

# Combined effect of work stress and impaired sleep on coronary and cardiovascular mortality in hypertensive workers: The MONICA/KORA cohort study

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<b>Background</b>	Although work stress and impaired sleep are established risk factors for cardiovascular disease (CVD) among healthy individuals, their impact on hypertensive workers is largely unknown.
<b>Design</b>	Prospective cohort study design.
<b>Methods</b>	Hypertensive workers (N=1959), derived from the population-based MONICA/KORA study in Southern Germany, who were free of any cardiovascular disease and diabetes were interviewed at baseline for work stress (high demand plus low control) and impaired sleep (difficulties falling asleep and/or maintaining sleep). Hazard ratios and 95% confidence intervals (CIs) were estimated by multivariate Cox proportional hazards models with adjustment for relevant covariates.
<b>Results</b>	During a mean follow-up of 17.8 years covering 34,900 person-years, 134 fatal CVD and 73 coronary heart disease (CHD) events were observed. In comparison to participants with low work stress and non-impaired sleep, participants with work stress (hazard ratio (HR) 1.56, 95% CI 0.81–2.98), or impaired sleep (HR 1.76, 95% CI 0.96–3.22) had an increased risk of CVD, while participants with both work stress and impaired sleep had the highest risk of CVD mortality (HR 2.94, 95% CI 1.18–7.33). Participants with both risk conditions had an absolute CVD mortality risk of 7.13 cases per 1000 person-years in comparison to 3.05 cases per 1000-person years in the reference group. Similar risk patterns were found for CHD mortality.
<b>Conclusions</b>	Our findings add a new piece of evidence that work stress together with impaired sleep increase risk of coronary and cardiovascular mortality in hypertensive workers.
<b>Keywords</b>	Work stress • impaired sleep • cardiovascular diseases • hypertension • mortality

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## Introduction

It is estimated that more than 30% of adults have hypertension, which is a major contributor to global mortality, largely through coronary heart disease (CHD) and a wide range of cardiovascular diseases (CVDs).<sup>1</sup> Notably, several psychosocial factors, such as work stress (particularly job strain) and impaired sleep (or sleep disturbances), are found to interplayed closely with hypertension.<sup>2,3</sup> Moreover, cumulative evidence has been gained that work stress and impaired sleep increase risk of CHD/CVD respectively among initially healthy populations,<sup>4,5</sup> but also further affect disease prognosis among patients, leading to recurrent events.<sup>6,7</sup> To our surprise, very few studies have been conducted to examine the contributions of work stress and impaired sleep to CVD among a particularly large high-risk population, that is, hypertensive workers, accounting for one-third of the entire working population.<sup>8</sup> For example, a large nine-year follow-up study in the USA among men with high CVD risk (i.e. high blood pressure, cholesterol and smoking) found that work stress increased risk of CVD mortality by 34%,<sup>9</sup> while a Japanese study among hypertensive workers indicated that work stress doubled the risk of incident CVD during 5.6-year follow-up.<sup>10</sup> Regarding impaired sleep among hypertensive patients, one small study from Russia indicated that obstructive sleep apnoea syndrome elevated odds of fatal and non-fatal CVD events during four-year follow-up by nine times;<sup>11</sup> another Japanese study also suggested that short sleep duration was associated with 1.5 higher risk of CVD incidence within maximal 116-month follow-up.<sup>12</sup>

Theoretically, in stress research, the important role of recovery has been emphasized, as 'a process of psychophysiological unwinding after effort expenditure' in the past years (Geurts and Sonnentag, p.482<sup>13</sup>). As an essential mechanism of recovery processes, sleep receives significant attention. It is certified that sleep contributes substantially to the recuperative process of the central nervous system, restoring not only brain physiology but also alertness, memory capacity and mood. Thus, it is crucial that good and normal sleep at night could stabilize the psychophysiological load reactions induced by stress in daytime, and could restore energy levels and personal resources.<sup>14</sup> Yet, to the best of our knowledge, no study has tested the joint effect of these two risk factors on the cardiovascular system. Therefore, we aimed to examine the prospective associations of both work stress and impaired sleep with CHD and CVD mortality risk in the high-risk group of hypertensive workers, using a large cohort with a representative working population in Germany. We assumed that workers who had both high work stress and impaired sleep would have the highest risk.

