Sleep Medicine 53 (2019) 115–123

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations

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ARTICLE INFO

Article history:
Received 17 March 2018
Received in revised form
14 August 2018
Accepted 27 August 2018
Available online 4 October 2018

Keywords:
High blood pressure
Insomnia
Benzodiazepines
Risk factor
Polysomnography

ABSTRACT

Introduction: Given conflicting data in the literature, the aim of this study was to examine the risk of high blood pressure (HBP) associated with sleep alterations, measured during polysomnography, and long-term use of benzodiazepine receptor agonists in a large sample of individuals with insomnia.
Methods: Demographic and polysomnographic data from 1272 individuals with insomnia recruited from the research database of the sleep laboratory of Erasme Hospital were analyzed. HBP status was defined by the presence of one of the following: self-report at interview of either a physician's diagnosis or taking antihypertensive medication; or an average systolic blood pressure ≥140 mm Hg or an average diastolic blood pressure ≥90 mm Hg at the medical examination. Logistic regression analyses were conducted to examine the risk of HBP associated with objective sleep alterations and long-term use of benzodiazepine receptor agonists in individuals with insomnia.
Results: The prevalence of HBP in individuals with insomnia is 30.03%. After adjustment for major confounding factors associated with HBP, multivariate logistic regression analysis revealed that short sleep duration (<5 h), severely reduced sleep efficiency (<65%), high sleep fragmentation (sleep fragmentation index ≥18/h), and long-term use of short or intermediate half-life benzodiazepine receptor agonists were significant risk factors for HBP in individuals with insomnia.
Conclusion: In individuals with insomnia, objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are associated with higher risk of HBP. Therefore, better management of these reversible risk factors is required to avoid the negative consequences of the co-occurrence of insomnia and HBP.

1. Introduction

The co-occurrence of insomnia and high blood pressure (HBP) is very frequent. Indeed, the prevalence of insomnia in individuals with HBP is estimated at 44.0%, and the prevalence of HBP may reach 43.1% in individuals with insomnia, in whom it appears to be more frequent than in the general population (24.1% in men and 20.1% in women) [1,2]. In addition, insomnia is a risk factor for HBP, whereas HBP is associated with a higher risk of insomnia [3,4]. The physiopathology of this particular relationship between insomnia and HBP is still unknown, although several hypotheses have been advanced. On one hand, HBP could lead to the development of insomnia by the use of antihypertensive medications (such as β-blockers) or by the negative impact of a chronic disease on psychological functioning [5,6]. Conversely, insomnia could induce the development of HBP via an increase in sympathetic activity, a dysregulation of the hypothalamic–pituitary–adrenal axis, or an increase in inflammation [7]. Furthermore, this co-occurrence of insomnia and HBP is associated with the development of antihypertensive drug resistance, which results in higher cardiovascular mortality and justifies the establishment of an effective treatment [8–11]. Thus, it would be noteworthy to study the actual prevalence

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https://doi.org/10.1016/j.sleep.2018.08.030
1389-9457/

of HBP with a larger sample of individuals with insomnia to better assess the importance of this co-occurrence.

Individuals with insomnia with objective sleep alterations (short sleep duration, reduced sleep efficiency, or sleep fragmentation) seem to have an increased risk of HBP [12,13] through several mechanisms (dysregulation of autonomic nervous system activity, hypothalamic–pituitary–adrenal axis, or pro-inflammatory mechanisms) [14]. However, in the majority of published studies, duration and continuity of sleep are not objectively measured during polysomnography or actigraphy but are instead self-reported [15], which may lead to some limitations (methodological and recruitment bias) [16], Moreover, among the few studies using polysomnography or actigraphy, there are conflicting results on the role played by duration and continuity of sleep in the occurrence of HBP [17–20]. Therefore, we investigated the risk of HBP associated with objective sleep alterations measured during polysomnography to better understand the involvement of these alterations in the pathophysiology of HBP in individuals with insomnia.

In the general population, it has been demonstrated that long-term use of benzodiazepine receptor agonists is associated with a reduction in systolic and diastolic blood pressure [21], which may be explained by peripheral vasodilatation [22]. Nevertheless, to avoid the occurrence of deleterious side effects (eg, tolerance, dependence, or abuse), for the pharmacological management of insomnia, short-term treatment with short or intermediate half-life benzodiazepine agonists is recommended as the first-line. Benzodiazepine receptor agonists with long half-life must be used in the second-line [23]. However, despite these risks, the long-term use of benzodiazepine receptor agonists is frequent, mainly when prescribed for complaints of severe insomnia [24,25]. Thus, it would be interesting to study the protective or deleterious effects of long-term benzodiazepine receptor agonist use on the risk of HBP in individuals with insomnia, which has not yet been studied.

Our first objective was to investigate the prevalence of HBP in individuals with insomnia. Our second objective was to examine the risk of HBP associated with objective sleep alterations measured during polysomnography and long-term use of benzodiazepine receptor agonists in this subpopulation. To achieve these goals, we recruited a large sample of individuals with insomnia and divided them into a control group without HBP and a patient group with HBP. The aim of this approach is to provide health professionals with reliable data concerning the risk of HBP associated with objective sleep alterations and long-term benzodiazepine receptor agonist use. We hoped, as a consequence, to enable better prevention of this pathology and avoiding the negative consequences related to the co-occurrence of insomnia and HBP in individuals with insomnia.

