population, long sleep duration is significantly associated with a decrease in hormone-related cancer risk (HR = 0.71) and an increase in colorectal cancer risk (HR = 1.29)(Zhao et al., 2013).

A similar meta-analysis of prospective cohort studies which used different study populations and defined short sleep as ≤6h per night and long sleep as ≥9 hours per night, supported these results (Lu, Tian, Yin, Shi, & Huang, 2013). There was no statistically significant association between both short or long sleep and cancer risk (RR=1.05 and RR=0.92, respectively). However, subgroup analysis showed that long sleep duration is positively associated with colorectal cancer risk, and inversely associated with prostate cancer and ovarian cancer risk (RR = 1.28, RR=0.36 and RR = 0.88, respectively).

Possible mechanisms

A few key mechanisms have been proposed to explain this relationship. Melatonin may aid in the prevention of cancer by inducing apoptosis, anti-proliferation and anti-angiogenesis of tumor cells (Zhao et al., 2013). Melatonin can inhibit sex hormone levels, and high levels of sex hormones have been associated with breast, endometrial, ovary, prostate and thyroid cancers. It also has an anti-oxidative effect, protecting against damage from carcinogenic substances, by eliminating free radicals (Zhao et al., 2013). Because melatonin increases with sleep duration, longer sleepers may have higher levels of melatonin and benefit from bigger protective effects against hormone-related cancers.

Conversely, long sleep duration may lead to an unbalanced body environment and a disturbed biological rhythm. Prolonged sleep may also reflect regular insufficient sleep, which can elevate levels of inflammation (Ma et al., 2016). The positive relationship between long sleep duration and colorectal cancer is still an obscure one. It may be explained by comorbidities or confounding.

Another systematic review and meta-analysis of cohort and experimental studies by (Irwin, Olmstead, & Carroll, 2016) suggest that chronic inflammation may predispose tumor development, and that short and long sleep duration increase the levels of inflammatory markers in the body. Cellular production of IL-6 and TNF-alpha, two inflammatory markers, is partly due to activation of TLR-4 activity, and sleep deprivation increases TLR-4 stimulated production of inflammatory cytokines, and increases activation of the key transcription control pathway in the inflammatory signaling cascade. Sleep also influences the HPA axis and the sympathetic nervous system, which shift basal gene expression profile toward increased pro-inflammatory skewing (Irwin et al., 2016). Activation of the beta-adrenergic signaling induces increases in NF-xB inflammatory gene expression, production of pro-inflammatory cytokines, and markers of systemic inflammation. Normal sleep is associated with a drop in sympathetic outflow; activation of the sympathetic effector pathways is one mechanism that could explain the associations between short sleep duration and an increase in markers of inflammation. The association between long sleep and inflammation may be the result of underlying comorbidities, as no other mechanisms have been proposed. Manoharan and Jothipriya (2016) also suggest in their systematic review of cohort studies that long and short sleep duration induces chronic inflammation through the effects of sleep duration on the endocrine, immune and metabolic systems of the body. Clinical evidence supports the previously mentioned result that in subjects with sleep deprivation, the levels of inflammatory markers like CRP and IL-6 are elevated (Manoharan and Jothipriya, 2016).

Some mechanisms behind the association between long sleep and mortality have also been proposed. Theories include (1) that long sleepers experience more sleep fragmentation, which has been

shown to be associated with negative health outcomes, (2) that there are changes in cytokine levels which influence mortality risk during long sleep, and (3) that there is a lack of physiological challenge, so that long sleepers are not exposed to potentially beneficial mild stressors (Gallicchio & Kalesan, 2009). Additionally, those with longer sleep duration have a shorter photoperiod, which, among other species, has been shown to increase risk of death. In contrast to the meta-analyses, the literature review suggests that short sleep duration may lead to oxidative stress, which may be causally linked to carcinogenesis (Noguti, Andersen, Cirelli, & Ribeiro, 2013). Oxidative stress occurs when there is an overproduction of reactive oxygen species (ROS), and a deficiency in antioxidants to neutralize these. This may lead to cell damage, and can evoke intracellular events such as proliferation, gene activation, cell-cycle arrest and apoptosis. It can thereby damage cellular lipids, protein, and DNA, inhibiting their function. Damage may also include somatic mutations, resulting in cancer. ROS has been shown to interact with initiation, progression and promotion of the mutation process. In various tumors, elevated levels of oxidative DNA lesions have been recorded, although their exact role in carcinogenesis is not clear. It is hypothesized that free radicals or ROS produced during waking are removed during sleep, giving sleep an antioxidant function that helps it relieve oxidative stress and possibly prevent or reduce carcinogenesis (Noguti et al., 2013).

Table 1. Sleep duration and cancer

Author	Study type	Number of studies	Outcome	Findings	Potential bias
Ma et al. (2016)	Meta-analysis of prospective studies, follow-up duration 6-18 years.	11, total of 622,429 participants	Cancer mortality	Long and short sleep duration associated with increased cancer mortality risk.	Corrected for publication bias long sleep duration; no bias in short duration. Little heterogeneity.
Zhao et al. (2013)	Systematic Review and Meta-analysis of prospective studies, with follow up duration of 7.5 – 22 years.	12 articles, 723,337 participants	Cancer risk	Short SD not associated with overall cancer risk (HR = 1.06). Long SD not related to all cancer risk (HR = 0.91). Long SD associated with hormone-related cancer (HR = 0.71)) and colorectal cancer (HR = 1.29) risk in Asian population.	Information through self-reports. High heterogeneity, different reference categories. Subgroup analysis based on small samples. Sleep duration measured at one point in time.
Lu et al. (2013)	Meta-analysis of prospective cohort studies, with follow-up period of 6-22 years.	9 articles with 10 studies (8392 incident cases, 555678 participants)	Cancer risk (breast, colorectal, prostate, endometrial, thyroid and ovarian)	Short SD not associated with increased cancer risk (RR=1.05).Long SD not associated with increased cancer risk. (RR=0.92) Long SD associated with colorectal cancer (RR=1.29), inversely associated with prostate cancer and ovarian (RR=0.36 and 0.80, respectively)	Significant Heterogeneity, subjective questionnaires to report sleep duration, different confounding variables controlled for between studies
Gallicchio and Kalesan (2009)	Systematic review and meta-analysis of prospective studies, follow up duration of 4-25 years	23 articles	Cancer-related mortality	Cancer-related mortality risk (RR) = 1.21	Self-reports used. Studies included varied in exclusion and inclusion criteria and adjustments; confounding bias.
Irwin et al. (2016)	Systematic-review and meta-analysis of cohort studies and experimental studies	72 included	Inflammation	Association between sleep disturbance and two markers of systemic inflammation	Not all studies reported adjustments for residual confounders. Sleep duration measured at 1 point in time. Sleep questionnaires as measurement.
Manoharan and Jothipriya (2016)	Systematic review of cohort studies	23 cohort studies	Inflammation	Strong association between sleep duration and inflammation, U-shaped association.	Self-reporting as measurement. Variation in exclusion criteria of studies. Different reference values used.

