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Mechanisms Linking Insomnia and Cardiometabolic Disease Risk

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ABSTRACT: About 10% to 15% of the adult population reports frequent, chronic insomnia symptoms of difficulty initiating or maintaining sleep associated with daytime impairment (ie, insomnia disorder). An additional 30% to 40% report insomnia symptoms at any given time. Not only is insomnia disproportionally more prevalent in individuals with cardiometabolic diseases, but evidence also demonstrates that insomnia, particularly when coupled with objective short sleep duration, increases the risk of developing cardiometabolic diseases. Insomnia is a disorder of 24-hour hyperarousal, a multidimensional construct ranging from cognitive to physiological dysregulation. Physiological hyperarousal in insomnia occurs in the form of hyperactivation of wake-promoting and emotion-regulating areas (eg, glucose metabolism in the ascending reticular activating system), hypothalamic-pituitary-adrenal axis (eg, cortisol levels), sympatho-adrenomedullary axis (eg, norepinephrine levels), cardiac sympathetic-parasympathetic system (eg, heart rate variability), and low-grade inflammation (eg, cytokine levels). Physiological hyperarousal in insomnia inhibits sleep ability, leading to objective short sleep and increasing cardiometabolic disease risk. This brief review summarizes the evidence on the pathophysiologic mechanisms associating insomnia with cardiometabolic disease risk, including current knowledge on the phenotypic heterogeneity of insomnia based on objective sleep duration. Future studies need to test the molecular, cellular, and behavioral mechanisms at play in increasing cardiometabolic disease risk across robustly identified insomnia phenotypes.

Key Words: blood pressure ■ cardiovascular diseases ■ phenotype ■ risk ■ sleep initiation and maintenance disorders

Insomnia is the most prevalent sleep disorder and is highly comorbidity with cardiometabolic diseases. This comorbidity suggests potentially shared pathophysiologic mechanisms. In fact, epidemiological data indicate that insomnia can precede and contribute to the development of cardiometabolic diseases. However, the extant evidence also shows that objectively measured sleep is heterogeneous in individuals with similar chronic insomnia complaints, reflecting individual differences in physiological sleep ability across insomnia phenotypes. Physiological data reviewed herein indicate that objectively defined insomnia phenotypes show elevated indices of hypothalamic-pituitary-adrenal and sympatho-adrenomedullary axis activation, reductions in cardiac autonomic modulation, among other pathophysiologic changes that are mechanistically linked to endothelial dysfunction, elevated blood pressure (BP), and insulin resistance, and, over time, to heart failure, cardiac arrhythmias, and myocardial infarction. This brief review summarizes evidence on the mechanistic pathways associating insomnia with cardiometabolic diseases. It includes current evidence on the heterogeneity of insomnia from an objectively measured sleep standpoint and discusses the pathophysiology of objective short sleep duration in chronic insomnia and its mechanistic role in cardiometabolic disease risk.

WHAT IS INSOMNIA?

Insomnia is a term used to refer to the symptoms and the disorder. Insomnia symptoms consist of self-reports of difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening.[1,2] About 30% to 40% of the

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Nonstandard Abbreviations and Acronyms

BDNF	brain-derived neurotrophic factor
BP	blood pressure
CBT-I	cognitive-behavioral therapy for insomnia
CBVD	cerebrovascular disease
CRP	C-reactive protein
CVD	cardiovascular disease
HR	heart rate
HRV	heart rate variability
IL-6	interleukin 6
INSD	insomnia with normal sleep duration
ISSD	insomnia with short sleep duration
T2D	type 2 diabetes
TNF-α	tumor necrosis factor alpha

What Are the Clinical Implications?

Insomnia, when frequent and chronic, is a disorder in its own right associated with cardiometabolic disease risk. Cardiometabolic disease risk is highest in insomnia with objective short sleep duration, the insomnia phenotype modeled in animal studies. Human and animal studies show that this insomnia phenotype is associated with hyperactivation of the arousal, stress, cardiac autonomic, metabolic, and immune systems, primary pathophysiologic mechanisms leading to cardiometabolic diseases. There is a need for prospective and proof-of-concept mechanistic studies, including randomized clinical trials, testing causal effects on cardiac, vascular, metabolic, and immune biomarkers in individuals with insomnia using objective sleep measures for their phenotyping.