2. Methods

2.1. Study population

The 1272 individuals with insomnia were recruited from the database of the sleep laboratory of Erasme Hospital, which contains data for 3511 individuals who completed sleep laboratory monitoring in the years 2002–2014. In our study, we did not recruit individuals without insomnia because our objective was to focus on the subpopulation of individuals with insomnia, in whom the co-occurrence of HBP may have a negative impact on cardiovascular outcomes.

These individuals with insomnia were referred to the sleep laboratory by physicians specializing in sleep medicine after an ambulatory consultation during which a preliminary assessment of complaints related to sleep, ongoing treatments, and somatic and psychiatric comorbidities was carried out systematically, making it possible to conduct a first diagnostic hypothesis. Following this first assessment, a sleep laboratory was offered to all individuals with insomnia to exclude the presence of other sleep pathology and to obtain an objective evaluation of their sleep. Thus, data for only those individuals with insomnia who accepted the sleep laboratory are in the database. Moreover, the data obtained during this ambulatory consultation are systematically checked when the subjects are admitted to the sleep laboratory.

The inclusion criteria were age ≥18 years, the presence of diagnostic criteria A (complaint of difficulty initiating [defined as sleep latency ≥30 min at least three times per week] or maintaining sleep [defined as three or more nocturnal awakenings or a long nighttime awakening (≥30 min) or early morning awakening (≥30 min before the usual time) at least three times per week], or nonrestorative sleep, for at least one month); and diagnostic criteria B (sleep disturbance or associated daytime fatigue causing clinically significant distress or impairment in social, occupational, or other important areas of functioning) of insomnia from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Text Revision (DSM-IV-TR) [26], which allowed us to recruit individuals with insomnia symptoms meeting strict diagnostic criteria.

The exclusion criteria included the presence of a major psychiatric disorder (psychotic disorder), presence of uncontrolled heavy somatic disease (chronic liver disease, chronic pancreatic disease, chronic pulmonary disease, severe cardiovascular disease, severe renal disease, autoimmune disease, and pathologies altering the activity of the hypothalamic–pituitary–adrenal axis such as Cushing's syndrome), presence of inflammatory or infectious disease, presence or history of cranial trauma, presence or history of central nervous system injury that could involve respiratory centres in the brain, presence or history of craniofacial or thoracic cavity malformations, current pregnancy, presence of obstructive sleep apnea syndrome (OSA) already known or course of treatment before sleep laboratory, presence of periodic limb movement (PLM) disorder/restless legs syndrome already known or course of treatment before sleep examinations, presence of predominantly central apnea syndrome, presence of narcolepsy or primary hypersomnia, presence of parasomnia, and presence or history of substance abuse.

2.2. Procedures

2.2.1. Medical and psychiatric evaluation of participants

All individuals upon admission to the sleep laboratory of Erasme Hospital had their medical records reviewed and a complete somatic examination performed, including a blood test, electrocardiogram, a daytime electroencephalogram, urinalysis, and a chest X-ray (only for those individuals >45 years of age). These steps allowed for a systematic diagnosis of potential somatic pathologies present in persons admitted to our unit.

HBP status was defined by the presence of one of the following: self-report at interview of either a physician's diagnosis or taking antihypertensive medication (including β-blockers, calcium channel blockers, diuretics, vasodilators, β-blockers with diuretics, angiotensin-converting enzyme inhibitors, angiotensin-converting enzyme inhibitors with diuretics, vasodilators with diuretics, angiotensin type 2 antagonists, or angiotensin type 2 antagonists with diuretics); or an average systolic blood pressure ≥140 mm Hg or an average diastolic blood pressure ≥90 mm Hg according to the World Health Organization diagnostic criteria [27]. Systolic and diastolic blood pressures were manually measured by well-trained nurses at the right arm after 5 min of rest in a sitting position. For individuals with a systolic blood pressure ≥140 mm Hg and/or a

diastolic blood pressure ≥90 mm Hg, blood pressures were measured again after an additional 5-min rest period.

Long-term use of benzodiazepine receptor agonists was defined as the use of benzodiazepines or Z-drugs (zolpidem, zopiclone, or zaleplon) for at least five days per week for a minimum period of six months before the sleep examination [28]. Benzodiazepine receptor agonists have been classified as short half-life (<6 h), intermediate half-life (6–24 h), and long half-life (>24 h) [29]. This study included no individuals with occasional or short-term benzodiazepine receptor agonist use because they had been instructed to stop this treatment at least 15 days prior to the sleep examination.

Patients also benefited on the day of admission from an appointment with a unit psychiatrist who potentially assigned psychiatric diagnoses per the DSM-IV-TR criteria [26].

On admission, patients completed a series of self-questionnaires to assess the severity of their subjective complaints of depression, poor sleep, and excessive daytime sleepiness as follows:

- The presence of depressive symptoms was investigated using the Beck Depression Inventory (BDI, reduced to 13 items). This scale consists of 13 items that can be scored from 1 to 3. The final score can vary from 0 to 39. A final score of 0–4 indicates an absence of depression, 5–7 slight depression, 8–15 moderate depression, and >16 severe depression [30].
- Daytime sleepiness was investigated using the Epworth Sleepiness Scale. This scale consists of eight questions that can be scored from 0 to 3 and assesses sleepiness during different daytime situations. The final score varies from 0 to 24. A final score of >10 indicates excessive daytime sleepiness [31].
- The presence of insomnia symptoms was investigated using the Insomnia Severity Index (ISI). This index consists of seven questions that can be scored from 0 to 4. The final score can vary from 0 to 28. A score of 0–7 indicates a lack of insomnia, 8–14 subclinical insomnia, 15–21 moderate insomnia, and 22–28 severe insomnia [32].