3.3 Sleep duration and the risk of cardiovascular disease

Table 2 shows the results of the data extraction from the six included reviews about the risk of cardiovascular disease. Four of these were systematic reviews with meta-analysis, and two were systematic reviews. Again, the meta-analyses all used prospective study designs.

A U-shaped association was found by Wang et al. (2016) in their systematic review and meta-analyses of prospective cohort studies, in which they investigated the effect of sleep duration on coronary heart disease. The bottom of the curve represented those who slept 7-8 hours a day. Short sleep duration was significantly associated with a higher risk of CHD. For every hour by which sleep duration is reduced, the risk increases by 11%. Long sleep duration was also associated with a higher risk of CHD, with a 7% increase in risk with every additional hour of sleep.

Another meta-analysis and systematic review of prospective studies investigated the effect of sleep duration on stroke and stroke mortality (Li et al., 2016). A J-shaped association was found. The lowest risk for stroke was at sleep duration of 6-7 hours a day. For ≤5 hours of sleep, the RR was 1.26. When compared to sleeping 7 hours a day, each 1-hour reduction in sleep duration results in an increased stroke risk of 7%. The RR for stroke mortality compared to the reference category of 7-8 hours was 1.19 for sleeping less than 6 hours a day. Compared to 7hours of sleep a day, the RR for stroke mortality was 1.05 per 1h reduction of sleep duration (Li et al., 2016).

Sleep duration of 8-9hours gives a RR of stroke incidence of 1.12, and ≥9hours gives a RR of 1.53 for stroke. With every hour increase in sleep duration, the RR increases by 1.17. Stroke mortality was 1.12 for 8-9 hours, and 1.53 for more than 9 hours. With every hour increase, stroke mortality RR was 1.17. Subgroup analyses suggest that an hour decrease was associated with an 8% increase in stroke risk in men, but no increase was found in women, suggesting women are more resilient to the effects of sleep loss on mortality risk (Li et al., 2016).

Da Silva et al. (2016) also looked at risk of cardiovascular mortality, and found an RR of 1.43 for long sleep duration and cardiovascular mortality. Another study showed strikingly similar results, with an RR of 1.38 for cardiovascular-related mortality (Gallicchio & Kalesan, 2009). The results were similar for males and females.

The systematic review of both prospective and cross-sectional studies done by Miller and Cappuccio (2013) looked at the effects of quantity of sleep on cardiovascular disease. Their results

suggest that short sleep duration is associated with an increased risk of developing or dying from coronary heart disease (CHD), stroke, and total CVD. Several studies included in their review also suggest that short sleep duration may contribute to the risk of developing hypertension.

Possible Mechanisms

One proposed mechanism behind this relationship suggests that changes in appetite control, insulin resistance, glucose homeostasis, endothelial function, sympathetic nervous system activation and inflammatory and hemostatic pathways play a role (Miller & Cappuccio, 2013). Sleep deprivation is also associated with a 30% reduction in phosphorylation of Akt, which is an important part of the insulin-signaling pathway in adipocytes. This can influence metabolism, adipose tissue and cardiovascular function. The endothelium is responsible for maintaining vascular tone, and a dysfunction, which is seen as a result of sleep deprivation, is associated with an increase in CVD risk.

A similar systematic review by Pepin et al. (2014) which included studies that have longitudinal, cross-sectional and retrospective designs also investigated the effect of quantity of sleep on CVD risk, and found contrasting results. Although one included study suggested that there is no association between sleep quality or duration and the development of risk factors of CVD, like dyslipidemia, hypertension and prediabetes, another showed a U-shaped relationship between sleep duration and risk of CVD (Pepin et al., 2014). Less than 6 hours per night and more than 9 hours of sleep per night were associated with an increased cardiovascular mortality.

The underlying mechanisms explaining the relationship between short sleep duration and CVD are hypothesized to be related to hormonal changes that promote weight gain, and therefore increase the risk of CHD (Wang et al., 2016; Miller & Cappucccio, 2013). Short sleep may also increase blood glucose concentrations, blood pressure, cholesterol level, the risk of coronary artery calcifications and the risk of atherosclerosis, which are all established risk factors for CHD (Wang et al., 2016). Additionally, the activation of the sympathetic nervous system, increased cortisol secretion and altered growth hormone metabolism may also have an effect. Short sleep duration may also result in an increase in inflammatory markers, like C-reactive protein and interleukins-6 (IL-6), which play a significant role in the development of CHD (Li et al., 2016; Wang et al., 2016).

Whereas several mechanisms have been proposed for the effect of short sleep duration on CVD risk, the mechanisms underlying the association between long sleep and CVD are not very well understood (Li et al., 2016; Wang et al., 2016). It may have to do with comorbidities like low socio-economic status, depression, unemployment, or low physical activity. Another suggestion is that long

sleep may increase fibrinogen, and promote inflammation and coagulation. Long sleep may also just reflect sleep need, which in turn reflects a decreased fitness and health status (Wang et al., 2016).

Table 2. Sleep duration and cardiovascular disease

Author	Study type	Number of studies included	Outcomes	Findings	Potential bias
Wang et al. (2016)	Systematic review & Meta-analysis, prospective cohort studies between 1997 and 2015, follow up duration ranged from 5-20 years	17 articles with 22 independent reports, 516440 cases, 17841 with CHD.	Coronary heart disease	U-shaped association, with the lowest risk at 7-8hours a day. Short SD: shortest and second shortest were significantly associated with risk of CHD. Combined RR of CHD was 1.11 for 1hr reduction, compared with 7h. Long sleep duration: pooled RR was 1.25 and 1.02 for longest and second longest. Combined RR of CHD 1.07 for increment of 1h a day compared to 7h.	Self reported sleep duration. Some heterogeneity. Most studies measured sleep duration at 1 point in time.
Li et al. (2016)	Systematic review and meta-analysis, prospective study designs with follow up duration ranged from 3-18 years	11 articles with 16 independent reports included	Stroke or stroke mortality	J-shaped association shown between SD and risk of stroke and stroke mortality; lowest risk at SD of 6-7h	Sleep duration self-reported. Sleep duration only measured at 1 point in time.
Miller and Cappuccio (2013)	Systematic Review of prospective and cross-sectional studies	10 studies,	CVD, stroke, coronary heart disease, hypertension	In prospective studies, short SD is associated with increased risk of developing or dying from CHD, stroke and total CVD. Also increased risk of developing diabetes II and obesity Risk of developing hypertension in short sleepers	Largely based on observation. No mention of length of follow-up duration of the prospective studies.
Pepin et al. (2014)	Systematic Review of longitudinal, cross-sectional and retrospective studies. Duration of follow up of prospective studies ranged from 6-16 years.	17 studies	Cardiovascular risk	No association between sleep quality or duration and CVD risk factors in women of same PA level. Cardiovascular mortality higher among individuals with sleep durations of less than 6h or more than 9h per night. Collectively: sufficient sleep makes unique contribution to reduction in CVD risk.	Mostly cross-sectional and observational, grouping values different per study, subjective sleep durations.