adult population reports insomnia symptoms regardless of frequency, chronicity, or associated daytime impairment.[2,3] The diagnostic criteria for insomnia disorder consists of self-reports of (1) at least 1 of the insomnia symptoms mentioned above, (2) associated with significant daytime functioning impairment, (3) despite adequate opportunity (ie, time allotted in bed) and circumstances (ie, safety, darkness, quietness, and comfort) for sleep, (4) occurring at least 3 nights per week, (5) for at least 3 months, and (6) not solely due to another current sleep, medical or mental disorder, or medication/substance use.[1] About 10% to 15% of the adult population meets criteria for chronic insomnia disorder.[3] Objective sleep criteria (eg, polysomnography) are not required for the diagnosis of insomnia disorder[1] and are not currently recommended for the routine diagnosis or severity assessment of chronic insomnia disorder, which is at odds with the other prevalent sleep-wake disorders (eg, disordered-breathing, hypersomnia, or circadian disorders) for which objective measures are either indicated or recommended.[1,2] This brief review will show how the heterogeneity in objective sleep among those with chronic insomnia complaints indexes the relative contribution of physiological versus behavioral factors to the pathophysiology of insomnia phenotypes and serves to stratify their cardiometabolic disease risk.[2,4,5]

INSOMNIA AND CARDIOMETABOLIC DISEASE RISK

This section briefly summarizes systematic reviews and meta-analyses on the association of insomnia, and its phenotypes, with hypertension, type 2 diabetes (T2D), cardiovascular diseases (CVD), and cerebrovascular diseases (CBVD).[6–24]

As it pertains to hypertension, its high comorbidity with insomnia had already been reported half a century ago; however, insomnia was considered a symptom of hypertension, thus, research on the association of insomnia with elevated BP or BP dysregulation remained stagnant for decades.[34] Currently, large studies,[8,13,15–17,21,23,24] have shown that the odds of prevalent hypertension associated with insomnia symptoms are about 1.41-fold,[16] and the longitudinal risk of incident hypertension is about 1.21-fold.[8,15] Meta-analyses[17,26,27] show that insomnia is associated with a 2% and 1.6% significantly attenuated dipping of systolic and diastolic BP during nighttime sleep; however, no study relied on objectively defined sleep to identify nighttime BP.[17] Despite adjusting for relevant factors (eg, sex, age, obesity, depression, or smoking), studies did not include polysomnography and were, thus, unable to control for sleep apnea or examine insomnia phenotypes based on objective sleep measures. Two seminal studies reported that the odds of prevalent and incident hypertension were 5.1-fold and 3.5-fold, respectively, in the insomnia with short sleep duration (ISSD) phenotype, defined as adults with chronic insomnia who sleep objectively <6 hours on polysomnography.[28,29] In contrast, the insomnia with normal sleep duration (INSD) phenotype was not associated with increased odds of prevalent or incident hypertension.[28,29] Five studies replicated these findings[30–35] and 2 meta-analyses[23,24] estimated that the ISSD phenotype is associated with 2.67-fold increased odds of prevalent hypertension and 1.95-fold increased longitudinal risk of incident hypertension.[24]

Multiple studies have reported an association between insomnia and T2D.[7,11,16,22,23] Although 2 case-control studies reported no association between chronic insomnia disorder and impaired metabolism,[36,37] large studies have estimated that the odds of prevalent T2D associated with insomnia symptoms are about 1.29- to 1.87-fold,[16,22] and longitudinal studies have estimated that the risk of incident T2D is about 1.55- to 1.84-fold.[11,16] Another seminal study reported that the ISSD, but not the INSD, phenotype was associated with 2- to 3-fold

increased odds of prevalent T2D.[38] Additional studies reported increased prevalence of T2D, multimorbidity, and metabolic syndrome in the ISSD, but not the INSD, phenotype,[35,39–42] with a meta-analysis reporting 1.63-fold increased odds of prevalent T2D in the ISSD phenotype.[23] No longitudinal meta-analytic data on the association of ISSD and INSD phenotypes with risk of incident T2D are available to date.