To avoid missing values, individuals who did not respond fully to these questionnaires were not included in our study.

2.2.2. Sleep evaluation and study

A unit psychiatrist conducted a sleep-specific medical record systematic review on the day of admission to complete an assessment of complaints related to sleep, including sleeping habits, severity of self-reported insomnia complaints (difficulty falling asleep, repeated nighttime awakenings, early morning awakening, and nonrestorative sleep), insomnia duration, symptoms of sleep apnea (snoring and self-reported apneas), symptoms of restless legs syndrome (drive to move the legs often, accompanied by abnormal leg sensations; symptom worsening at rest, that is, sitting; partial or temporary relief by activity, at least as long as the activity continues; worsening of the symptoms later in the day or night) [33], and nocturnal movements (eg, periodic limb movements [PLMs]). Restless legs syndrome was defined as occasional (<2 episodes/wk) and frequent (≥2 episodes/wk) based on the frequency of episodes for one week [34]. Insomnia was diagnosed after this appointment if the diagnostic criteria A and B for insomnia according to DSM IV-TR [26] were met.

Participants stayed in a sleep laboratory for two nights, including a first night of habituation and a night of polysomnography from which the data were collected for analysis. The patients went to bed between 22:00 and 24:00 and arose between 6:00 and 8:00, following their usual schedule. During bedtime hours, the subjects were recumbent and the lights were turned off. Daytime naps were not permitted.

The polysomnographic recordings from our unit met the guidelines of the American Academy of Sleep Medicine (AASM) [35]. The applied polysomnography-montage was as follows: two electro-oculogram channels, three electroencephalogram channels (Fz-Ax, Cz-Ax, and Oz-Ax, where Ax was a contralateral mastoid reference), one submental electromyogram channel, electrocardiogram, thermistors to detect the oro-nasal airflow, finger pulse oximetry, a microphone to record breathing sounds and snoring, piezoelectric sensors, and leg movement electrodes. In addition, the applied polysomnography montage also included strain gauges to measure thoracic and abdominal breathing. Polysomnographic recordings were visually scored by specialized technicians using AASM criteria [36] (inter-judge agreement score of 85%).

Objective sleep alterations were defined based on polysomnographic parameters:

- Sleep efficiency was divided into three categories: ≥85% (absence of reduced sleep efficiency), 65 and <85% (slightly reduced sleep efficiency), and <65% (severely reduced sleep efficiency).
- Total sleep time was divided into three categories: <5 h (short sleep duration), ≥5 and <7 h (intermediate sleep duration), and ≥7 h (long sleep duration).
- Sleep fragmentation index was divided into two categories: <18/h (low sleep fragmentation) and ≥18/h (high sleep fragmentation). A sleep fragmentation index was obtained by adding the micro-arousals and awakenings indices.

Apneas were scored if the decrease in airflow was ≥90% for at least 10 s and hypopneas were scored if the decrease in airflow was ≥30% for at least 10 s with a decrease in oxygen saturation of 3% or followed by a micro-arousal [37]. The apnea–hypopnea index (AHI) corresponds to the total number of apneas and hypopneas divided by period of sleep in hours. OSA was considered absent when AHI was <5/h, mild when AHI was ≥5 and <15/h, moderate when AHI was ≥15 and <29/h, and severe when AHI was ≥30/h [38]. PLMs were scored by the following strict criteria: duration between 0.5 and 10 s, interval between 5 and 90 s from leg movement onset, and movements had to be part of a series of ≥4 consecutive movements meeting these criteria [39]. A PLM index corresponds to the total number of PLMs divided by period of sleep in hours. Moderate to severe PLM disorder was present when PLMs index was ≥26/h [40].

After the sleep examination, the diagnosis of primary insomnia was made by a unit psychiatrist when the diagnostic criteria of the primary insomnia of the DSM-IV-TR [26] were present, which allowed the realization of the analyses on the particular subpopulation of primary insomnia patients.

2.3. Statistical analyses

Statistical analyses were performed using Stata 14 (StataCorp LLC, College Station, TX). The normal distribution of the data was verified using histograms, boxplots, and quantile–quantile plots, and the equality of variances was checked using the Levene test.

In order to allow our analyses, we subdivided into a control group without HBP and a patient group with HBP both the whole sample of individuals with insomnia and the particular subgroup of primary insomnia patients. Only individuals with a diagnosis of HBP according to the diagnostic criteria of the World Health Organization at admission were included in the HBP group.

Categorical data were described with percentages and numbers, and continuous data were described with means and standard deviations or as median and P25–P75 (25th to 75th percentile). Normally distributed variables were analyzed with a *t*-test. A

Wilcoxon test or χ^2 test was used on asymmetric distributed or dichotomous variables.

Univariate binary logistic regression models were used to study the risk of HBP associated with objective sleep alterations, long-term use of benzodiazepine receptor agonists, and potential confounding factors. After a review of the literature on risk factors for HBP in the general population [19,41–49], potential confounding factors included for this analysis were Epworth Sleepiness Scale (ESS) score (categorical: ≤10, >10), ISI score (categorical: <15, ≥15, and <22, ≥22), BDI score (categorical: ≤4, >4, and <16, ≥16), BMI (categorical: <25 kg/m^2, ≥25 and <30 kg/m^2, ≥30 kg/m^2), age (categorical: <30 years, ≥30 and <50 years, ≥50 years), alcohol (categorical: 0 unit/d, ≥1 and <4 unit/d, ≥4 unit/d), AHI (categorical: <5/h, ≥5 and <15/h, ≥15 and <30/h, ≥30/h), PLMs index (categorical: <26/hour, ≥26/hour), frequency of restless legs syndrome (categorical: no, occasional, frequent), insomnia duration (categorical: 1–5 months, ≥6 months) and as binary variables gender, snoring, antidepressant therapy, smoking, caffeine, type 2 diabetes, and hypertriglyceridemia.

