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Review Article

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# Sleep Disorders, Sleeping Pills and Hypertension: A Systematic Review

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**Abstract:** Hypertension and insomnia or sleep loss is very common and often co-exists together. There are evidences suggesting that the increase in the prevalence of arterial hypertension in the past decade might be related both to an increased prevalence of insomnia and to the decline of sleep duration due to modern lifestyle. However, there is a lack of studies in detailed investigation of the effect of sleeping pills on blood pressure. The aim of this study was to reconsider both the clinical evidence of the relationship between conditions of sleep loss, sleeping pills, and hypertension and the potential pathophysiological mechanisms underlying the biological plausibility of their relationship**.** Through a systematic search from MEDLINE, EMBASE, and PubMed, we selected 20 articles, which reported sleep disorders, or studied sleep duration or insomnia and sleeping pills and their relationship with blood pressure or hypertension in participants over 18 years**.** Sleep loss or sleep disorders due to persistent insomnia or sleep apnea seems to be associated with an increased risk for hypertension, even after controlling for other hypertensive risk factors. For sleeping pills, it is still a controversy whether they increase or decrease blood pressure in patients with sleeping disorders. Chronic sleep loss or alterations of sleep quality can act as a physiological stressor or that impairs brain functions and contributes to hypertension. However, further studies need to measure the relationship between sleeping pills and blood pressure.

**Keywords:** Sleep disorders, sleep duration, insomnia, sleeping pills, and hypertension.

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## 1. INTRODUCTION

Insomnia is considered a very complex disorder. Several studies revealed that it is a very common problem among the general population.[1,2] Primary insomnia is not usually associated with other diseases.[3] Secondary insomnia is contributed to another disease or disorder.[4] Recent studies suggested that insomnia and other sleeping disorders have more complex attribution to co-morbid diseases.[5] Suke et al revealed that chronic insomnia can be a useful predictor for future hypertension in Japanese workers.[6] Some other scientists elucidate that insomnia can be a predictor for psychiatric disorders.[7] However, the exact mechanism is still not very clear. A sleeping pill is a tablet that helps to stimulate sleep.[1] It is a fact that using sleeping pills is common in -adults due to psychological or physiological factors. In general, the National Heart, Lung, and Blood Institute defines the normal sleeping hours in elderly adults to be around 7–8 hours.[2] Common medications for both primary and secondary insomnia include benzodiazepine, antidepressants, over the counter medications and cognitive behavioral therapy[6] as well as complementary or herbal medications.[8] Several studies have reported that sleeping pills were associated with hypertension.[9] Sleeping pills are commonly used for the treatment of sleeping disorders, for example Circadian rhythm disorders, Snoring, Sleep apnea, Narcolepsy, Restless leg syndrome, Insomnia and Nightmares.[9] Over-the-counter (OTC) sleeping pills drugs such as Antihistamines, Melatonin and Valerian are also prescription drugs for instance tricyclic antidepressants which act by increasing levels of norepinephrine and serotonin and blocking the action of acetylcholine, benzodiazepines that bind to receptors in various regions of the brain and spinal cord. Moreover, this binding increases the inhibitory effects of gamma-aminobutyric acid (GABA) and non-benzodiazepines, that control its binding to brain GABA-A receptors. GABA-A receptors are ligand gated chloride channels mediating inhibitory signals.[10] On the other hand, sleeping pills can cause severe side effects including oversleeping, drowsiness, allergic reaction (anaphylaxis) and facial swelling (angioedema).[11] However, the relationship between sleep disorders, sleeping pills and hypertension is very complex. Moreover, cardiovascular risk factors and other conditions, such as gender, age, body weight, alcohol consumption, depression, might contribute to both insomnia and hypertension; thus, it is difficult to unravel whether a cause-effect relation exists independently of common causing factors.[12] Therefore, it is an important subject to examine and learn more about the exact cause and pathways. Thus, our aim of this study was to systematically review the literature about clinical evidence of the association between different sleep disorders, sleeping pills and hypertension.