As it pertains to CVD and CBVD, large studies have estimated that insomnia symptoms are associated with a 1.28-fold to 1.69-fold increased longitudinal risk of incident CVD or CBVD,[9,10,12,14,18–21] Five studies have shown that the ISSD, but not the INSD, phenotype is associated with risk of CVD and CBVD.[40,43–46] These studies showed that the ISSD was associated with a 29% increased longitudinal risk of incident CVD or CBVD,[43] 2.5-fold increased longitudinal odds of incident CVD or CBVD,[44] and 2.3-fold increased odds of possible vascular cognitive impairment.[47]

Collectively, the evidence briefly reviewed above supports an association of insomnia with cardiometabolic diseases that is driven by the ISSD phenotype. The validity of this insomnia phenotype has been supported by unsupervised data-driven[48–52] and stability studies.[53,54]

PATHOPHYSIOLOGIC MECHANISMS OF CARDIOMETABOLIC DISEASE RISK

The cause of insomnia is explained by the interaction between diathesis (predisposing traits) and stress (precipitating events).[55,56] As shown in the Figure, the chronicity of chronic insomnia complaints is primarily explained by cognitive-behavioral (perpetuating) factors.[56] Neurobiological evidence indicates, however, that dysregulation of the arousal and stress systems is also involved in perpetuating insomnia, specifically the ISSD phenotype,[4,57] and that these pathophysiological mechanisms may be responsible for the association of this insomnia phenotype with cardiometabolic disease risk. This section briefly reviews evidence on these potential mechanistic links, from genetics to peripheral physiology and health behaviors.

Although genetic and epigenetic studies of insomnia in humans still need to address the interaction between genetic predisposition and environmental precipitating events,[58] genome-wide association studies have identified between 200 and 500 loci associated with insomnia symptoms, which suggests extreme polygenicity, and include metabolic pathways involved in T2D risk.[59,60] Mendelian randomization studies have identified causal effects between genetically predicted insomnia symptoms with hypertension, CVD, and CVBD.[21] Nonhuman models of insomnia have aimed at disentangling its genetic cause and pathophysiology.[61] These model organisms have shown that psychosocial stress in male rats induces sleep continuity disturbances with short sleep via activation of cerebral cortex, limbic system, and parts of the arousal and autonomic nervous system (wake-promoting areas) with simultaneous activation of the ventrolateral and median preoptic nuclei of the anterior hypothalamus (sleep-promoting areas).[62] In *Drosophila*, selectively bred short sleep is associated with sleep continuity disturbances, a phenotype with high heritability and associated with hyperactivation, elevated levels of dopamine, triglycerides, cholesterol, and free fatty acids, and early mortality.[63] In addition, mutant short-sleeping *Drosophila* exhibit a mismatch between sleep opportunity and sleep ability, whereas experimentally mismatching sleep opportunity and ability in short-sleeping *Drosophila* produces sleep continuity disturbances.[64] These nonhuman organisms clearly model the human ISSD phenotype and provide support for its pathophysiology and adverse health outcomes. However, they need to be expanded to understand the cellular and molecular mechanisms linking the ISSD phenotype to cardiometabolic disease risk.[65]

Several neuroimaging studies in humans with chronic insomnia have aimed to uncover how 24-hour hyperarousal is reflected in the sleeping brain. Meta-analyses of studies using different types of brain imaging methods found no significant convergent evidence for a combination of structural atrophy or functional disturbances in individuals with chronic insomnia,[66,67] despite resting-state functional data suggesting that the salience network may be crucial in hyperarousal.[68] Inconsistencies across neuroimaging studies might be related to multiple factors, including phenotypic heterogeneity among those with chronic insomnia.[66] One study showed decreased functional connectivity of the left inferior occipital gyrus with bilateral occipital, parietal, and temporal regions in the ISSD phenotype.[69] Magnetic resonance spectroscopy has been used to study neurotransmitters and amino acids in the brain of individuals with chronic insomnia. Five studies showed decreased γ-aminobutyric acid or increased glutamate/glutamine concentrations in chronic insomnia,[70–74] and a sixth study found that glutamate/glutamine levels in the dorsolateral prefrontal cortex increased across the day in those with chronic insomnia and that shorter sleep duration was associated with lower γ-aminobutyric acid levels in the anterior cingulate cortex;[75] these findings suggested that reduced γ-aminobutyric acid levels may be a trait marker of the ISSD phenotype.[75] Another study found that the ISSD phenotype was associated with reduced aspartate and glutamine concentrations in the left occipital cortex.[49] In addition, studies have shown that insomnia is associated with significantly reduced BDNF (brain-derived neurotrophic factor) levels,[76] with 2 studies showing that these reduced BDNF levels are found in the ISSD, but not the INSD, phenotype.[77,78] Together, these data suggest that changes in brain biochemistry and functional