Da Silva et al. (2016)	Systematic review and meta-analysis of population based cohort studies, follow up duration of 3.4-35 years	27 cohort studies, over 77,000 individuals,	Mortality in the elderly	Long sleep duration associated with greater risk of death (RR= 1.33). Long sleep duration and cardiovascular mortality: RR = 1.43. Short sleep also significantly associated with risk of death (RR=1.07	Some heterogeneity for long sleep duration studies. Possible confounding bias. Population bias. Different reference categories among studies.
Gallicchio and Kalesan (2009)	Systematic review and meta-analysis of prospective studies, follow up duration of 4-25 years	23 articles		Pooled all-cause mortality for short sleep to reference category was 1.10. Similar for males (RR=1.13 and females, RR=1.10). Pooled RR for cardiovascular-related mortality = 1.06 and 0.99 for cancer-related mortality. Pooled all-cause mortality RR comparing long sleep duration with reference was 1.23. Similar for males (1.23 and females 1.27). Cardiovascular-related = 1.38 and cancer-related = 1.21.	Little heterogeneity. Self-reports used. Studies included varied in exclusion and inclusion criteria and adjustments; confounding bias.

3.4. Sleep duration and mental health

Table 3 shows the results of the data extraction from the three included articles about the risk of mental health issues. Two were systematic reviews, and one was a meta-analysis.

Zhai, Zhang, and Zhang (2015) concluded from their meta-analysis of prospective studies that shorter sleep duration was associated with an increased risk of depression, with a risk ratio of 1.31. A long sleep duration showed an even bigger risk ratio, of 1.42 (Zhai et al., 2015). In the short term, however, an opposite effect is seen, as sleep deprivation is still the only intervention in depression that shows antidepressant effects within 24 hours (Tsuno, Besset, & Ritchie, 2005).

Sleep has also been associated with schizophrenia (Lunsford-Avery & A. Mittal, 2013). Particularly, sleep problems in early childhood may predispose individuals to developing schizophrenia. However, as sleep loss is also considered an intrinsic feature of the disorder, regardless of medication status or illness phase, it is difficult to state with certainty that sleep loss is an antecedent of psychosis development.

In addition to schizophrenia and depression, studies have shown that sleep loss may also increase the risk of suicidal behavior. In studies controlling for psychopathology, sleep duration was associated with suicidal ideation in about ¾ of the studies (Pigeon, Bishop, & Titus, 2016). In studies in which adjustment for psychopathology was included, about ¼ studies found an association between suicidal ideation and sleep duration. When looking at actual suicides, there are positive associations among sleep disturbances in some form and increased risk of suicide, when adjusting for co-occurring psychopathology (Pigeon et al., 2016).

Possible Mechanisms

Short sleep duration may increase tiredness throughout the day, which has been shown to be predictive of depression. Increased negative emotions and events caused by tiredness could predispose depression, which is one of the mechanisms which may explain the relationship between short sleep duration and depression, and possibly suicide risk (Zhai et al., 2015). Long sleep duration has been correlated to low physical activity levels, and physical activity increases levels of neurotransmitters like dopamine and serotonin that stimulate the excretion of endorphins, which improves self-efficacy and self-esteem and thereby reduces depression. However, these are mostly hypothesis, as sleep factors may predispose, precipitate, or perpetuate depression, and it is hard to determine the direction of causality (Zhai et al., 2015).

The relationship between sleep duration and schizophrenia may be explained by evidence which suggests that many structures and pathways involved in sleep are compromised in individuals with

schizophrenia, and that these abnormalities may have been present before the onset of the disorder, suggesting they may play a role in the pathophysiology of schizophrenia.

Table 3. Sleep duration and mental health

Author	Publication Type	Number of studies	Outcomes	Findings	Potential bias
Zhai et al. (2015)	Meta-analysis of prospective studies follow-up duration 3.4-34 years	6 articles with 7 studies included	Depression risk	Short sleep duration significantly associated with risk of depression (RR=1.31) Pooled RR of overall data for long sleep duration was 1.42. Sleep factors could predispose, precipitate, and perpetuate depression. Any distinction is difficult and arbitrary.	Differing methods to assess SD, possible confounders, different criteria used for short and long sleep duration.
Lunsford-Avery and A. Mittal (2013)	Systematic review, mostly retrospective studies	26 articles	Schizophrenia	Sleep problems in early childhood may differentiate individuals who others. Sleep duration abnormalities may represent and intrinsic feature of the disorder.	No mention of follow-up/retrospective analysis duration
Pigeon et al. (2016)	Systematic review, mostly cross-sectional, some longitudinal studies	36 articles	Suicidal ideation and attempts	Significant association between a sleep measure and suicidal ideation in 77% of unadjusted comparisons and in 74% of comparisons in which some adjustment for psychopathology was included. In studies controlling for psychopathology, SD was associated with SI in only 1 of 4 studies. Suicide attempts: inconclusive, prospective research using validated measures needed Suicide: positive associations among sleep disturbances and increased risk of suicide. All controlled for co-occurring psychopathology.	No mention of follow up duration

3.5. Sleep duration and obesity, diabetes and metabolic syndrome

Table 4 shows the results of the data extraction from the eight included articles about the risk of metabolic syndrome, diabetes and obesity. Three were meta-analyses with systematic reviews, two were systematic reviews, and three were meta-analyses. Obesity, diabetes and metabolic syndrome are grouped together, as they have similar underlying mechanisms and are all inter-related concerning causes and effects.