## Methods

### Study design

The data of our current study was drawn from three surveys (S1, S2, S3) of the population-based MONICA/KORA cohort study, which were conducted between 1984 and 1995 in the region of Augsburg, southern Germany, and followed up within the KORA research platform. The MONICA/KORA cohort study was one part of the multinational World Health Organization's MONICA project aimed to estimate the prevalence and distribution of cardiovascular risk factors among men and

women aged 25–64 (S1) or 25–74 years (S2, S3).<sup>15</sup> All procedures were subjected to constant quality assessment. The study was approved by the local authorities and followed the Declaration of Helsinki. Written informed consent was obtained from all participants.

### Study sample

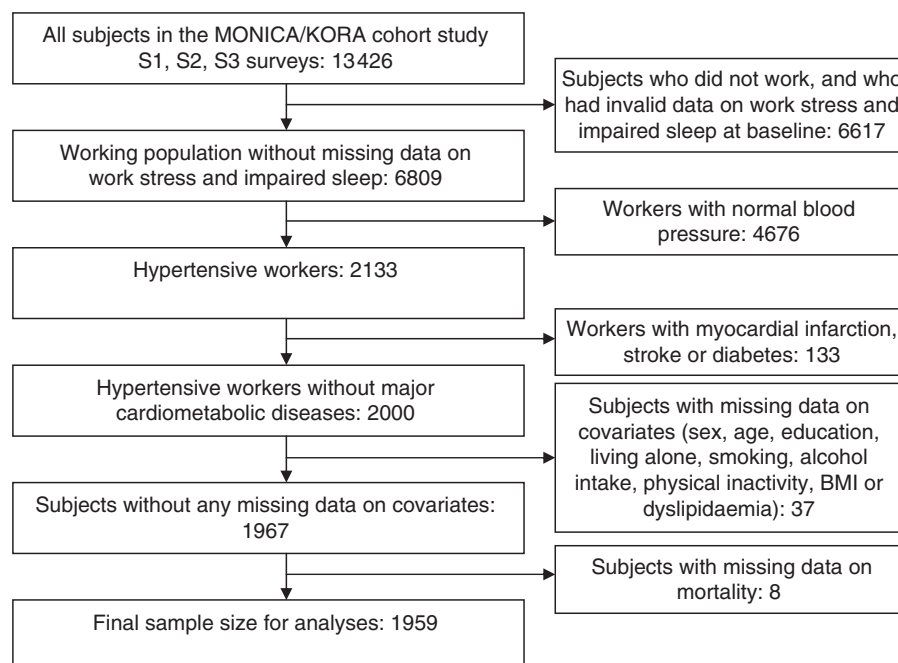
Among all 13,426 participants of the MONICA/KORA cohort study, we restricted the sample to those who were working, had valid data on work stress and impaired sleep and who had hypertension at baseline as well. In this study, hypertension was defined as blood pressure  $\geq 140/90$  mmHg and/or use of antihypertensive medication. As a result, 2133 hypertensive workers aged 25–65 years without missing values on key risk factors (i.e. work stress and impaired sleep) were identified. We then further excluded subjects who had self-reported and medically confirmed CVD ( $n = 48$ ) and diabetes at baseline ( $n = 85$  diabetes patients were excluded due to cardiovascular protection of antidiabetic drugs),<sup>16</sup> who had missing data on co-variables ( $n = 37$ ) and who were lost during follow-up or death ( $n = 8$ ). Finally, data from 1959 participants were used for our analyses (see Figure 1).

### Measures

Using the well-established job strain model, work stress at baseline was composed of two psychosocial working conditions: demand and control.<sup>17</sup> In the MONICA study, demand was measured by five items and control was measured by six items with a four-point Likert response scale (Cronbach's alpha coefficients were 0.70 and 0.71, respectively). We used median points of the sample, that is, 12 for demand and 18 for control, to define different levels of work stress. Workers whose demand was  $>12$  and control  $<18$  were classified as high work stress group (WS (+)), the rest as low work stress group (WS (-)). Baseline sleep quality was assessed by two questions with a three-point Likert response scale, asking about difficulties initiating sleep and difficulties maintaining sleep. The three possible responses were 'sometimes', 'often' and 'almost never'. Subjects who claimed to often have difficulties falling asleep or/and maintaining sleep were combined into the category of high impaired sleep (IS (+)), otherwise (IS (-)).<sup>18</sup>

