Association between job strain and risk of incident stroke

A meta-analysis

Yuli Huang, MD, PhD*
Shuxian Xu, MD*
Jinghai Hua, MD
Dingji Zhu, MD
Changhua Liu, MD
Yunzhao Hu, MD, PhD
Tiebang Liu, MD, PhD
Dingli Xu, MD

Correspondence to Dr. Dingli Xu: dinglixu@fimmu.com or Dr. Tiebang Liu: liutbsz@sina.com

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ABSTRACT

Objective: Prospective cohort studies regarding job strain and the risk of stroke are controversial. This meta-analysis aimed to evaluate the association between job strain and the risk of stroke.

Methods: The PubMed, Embase, and PsycINFO databases were searched for prospective cohort studies with data on job strain and the risk of stroke. Studies were included if they reported adjusted relative risks (RRs) with 95% confidence intervals (CIs) of stroke from job strain. Subgroup analyses were conducted according to sex and stroke type.

Results: Six prospective cohort studies comprising 138,782 participants were included. High strain jobs were associated with increased risk of stroke (RR 1.22, 95% CI 1.01–1.47) compared with low strain jobs. The result was more pronounced for ischemic stroke (RR 1.58, 95% CI 1.12–2.23). The risk of stroke was significant in women (RR 1.33, 95% CI 1.04–1.69) and nonsignificant in men (RR 1.26, 95% CI 0.69–2.27), but the difference in RRs in sex subgroups was not significant. Neither active (RR 1.07, 95% CI 0.90–1.28) nor passive (RR 1.01, 95% CI 0.86–1.18) job characteristics were associated with an increased risk of stroke compared with low strain jobs.

Conclusions: Exposure to high strain jobs was associated with an increased risk of stroke, especially in women. Further studies are needed to confirm whether interventions to reduce work stress decrease the risk of stroke. *Neurology*® 2015;85:1–7

GLOSSARY

CHD = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **DCM** = demand-control model; **HR** = hazard ratio; **PAR** = population attributable risk; **RR** = relative risk.

Studies have shown that psychological stress at work can increase the risk of cardiovascular disease (CVD).[1,2] The job strain model, also known as the demand–control model (DCM), is one of the most widely validated occupational stress models used in epidemiologic research. The DCM assesses job characteristics on the basis of psychological job demand and job control.[3,4] Psychological job demand refers to time pressure, mental load, and coordination responsibilities, which is constructed to evaluate the aggregate of psychological stressors for work stress. Job control is defined as an individual's potential control over work-related decision-making, which contains 2 components: skill discretion and decision authority. By combining the scales of job demand and job control, 4 categories are obtained: low strain jobs (low demand, high control), passive jobs (low demand, low control), active jobs (high demand, high control), and high strain jobs (high demand, low control) (figure 1).[3,5]

Epidemiologic studies have shown that high strain jobs are associated with an increased risk of CVD, especially hypertension,[6,7] and coronary heart disease (CHD).[8–10] However, prospective cohort studies that examined the association between job strain categories and the risk of stroke are inconsistent.[5] A Japanese prospective study found that the risk of stroke was significantly increased among men with active, passive, or high strain jobs, but the same was not observed in women.[11] However, a recent longitudinal, general population-based study in Swedish men

*These authors contributed equally to this work.

From the Department of Cardiology (Y. Huang, J.H., D.Z., C.L., D.X.), Nanfang Hospital, Southern Medical University, Guangzhou; Shenzhen Psychiatric College (S.X.), Anhui Medical University; Department of Psychiatry (S.X., T.L.), Shenzhen Key Laboratory of Psychological Health Center, Shenzhen; and Clinical Medicine Research Center (Y. Huang, Y. Hu), the First People's Hospital of Shunde, Foshan, PR China.