## 2. METHODS

### *2.1 Search strategy*

We performed a systematic search of MEDLINE, EMBASE and PubMed. The search strategies used headings and keywords for "sleep disorders" or "insomnia" or "sleep loss" or "sleep duration" or "sleep deprivation" or "sleeping pills" and "hypertension" or "blood pressure" or "sleeping pills". The searches were limited to the English Language and to studies conducted on adult human populations. Studies conducted with children were excluded from the analysis. We examined 20 articles.

### *2.2 Inclusion criteria*

-Studies involved adult participants over 18 years;
- Longitudinal, cross-sectional, or case control studies;
- Systematic reviews or meta-analyses;
- Studies that analyzed the relationship between insomnia, sleep duration, sleeping pills and Blood pressure as side effect;
- Studies published between February 2000 to February 2020.

### *2.3 Exclusion criteria*

- Children
- Studies not available in full text through library access.
- Studies not available in English language.

## 3 RESULTS

Multiple studies have found that experimental sleeping pills leads to increased BP. Among the articles initially identified, 20 studies met the inclusion criteria (Table 1). Sample size ranged from 5 to more than 20 thousand subjects: 10 studies were performed in young adults (mean age 23- 48) and only one study looked at healthy elderly subjects (age 60- 69); 9 studies encompassed both male and female subjects and two studies only males. Few studies analyzed the effects of partial Sleeping pills on BP and among them only 4 studies met inclusion criteria. The majority of the studies used total sleeping evaluation. Ten of the 20 studies looked at healthy subjects, whereas one study reported on pre-hypertensive or hypertensive subjects.

**Table1. Summarizing results from studies assessing sleep disorders, sleep duration, sleeping pills and risk for Hypertension in General Populations.**

| Authors | Study Design | Study Size (N) | Study Population | Sleep disorder | Sleeping hours | Sleeping evaluation | Blood pressure status |
|---|---|---|---|---|---|---|---|
| Michiaki Nagai, Satoshi Hoshide, Mami Nishikawa, Kazuyuki Shimada, Kazuomi Kario | cross-sectional design | 201 elderly individuals | 79.9± 6.4 years old | Persistent insomnia | ≥ 9 hours per night | Self-reported sleep duration and insomnia questionnaires were used to classify the patients according to sleep duration period and insomnia status. | Average SBP 140 ± 16 Average DBP 80 ± 8 |
| Kristen L. Knutson, Eve Van Cauter; Paul J. Rathouz, et al | cross-sectional and longitudinal associations | 578 African Americans and whites | 33 to 45 years old | Persistent insomnia | | Sleep was measured twice using wrist actigraphy for 3 consecutive days between 2003 and 2005. | SBP greater than or equal to 140 mm Hg, a DBP greater than or equal to 90 mm Hg |
| Rébecca Robillard, Paola A. Lanfranchi, François Prince, Daniel Filipini, and Julie Carrier, | Crossover counterbalanced design. | 8 Young adult, 8 Elderly | 20 - 69 years old | Sleep deprivation. | | Each subject underwent two counterbalanced homeostatic sleep pressure conditions | BP in young participants SBP 118.9/ DBP 77.9 and in elderly participants SBP 139.4/ DBP 83.6 |
| F. Javier Nieto, MD, PhD; Terry B. Young, PhD; Bonnie K. Lind, MS; et al | Cross-sectional analyses | 6132 | ≥40 years | Sleep-disordered breathing (SDB) and sleep apnea | | Self-administered sleep habits questionnaire | 140/90 mm Hg |
| Alexa dros N. Vgontzas, Duanping Liao, Edward O. Bixler, George P. Chrousos, Antonio Vela- Bueno, | Representative cross-sectional study | 1741 men and women | (≥20 years) | Insomnia | Sleep duration was classified into 3 categories: ≥ 6 h sleep (top 50% of the sample); 5-6 h (approximately the third quartile of the sample); and ≤ 5 h (approximately the bottom quartile of the sample). | Standardized questionnaire. Questionnaire consists of 53 questions (7 demographic, 20 sleep-related, and 26 general health questions). | Diastolic blood pressure>90 mm Hg or a Systolic blood pressure > 140 mm Hg at the time of the sleep laboratory evaluation. Insomnia with short sleep duration is associated with increased risk of hypertension, to a degree comparable to that of other common sleep disorders, |
| Daniel J. Gottlieb, Susan Redline, F. Javier Nieto, Carol M. Baldwin,; Anne B. Newman, | Cross-sectional observational study | 2813 men and 3097 women. | (40 to 100 years) | Sleep duration | Sleep durations were | Sleep Habits Questionnaire | Hypertension was defined as a systolic blood pressure of 140 mm Hg or |