In the MONICA/KORA cohort study, information on covariates was collected at baseline, such as sex (male vs. female), age (years), education (years) and blood pressure (mmHg). Subjects were coded as living alone if they stated that they lived in a single-person household. The participants also provided information about whether they had ever smoked cigarettes (never, former smoker, or current smoker). Assessment of alcohol intake was based on questionnaire data regarding weekday and weekend consumption of beer, wine and spirits. Each participant was asked about his or her leisure-time physical activity with four-point Likert response scale (0,  $<1$ , 1–2, and  $>2$  h/week) during winter and summer. Participants were classified as physically active if they exercised in both the summer and winter seasons, and on average at least 1 h/week in the course of a year. Body mass index (BMI) was calculated as  $\text{kg/m}^2$ . Dyslipidaemia was defined as the ratio of total cholesterol to high-density lipoprotein cholesterol of 5.0 or greater, in line with previous research.<sup>19</sup>

The health outcome of the present study was CHD (using codes of the ninth revision of the International Classification of Diseases: ICD-9 410–414, 798) and CVD mortality (ICD-9 390–459) that occurred until General Morbidity Follow-up in 2008/2009. Deaths were ascertained by regularly checking the vital status of participants of the MONICA/KORA cohort study through the population registries inside and outside the study area. Death certificates were obtained from local health authorities.



**Figure 1** Flow chart of the study sample derived from the MONICA/KORA cohort study. BMI: body mass index.

## Statistical analyses

First, the dichotomized information on work stress and impaired sleep was combined in one composite variable with four groups. The group WS (–) IS (–) was set as reference to be compared with the other groups WS (+) IS (–), WS (–) IS (+), and WS (+) IS (+). Second, statistical differences in covariates among the four groups mentioned above were determined by analysis of variance for continuous variables presented as means and standard deviations (SDs), or by  $\chi^2$  test for categorical variables presented as relative proportions. Third, prospective associations of work stress and impaired sleep with CHD and CVD mortality were examined with Cox proportional hazards models. Results are displayed as hazard ratios with 95% confidence intervals. We adjusted for sex, age and baseline survey in Model I; additional adjustments were conducted for education and living alone (Model II), for smoking, alcohol intake and physical inactivity (Model III) and for BMI, dyslipidaemia and blood pressure (Model IV) in order to assess robustness of associations. Finally, the fully adjusted Model V took all the covariates into account. Analyses were performed with the statistical program SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

## Results

Among these 1959 hypertensive workers who were free of any CVD and diabetes at baseline, 1353 individuals were in the WS (–) IS (–) group, 279 in WS (+) IS (–), 255 in WS (–) IS (+) and 72 in WS (+) IS (+). Baseline characteristics of the study sample stratified by four groups are shown in [Table 1](#). Compared with those with WS (–) IS (–), the subjects exposed to WS (+) IS (+) were more frequently female, averagely older, less educated and more physically inactive, and had a higher percentage of obesity. The distribution of other characteristics such as living alone, smoking, alcohol intake,

dyslipidaemia and blood pressure did not significantly differ across the four groups.

During the average follow-up period of 17.8 years (34,900 person-years), 73 and 134 deaths from CHD and CVD were observed, respectively. [Figure 2](#) presents the absolute mortality risks, which were the highest in the group WS (+) IS (+) (approximately five cases for CHD and seven for CVD mortality per 1000 person-years), followed by those who were exposed to WS (–) IS (+), WS (+) IS (–) and the reference group, WS (–) IS (–). As shown in [Table 2](#), the basic Model I indicated that the risk of CHD death was elevated by 222% among those who were exposed to WS (+) IS (+). Further adjustment for socio-demographic factors and health-related behaviours, as well as clinical risk factors, did not substantially alter the associations. The fully adjusted Model V revealed that the condition of WS (+) IS (+) was associated with nearly two-times higher risk. Interaction analysis indicated potential additive effect between work stress and impaired sleep on CHD mortality, as evidenced by relative excess risk due to interaction equalling 0.63. A similar combined effect on CVD mortality was observed.

Moreover, with respect to all-cause mortality or other definition of impaired sleep (i.e. with three levels), we found the overall pattern of associations was unchanged (results are available upon request).