In multivariate binary logistic regression models, the risk of HBP associated with objective sleep alterations, and long-term use of benzodiazepine receptor agonists was adjusted only for confounding factors significantly associated with HBP. These confounding factors were entered in a hierarchical way, adjusting for gender, age, and BMI in model 1, and adding antidepressant therapy, smoking, alcohol, and caffeine in model 2. Model 3 further included hypertriglyceridemia and type 2 diabetes. Finally, model 4 added snoring, PLM disorder severity, OSA severity, and insomnia duration.

The adequacy of model 4 was verified by the Hosmer and Lemeshow test and the specificity of the model by Link test. The numbers of subjects by risk factors, outliers, and collinearity between risk factors that may cause problems were been verified.

A p value of <0.05 was considered significant.

3. Results

3.1. Polysomnographic data

Polysomnographic data for the whole sample are available in Table 1. Compared to those without HBP, individuals with HBP have a decrease in sleep efficiency, sleep period time, total sleep time, slow-wave sleep, and rapid eye movement (REM) sleep, whereas they show an increase in stage 1, wake after sleep onset, REM latency, number of awakenings, micro-arousal index, sleep fragmentation index, AHI, oxygen desaturation index, total time under 90% of SaO2, and PLMs index. There are no significant differences for sleep latency and stage 2.

3.2. Demographic data

Demographic data are provided in Table 2. Male gender, snoring, antidepressants therapy, type 2 diabetes, hypertriglyceridemia, caffeine consumption, alcohol consumption, severely reduced sleep efficiency, short sleep duration, high sleep fragmentation, AHI ≥5 and <15/h, AHI ≥15 and <30/h, AHI ≥30/h, PLMs index ≥26/h, insomnia duration ≥6 months, and long-term use of short or intermediate half-life benzodiazepine receptor agonists are more frequent in individuals with HBP. These individuals also present with an age/BMI greater than those of the individuals without HBP. In addition, compared to those without HBP, smoking is less frequent in individuals with HBP. There was no significant difference in BDI score, ISI score, ESS score, frequency of restless legs syndrome, and long-term use of long half-life benzodiazepine receptor agonists.

3.3. Prevalence of HBP in individuals with insomnia

The prevalence of HBP in our sample of individuals with insomnia is 30.03% (n = 382) (Table 2).

3.4. Univariate analysis

Results of the univariate analysis are provided in the Supplementary Data. Male gender, snoring, antidepressant therapy, type 2 diabetes, hypertriglyceridemia, no smoking, alcohol consumption ≥1 and <4 unit/d, alcohol consumption ≥4 unit/d, caffeine consumption, BMI ≥25 and <30 kg/m^2, BMI ≥30 kg/m^2, age ≥30 and <50 years, age ≥50 years, AHI ≥5 and <15/h, AHI ≥15 and <30/h, AHI ≥30/h, PLMs index ≥26/h, slightly reduced sleep efficiency, severely reduced sleep efficiency, short sleep duration, intermediate sleep duration, high sleep fragmentation, insomnia duration ≥6 months, and long-term use of short or intermediate half-life benzodiazepine receptor agonists were

Table 1
Polysomnographic data of study subjects.

	Whole sample (N = 1272)	Subjects without HBP (n = 890)	Subjects with HBP (n = 382)	p
SL (min)	24.67 (14.33–42.59)	24.00 (14.00–42.00)	26.00 (14.50–46.50)	0.080[a]
SE (%)	79.98 (71.38–86.21)	81.24 (72.95–86.99)	76.58 (65.65–84.04)	<0.001[a]
SPT (min)	448.74 ± 63.58	451.46 ± 61.67	442.40 ± 67.48	0.020[b]
TST (min)	384.67 ± 74.00	392.65 ± 68.97	366.06 ± 81.70	<0.001[b]
% Stage 1	7.05 (4.63–9.89)	6.83 (4.60–9.46)	7.57 (4.77–11.61)	0.001[a]
% Stage 2	54.88 ± 10.58	55.24 ± 9.87	54.02 ± 12.05	0.061[b]
% SWS	3.48 (0.32–9.54)	4.91 (0.80–11.35)	1.30 (0.00–6.20)	0.001[a]
% REM	16.82 ± 6.32	17.33 ± 6.13	15.63 ± 6.60	<0.001[b]
% WASO	11.59 (6.90–18.58)	10.67 (6.31–16.95)	14.14 (8.73–22.48)	<0.001[a]
REM latency (min)	79.67 (57.00–128.00)	77.00 (57.00–122.00)	87.00 (57.42–142.00)	0.019[a]
Number of awakenings	31 (21–46)	31 (21–45)	32 (22–48)	0.035[a]
Micro-arousal index	7 (5–12)	7 (4–11)	9 (5–15)	<0.001[a]
Sleep fragmentation index	11.98 (8.72–17.35)	11.49 (8.34–16.11)	13.88 (9.90–21.59)	<0.001[a]
AHI	2 (1–7)	2 (1–5)	4 (1–14)	<0.001[a]
ODI	1 (0–3)	1 (0–2)	2 (1–6)	<0.001[a]
Total time <90% of SaO_2 (min)	0.50 (0.00–14.17)	0.00 (0.00–6.00)	4.33 (0.00–47.50)	<0.001[a]
PLM index	17.80 (8.66–32.63)	16.96 (8.57–31.74)	19.52 (8.94–37.58)	0.041[a]

AHI, apnea–hypopnea index; HBP, high blood pressure; ODI, oxygen desaturation index; PLM, periodic limb movement; REM, rapid eye movement; SaO_2, oxygen saturation; SE, sleep efficiency; SL, sleep latency; SPT, sleep period time; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset.
[a] Wilcoxon test.
[b] t-Test.