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| Helaine E. Resnick, Naresh M. Punjabi | | | | | categorized as less than 6, 6 to less than 7, 7 to less than 8, 8 to less than 9, and 9 or more hours per night. | | greater, a diastolic blood pressure of 90 mm Hg or greater, or use of medication to treat hypertension. Usual sleep duration above or below the median of 7 to less than 8 hours per night is associated with an increased prevalence of hypertension, particularly at the extreme of less than 6 hours per night. |
| Meng Li,Shoumeng Yan, Shan Jiang, Xiaoyu Ma, Tianyu Gao, | Cross-sectional study | 19407 adult | (18–79 years) | Sleep duration | Three groups were divided into (<7 hours/day, 7–8 hours/day and >8 hours/day) | Self-reported sleep duration | Systolic blood pressure≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Short sleep duration was significantly associated with hypertension among people aged 18–44 years in northeast China. |
| Rong Ren,Naima Covassin,Linghui Yang,Yun Li, YeZhang, JunyingZhou, Lu Tan,Taomei Li,Xiao Li, YanyanWang, JihuiZhang, Yun-Kwok Wing,Weimin Li,Virend K.Somers,Xiangdong Tang | Cross-sectional | A total of 7107 OSA patients and 1118 primary snorers | (age >18 years) | Sleep duration and obstructive sleep apnea | Five categories of sleep duration were then derived (>8, 7–8, 6–7, 5–6, and <5 hours). | At the sleep center for suspected OSA, subjective sleep duration was assessed during the face-to-face clinical interview . Objective sleep duration was defined as total sleep time (TST) as recorded during overnight polysomnogra- phy. | Diastolic BP ≥90 mm Hg or systolic BP ≥140 mm Hg. Objective short sleep duration is independently associated with hypertension in OSA patients. Extremely short objective sleep duration (<5 hours) in itself may actually be even more detrimental thanOSA, at least for hypertension risk. |
| -Jamshid Najafian,Fatemeh Nour - Nooshin Mohammadifard | cross-sectional survey | 12492 | < 19 years | Sleep duration | ≥ 5h | Questionnaire. | Diastolic BP ≥90 mm Hg or systolic BP ≥140 mm Hg |
| -Yan Wang -Hao Mei -Yan-Rui Jiang -Wan-Qi Sun -Yuan-Jin Song -Shi-Jian Liu -Fan Jiang | Meta-Analysis | 13 Articles :352340 | <45–60> | Sleep duration | ≤ 5 h, 6 h, 7 h, 8 h, and ≥ 9 h | Self-reports of average sleep during the day and night over the course of one week | systolic blood pressure readings ≥ 140 mm Hg or diastolic readings ≥ 90 mm Hg |
| -Lu K -Chen J -Wu S -Chen J | cross-sectional | 4144 | <18 | Sleep duration | <8 h | Pittsburgh Sleep Quality Index | Systolic blood pressure≥ 130 mm Hg or diastolic ≥ 85 mm Hg |