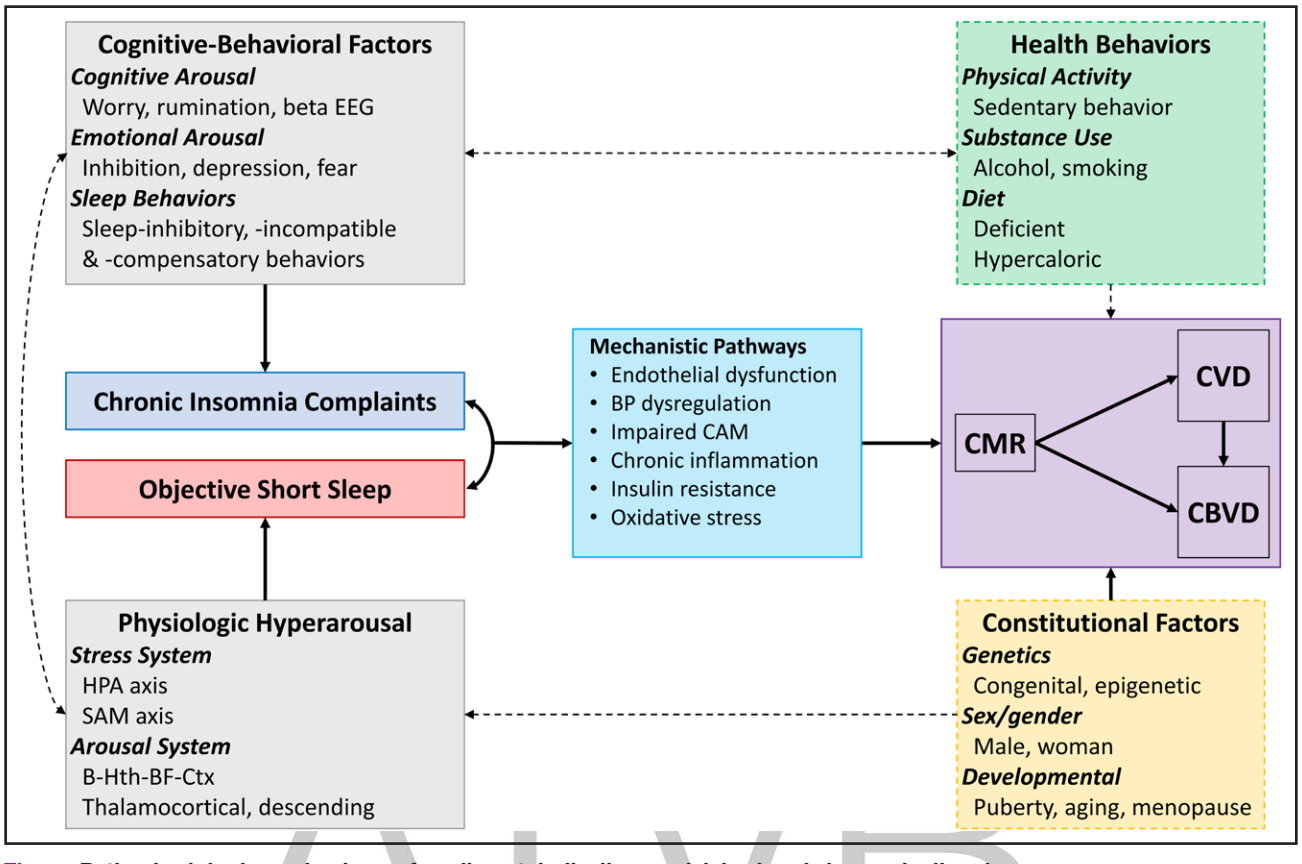

Figure. Pathophysiologic mechanisms of cardiometabolic disease risk in chronic insomnia disorder. This diagram depicts the pathophysiology of chronic insomnia with objective short sleep duration and its associated adverse cardiometabolic health outcomes. Chronic insomnia complaints are primarily the result of cognitive-behavioral perpetuating factors, including cognitive arousal (eg, worry, underlying high electroencephalography [EEG] frequency power) and specific sleep-inhibitory (eg, cognitively/emotionally arousing activities before bedtime), sleep-incompatible (eg, activities in bed other than sleep and sex), and sleep-compensatory (eg, excessive time in bed, catch-up sleep) behaviors. Objective short sleep duration in individuals with chronic insomnia complaints is primarily the result of physiological hyperarousal; that is, the inhibition of physiological sleep ability via hyperactivation of ascending projections from the brainstem and hypothalamus to the diencephalon, limbic system, basal forebrain, and neocortex (B-Hth-BF-Ctx), as well as descending projections regulating the autonomic nervous system. Ascending and descending projections interact with activation of the hypothalamic-pituitary-adrenal (HPA) and sympatho-adrenomedullary (SAM) axes of the stress system. Chronic insomnia and objective short sleep duration therefore intersect in a synergistic manner into a specific phenotype associated with cardiometabolic disease risk. This elevated risk is the result of physiological mechanistic pathways, including endothelial dysfunction, blood pressure (BP) dysregulation, impaired cardiac autonomic modulation (CAM), chronic low-grade inflammation, and insulin resistance or oxidative stress, which lead to cardiometabolic risk factors (CMR), cardiovascular disease (CVD), and cerebrovascular diseases (CBVD) via coronary artery calcification, carotid intima media thickness or vascular insults, among many other central and peripheral subclinical changes. The diagram considers the potential relative contribution of known constitutional factors and inadequate health behaviors in increasing cardiometabolic disease risk. Adapted from Fernandez-Mendoza.[128]

connectivity, reflective of physiological hyperarousal with downstream effects on other systems, such as the autonomic nervous system, are found in the ISSD phenotype, but not the INSD phenotype.

Since the 1960s,[79] studies have reported increased hypothalamic-pituitary-adrenal axis activation (eg, increased cortisol levels)[4,57,80–83] or sympatho-adrenomedullary axis activation (eg, increased norepinephrine levels) in individuals with chronic insomnia, which were found to correlate with the degree of objective sleep disturbance or only in the ISSD phenotype.[4,57,80,81,83–85] Insomnia has been associated with elevated whole-body metabolic rate, increased nighttime heart rate (HR), blunted HR variability (HRV), or altered impedance cardiography.[86–94] The association of insomnia with indices of cardiac autonomic modulation has been examined in multiple studies.