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REPLY

Sleep is unlikely to be the key mediator between stress and CVD

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We are pleased that our paper on stress and cardiovascular disease (CVD; Steptoe, A. & Kivimäki, M. Stress and cardiovascular disease. *Nat. Rev. Cardiol.* 9, 360–370 [2012]) has attracted the interest of *Nature Reviews Cardiology* readers.[1] Huang and colleagues (Huang, Y., Hu, Y. & Mai, W. Correspondence: Stress and sleep disturbance—a connection in CVD. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2012.45-c1) suggest that the increased risk of CVD among people suffering from stress could be caused by stress-induced sleep disturbance.[2] We agree that a link exists between stress and sleeping problems. In the Whitehall II study,[3] for example, people who reported working an excessive number of hours over several years had an almost eightfold increased risk of developing difficulty in falling asleep. In addition, these individuals were twice as likely to wake early compared with those without such work-related stress.[3] Despite these findings, we consider that the overall evidence for sleep disturbance being a key mediator between stress and CVD is weak.

Sleep is known to affect health. Rats deprived of sleep die after approximately 1 month.[4] Evidence from studies of humans suggests that short sleep duration and poor sleep quality are independent risk factors for the development and exacerbation of insulin resistance, and could lead to increases in adiposity.[5,6] Shift work, which interferes with normal sleeping patterns and thus represents a quasi-experiment of the effects of disturbed sleep, has been shown to increase the risk of obesity and type 2 diabetes mellitus.[7] Data from genetic studies support these pathways. Risk variants from genes that have traditionally been related to sleep regulation, such as melatonin receptor type 1B (*MTNR1B*), brain-derived neurotrophic factor (*BDNF*), and a circadian pacemaker gene cryptochrome-2 (*CRY2*), have been found to be associated with markers of glycemic homeostasis, obesity, and type 2 diabetes.[8,9] As these metabolic conditions are established risk factors for CVD, this evidence is consistent with the hypothesis that sleep, in principle, could also mediate the association between stress and CVD.

However, several other findings cast doubts on the validity of this mediation hypothesis. First, as we demonstrate in our Review,[1] stress is also associated with adverse metabolic changes and increased risk of obesity and coronary heart disease. The stress response could, therefore, mediate the association between sleep and CVD rather than the other way round. Second, several cardiovascular risk factors, such as obesity, tobacco smoking, and depression, induce sleep disturbance.[10,11] Thus, rather than mediating the association between stress and CVD, sleep disturbance could be an innocent bystander marking other stress mediators. Indeed, Matthews *et al.* found little evidence that sleep was associated with atherosclerosis independently of obesity[12] and, similarly, interventions to treat sleep disorders have produced little improvement in cardiovascular health.[13] Third, studies involving objective measures of sleep quality show that stress is more-strongly associated with reported sleep disturbance than with these objective indicators.[14] Finally, and perhaps most importantly, some direct evidence exists on stress (indexed as working an excessive number of hours), sleep, and incident coronary heart disease, all assessed within a single setting—the Whitehall II study.[15] Although analyses of these data show that stress is associated with an elevated risk of coronary heart disease, this association was not explained by measures of sleep.[15] Thus, sleep disturbance does not seem to be the reason why people who experience stress have an increased risk of CVD.

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Competing interests
The authors declare no competing interests.

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