## Discussion

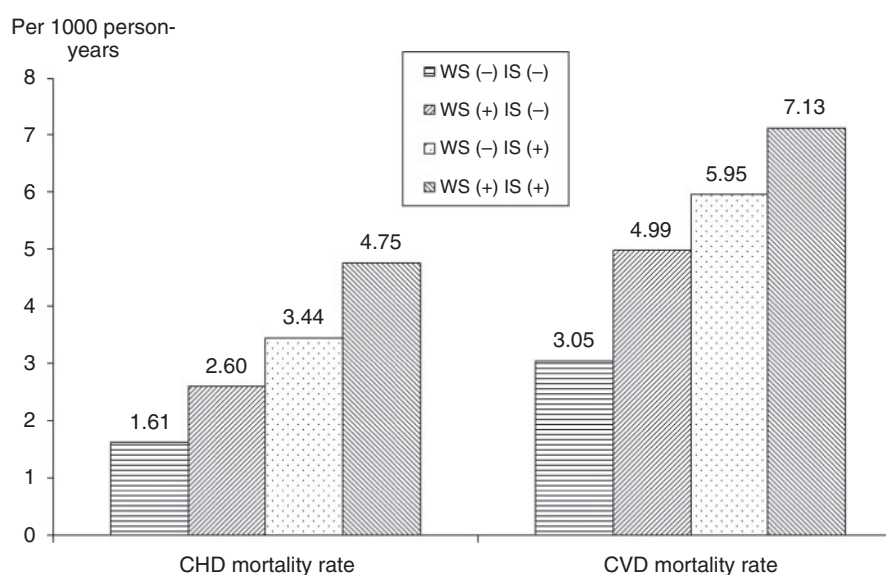
Much research on work stress-hypertension-CVD<sup>2,4</sup> and impaired sleep-hypertension-CVD<sup>3,5</sup> has been conducted for decades, while very few studies have tested combined effects of work stress and impaired sleep on CVD among hypertensive individuals.<sup>9–12</sup> To our knowledge, our present study is the first to examine the

**Table 1** Baseline characteristics of the study sample.

Variables	WS (–) IS (–) n = 1353	WS (+) IS (–) n = 279	WS (–) IS (+) n = 255	WS (+) IS (+) n = 72	p-value <sup>a</sup>
Male sex, %	77.53%	75.99%	72.55%	51.39%	<0.001
Age, years (SD)	45.24 (9.66)	46.53 (9.00)	49.38 (8.59)	49.30 (8.28)	<0.001
Education, years (SD)	11.69 (2.65)	10.42 (1.75)	11.10 (2.28)	9.75 (1.11)	<0.001
Living alone, %	20.69	20.79	14.51	20.83	0.1473
Smoking					
Never, %	36.21	39.43	38.04	44.45	0.2900
Former, %	31.86	31.90	35.29	22.22	
Current, %	31.93	28.67	26.67	33.33	
Regular alcohol intake, %	19.66	18.64	19.61	27.78	0.5364
Men (0–40), women (0–20), %	41.69	43.37	44.71	43.06	
Men (≥ 40), women (≥ 20), %	38.65	37.99	35.68	29.16	
Physical inactivity, %	55.65	67.03	58.43	66.67	0.0022
Body weight, based on BMI kg/m <sup>2</sup>					
Normal: BMI < 25, %	23.95	17.56	22.75	25.00	0.0025
Overweight: BMI ≥ 25 and < 30, %	54.25	50.18	51.76	41.67	
Obese: BMI ≥ 30, %	21.80	32.26	25.49	33.33	
Dyslipidaemia, %	43.90	46.24	44.31	34.72	0.3711
Diastolic blood pressure, mmHg (SD)	91.40 (9.60)	92.15 (9.04)	91.85 (9.23)	91.14 (8.89)	0.5980
Systolic blood pressure, mmHg (SD)	145.70 (13.53)	147.45 (15.34)	146.27 (15.07)	145.11 (12.64)	0.2599

<sup>a</sup>p-values derived from analysis of variance for continuous variables and  $\chi^2$  test for categorical variables.