Table 2
Sample description ($N = 1272$).

Variable		Category	%	Subjects without HBP	Subjects with HBP	p (χ^2)
Gender		Female (n = 604)	47.48%	50.22%	41.10%	0.003
		Male (n = 668)	52.52%	49.78%	58.90%	
Snoring		No (n = 635)	49.92%	54.94%	38.22%	<0.001
		Yes (n = 637)	50.08%	45.06%	61.78%	
Benzodiazepine receptor agonists		No (n = 984)	77.36%	81.01%	68.85%	<0.001
		Short (n = 129)	10.14%	8.20%	14.66%	
		Intermediate (n = 85)	6.68%	4.61%	11.52%	
		Long (n = 74)	5.82%	6.18%	4.97%	
Antidepressant therapy		No (n = 894)	70.28%	73.03%	63.87%	0.001
		Yes (n = 378)	29.72%	26.97%	36.13%	
Type 2 diabetes		No (n = 1007)	79.17%	86.85%	61.26%	<0.001
		Yes (n = 265)	20.83%	13.15%	38.74%	
Hypertriglyceridemia		No (n = 911)	71.62%	76.74%	59.69%	<0.001
		Yes (n = 361)	28.38%	23.26%	40.31%	
Smoking		No (n = 981)	77.12%	75.51%	80.89%	0.036
		Yes (n = 291)	22.88%	24.49%	19.11%	
Alcohol (unit/d)		0 (n = 981)	77.12%	80.90%	68.32%	<0.001
		≥1 and < 4 (n = 251)	19.73%	17.30%	25.39%	
		≥4 (n = 40)	3.15%	1.80%	6.28%	
Caffeine		No (n = 363)	28.54%	31.24%	22.25%	0.001
		Yes (n = 909)	71.46%	68.76%	77.75%	
RLS		No (n = 878)	69.03%	67.87%	67.73%	0.197
		Occasional (n = 203)	15.96%	15.96%	15.97%	
		Frequent (n = 191)	15.01%	16.18%	12.30%	
Reduced sleep efficiency		Absent (n = 391)	30.74%	34.27%	22.51%	<0.001
		Slightly (n = 695)	54.64%	55.28%	53.14%	
		Severely (n = 186)	14.62%	10.45%	24.35%	
Sleep duration		Long (n = 416)	32.70%	35.39%	26.44%	<0.001
		Intermediate (n = 737)	57.94%	58.43%	56.81%	
		Short (n = 119)	9.36%	6.18%	16.75%	
Sleep fragmentation		Low (n = 977)	76.81%	82.02%	64.66%	<0.001
		High (n = 295)	23.19%	17.98%	35.34%	
AHI		<5 (n = 839)	65.96%	71.80%	52.36%	<0.001
		≥5 and < 15 (n = 258)	20.28%	18.88%	23.56%	
		≥15 and < 30 (n = 84)	6.60%	4.72%	10.99%	
		≥30 (n = 91)	7.15%	4.61%	13.09%	
PLMs index		<26/h (n = 837)	65.80%	68.54%	59.42%	0.002
		≥26/h (n = 435)	34.20%	31.46%	40.58%	
Insomnia duration		1–5 mo (n = 781)	61.40%	63.26%	57.07%	0.038
		≥6 mo (n = 491)	38.60%	36.74%	42.93%	
HBP		No (n = 890)	69.97%			
		Yes (n = 382)	30.03%			
	Mean ± SD					t Test
BMI (kg/m^2)	26.90 ± 5.78			25.60 ± 5.15	29.91 ± 6.03	<0.001
		<25 (n = 542)	42.61%	51.69%	21.47%	
		≥25 and < 30 (n = 409)	32.15%	31.69%	33.25%	
		≥30 (n = 321)	25.24%	16.63%	45.29%	
Age (y)	44.93 ± 12.28			41.79 ± 11.65	52.25 ± 10.49	<0.001
		<30 (n = 182)	14.31%	19.44%	2.26%	
		≥30 and < 50 (n = 667)	52.44%	57.30%	41.10%	
		≥50 (n = 423)	33.25%	23.26%	56.54%	
Systolic blood pressure (mm Hg)	121.45 ± 14.92			117.88 ± 12.37	129.78 ± 16.92	<0.001
Diastolic blood pressure (mm Hg)	74.21 ± 10.69			72.50 ± 9.81	78.18 ± 11.58	<0.001
	Median (P25–P75)					Wilcoxon test
BDI score	6 (3–11)			6 (3–11)	6 (3–11)	0.779
		≤4 (n = 459)	36.09%	36.29%	35.60%	
		>4 and < 16 (n = 657)	51.65%	51.12%	52.88%	
		≥16 (n = 156)	12.26%	12.58%	11.52%	
ISI score	18 (16–21)			19 (16–21)	18 (16–21)	0.143
		<15 (n = 175)	13.76%	13.48%	14.40%	
		≥15 and < 22 (n = 824)	64.78%	63.60%	67.54%	
		≥22 (n = 273)	21.46%	22.92%	18.06%	
Epworth Sleepiness Scale score	10 (6–14)			10 (6–14)	10 (6–14)	0.929
		≤10 (n = 689)	54.17%	54.16%	54.19%	
		>10 (n = 583)	45.83%	45.84%	45.81%	