[87,88,93] Although a meta-analysis reported that chronic insomnia disorder was not significantly associated with blunted HRV indices,[87] a systematic review indicated that 80% of the studies found significant differences in cardiac autonomic balance, including blunted HRV,[88] and that the ISSD phenotype presented the most consistent findings across 5 well-controlled studies.[88–94] For example, chronic insomnia disorder, when defined solely using subjective diagnostic criteria, is not associated with blunted HRV; however, when subjects are split into the ISSD versus INSD phenotypes, the ISSD phenotype shows lower HRV, while the

INSD phenotype shows similar HRV as good sleepers.[94] These findings were replicated in another case-control study with robust methodology.[92] In addition, the ISSD, but not the INSD, phenotype has been associated with elevated levels of cardiac troponin T in a large population-based study.[46] However, no study has examined whether activation of the renin-angiotensin-aldosterone system is altered in insomnia or its phenotypes and whether it is mechanistically linked to nondipping BP and hypertension risk.

There is evidence for the association of insomnia with immune system biomarkers.[95–99] Large studies show significant associations between insomnia symptoms with elevated IL-6 (interleukin-6) and CRP (C-reactive protein) levels, but not with TNF-α (tumor necrosis factor alpha) levels.[95] In-laboratory controlled studies found increased inflammation in individuals with chronic insomnia disorder compared with good sleepers, as measured by mid-afternoon-to-evening levels[97] and diurnal circadian pattern[98] of IL-6 and TNF-α secretion. Another controlled study found that the ISSD phenotype was associated with 4.2-fold increased odds of short leukocyte telomere length.[99] These findings of elevated stress and immune system activation in individuals with the ISSD phenotype, but not in those with the INSD phenotype, have been replicated in studies of adults and youths.[100–107] In addition, the ISSD phenotype has been associated with glucose metabolism dysregulation and insulin resistance, which is not observed in the INSD phenotype.[41,107,108] Despite the robust associations found, no longitudinal or intervention study has examined whether chronic low-grade inflammation is mechanistically linked to cardiometabolic disease risk in insomnia and its phenotypes.

More recently, 2 studies have shown that the ISSD phenotype is associated with higher concentrations of acetate, butyrate, propionate, and total short-chain fatty acids, as well as with higher levels of 8 microbiota metabolites as assayed in fecal samples, which speaks to potential pathways in the gut-brain axis contributing to adverse cardiometabolic health outcomes in the ISSD phenotype.[109,110] One study found 52 serum metabolites related to the ISSD phenotype compared with good sleepers, of which indoxyl sulfate was positively associated with BP levels and bacteroidetes abundance and negatively with firmicutes abundance.[111] Studies are needed to replicate these findings and uncover the molecular underpinnings of increased cardiometabolic disease risk using mechanistic longitudinal designs or proof-of-concept randomized clinical trials.