WS: work stress; IS: impaired sleep; SD: standard deviation; BMI: body mass index



**Figure 2** Absolute CHD and CVD mortality risks according to work stress and impaired sleep. WS: work stress; IS: impaired sleep; CHD: coronary heart disease; CVD: cardiovascular disease.

combined effects of work stress and impaired sleep on CHD and CVD mortality in hypertensive workers, which is in line with a recent review indicating that the effect of psychosocial factors is stronger among individuals with pre-existing CVD risks than

those who were healthy initially.<sup>20</sup> As assumed, we found that those workers who experienced both harmful conditions were under substantially higher risk of death due to CHD/CVD among this high-risk population.

**Table 2** Hazard ratios and 95% confidence intervals by work stress and impaired sleep for CHD mortality and CVD mortality.<sup>a</sup>

	Model I <sup>b</sup>	Model II <sup>c</sup>	Model III <sup>d</sup>	Model IV <sup>e</sup>	Model V <sup>f</sup>
CHD mortality					
WS (–) IS (–)	1.00	1.00	1.00	1.00	1.00
WS (+) IS (–)	1.57 (0.84, 2.94)	1.49 (0.78, 2.83)	1.68 (0.89, 3.17)	1.52 (0.80, 2.86)	1.56 (0.81, 2.98)
WS (–) IS (+)	1.72 (0.95, 3.14)	1.72 (0.94, 3.15)	1.77 (0.97, 3.24)	1.76 (0.97, 3.21)	1.76 (0.96, 3.22)
WS (+) IS (+)	3.22 (1.35, 7.68)	3.12 (1.28, 7.61)	2.87 (1.20, 6.87)	3.52 (1.45, 8.56)	2.94 (1.18, 7.33)
CVD mortality					
WS (–) IS (–)	1.00	1.00	1.00	1.00	1.00
WS (+) IS (–)	1.58 (1.00, 2.49)	1.47 (0.93, 2.34)	1.56 (0.99, 2.47)	1.49 (0.94, 2.35)	1.44 (0.90, 2.30)
WS (–) IS (+)	1.56 (0.99, 2.46)	1.56 (0.99, 2.46)	1.65 (1.05, 2.59)	1.57 (1.00, 2.46)	1.67 (1.06, 2.63)
WS (+) IS (+)	2.45 (1.22, 4.93)	2.38 (1.17, 4.85)	2.22 (1.10, 4.46)	2.42 (1.19, 4.93)	2.17 (1.05, 4.48)

<sup>a</sup>Cox proportional hazards regression.  
<sup>b</sup>Model I: adjusted for sex, age and baseline survey.  
<sup>c</sup>Model II: Model I + additionally adjusted for education and living alone.  
<sup>d</sup>Model III: Model I + additionally adjusted for smoking, alcohol intake and physical inactivity.  
<sup>e</sup>Model IV: Model I + additionally adjusted for BMI, dyslipidaemia and blood pressure.  
<sup>f</sup>Model V: fully adjusted.  
WS: work stress; IS: impaired sleep; CHD: coronary heart disease; CVD: cardiovascular disease

According to our results, it seems the classic risk factors (such as unhealthy behaviours and clinical indicators) did not play important roles. Still, there are several lines to outline possible mechanisms explaining the impact of work stress and impaired sleep on CHD/CVD. Psychologically, according to the Effort–Recovery theory,<sup>21</sup> stress in the workplace requires effort of workers during working hours and causes acute load reactions. Under optimal circumstances, a sleep-induced recovery process during after-work hours helps the human body to reset the stress-related acute load reactions to pre-stress levels.<sup>14</sup> However, when work stress is too high or persists for too long, short or low quality sleep would provide incomplete recovery. Consequently, the workers begin to work in a suboptimal condition, and need to invest compensatory efforts for coping with stress on the following day. In turn, this would lead to elevated intensity of load reactions, and higher requirement of the subsequent recovery process. Such an accumulatively inter-related course would, in the long run, lead to chronic load reactions or allostatic load.<sup>22</sup> In recent years, empirical evidence also suggests that the relationship between work stress and impaired sleep is not one-directional only, but also reciprocal.<sup>23</sup> On the other hand, bio-medical mechanisms from work stress to CVD have been explored for years, majorly through the sympatho-adrenal medullary axis and the hypothalamic–pituitary–adrenocortical axis, altering secretion patterns of catecholamines and cortisol, and decreasing cardiac vagal tone;<sup>24</sup> disrupted immune and inflammatory responses are additionally involved.<sup>25</sup> Similarly, impaired sleep stimulates the biological systems mentioned above via the central nervous system, dysregulating neuroendocrine, autonomic and immune responses.<sup>26</sup> As well, stress-induced myocardial ischaemia has been proposed as an alternative explanation.<sup>27</sup> These psycho-physiological pathways increase the risk of CHD and CVD. It is worth mentioning that studies have added new evidence that dual exposure to high stress and impaired sleep exerts a remarkable impact on biomarkers.<sup>28</sup>