Wu, Zhai, and Zhang (2014) found a significant association between short sleep and obesity in their meta-analysis of prospective studies. The OR they found was 1.45, with 1.65 and 1.25 for males and females, respectively. In subgroup analysis, the association was only significant among adults in North America (OR = 1.46) and in Japan (OR = 1.47), but not in Europe (1.45). When short sleep was identified as <6h, the OR was 2.74. No significant association was initially found between long sleep duration and obesity, but after excluding three studies with high heterogeneity, the pooled OR was 1.25. This was supported by another review of prospective studies which looked at short sleep duration and weight gain, who found that most of the prospective studies they reviewed found a significant association between short sleep and weight gain (Magee & Hale, 2011). The prospective studies used in the review by Patel & Hu (2008) also suggested a modest association between short sleep duration and weight gain. Adjusting for differences in baseline weight, weight gain was 1.14 times greater over 16 years among those who slept ≤5h or 6h a day, compared to those who slept 7 hours a day. The hazard ratios for obesity were 1.15 and 1.06 for ≤5 and 6 hours, respectively. The hazard ratio for a 15kg weight gain in these 16 years were 1.28 and 1.10 for ≤5h and 6 hours, respectively (Patel & Hu, 2008). Individuals who slept 5 hours or less were twice as likely to be obese within 9 years compared to those who sleep 7 hours per night. The strength of the sleep duration/obesity relationship appears to decrease with age.

These findings were supported by the meta-analysis and review of randomized controlled trials of (Al Khatib, Harding, Darzi, & Pot, 2016). When looking at the effects of sleep deprivation on energy expenditure and energy intake, they found that partial sleep deprivation can lead up to a net positive energy balance of up to 385kcal per day. Cappuccio et al. (2008) supported these findings in their meta-analyses of cross-sectional and prospective studies by concluding that short sleep, defined as five hours or less per 24 hours, was significantly associated with obesity. The pooled OR was 1.55, and all studies showed a consistent negative association between sleep time and BMI. Per hour of sleep lost, there was a 0.35 unit of change, measured in kg.m2 in BMI. This result was consistent across different populations (Cappuccio et al., 2008).

Besides just obesity, evidence has also been found for risk of diabetes in a meta-analysis of prospective cohort studies. Shan et al. (2015) found **a** u-shaped association between sleep duration and risk of type II diabetes. The lowest risk was found at 7-8 hours of sleep per day. The pooled RR was 1.06 for 6 hours of sleep, and 1.37 for less than five hours per day. Compared with 7 hours, the pooled RR for type II diabetes was 1.09 for every additional hour of sleep reduction. Sixty-eight additional cases per 100,000 people would occur every year with every one-hour reduction of habitual sleep duration. For long sleep duration, the pooled RR for risk of type II diabetes was 1.11 for 8 hours per day, and 1.40 for ≥9 hours per day. The pooled RR was 1.14 for every hour increase in sleep duration. 106 individuals per 100,000 would get diabetes for every hour increment of sleep (Shan et al., 2015).

These findings were supported by Anothaisintawee, Reutrakul, Van Cauter, and Thakkinstian (2016), in their systematic review and meta-analyses of prospective studies. The pooled RR's of diabetes were 1.48, 1.18, and 1.36 for sleep duration of ≤5h, ≤6h and ≥9 hours per day, respectively. The effect of short sleep duration on diabetes is comparable to that of being inactive. Lifestyle modifications, with diet and exercise, in people with impaired glucose tolerance have shown to eliminate the relationship between long sleep and diabetes (Anothaisintawee et al., 2016).

Another example of a detrimental effect of sleep restriction is the increased risk of metabolic syndrome (Xi, He, Zhang, Xue, & Zhou, 2014). A systematic review and meta-analyses of prospective and cross-sectional studies found that short sleep duration is significantly associated with increased risk of metabolic syndrome (OR = 1.27). The effect in men and women was similar. Long sleep duration was not associated with an increased risk of metabolic syndrome, when controlled for age, sex and BMI. Several meta-analyses support the association between sleep duration and obesity, hypertension, and type II diabetes, as mentioned before, and these are all important components of metabolic syndrome. Therefore, similar mechanisms explain the increased risk of metabolic syndrome.

Possible Mechanisms

Al Khatib et al. (2016) suggest that weight-gain due to sleep duration is explained by increase in calorie intake per 24 hours, and no change in energy expenditure. Short sleep duration can therefore contribute to weight gain. Additionally, shifts in macronutrient distribution were found, as those who experienced partial sleep deprivation favored fat intake at the expense of protein consumption. This may be due to the hormones leptin and ghrelin, or be hedonically driven. Sleep deprivation leads to greater neuronal activation in response to food stimuli, particularly in reward-related areas of the brain. Short sleep can heighten motivation to find food as a reward, particularly those high in fat and sugar (Al Khatib et al., 2016). Cappuccio

et al. (2008) also suggested that the association may be caused by changes in the hormones leptin and ghrelin, as they increase appetite and lead to obesity. Additionally, they suggest that short sleep may activate an inflammatory pathway that is also implicated in the development of obesity. It may also just be a marker of an unfavorable health status and lifestyle, of which poor sleep is one (Cappuccio et al., 2008). Patel & Hu, (2008) also suggest that the hormones leptin and ghrelin are indicated to be responsible for the weight gain. Additionally, people who sleep less have more time to eat, so when they find themselves in an environment where food is readily available, and if they are partaking in common late-night sedentary activities where snacking is often seen, they will eat more. Tiredness also leads to less physical inactivity and lower energy expenditure. The same mechanisms were proposed and thus supported by Wu et al. (2014). Magee & Hale (2011) propose, contrary to the other studies, that increased media use may result in less time to sleep, contributing to hunger and increased caloric intake, and decreased energy expenditure (Figure 2).