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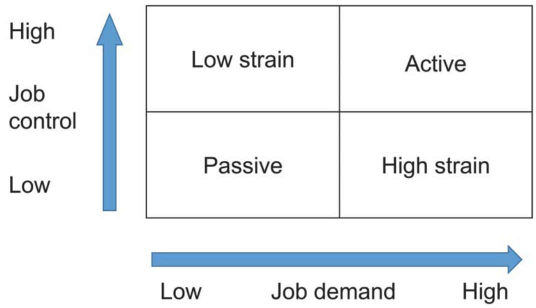
Figure 1 **Classification of job strain by the demand-control model**



By combining the scales of job demand and job control, 4 categories are obtained: low strain jobs (low demand, high control), passive jobs (low demand, low control), active jobs (high demand, high control), and high strain jobs (high demand, low control).

concluded that there was no increased risk of stroke in any of the 4 DCM job categories.[8] Furthermore, job demand and job control may affect the risk of stroke independently. Two large-scale studies showed that low job control was associated with an increased risk of stroke.[12,13] These studies emphasized the importance of low job control rather than its interaction with high demand. However, other studies have shown that the combination of high demand and low control (high strain jobs) was much more important for classifying CVD risks than low control alone.[14]

Given these inconsistent results, a comprehensive systematic review and meta-analysis based on prospective cohort studies may help to clarify this issue. In this study, we aimed to assess the association between job strain and the risk of incident stroke.

METHODS

Literature search and study selection. The potentially relevant studies were identified according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group.[15] We searched PubMed, Embase, and PsycINFO for prospective cohort studies to July 20, 2014, using the search strategy with the following terms: "burnout, professional," "stress at work," "work stress," "job stress," "occupational stress," "occupational strain," "job strain," "job control," "decision latitude," "job demand," "demand-control model," and "cardiovascular disease," "cerebrovascular disorder," "cardiocerebrovascular disease," "cardiovascular event," "cerebrovascular disease," "cerebrovascular attack," "stroke," "cerebral infarction," "intracranial hemorrhage." We restricted the search to human studies. The detailed strategy for the PubMed search is presented in table e-1 on the *Neurology®* Web site at Neurology.org. The strategies for Embase and PsycINFO databases were similar but were adapted where necessary.

Titles and abstracts of the reports were screened for further assessment and full copies of potentially suitable studies were obtained if needed. We included studies if they met the following criteria: (1) prospective cohort study; (2) baseline status of job strain categories was measured; (3) all participants aged 18 years or older and follow-up duration ≥2 years; and (4) relative risks (RRs) or hazard ratios (HRs) and 95% confidence intervals (CIs) for risks of incident stroke in high strain, active, or passive jobs were reported vs low strain jobs.

The exclusion criteria were: (1) the enrollment of participants depended on having a specific risk factor condition (e.g., diabetes mellitus, hypertension, or other baseline chronic disease), or (2) multiple reports were from the same cohort. If there were multiple articles from the same cohort, the most recently published data were used for analysis. However, if duplicate articles reported additional data for subgroup analysis, which were not reported in the primary included reports, these data were included for subgroup analysis.

Data extraction and assessment of study quality. Two reviewers (Y. Huang and S.X.) assessed the studies and extracted the data according to the predefined criteria independently. Study information such as participant number, sex, follow-up duration, adjusted risk factors, and events assessment were recorded in pretested, specially designed forms.

The quality of each study was assessed using the Newcastle–Ottawa Quality Assessment Scale for prospective cohort studies,[16] in which the quality of a study was evaluated based on selection (up to 4 stars), comparability (up to 2 stars), and exposure/outcome (up to 3 stars). In our analysis, studies were graded with good quality if ≥7 stars were awarded.

Statistical analysis. We analyzed the RR of stroke in individuals with high strain, active, or passive jobs compared with low strain jobs. Furthermore, we analyzed the RR of stroke in subjects with low control or high demand jobs, respectively. Subgroup analyses of the high strain group were conducted according to sex (women vs men) and stroke type (ischemic vs hemorrhagic stroke).