Our present study has several obvious strengths. For instance, this is a large population-based prospective cohort study, including both sexes, with a long follow-up period. The study endpoint was death from CHD and CVD, which was certified by authorized records, and many well-established risk factors were considered in our regression modelling. Some limitations should be addressed as well. The major one is the single measurement of work stress and impaired sleep at baseline only. Therefore, we might run the risk of misclassification because exposure conditions could be changed during the follow-up. In particular, the average baseline age of the study cohort was nearly 50 years, and the average follow-up time was close to 20 years. A majority of the participants were likely to have retired within the observational period. It is assumed that exposure to work stress is discontinued at the moment of retirement, and health status will be improved afterwards. Indeed, one French study suggested a significant decrease in sleep disturbances following retirement.<sup>29</sup> However, more studies from Europe and the USA found that retirement would increase the risk of CVD.<sup>30,31</sup> This might be due to other sources of stress originated from the retirement, such as loss of status and feeling of worthlessness. Another limitation relates to non-fatal CHD and CVD, which are not within the scope of the current investigation. In future research, approaches of life course epidemiology could be considered for tackling these major life events such as retirement or CVD morbidity.<sup>32</sup> In addition, given the relatively small sample size, some power consideration should be taken into account. In this current study, we applied the generally accepted rule of thumb for regression equations using six or more predictors, that an absolute minimum of 10 participants per predictor variable is appropriate.<sup>33</sup> Last, lacking of universal definition of dyslipidaemia, total cholesterol and high-density lipoprotein cholesterol were used in our study, while other lipids, such as low-density lipoprotein cholesterol, were not taken into consideration.

If supported by further studies, the current findings may provide evidence for several evidence-based implications in clinical practice.



As for work stress reduction, stress management interventions in the workplace have received increasing attention.<sup>34</sup> Among several successful interventions, a study on work stress management in German workers, using psychotherapeutic techniques, reported long-term effectiveness over a period of nine years, which is the longest follow-up in this regard.<sup>35</sup> Preliminarily exciting evidence is also reported among hypertensive workers from the USA, where an individual level stress management training programme resulted in a lower systolic blood pressure of 10.6 mmHg and lower diastolic blood pressure of 6.3 mmHg three months after the intervention.<sup>36</sup> With respect to sleep treatment, cognitive behavioural therapy has been repeatedly proved to be effective in the treatment of sleep disorders with clinically meaningful effect sizes.<sup>37</sup> Even among individuals with CVD and insomnia, cognitive behavioural therapy was approved, promising to reduce cardiovascular morbidity and symptom burden.<sup>38</sup> Recent evidence suggests that particularly cognitive behavioral therapy-based stress management improves CVD outcomes.<sup>39</sup> It is worth noting that, in the 2016 European Guidelines on CVD prevention in clinical practice,<sup>40</sup> the class of recommendation regarding psychosocial factors was justified as IIa. Specifically, 'psychosocial risk factor assessment, using clinical interview or standardized questionnaires, should be considered to identify possible barriers to lifestyle change or adherence to medication in individuals at high CVD risk or with established CVD' (Piepoli et al.,<sup>40</sup> p.NP19). In accordance with the latest guidelines on CVD prevention in Europe, our study adds a new piece of evidence focusing on work stress and impaired sleep.

In conclusion, the findings of our study indicate that the combination of work stress and impaired sleep increases the risk of CHD and CVD mortality in hypertensive workers. Future interventions in the workplace to promote cardiovascular health, that is, stress management and sleep treatment, should be considered, especially among workers with chronic conditions, such as hypertension.

## Author contribution

JL, PA and KHL contributed to the conception or design of the work. KHL contributed to the data acquisition. JL contributed to the data analysis. JL, PA, KHL, SA and XF contributed to the interpretation of results. JL drafted the manuscript. JL, PA, KHL and SA critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## Declaration of conflicting interests

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