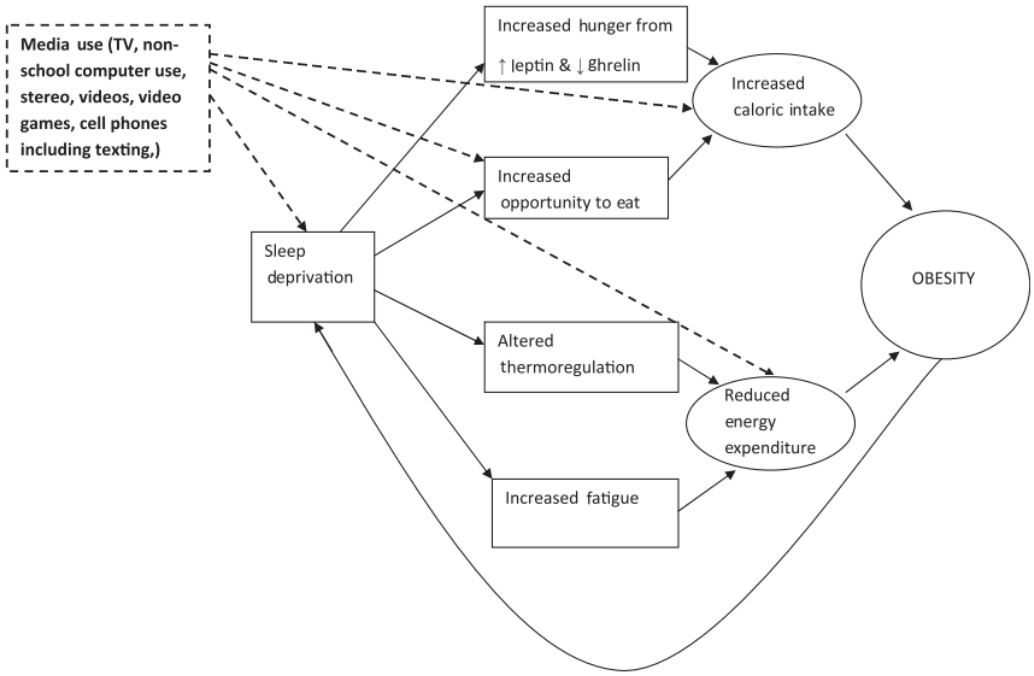

Figure 2. Proposed mechanisms through which short sleep duration may lead to obesity (Magee & Hale, 2011)

Similar to Patel & Hu (2008), they also suggest that the associations may weaken with age. As for the mechanisms underlying sleep duration and diabetes, findings from lab studies suggest that a few days of sleep restriction is enough to cause a significant reduction of insulin sensitivity, without adequate compensation by increased insulin release, resulting in decreased glucose tolerance (Anothaisintawee et al., 2016).The adverse impact of insulin secretion and beta-cell responsiveness is thought to be mediated by heightened sympathetic nervous system activity, increased cortisol levels at night, and alterations in hormone secretions and elevations in systemic inflammatory responses. The mechanisms behind long sleep

and diabetes remain poorly understood. Depression, undiagnosed obstructive sleep apnea, or poor health may also cause long sleep and diabetes (Anothaisintawee et al., 2016). (Shan et al., 2015) propose that is a decrease in glucose tolerance and insulin sensitivity after sleep restriction, combined with increased hepatic glucose production and reduced peripheral glucose disposal. These changes in sensitivity of the neuroendocrine systems are the major mediators of the detrimental metabolic effects of insufficient sleep. Increased sympathetic nerve activity may reduce b-cell responsiveness, and insufficient pancreatic insulin secretion. Increased uptake of glucose by the sleep-deprived brain may result in increased levels of circulating glucose and postprandial insulin-to-glucose ratio (Shan et al., 2015).

Table 3. Sleep duration and risk of obesity, diabetes and metabolic syndrome

Author	Publication Type	Number of studies	Outcome	Findings	Potential bias
Wu et al. (2014)	Meta-analysis of prospective studies , follow-up duration ranged from 3-12 years	11 articles with 197,906 participants for short SD and 164,016 participants for long SD.	Obesity	Short sleep duration significantly associated with risk of future obesity. OR = 1.45. Males = 1.65, females = 1.25. For using ≤6h, or = 2.74. Significant association was found among adults in North America (OR = 1;46), and Japan (1.47) but not in Europe (1.45) Long sleep duration: no significant association. After excluding 3 studies causing heterogeneity, pooled OR was 1.25.	No standard definition Different study populations; between-study heterogeneity Self-reported sleep durations. Different confounders controlled for between studies.
Magee and Hale (2011)	Systematic review of longitudinal studies, follow up duration ranged from 1-14 years	13 adult studies	Weight gain	4/13 found association between short sleep and weight gain, no association between long sleep. Four found both associations, and 5 found no association.	Possible publication bias. Not all studies used standardized measures.
Shan et al. (2015)	Meta-analysis, prospective studies, follow up period ranged from 2.5-16 years (median 7.5)	10 studies, 11 independent reports.	Diabetes risk	U-shaped association show between SD and risk of type II diabetes. Lowest risk at duration of 7-8hrs per day. Reference category = 7h/day. Pooled RR was 1.06 for 6h per day and 1.37 for ≤5hrs/night. - Pooled RR = 1.11 for long sleep duration and T2DM risk for 8h per day and 1.40 for ≥9h per day Compared to 7h/day, hour decrease = 9% and hour increase = 14% increased risk of diabetes.	Substantial between-study heterogeneity. Self-reported sleep duration. In most studies sleep duration assessed at only 1 time point. Possible residual confounders.
Anothaisintawee et al. (2016)	Systematic review and meta-analysis of prospective cohort studies, follow up duration 2-32 years	36 studies (37 cohorts) with 1,061,555 participants	Diabetes risk	Pooled RRs were 1.48, 1.18 and 1.36 for sleep duration ≤5h/d, 6h/d and ≥9h/day, respectively. The effect of short sleep duration is comparable to that of being inactive.	Self-reported sleep duration. Diabetes not systematically specified as type II. Moderate to high heterogeneity for some sleep factors.

Xi et al. (2014)	Systematic review and meta-analysis, case-control and cohort designs	10 papers, 12 studies with 18720 MS cases, 70833 controls.	Metabolic syndrome	Short SD significantly associated with increased risk of MS (OR = 1.27) Effect in men (OR=1.24) and women (OR=1.35) was similar. Long SD not associated with increased risk of MS (OR =1.07). Similar in men and women. Several meta-analyses supported associated between SD and obesity, hypertension and T2DM; obesity, hypertension and impaired fasting glucose all components of MS	Unexplained between-study heterogeneity. Different confounders were controlled for. No mention of follow-up duration prospective studies. Self-reported sleep duration. Mostly cross-sectional.
Cappuccio et al. (2008)	Meta-analysis of cross-sectional and longitudinal studies	45 studies, 26 on adults, 604,509 adults from around the world.	Obesity or BMI.	Significant association between short SD and obesity: pooled OR = 1.55, all studies showed consistent significant negative association between SD and BMI. -0.35 unit of change ($kg.m^2$) in BMI per hours of sleep. Consistent in different populations	No publication bias, possible confounding bias. Significant heterogeneity. Pooled studies are cross-sectional.
Al Khatib et al. (2016)	Systematic review and meta-analysis of randomized control trials	17SR, 11MA. Total of 496 subjects	Energy expenditure and intake	PSD may lead to a net positive energy balance of 385kcal per day, because of significant increase in total 24-h I, and no effect on total 24h EE. May therefore contribute to the occurrence of weight gain in those with short sleep duration.	Mainly based on studies with highly restrictive sleep schedules conducted in controlled lab conditions over a short period of time. Some heterogeneity.
Patel and Hu (2008)	Systematic review of cross-sectional and prospective studies, follow up duration of 4-16 years	1966-2007. 36 publications, 23 about adults.	weight gain, obesity or both	U-shaped association between sleep duration and BMI in women, minimum at 7h. Men = monotonic trend, longer sleep durations = lower BMI. (Largest study). Literature supports the presence of an association between sleep duration and weight Relationship may weaken with age.	Self-reported sleep duration. Possible reverse causation. Possible residual confounding.