Multivariate-adjusted outcome data (expressed as RRs or HRs) were used for analysis. We logarithmically transformed these data in each study and calculated the corresponding standard errors for meta-analysis.

The I^2 statistic was used to test heterogeneity ($p < 0.10$ or $I^2 > 50\%$ represented significant heterogeneity). If there was no significant heterogeneity among studies, a fixed-effects model was used for analysis. Otherwise, we used a random-effects model for analysis. Publication bias was assessed by inspecting funnel plots, and Egger test.

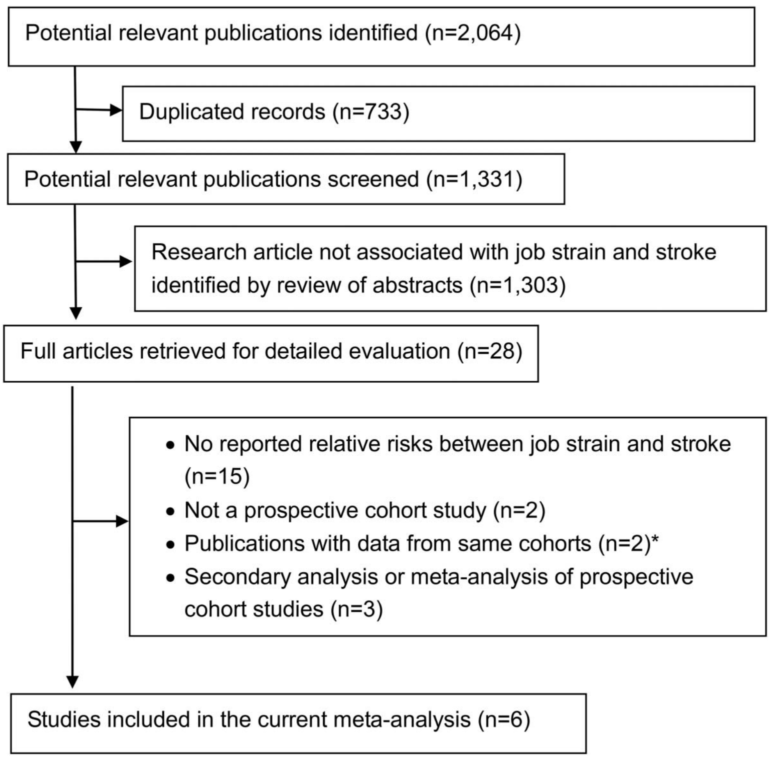
If the pooled RR of stroke for job strain was statistically significant, the population attributable risk (PAR), which expresses the proportion of events attributable to the exposure, was determined. The formula for PAR calculation was as follows: PAR% = (Pe) (RR − 1)/([Pe] [RR − 1] + 1) × 100, where Pe indicates the proportion of participants exposed to the risk factor and RR indicates the estimated relative risk.[17]

We used RevMan version 5.2 (Cochrane Collaboration, Copenhagen, Denmark) and Stata version 12.0 (Stata Corp LP, College Station, TX) to perform all analyses. The p values are 2-tailed, and the statistical significance was set at 0.05.

RESULTS

Studies retrieved and characteristics. After screening the titles and abstracts of 1,331 reports retrieved in the initial search, 28 qualified for full review. Finally, 6 prospective cohort studies[8,11,18–21] comprising 138,782 individuals satisfied the study inclusion criteria and were analyzed (figure 2). One article from Japan was excluded for primary outcome

Figure 2 Flowchart of selection of studies



*Only the latest published data from the same cohort was included if duplicated reports offered the same information. However, one of these reports offered additional information for subgroup analysis according to stroke type,[22] which was not reported in the primary included publication,[11] and it was only reincluded for subgroup analyses.

analysis,[22] as more recent data[11] from the same cohort were included in primary analysis. However, because this article[22] reported additional information for subgroup analyses according to stroke type, these data were re-entered for subgroup analyses.