AHI, apnea–hypopnea index; BDI, Beck Depression Inventory; BMI, body mass index; HBP, high blood pressure; ISI, Insomnia Severity Index; PLM, periodic limb movement; RLS, restless legs syndrome; SD, standard deviation. P25–P75, 25th to 75th percentile.

associated with an increased risk of HBP in individuals with insomnia.

3.5. Multivariate analysis for the whole sample

Results of the multivariate analysis for the entire sample are shown in Table 3. In the four models studied, the risk of hypertension associated with short sleep duration (odds ratio [OR] 1.91, 95% confidence interval [CI] 1.15–3.16), severely reduced sleep efficiency (OR 1.57, (95% CI 1.01–2.45)), high sleep fragmentation (OR 1.59, 95% CI 1.10–2.30), and long-term use of short (OR 1.78, 95% CI 1.03–3.09) or intermediate (OR 2.10, 95% CI 1.12–3.92) half-life benzodiazepine receptor agonists remains significant, whereas the risk of HBP associated with intermediate sleep duration (OR 0.89, 95% CI 0.65–1.23) and slightly reduced sleep efficiency (OR 0.92, 95% CI 0.65–1.29) becomes nonsignificant. Despite the adjustment for major confounding factors associated with HBP in the four models studied, multivariate logistic regression analysis revealed that long-term use of long half-life benzodiazepines receptor receptors (OR 0.92, 95% CI 0.46–1.86) was not significantly associated with higher risk of HBP.

3.6. Multivariate analysis for primary insomnia patients individuals with insomnia

Results of the multivariate analysis for primary insomnia patients are shown in Table 4. In order to keep only the 641 primary insomnia patients included in this analysis, we excluded 156 individuals with psychiatric comorbidity, 387 individuals with PLM disorder and/or restless legs syndrome, and 88 individuals with OSA from our initial sample of 1272 individuals with insomnia. In the four models studied, the risk of hypertension associated with high sleep fragmentation (OR 1.82, 95% CI 1.02–3.25) and long-term use of short or intermediate (OR 2.71, 95% CI 1.25–5.87) half-life benzodiazepine receptor agonists remains significant, whereas the risk of HBP associated with short sleep duration (OR 1.80, 95% CI 0.82–3.92) and severely reduced sleep efficiency (OR 1.21, 95% CI 0.62–2.38) becomes nonsignificant. Despite the adjustment for major confounding factors associated with HBP in the four models studied, multivariate logistic regression analysis revealed that intermediate sleep duration (OR 0.96, 95% CI 0.60–1.53), slightly reduced sleep efficiency (OR 0.84, 95% CI 0.51–1.36), and long-term use of long half-life benzodiazepines receptor receptors (OR 0.92, 95% CI 0.30–2.85) remains not significantly associated with higher risk of HBP.

4. Discussion

In our sample of individuals with insomnia, we demonstrated a prevalence of HBP of 30.03%, which highlights the importance of this problem to the health care professionals treating this particular subpopulation. This prevalence is less important than those of 43.1% and 52.0% highlighted by Taylor et al., [1] and Vgontzas et al., [50], which may be explained by the fact that in these studies, the diagnosis of insomnia was not based on DSM-IV-TR [26] criteria but based instead on self-questionnaires, which may lead to a recruitment bias resulting in overestimation of HBP. In addition, it is higher than that of the 16.90% shown by Li et al., [3]. However, in this study, the criteria used for the diagnosis of insomnia were those of the primary insomnia of DSM-IV-TR [26], which may lead to underestimation of HBP because individuals with secondary insomnia were excluded from this analysis. On the other hand, it seems relatively similar to that of 25.5% demonstrated by Bathgate et al., [17], which may be explained by the use in that study of diagnostic criteria for insomnia similar to those applied in our study. Finally, this prevalence is higher than that demonstrated in the general population (22.6%) [51] and seems to confirm that HBP is more frequent in the subpopulation of individuals with insomnia. However, the co-occurrence of insomnia and HBP is associated with many negative consequences [52] that may have a detrimental impact on the prognosis of these individuals [53] and justifies the need for effective treatment [10,11]. Therefore, in individuals with insomnia, it is important to identify the specific risk factors for HBP to enhance the detection and management of this pathology and to reduce complications and mortality for these individuals.

Among the few studies using polysomnography, there are contradictory results regarding the role of sleep duration in HBP occurrence in individuals with insomnia. The variation may be explained by the recruitment of different populations of individuals

Table 3
Multivariate analysis results ($N = 1272$).