4. Conclusion

This study has provided a comprehensive review of the literature and quantitative estimates of associations between sleep and the four investigated health outcomes: cancer, mental health, cardiovascular disease and obesity, diabetes & metabolic syndrome. Overall, the published literature supports the presence of an association between sleep duration and these health outcomes. The conclusions are based on the analysis of prospective cohort studies, and are supported by possible mechanisms that are proposed in the reviews of both prospective and cross-sectional or retrospective studies.

Sleeping more than 9 to 10 hours per night can increase risk of cancer mortality by up to 11%, and risk of colorectal cancer by up to 29%, whereas it decreases the risk of prostate and ovarian cancer with 64% and 12% respectively (Lu et al., 2013; Ma et al., 2016; Noguti et al., 2013; Zhao et al., 2013). The literature also suggested that short sleep might lead to carcinogenesis (Irwin et al., 2016). Mechanisms have been proposed to explain the association between long sleep duration and a reduced risk of hormone-related cancers. Melatonin levels increase with long sleep duration and has protective effects against this cancer type (Zhao et al., 2013). More evidence is needed to elucidate mechanisms underlying long sleep duration and colorectal cancer. Short sleep duration is hypothesized to increase oxidative stress and raise levels of inflammatory markers in the body, which may predispose carcinogenesis (Irwin et al., 2016; Noguti et al., 2013).

Sleep duration also has an effect on cardiovascular disease; despite some conflicting evidence, most studies agree that short sleep duration and long sleep duration (less than six hours or more than 9 hours) significantly increases risk of cardiovascular diseases like CHD, stroke and hypertension (Li et al., 2016; Miller & Cappuccio, 2013; Pepin et al., 2014; Wang et al., 2016). Mechanisms explaining the relationship between short sleep duration and cardiovascular risk include hormonal responses to sleep loss, such an increased cortisol and appetite-regulating hormone secretion, and altered growth hormone metabolism. Additionally, blood glucose concentrations, blood pressure and cholesterol levels are all influenced by short sleep, influencing cardiovascular risk factors (Li et al., 2016; Wang et al., 2016). The mechanisms underlying long sleep duration and cardiovascular disease are still poorly understood. Because no other explanations have been proposed, comorbidities and confounders are currently suspected to cause the relationship (Wang et al., 2016).

When looking at sleep duration and mental disorders, it has been suggested that short sleep duration increases the risk of depression by 31% and long sleep duration increases the risk by 42% (Zhai et al., 2015). In the short term, however, sleep deprivation can relieve depressive symptoms (Tsuno et al., 2005). It is also

related to anxiogenesis and schizophrenia, but it is hard to determine whether it is a cause of or a side effect of these conditions. Suicide risk has also been implicated to be affected by sleep loss (Pigeon et al., 2016). A few mechanisms have been proposed in an attempt to explain this relationship. Short sleep duration increases tiredness throughout the day, which can stimulate negative emotions and events, predisposing depression and possibly suicide (Zhai et al., 2015). Long sleep duration is correlated with low physical activity, and therefore a reduced production of neurotransmitters like dopamine and serotonin which stimulate endorphin secretion, which can enhance self-efficacy and self-esteem and elevate your mood. Lack of these endorphins can therefore encourage depressed feelings (Zhai et al., 2015).

The evidence for the effects of sleep deprivation on obesity, and associated risk of diabetes and metabolic syndrome, was the most overwhelming. Short sleep duration or sleep deprivation can lead to weight gain, shifts in macronutrient distribution, increased obesity risk by up to 55% when sleeping less than 5 hours per night, increased risk of diabetes up to 48%, and increased risk of metabolic syndrome by up to 27% (Al Khatib et al., 2016; Cappuccio et al., 2008; Shan et al., 2015; Wu et al., 2014).. For long sleep, defined as 9 or more hours, it was found that there is an increased risk of weight gain, especially in women (Patel & Hu, 2008). The risk of obesity also increases by up to 25%, and the risk of diabetes increases by up to 40% (Anothaisintawee et al., 2016; Magee & Hale, 2011; Shan et al., 2015; Wu et al., 2014). Several mechanisms have been proposed to underlie the association between short sleep duration and obesity, diabetes and metabolic syndrome, which are mostly related to variations in hormone levels of leptin and ghrelin that regulate appetite, increasing caloric intake and increasing fat and sugar consumption (Al Khatib et al., 2016). People who sleep less also have more time to eat, during common late-night sedentary activities (Patel & Hu, 2008). Sleep restriction also reduces insulin sensitivity, resulting in decreased glucose tolerance, contributing to diabetes risk (Anothaisintawee et al., 2016). The mechanisms behind long sleep duration and increased risk of obesity, diabetes and metabolic syndrome remain poorly understood.

To conclude, sleep duration potentially has a great impact on human health. It influences many processes and mechanisms in the body, which can lead to adverse health outcomes in both the short and the long term. Many of these mechanisms are interrelated, as an increased risk of weight gain may also lead to an increased risk of obesity, diabetes, cardiovascular disease(s), and metabolic syndrome. The same mechanisms that may increase the risk of cancer, like inflammation, may also contribute to an increased risk of cardiovascular disease and diabetes. This also makes it hard to establish causation, as all these mechanisms are linked and it is hard to determine an independent underlying factor for these conditions.

5. Discussion

As proven by an extensive literature search, this is the first systematic review to provide a summary of all the effects that sleep has on the most prominent health outcomes. This is important because of the steady increase in the occurrence of these health outcomes in our modern society, and because there is a general lack of attention for sleep as a health determinant in health policy. This review has shown that both a short and long sleep duration significantly affects the risk of various negative health outcomes, and that sleeping an average amount, usually described as 7-9 hours per day, significantly reduces the risk of cancer, cardiovascular disease, mental health issues, and obesity, diabetes & metabolic syndrome. As seen in this review, long sleep duration is sometimes even more detrimental to health than short sleep duration, and therefore poses just as big of a risk for health, if not bigger, than short sleep duration. Consequently, evidence is provided that sleep duration should be taken into consideration as an important determinant of health, and promoting healthier sleeping habits should become a bigger focus for health institutes.