Table 1 summarizes the key characteristics of the included studies. Ages ranged between 18 and 75 years, the follow-up duration ranged from 3.4 years[19] to 16.7 years.[8] One study was from Asia,[11] one was from the United States,[18] and the other 4 studies were from European countries (Sweden and Finland).[8,19–21] All studies were graded as good quality according to the Newcastle–Ottawa Quality Assessment Scale. Details of the quality assessment are presented in table e-2.

Association between job strain categories and the risk of stroke. All studies reported the RR of stroke in individuals with high strain, active, or passive groups compared with the low strain group. We used fixed-effects models for the analyses, as there was no significant heterogeneity among all studies.

High strain jobs were associated with an increased risk of stroke (RR 1.22, 95% CI 1.01–1.47; figure 3A), while there were no significant associations in the active (RR 1.07, 95% CI 0.90–1.28; figure 3B) or passive (RR 1.01, 95% CI 0.86–1.18; figure 3C) job groups compared with low strain jobs. We did not find any evidence of publication bias by visual inspection of the funnel plot (figures e-1–e-3), or using Egger test (all $p > 0.05$).

All included studies reported the proportion of job strain in the studied participants (range from 11.1%[8] to 26.6%[19]). On the basis of the pooled RR and percent of high strain in the studied population, we found that the PAR of stroke for high strain jobs was 4.4%.

Association between high strain components and the risk of stroke. Three studies reported data for individuals with low control and high demand jobs separately.[8,19,20] Data were pooled from these studies and calculated using the random-effects model, as there was significant heterogeneity ($I^2 = 74\%$) in the high demand group. Neither low control (RR 1.04,

Table 1 Study characteristics

Study ref.	Country	Percent of high strain	Scale	Sample size (% women)	Age, y, average (range or SD)	Follow-up, y	Participants with baseline CVD excluded	Risk factors adjusted	Events for analysis
8	Sweden	11.1	Demand-Control Questionnaire	6,070 (0)	55.3 (2.1)	16.7	Yes	Age, adiposity, diabetes, smoking, and hypertension	All stroke
11	Japan	25.0	Demand-Control Questionnaire	6,553 (51)	NA (≤65)	11.0	Yes	Age, educational attainment, smoking status, alcohol consumption, physical activity index, and study area	All stroke
18	United States	20.4	Job Content Questionnaire	22,086 (100)	57.2 (5.2)	10	Yes	Age, race, study drug randomization, education, income	Ischemic stroke
19	Finland	26.6	Job Content Questionnaire	48,361 (100)	43.5 (18-65)	3.4	No	Age and history of cerebrovascular disease	All stroke
20	Sweden	16.2	Demand-Control Questionnaire	47,942 (100)	40.3 (5.8)	11.2	Yes	Age	All stroke/ hemorrhagic/ ischemic
21	Sweden	19.8	Demand-Control Questionnaire	7,770 (60.6)	54.7 (NA)	7.8	Yes	Unadjusted	All stroke

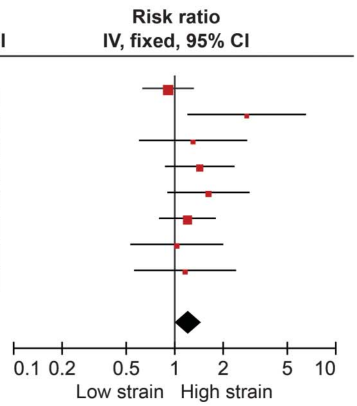
Abbreviations: CVD = cardiovascular disease; NA = not available; ref. = reference.

