Illuminating the sleep-heart failure connection – time to be woken up by the evidence

Philipp Markwirth[1,2]*, Michael Böhm[1,2]

[1]Klinik für Innere Medizin III, Kardiologie, Angiologie und internistische Intensivmedizin, Universtiätsklinikum des Saarlandes, Homburg, Germany
[2]HOMICAREM (HOMburg Institute for CArdio-REnal-Metabolic Medicine), Universitätsklinikum des Saarlandes, Homburg, Germany

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***Corresponding author:**
Philipp Markwirth
Klinik für Innere Medizin III
Kardiologie, Angiologie
und internistische
Intensivmedizin
Universtiätsklinikum
des Saarlandes
Homburg, Germany
E-mail: Philipp.Markwirth@uks.eu

Sleep disturbance is a ubiquitous yet often under-recognized burden in patients with heart failure (HF) [1, 2], manifesting not only as a sequela of HF but potentially as a contributing factor to its onset and progression. Sleep-disordered breathing, for example, has been associated independently with higher mortality in patients with cardiovascular disease [3]. Despite mounting observational evidence linking poor sleep to adverse cardiovascular outcomes, however, causality has remained elusive. Traditional observational studies are inherently limited by residual confounding and reverse causation due to their non-randomized nature.

To address these limitations, Wang *et al.* examine this crucial bidirectional relationship with a robust dual-method approach, combining data from a large observational cohort (National Health and Nutrition Examination Survey, NHANES) with Mendelian randomization (MR) analysis to infer a causal link between sleep disturbances and HF [4]. In this issue of *Archives of Medical Science*, the authors leverage genetic variants (single nucleotide polymorphisms, SNPs) identified from genome-wide association studies (GWAS) as "instrumental variables" for the exposure of interest, sleeplessness. Because these variants are randomly assigned at conception, MR is less susceptible to confounding and reverse causation, providing stronger evidence for causality than traditional epidemiologic methods.

The study's findings are compelling: In the NHANES analysis, the presence of a sleep disorder was associated with an odds ratio (OR) of 3.51 (p = 0.002) for HF after multivariable adjustment for baseline characteristics and cardiovascular risk factors. The MR analysis supported a causal relationship, yielding an OR of 1.53 (p = 0.016) with the inverse-variance weighted (IVW) method and 3.33 (p = 0.023) with MR-Egger analysis.

These results are not merely of academic interest, they resonate deeply with clinical reality. Sleep disorders are frequently encountered in HF management but are often dismissed as secondary symptoms or comorbid noise rather than primary contributors. This study challenges this narrative, suggesting that sleep health may be a modifiable risk factor for both preventing HF and improving outcomes in patients already diagnosed. A key concern in MR studies is horizontal pleiotropy, where genetic variants influence the outcome through pathways other than the exposure of interest, thus introducing confounding bias. To address this, Wang *et al.* applied several complementary MR methods: the stan-

dard inverse-variance weighted (IVW) model, MR-Egger regression, and the weighted median estimator. The consistency of findings across these approaches, together with the MR-Egger intercept test showing minimal pleiotropy and sensitivity analyses (leave-one-out testing), strengthens confidence that the observed association between insomnia and HF is not driven by biased genetic instruments.

From a mechanistic standpoint, the findings are biologically plausible. Sleep deprivation is known to trigger neurohormonal activation [5], sympathetic overdrive [6], systemic inflammation [7], and endothelial dysfunction [8] – all of which are pathophysiological hallmarks of HF. But while the science is compelling, clinical implementation remains challenging. Cardiologists and HF specialists must now consider whether sleep assessment should be a routine component of cardiovascular risk stratification and disease management. Tools such as actigraphy, polysomnography, and validated insomnia scales may become increasingly relevant.

Moreover, if sleep disturbances are causal, then intervention becomes imperative. Non-pharmacologic approaches such as cognitive behavioral therapy for insomnia (CBT-I) [9], along with pharmacologic options like orexin antagonists [10] have shown benefit in the general population. Specifically, the use of $5HT_{1A}$ receptor antagonists [11] or intravenous iron [12] have been shown to improve HF-related sleep apnea. Whether these strategies reduce HF incidence or improve clinical endpoints in patients with existing HF is unknown, but should now be the subject of urgent clinical investigation. This study also opens new directions for prevention. Could early identification of sleep disorders among individuals with other cardiovascular risk factors forestall the development of HF? Should sleep be considered alongside hypertension, dyslipidemia, and diabetes in primary prevention frameworks?

Of course, limitations remain. As the authors acknowledge, self-reported sleep metrics can introduce bias, and the MR analysis, while elegant, is limited to genetic instruments for insomnia, a specific but not comprehensive marker of sleep health. Future work should aim to disentangle the unique contributions of sleep apnea, circadian misalignment, and other sleep phenotypes to HF pathogenesis.

In conclusion, this study by Wang *et al*. delivers an important message to the cardiovascular community: sleep is not a passive state but a dynamic regulator of cardiovascular health. Insomnia is no longer just a symptom; it may be a driver. It is time for sleep disturbances to be recognized not only as comorbidities but as potential causal and modifiable risk factors in HF prevention and management. The evidence is mounting, and it demands that we wake up to its implications.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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