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| -Hu D | | | | | | | |
| -Xun-ming Sun<br>-Shun Yao<br>-Shu-juan Hu<br>-Zu-yun Liu<br>-Ya-jun Yang<br>-Zi-yu Yuan<br>-Wei-min Ye<br>-Li Jin<br>-Xiao-feng Wang | Cross-sectional | 20505 | <35– 64 > | Short sleep duration | <7–8h | Questionnaire | Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg |
| Christina J. Bathgate, Julio Fernandez-Mendoza | longitudinal | | | Insomnia, Short Sleep Duration | < 6 h | | Elevated blood pressure |
| Aleksander Prejbisz, Marek Kabat, Andrzej Januszewicz,Waldemar Szelenberger, Anna J. Piotrowska, Walerian Piotrowski, Jerzy Piwon´ Ski, Magdalena Makowiecka-Cies , Krystyna Widecka, Boz ˙ Ena Patera, Leszek Bieniaszewski6, Krzysztof Narkiewicz, Andrzej Tykarski, Anna Piejko, Tomasz Grodzicki,Beata Czerwien´ Ska & Andrzej Wie ˛ Cek | cross-sectional | 432 | 47+ or - 13 years; 253 males, 179 females | insomnia | | Athens Insomnia Scale (AIS) | Hypertension was diagnosed according to WHO criteria (BP 140/90 mmHg or current antihypertensive treatment). |
| Pooja Bansil | cross-sectional survey | 10,308 | 18 years and older | sleep apnea, insomnia, restless legs | <7 hours | the reported number of hours and minutes usually slept on weekday or workday nights. | mean systolic BP (SBP) ≥ 140 mm Hg, mean diastolic BP (DBP) ≥ 90mm Hg, or currently taking prescription medication to lower high BP. |
| Yuki Morinaga, Kiyoshi Matsumura, Yasuo Kansui, Satoko Sakata. | cross-sectional | 2208 male | ranging in age from 18 to 69 years old (mean age, 44.8 ± 0.2 years), of a bus and railway company in Japan. | obstructive sleep apnea | | A screening test of OSA and blood examinations | Both SBP and DBP were significantly higher in the subjects with severe OSA than in those without OSA. |

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| Nobuo Sasaki Ryoji Ozonob, Hidehisa Yamashitac, Hirofumi Ashimena, Yoshiko Miyamotoa, Sumi Iwamia, Naomi Yuzonoa, Saeko Fujiwaraa, and Yasuki Kiharad | Cross sectional | 4459 | 18 and older Elderly | Insomnia Sleep habits and sleeping pills | Short<= 6 h Medium >6h to <=8h Long >8h | Japanese version of the PSQI Pittsburgh Sleep Quality Index assessed the bed time, using the following question: "What time have you usually gone to bed at night?" TIB was calculated from bed time and wake up time (the wakeup time was obtained, using the following question: "What time have you usually gotten up in the morning?"). | Lower in those who take sleeping pills In both the short and the long TIB groups, systolic BP was significantly higher than that of the medium TIB group (134.2 ± 17.5, 134.8 ± 19.6 vs. 130.1 ± 17.7, $p < 0.05$, $p < 0.0001$, respectively). Diastolic BP was significantly higher in the long TIB group than that of the medium TIB group (75.8 ± 11.8 vs. 74.2 ± 10.8, $p < 0.01$) close relationship between insomnia and hypertension has been reported |
| Guo X,Zheng L, Wang J, Zhang X, Zhang X, Li J, Sun Y. | cross sectional and longitudinal studies | 225,858 subjects were included in the metaanalysis | 18-106 years | habitual sle ep duratio n | | pooled odds ratios (ORs) or relative risks (RRs) were estimated using a random-effects model or a fixed-effects model. | Short sleep duration was associated with a higher risk for hypertension even longitudinally. |
| Jihye Kim, Inho Jo | cross-sectional | 5,393 | 19–99 | Sleep Duration | categorized into five groups: ≤5, 6, 7, 8, and ≥9h. | Korean National Health and Nutrition Examination Survey(KNHANES III) Sleep duration was defined as the response to the question: "How many hours of sleep do you usually get in a day on average?" | Short sleep duration (≤5h) is independently associated with hypertension in young and middle-aged Korean adults. |
| Dayna A. Johnson , S. Justin Thomas, Marwah Abdalla, Na Guo, Yuichiro Yano, Michael Rueschman, Rikki M. Tanner, Murray A. Mittleman, David A. Calhoun, James G. Wilson, Paul Muntner, Susan Redline, | longitudinal study | 5306 | 21 to 95 | sleep apnea | | Type 3 home sleep apnea device (Embletta-Gold device; Embla, Broomfield, CO | Moderate or severe OSA and hypoxemia was associated with a >2-times higher odds of having resistant hypertension untreated OSA may contribute to hard-to-control BP in blacks. |