Figure 3 Association between job strain categories and the risk of stroke

A

Study or subgroup	Log (Risk ratio)	SE	Weight (%)	Risk ratio IV, fixed, 95% CI
Reference 08	-0.0943	0.1876	26.8	0.91 [0.63, 1.31]
Reference 11 men	1.0296	0.4323	5.0	2.80 [1.20, 6.53]
Reference 11 women	0.2624	0.3945	6.1	1.30 [0.60, 2.82]
Reference 19	0.3577	0.2536	14.6	1.43 [0.87, 2.35]
Reference 20	0.4824	0.2999	10.5	1.62 [0.90, 2.92]
Reference 21	0.1823	0.2069	22.0	1.20 [0.80, 1.80]
Reference 22 men	0.0296	0.339	8.2	1.03 [0.53, 2.00]
Reference 22 women	0.1484	0.3716	6.8	1.16 [0.56, 2.40]
Total (95% CI)			**100.0**	**1.22 [1.01, 1.47]**

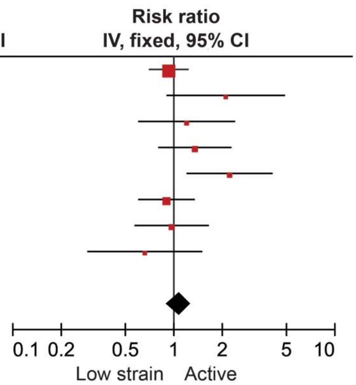
Heterogeneity: Chi² = 7.72, df = 7 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.04 (P = 0.04)



B

Study or subgroup	Log (Risk ratio)	SE	Weight (%)	Risk ratio IV, fixed, 95% CI
Reference 08	-0.0726	0.145	37.2	0.93 [0.70, 1.24]
Reference 11 men	0.7419	0.4323	4.2	2.10 [0.90, 4.90]
Reference 11 women	0.1823	0.3537	6.3	1.20 [0.60, 2.40]
Reference 19	0.3001	0.267	11.0	1.35 [0.80, 2.28]
Reference 20	0.7975	0.3139	7.9	2.22 [1.20, 4.11]
Reference 21	-0.1054	0.2069	18.3	0.90 [0.60, 1.35]
Reference 22 men	-0.0305	0.2713	10.6	0.97 [0.57, 1.65]
Reference 22 women	-0.4155	0.4196	4.4	0.66 [0.29, 1.50]
Total (95% CI)			**100.0**	**1.07 [0.90, 1.28]**

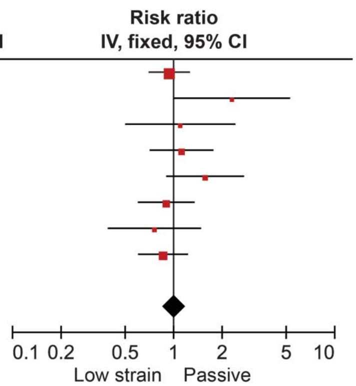
Heterogeneity: Chi² = 11.79, df = 7 (P = 0.11); I² = 41%
Test for overall effect: Z = 0.80 (P = 0.42)



C

Study or subgroup	Log (Risk ratio)	SE	Weight (%)	Risk ratio IV, fixed, 95% CI
Reference 08	-0.0619	0.1504	29.7	0.94 [0.70, 1.26]
Reference 11 men	0.8329	0.425	3.7	2.30 [1.00, 5.29]
Reference 11 women	0.0953	0.4023	4.1	1.10 [0.50, 2.42]
Reference 19	0.1133	0.2326	12.4	1.12 [0.71, 1.77]
Reference 20	0.4511	0.2839	8.3	1.57 [0.90, 2.74]
Reference 21	-0.1054	0.2069	15.7	0.90 [0.60, 1.35]
Reference 22 men	-0.2744	0.3404	5.8	0.76 [0.39, 1.48]
Reference 22 women	-0.1508	0.182	20.3	0.86 [0.60, 1.23]
Total (95% CI)			**100.0**	**1.01 [0.86, 1.18]**

Heterogeneity: Chi² = 8.42, df = 7 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.06 (P = 0.95)



Forest plot for risk of stroke in different job strain categories. (A) Risk of stroke in high strain jobs vs low strain jobs. (B) Risk of stroke in active vs low strain jobs. (C) Risk of stroke in passive vs low strain jobs. In every forest plot, the square box in the graph portrays the weight that each study contributed to the analysis. The overall summary estimate of relative risk is shown on the last row of the graph. CI = confidence interval; IV = inverse variance; SE = standard error.