The study presents several notable strengths. A large number of exclusively high-quality studies were included, giving the study a large power to detect associations between exposures and outcomes. Article selection was done systematically in multiple databases to ensure that no important articles were left out, and only meta-analyses and systematic reviews were included, giving the results more credibility as their conclusions are already based on very large populations. The review was reported according to the PRISMA guidelines, ensuring internal validity. The studies used for the main conclusions were all longitudinal and prospective in nature, making results more reliable and causation easier to establish. Although several cross-sectional studies were also included, these were used only to provide information on the underlying mechanisms. Studies that included populations that suffered from sleep disorders or other comorbidities were excluded, to reduce confounders.

Several limitations should be considered. First, the quality of the data is restricted to the quality of each individual study included in the meta-analyses and systematic reviews that were included in this review. The results can only be representative of those studies that have been included. The effect of residual confounders on the results cannot be completely excluded. Although most studies controlled for possible confounders, the variables that were controlled for might have been different between studies. Publication bias may also influence results, as some small studies with null effects may have been excluded or may not have been published.

Second, the included studies have substantial differences in study designs, including how sleep duration was measured (through self-reporting, actigraphy or polysomnography), what was considered 'long' or 'short' sleep duration, what reference value (or 'average' sleep duration) of sleep was used, whether the studies had a prospective, cross-sectional or retrospective study design, which countries were included in the analysis, what confounding variables were controlled for to prevent confounding bias, the length of follow-up in case of prospective studies, and the number of participants that were used. These factors may have lead to heterogeneity both within the meta-analyses and systematic reviews used and between the various studies analyzed. Several studies, like Zhao et al. (2013), Wu et al. (2014), Irwin et al. (2016), Da Silva et al. (2016), Cappuccio et al. (2008), and Al Khatib et al. (2016) did use regression analyses and sub-group analysis to explore sources of heterogeneity and excluded those studies causing it. Despite these variabilities in study design and how exposure was assigned, the results were still fairly uniform.

Third, many of the studies used questionnaires and self-reporting to assess sleep duration, rather than objective measures such as polysomnography or actigrapy. Objective measures more accurately measure sleep duration as they also take into account time spent awake during the night which subjectively may not be recalled. However, there is evidence that subjective and objective measurements of sleep duration correlate substantially, giving similar results. However, differences in measurement methods may still influence study results (Zhao et al., 2013). Individuals who self-reported longer or shorter sleep duration may also have been in general poorer overall health or in a bad mood, leading to potential information bias. In some studies, sleep duration was only measured at one or a few points in time, which may not accurately reflect the average sleep duration a person has in the long term, possibly changing the outcomes. Whereas for the results only results from prospective studies were used, the length of follow-up still differed substantially between studies that were included, ranging from one year to over thirty years. There is large night-to-night variability in the sleep duration of many people, and sleep habits vary greatly between weekdays and weekends as well. Additionally, very few studies measured the effect of sleep quality which may also substantially influence the results.

Despite the general consistency in the presence of associations between sleep and health outcomes, the power to definitively conclude causation is limited. Reverse causation cannot be excluded, as for example obesity can cause risk of medical conditions like osteoarthritis, asthma and heart failure, which can in turn disrupt sleep and lead to insomnia. However, most studies controlled for such comorbidities. Therefore, while definitive conclusions about causality cannot be drawn, the evidence does strongly support the presence of causal relationships between sleep duration and the various health outcomes researched.

These results are important in guiding the assessment of current evidence and defining what still needs to be researched and which methods should be used. From this review it became evident that more studies need to be done to investigate the mechanisms underlying the relationship between long sleep duration and colorectal cancer, cardiovascular disease, mental health problems and obesity, diabetes and metabolic syndrome. So far most of the research has looked at short sleep duration and the mechanisms causing disease, as only recently research has been done to show long sleep duration also negatively impacts health. Especially research about schizophrenia and suicide in relation to sleep duration is mostly based on cross-sectional or retrospective studies, so more longitudinal prospective studies are needed to establish causality.

Additionally, this research in this paper could be complemented by investigating whether circadian misalignment due to night shifts and altered lifestyles also impacts health in similar ways as sleep duration can. Initially, the effect of sleep duration on cognition and the immune response were also included in this review. However, because these were not considered as direct health outcomes but as mechanisms leading to other health outcomes (such as dementia or illness due to impaired immunity) they fell outside the scope of this research and were not included in the analysis. Nevertheless, a growing body of research has investigated both cognition and illness in relation to sleep duration and should be considered in future research regarding this topic. Also, more studies should look into the effects of napping and whether or not you can 'compensate' for sleep loss of excessive sleep. Most importantly, these studies should be based on longitudinal, prospective cohort studies, which correct for comorbidities and common confounders, so as to ensure that causality can be established.

As an interesting addition to this current review, several Dutch authors were contacted to request unpublished data and population studies from the Netherlands were searched, to give an insight into how much research is being done in the Netherlands and what the current level of knowledge on this topic is. The authors that were contacted were not able to provide any relevant unpublished articles, and the longitudinal prospective population studies were found, like the Doetinchem Cohort Study, the Lifelines study and the PIAMA birth cohort study, contained no useful information for this review (Berentzen et al., 2014; Picavet et al., 2016; van Maanen et al., 2013). This reflects and thereby supports the previously described need for more longitudinal prospective research about the effects of sleep duration on health, especially because chronic diseases like obesity, diabetes, and cardiovascular disease are becoming more and more prominent in our society (WHO, 2014).