## 4 DISCUSSION

Main objective of this study was to assess the relationship between sleeping disorders, sleeping pills and hypertension by reviewing the literature. We found in the cross-sectional studies with sample size of 4459 subjects, concluded that the group who took sleeping pills for insomnia, their systolic blood pressure was lower than the group with no sleeping pills.[12-14] Interestingly, several studies concluded that there is a close relationship between insomnia and hypertension. Patients who took sleeping pills for this insomnia were found to improve the quality and quantity of sleep, leading to a reduction in their blood pressure.[15,16] On the contrary, a prospective cohort study with a sample size of 752 participants found that the use of sleeping pills was prospectively associated with an increased number of antihypertensive drugs. [17,18] However, the question remains unanswered about whether the sleeping pill is the cause of hypertension or not in patients with sleeping disorders. For the sleep duration we found, 8 out of 20 research studies mentioned that sleeping disorder and hypertension have an opposite relationship between sleep duration and hypertension.[19,20] These studies included 7 cross-sectional and one Meta-Analysis with a total sample size of 646, 049 adults. They found that short sleep duration was associated with increased blood pressure and increased risk of hypertension. [21] In these studies hypertension was defined as a diastolic blood pressure >90 mm Hg or a systolic blood pressure >140 mm Hg or the use of antihypertensive medications.[22] In addition, eight studies out of twenty were mainly cross sectional, one out of these eight was a cross-sectional and longitudinal associations, another one was a representative cross-sectional with a total sample size of 17, 719 participants. They suffered from insomnia which resulted in participants complaining from raised blood pressure.[23] Also, 16 participants in crossover counterbalanced design suffered from sleep deprivation, that resulted in an elevation of their blood pressure for elderly and decreased blood pressure in young adults.[24,25] Moreover, there were five studies looking at the relationship between obstructive sleep (OSA) apnea and hypertension using a screening test of OSA.[26] Four studies were cross-sectional with a sample size of 25. 755 participants and one longitudinal study with a sample size of 5,306 participants. The majority of the studies found a significant relationship between obstructive sleep apnea and hypertension; blood pressure was higher in the subjects with severe OSA than in those without OSA.[26,27] There is a different process by which we can explain the underlying relationship between sleeping disorders, short sleep duration, insomnia, and hypertension. Since sleep has important homeostatic functions, including suppressive effects on the stress system[12,11], and on the immune system[10], both sleep loss and insomnia have been attributed with changes related to stress function, sympathetic nervous system activation and inflammatory pathways.[12] Chronic insomnia has been shown to be associated with an activation of the stress system. The pathophysiology of chronic insomnia and its related effects on the brain is now considered the main pathway through which insomnia and hypertension could be linked.[13] For the relationship between sleeping pills and hypertension the impact of sleeping pills on the blood pressure and blood pressure medications, there was no large-scale study or trial that examined this association in details yet. In summary, sleep loss or sleep disorders due to persistent insomnia or sleep apnea seems to be associated with an increased risk for hypertension, even after controlling for other hypertensive risk factors. The effect might be more pronounced when sleep complaints are associated with objectively measured short sleep duration and may vary by age since this relationship is not confirmed in both young or old age. It is still controversial for sleeping pills whether they increase or decrease blood pressure in patients with sleeping disorders. Nevertheless, further studies are needed to clarify the influence of confounding factors and the degree of insomnia, and the use of sleeping pills related to hypertension.

## 5 CONCLUSION

Sleep loss or sleep disorders due to persistent insomnia or sleep apnea was found to be associated with an increased risk for hypertension even after controlling other hypertensive risk factors. However, it is still under-investigated whether I sleeping pills can increase or decrease blood pressure in patients suffering from sleeping disorders. Therefore, it is recommended to apply more future research, that study in depth the relationship between sleeping pills and their effect on blood pressure in large scale studies.

## 6 AUTHORS CONTRIBUTION STATEMENT

Yosra Alhindi, Arwa Fairaq and Sahar El-ashmony conceptualized and gathered the data with regard to this work. Sara Khalid Alrimi, Raghad Abdulrahman Aljeffry, Raghad Ishag Isa, Jumanah Ahmed Sharkar, Rawah Mohammad Bokhari analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript writing.

## 7 CONFLICT OF INTEREST

Conflict of interest declared none.

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