Variable	Model 1 OR adjusted (95% CI)	p	Model 2 OR adjusted (95% CI)	p	Model 3 OR adjusted (95% CI)	p	Model 4 OR adjusted (95% CI)	p
Benzodiazepines receptor agonists		0.003		0.007		0.017		0.030
No	1		1		1		1	
Short	1.83 (1.20–2.77)		1.75 (1.14–2.71)		1.64 (1.06–2.55)		1.78 (1.03–3.09)	
Intermediate	1.97 (1.19–3.26)		1.90 (1.13–3.19)		1.87 (1.11–3.18)		2.10 (1.12–3.92)	
Long	0.91 (0.51–1.65)		0.83 (0.45–1.53)		0.82 (0.44–1.54)		0.92 (0.46–1.86)	
Reduced sleep efficiency		0.012		0.013				0.022
Absent	1		1		1		1	
Slightly	0.95 (0.69–1.32)		0.95 (0.68–1.32)		0.95 (0.68–1.33)		0.92 (0.65–1.29)	
Severely	1.65 (1.08–2.54)		1.65 (1.07–2.54)		1.62 (1.04–2.52)	0.021	1.57 (1.01–2.45)	
Sleep duration (h)		0.002		0.002		0.004		0.005
Long	1		1		1		1	
Intermediate	0.94 (0.69–1.28)		0.93 (0.68–1.26)		0.91 (0.67–1.25)		0.89 (0.65–1.23)	
Short	2.07 (1.28–3.35)		2.09 (1.28–3.39)		1.98 (1.21–3.26)		1.91 (1.15–3.16)	
Sleep fragmentation		0.001		0.004		0.009		0.014
Low	1		1		1		1	
High	1.66 (1.22–2.27)		1.59 (1.16–2.18)		1.53 (1.11–2.11)		1.59 (1.10–2.30)	

Model 1: adjustment for gender, age, and BMI.
Model 2: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, and caffeine.
Model 3: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, caffeine, hypertriglyceridemia, and type 2 diabetes.
Model 4: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, caffeine, hypertriglyceridemia, type 2 diabetes, snoring, PML index, AHI, and insomnia duration.
AHI, apnea–hypopnea index; BMI, body mass index; CI, confidence interval; HBP, high blood pressure; OR, odds ratio; PLM, periodic limb movements.

Table 4
Multivariate analysis results for primary insomnia patients ($n = 641$).

Variable	Model OR unadjusted (95% CI)	p	Model 1 OR adjusted (95% CI)	p	Model 2 OR adjusted (95% CI)	p	Model 3 OR adjusted (95% CI)	p	Model 4 OR adjusted (95% CI)	p
Benzodiazepine receptor agonists		<0.001		0.007		0.002		0.018		0.015
No	1		1		1		1		1	
Short/Intermediate	2.77 (1.77–4.34)		2.17 (1.31–3.60)		2.07 (1.27–3.37)		2.02 (1.18–3.45)		2.71 (1.25–5.87)	
Long	1.01 (0.43–2.38)		0.78 (0.30–2.00)		0.57 (0.26–1.28)		0.69 (0.26–1.82)		0.92 (0.30–2.85)	
Reduced sleep efficiency		<0.001		0.226		0.306		0.419		0.426
Absent	1		1		1		1		1	
Slightly	1.25 (0.82–1.90)		0.84 (0.53–1.34)		0.85 (0.53–1.36)		0.86 (0.53–1.39)		0.84 (0.51–1.36)	
Severely	3.33 (1.92–5.77)		1.38 (0.73–2.62)		1.33 (0.69–2.54)		1.27 (0.66–2.47)		1.21 (0.62–2.38)	
Sleep duration		<0.001		0.097		0.100		0.177		0.227
Long	1		1		1		1		1	
Intermediate	1.30 (0.86–1.95)		1.01 (0.64–1.57)		0.99 (0.63–1.56)		1.00 (0.63–1.57)		0.96 (0.60–1.53)	
Short	4.48 (2.35–8.52)		2.10 (1.00–4.40)		2.09 (0.99–4.39)		1.92 (0.90–4.11)		1.80 (0.82–3.92)	
Sleep fragmentation		0.010		0.017		0.039		0.037		0.044
Low	1		1		1		1		1	
High	1.92 (1.17–3.16)		1.96 (1.13–3.42)		1.83 (1.03–3.23)		1.85 (1.04–3.29)		1.82 (1.02–3.25)	

Model 1: adjustment for gender, age, and BMI.
Model 2: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, and caffeine.
Model 3: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, caffeine, hypertriglyceridemia, and type 2 diabetes.
Model 4: adjustment for gender, age, BMI, antidepressant therapy, smoking, alcohol, caffeine, hypertriglyceridemia, type 2 diabetes, snoring, and insomnia duration.
AHI, apnea–hypopnea index; BMI, body mass index; CI, confidence interval; HBP, high blood pressure; OR, odds ratio.

with insomnia in these studies according to the diagnostic criteria used (insomnia disorder or primary insomnia) [54]. Indeed, in studies recruiting individuals with insomnia disorder, short sleep duration is a risk factor for HBP [12,17,50]. In contrast, studies recruiting primary insomnia patients found that short sleep duration is not a risk factor for HBP [19]. Moreover, even though the majority of studies have focused only on the relationship between short sleep duration and cardiometabolic complications in individuals with insomnia [55,56], alterations in sleep continuity may also be considered a marker of cardiometabolic severity in insomnia [57]. Here, we found that short sleep duration and reduced sleep efficiency are associated with higher risk of HBP in individuals with insomnia disorder, whereas in primary insomnia patients, short sleep duration and reduced sleep efficiency are not associated with increased occurrence of HBP. Our results seem to confirm that among individuals with insomnia, the role played by short sleep duration and reduced sleep efficiency in the pathophysiology of HBP differs according to the diagnostic criteria of insomnia used [58]. One possible explanation for this difference could be a synergy between short sleep duration and sleep disorders (OSA and/or PLM disorder) in individuals with insomnia disorder, which may potentiate the occurrence of biological alterations associated with increased cardiometabolic risk (dysregulation of autonomic nervous system activity, hypothalamic–pituitary–adrenal axis, or pro-inflammatory mechanisms). In primary insomnia patients, however, the lack of this synergy could explain the absence of a higher risk of HBP associated with short sleep duration and reduced sleep efficiency [59]. Yet, we have shown that primary insomnia patients with excessive sleep fragmentation have a higher risk of HBP, which could be explained by overactivation of the stress system secondary to a greater tendency toward nocturnal awakenings induced by hyperarousal [60–62]. Thus, regardless of the subgroup of individuals with insomnia who are studied (insomnia disorder or primary insomnia), adequate management of objective sleep alterations and associated sleep disorders (OSA and PLM disorder) is necessary to improve cardiovascular outcomes in these individuals with insomnia.