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7. Appendix

Appendix A – Full Electronic Search Embase/Medline

Embase Session Results

No.	Query	Results
#25	**#23** NOT **#24**	**2,103**
#24	**protocol**:ti OR **therap***:ti OR **pharmacotherap***:ti OR **treatment***:ti OR **treating**:ti OR **treat**:ti OR **acute**:ti OR **benzodiazep***:ti OR **management**:ti OR **managing**:ti OR **manage**:ti OR **screening**:ti OR **education**:ti AND **ot** AND **medication***:ti OR **antidepressant**:ti OR **intervention***:ti OR **outcome***:ti OR **patient***:ti OR **training**:ti OR **exercise**:ti	**2,682,298**
#23	**#22** AND (**english**:la OR **dutch**:la)	**2,531**
#22	**#21** AND (**review***:ti OR (**literature** NEAR/3 **review***):ab OR '**review**'/de OR '**systematic review**'/de OR '**meta analysis**'/de OR '**meta analysis**':ti,ab OR **metaanalysis**:ti,ab)	**3,027**
#21	**#20** NOT (**letter**:it OR **note**:it OR **erratum**:it OR **news**:it OR '**conference abstract**':it OR '**conference paper**':it OR '**conference review**':it OR ('**animal**'/exp NOT '**human**'/de))	**22,787**
#20	**#4** AND (**#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19**)	**36,906**
#19	'**cell regeneration**':ti OR '**cell restoration**':ti OR **recovery**:ti OR '**regeneration**'/mj OR '**cell regeneration**'/mj OR '**energy recovery**'/mj	**88,579**
#18	'**immune response**':ti OR '**immune function**':ti OR '**susceptibility to diseases**':ti OR '**disease susceptibility**':ti OR '**immunity**'/mj OR '**immune response**'/mj OR '**immune system**'/mj OR '**disease predisposition**'/mj OR '**life expectancy**'/mj OR '**daily life activity**'/mj OR '**quality of life**'/mj	**187,624**
#17	'**cardiovascular disease**'/mj OR '**coronary disease**'/mj/exp OR '**coronary artery disease**'/mj OR '**vascular disease**'/mj OR '**blood pressure**'/mj OR '**hypertension**'/mj OR '**hypercholesterolemia**'/mj OR '**cholesterol**'/mj	**579,157**
		658,385

#16
cardiovascular:ti OR **cardiometabolic***:ti OR **coronary**:ti OR '**heart disease**':ti OR **hypertension**:ti OR '**blood pressure**':ti OR '**arterial pressure**':ti OR '**high cholesterol**':ti OR **hypercholesterol***:ti OR '**serum cholesterol**':ti
640,500
#15
'**obesity**'/mj OR '**abdominal obesity**'/mj OR '**body weight**'/mj OR '**overweight**'/mj OR '**weight reduction**'/mj OR '**weight gain**'/mj OR '**intraabdominal fat**'/mj OR '**metabolic syndrome x**'/mj OR '**diabetes mellitis**' OR '**blood glucose level**'/mj OR '**hyperglycemia**'/mj OR '**hypoglycemia**'/mj OR '**insulin**'/mj OR '**hyperlipidemia**'/mj OR '**dyslipidemia**'/mj OR '**metabolism**'/mj OR '**energy metabolism**'/mj OR '**energy balance**'/mj OR '**metabolic disorder**'/mj OR '**disorders of carbohydrate metabolism**'/mj OR '**digestion**'/mj OR '**digestive system disease**'/mj OR '**insulin resistance**'/mj OR '**leptin**'/mj OR '**lipid metabolism**'/mj OR '**disorders of lipid metabolism**'/mj OR '**hormonal regulation**'/mj OR '**ghrelin**'/mj OR '**homeostasis**'/mj
885,871
#14
obesity:ti OR **overweight**:ti OR **diabet***:ti OR **metabol***:ti OR **digestion**:ti OR '**hormonal regulation**':ti OR **homeostasis**:ti
2,826,720
#13
cancer*:ti OR **neoplasm***:ti OR '**neoplasm**'/mj/exp NOT (**survivor***:ti OR **patient***:ti)
369,185
#12
'**concentration loss**'/mj OR '**attention**'/mj OR '**cognition**'/mj OR '**cognitive defect**'/mj OR '**creativity**'/mj OR '**alertness**'/mj OR '**thinking**'/mj OR '**learning**'/mj OR '**memory**'/mj OR '**memory disorder**'/mj OR '**mental function**'/mj OR '**intelligence quotient**'/mj OR '**decision making**'/mj OR '**emotion**'/de OR '**emotional disorder**'/mj OR '**emotional stress**'/mj
358,608
#11
concentration:ti OR **focus**:ti OR **attention**:ti OR **cognition**:ti OR '**cognitive functioning**':ti OR '**cognitive performance**':ti OR **creativity**:ti OR **alertness**:ti OR '**reaction speed**':ti OR **memory**:ti OR **learning**:ti OR **iq**:ti OR **intelligence**:ti OR '**decision-making**':ti OR **motivation**:ti OR '**emotional regulation**':ti
316,294
#10
'**mood**'/mj OR '**mood disorder**'/mj OR '**depression**'/mj OR '**anxiety**'/mj OR '**anxiety disorder**'/mj OR '**irritability**'/mj OR '**annoyance**'/mj OR '**anger**'/mj OR '**stress**'/mj OR '**mental stress**'/mj OR '**emotional stress**'/mj OR '**burnout**'/mj OR '**fatigue**'/mj OR '**suicide**'/mj
428,205
#9
mood:ti OR **depression**:ti OR **anxiety**:ti OR **irritability**:ti OR **annoyance**:ti OR **anger**:ti OR **stress**:ti OR **burnout**:ti OR '**burn-out**':ti OR **fatigue**:ti OR '**social jetlag**':ti OR **suicide***:ti OR **suicidality**:ti
35,146
#8
'**development**'/mj OR '**human development**'/mj OR '**child development**'/mj OR '**adolescent development**'/mj OR '**psychosocial development**'/mj
2,128
#7
'**child development**':ti OR '**infant development**':ti OR '**adolescent development**':ti
401,116
#6

'health'/mj OR **'health status'**/mj OR **'physical health'**/mj OR **'mental health'**/mj OR **'mental disease'**/mj OR **'psychosomatic disorder'**/mj OR **'somatoform disorder'**/mj OR **'psychophysiology'**/mj OR **'diseases'**/mj OR **'mortality'**/mj OR **'morbidity'**/mj OR **'wellbeing'**/mj OR **'physical wellbeing'**/mj OR **'fitness'**/mj

763,811

#5

health*:ti OR **illness***:ti OR **complaints**:ti OR **'psychological effects'**:ti OR **'physiological effects'**:ti OR **'well being'**:ti OR **wellbeing**:ti OR **fitness**:ti

134,606

#4

#1 OR **#2** OR **#3**

90,055

#3

'sleep'/mj OR **'night sleep'**/mj OR **'sleep disorder'**/mj OR **'insomnia'**/mj OR **'circadian rhythm sleep disorder'**/mj OR **'sleep deprivation'**/mj OR **'sleep time'**/mj OR **'sleep quality'**/mj OR **'sleep pattern'**/mj OR **'sleep waking cycle'**/mj OR **'wakefullness'**/mj

267

#2

'circadian disruption':ti OR **chronodisruption**:ti OR **'circadian desynchron*'**:ti OR **'circadion dysfunct*'**:ti OR **'circadian dysregulation*'**:ti OR **'abnormal circadian'**:ti

113,521

#1

sleep*:ti OR **sleeping**:ti OR **sleeplessness**:ti OR **insomnia**:ti OR **dyssomnia***:ti OR **wakefullness**:ti

Appendix B – Prisma 2009 Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	