Finally, although the above evidence suggests that pathophysiologic changes play a mechanistic role in the increased cardiometabolic risk observed in the ISSD phenotype, it is possible that health behaviors may be present in these pathways (Figure). Individuals with insomnia are more likely to report smoking, excessive alcohol or caffeine use, inadequate diets, or sedentarism.[112] However, little evidence is available on how these health behaviors distribute across insomnia phenotypes and whether they play a relevant role.[113] In fact, most studies reviewed above controlled for many of these health behaviors in their design or analyses. Nevertheless, more work is needed to establish the relative contribution and potential causal role of inadequate health behaviors to the increased cardiometabolic risk associated with insomnia, above and beyond the examined pathophysiologic mechanisms.

In summary, biomarkers of ascending arousal and stress system activation, neuroendocrine dysregulation, cardiac autonomic imbalance, subclinical myocardial abnormalities, chronic low-grade inflammation, and insulin resistance are found in the ISSD phenotype, for which 24-hour physiological hyperarousal is the primary pathophysiologic mechanism increasing cardiometabolic disease risk (Figure).

DO INSOMNIA TREATMENTS IMPROVE CARDIOMETABOLIC DISEASE RISK?

The importance of cognitive-behavioral factors in perpetuating chronic insomnia complaints is depicted in the Figure. Cognitive-behavioral therapy for insomnia (CBT-I) is the guideline-recommended first-line treatment as it improves subjective insomnia severity and sleep continuity in individuals with chronic insomnia, including those with comorbid cardiometabolic diseases, at similar clinically meaningful efficacy.[114–117] However, whether CBT-I improves cardiometabolic health outcomes or biomarkers is inconclusive.[118–121] Although CBT-I appears to improve insulin resistance (ie, hemoglobin A1c) and inflammation (ie, CRP), the majority of clinical trials were pilot studies, in specific patient populations (eg, cancer, hemodialysis, bipolar disorder, T2D), and presented a high risk of bias.[118,121] Only 2 randomized clinical trials have examined the effect of hypnotics/sedatives on cardiometabolic outcomes, with no meta-analyses available on the topic. One study found that estazolam, compared with a placebo, improved systolic and diastolic BP levels in individuals with comorbid hypertension and chronic insomnia disorder.[122] Another study found that zolpidem, compared with placebo, reduced norepinephrine levels and increased the number of BP-dippers in individuals with comorbid nondipping hypertension and poor sleep quality.[123] As it pertains to insomnia phenotypes, recent meta-analytic data show that the ISSD phenotype has a 29% lower response rate, a 26% lower remission rate, and benefits less with CBT-I, in terms of objective sleep duration, insomnia severity index, and dysfunctional cognitions, than the INSD phenotype.[124] No physiological or cardiometabolic outcomes have been meta-analyzed. However, a pilot study showed that trazodone, but not CBT-I, significantly lengthened objective sleep duration

and decreased cortisol levels in the ISSD phenotype;[125] a finding consistent with the cortisol-lowering effects of doxepin in chronic insomnia[126] and the effect of dual orexin antagonists on the ISSD phenotype.[127] Collectively, these data suggest that future proof-of-concept and effectiveness studies on cardiometabolic disease biomarkers should objectively phenotype chronic insomnia.

CONCLUSIONS

Once frequent and chronic, insomnia is a disorder in its own right that puts individuals at risk of cardiometabolic diseases. Current evidence indicates that this risk is present in the ISSD phenotype, but not the INSD phenotype. There is a need for experimental studies using state-of-the-art methods to assess cardiac physiology, metabolic regulation, and vascularity, among many other domains, in individuals with chronic insomnia using objective sleep duration for their phenotyping. There is also a need for longitudinal studies and proof-of-concept mechanistic trials capable of testing causal mediating effects, and not solely associations, with relevant pathophysiologic biomarkers of cardiometabolic disease. There is, thus, a need to identify the most reliable cardiac, vascular, and metabolic biomarkers and incorporate them into prospective clinical trials.

ARTICLE INFORMATION

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Disclosures

None.

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