We found that long-term use of short or intermediate half-life benzodiazepine receptor agonists was associated with a higher risk of HBP in individuals with insomnia. Although a short treatment with short or intermediate half-life benzodiazepine receptor agonists is a first-line recommendation for the pharmacological management of insomnia [63], it is not followed in many individuals. Indeed, in the case of a prescription as hypnotic, the long-term use of short or intermediate half-life benzodiazepine receptor agonists is frequent, despite the risks of dependence, tolerance, and abuse [64]. As their duration of action is not sufficient to cover the period between administrations, short or intermediate half-life benzodiazepine receptor agonists may result in transient withdrawals [65], which may become recurrent with long-term use and may be associated with the repeated occurrence of withdrawal symptoms such as anxiety [66]. However, this repeated occurrence of anxiety may increase autonomic arousal via overactivation of the hypothalamic–pituitary–adrenal axis, which may lead to an increase in circulating catecholamines and increased HBP risk [67]. Thus, the long-term prescription of short or intermediate half-life benzodiazepine receptor agonists as hypnotics is not trivial because it is associated with increased HBP risk, which could partly explain the excess cardiovascular mortality present in individuals with insomnia [68] and justifies a strict adherence to the recommendations for the pharmacological treatment of insomnia.

Short or intermediate half-life benzodiazepine receptor agonists reduce sleep latency but only slightly increase sleep duration or efficiency [69,70]. Given their limited duration of action, they act mainly at the beginning of the night by facilitating falling asleep, whereas their action is less effective for the occurrence of awakenings at the end of the night [69,70]. Nevertheless, in primary insomnia, hyperarousal has a specific dynamic during the night whereby it occurs primarily during sleep onset, the first third of the night, and the last third of the night [71]. Short or intermediate half-life benzodiazepine receptor agonists only partially block hyperarousal during the night and do not prevent the long-term occurrence of biological alterations (overactivity of the sympathetic system and hypothalamic–pituitary–adrenal axis) [72,73] associated with the somatic component of hyperarousal [74], which may promote the development of HBP [75,76] in primary insomnia patients. In the case of chronic treatment in primary insomnia, it is therefore important to favor a treatment that completely blocks hyperarousal and to prevent the occurrence of cardiovascular complications in this particular subpopulation of primary insomnia patients individuals with insomnia..

In the future, prospective studies should be conducted with the subpopulation of individuals with insomnia to validate the risk factors of HBP highlighted in our study.

4.1. Study limitations

The results obtained in our study come from retrospective data that, even if they have been encoded in a systematic manner, cannot be verified directly with the subject in most cases, which means that our results need to be replicated in prospective studies. Moreover, we focused only on HBP, which means that our results cannot be generalized to other cardiovascular pathology, such as myocardial infarction and stroke. In addition, our database contains only individuals with insomnia who have agreed to perform sleep laboratory testing, which may also limit the generalization of results. Finally, another limitation of our study is the absence of a scale for anxiety.

5. Conclusion

We found a 30.03% prevalence rate of HBP in a large sample of individuals with insomnia. In this subpopulation, objective sleep alterations measured during polysomnography and long-term use of short or intermediate half-life benzodiazepine receptor agonists are associated with increased HBP risk. Thus, sleep alterations must be adequately managed, and recommendations for the pharmacological treatment of insomnia must be strictly followed in order to avoid the negative consequences of the co-occurrence of insomnia and HBP.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

This research protocol was approved by the Hospital and Medical School Ethics Committee of the Erasme Hospital (Brussels University Clinics) (Erasme Reference: P2017] 186). At Erasme Hospital, all patients are informed that their data could be used retrospectively for scientific research. If patients do not wish for their data to be used, they must inform the hospital, at which time, this directive is indicated in their medical records, and any future use of their data is prohibited.

Availability of data and material

The datasets used and] or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

MH: principal investigator of the study with active participation in the encoding of data, statistical analysis, interpretation of results and writing of the article. JL: Active participation in the extraction and calculation of data from polysomnography for the realization of the database. GL: Support in the English translation of the manuscript and supervised the research work as a thesis promoter. PL: Support in drafting the manuscript and supervision of the research work as a thesis co-promoter. PH: Support in drafting the manuscript and supervision of research work as a member of the accompanying thesis committee. All authors read and approved the final manuscript.

Acknowledgements

The authors thank Christelle Bouchart, MD, for her support and the sleep laboratory team from the Erasmus Hospital for technical support.

Conflict of interest

The authors have no conflicts of interest with the work carried out in this study.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.08.030.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2018.08.030.

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