95% CI 0.90–1.20) nor high demand (RR 1.14, 95% CI 0.78–1.68) job groups were associated with an increased risk of stroke as compared with high control and low demand, respectively.

Subgroup analyses. Five studies with data for 126,459 women[11,18–21] and 3 studies with data for 12,323 men[8,11,21] were included in the subgroup analysis according to sex. The random-effects model was used because the data for men showed significant heterogeneity (I^2 = 65%). High strain jobs were associated with an increased risk of stroke in women (RR 1.33, 95% CI 1.04–1.69) but not in men (RR 1.26, 95% CI 0.69–2.27). However, the difference between men and women was not significant (figure e-4). The PAR of stroke for high strain jobs in women was 6.5%.

Three studies comprising 76,000 participants for ischemic stroke[18,20,22] and 2 containing 54,495 individuals for hemorrhagic stroke (intracerebral and subarachnoid hemorrhage) were included in the subgroup analysis according to stroke type.[20,22] Data were pooled from these studies and calculated using a fixed-effects model for the analyses (I^2 = 0%). High strain jobs significantly increased the risk of ischemic stroke (RR 1.58, 95% CI 1.12–2.23) but not of hemorrhagic stroke (RR 1.37, 95% CI 0.73–2.58). The PAR of ischemic stroke for high strain jobs was 9.5%. However, we did not detect a significant difference between ischemic and hemorrhagic stroke (figure e-5).

Sensitivity analyses. We used several methods to test the sensitivity. First, we confirmed that the outcomes were not influenced by the use of fixed-effect (RR 1.22, 95% CI 1.01–1.47) or random-effect (RR 1.23, 95% CI 1.01–1.51) models. We also performed a sensitivity analysis by omitting a Swedish study,[21] which was unadjusted for confounding factors, and found that the risk of stroke in high strain jobs remained significant (RR 1.24, 95% CI 1.01–1.53) compared with low strain jobs. Furthermore, we omitted another study from Sweden,[20] which was only age-adjusted, from the rest of the studies and found that the association between high strain jobs and risk of stroke was almost significant (RR 1.26, 95% CI 0.99–1.60).

DISCUSSION In this meta-analysis of 138,782 individuals, we found that being exposed to high strain jobs was associated with an increased risk of stroke. The results were particularly pronounced for ischemic stroke and among women with high strain jobs. To our knowledge, this is the first meta-analysis to evaluate the association between job strain and the risk of stroke.

Several mechanisms may be involved in the association between having a high strain job and the risk of stroke. First, work stress may foster unhealthy behavior such as smoking, reduced physical activity, lower help-seeking behavior, and poor eating habits, all of which are also important risk factors for stroke.[23,24] A meta-analysis of data on 102,128 participants showed that the risk of CHD was highest among participants who reported high job strain and an unhealthy lifestyle (HR 2.55, 95% CI 2.18–2.98). However, those with job strain and a healthy lifestyle also had a 25% higher risk of CHD compared with those who had no job strain.[9] These results indicate that unhealthy lifestyles do not fully explain the CVD risks in people exposed to high job strain. Second, work stress is often associated with certain cardiovascular risk factors, such as metabolic syndrome, high body mass index, impaired glucose metabolism, and dyslipidemia, which are also known to be risk factors for stroke.[25,26] Third, long-term work stress could lead directly to neuroendocrine perturbations, such as enhanced activation of the hypothalamic pituitary adrenal axis and sympathetic nervous system, which may result in an elevated inflammatory response, destabilization of atherosclerotic plaques, accelerated cellular aging, enhanced cortisol secretion, and hemodynamic perturbations, as well as other risk factors for stroke.[18,27–29]

It is controversial whether the classification of "job strain" has stronger effects on CVD than when the 2 scales of job demands or control are observed separately.[30] A Japanese study reported that in treated hypertensive workers, those facing a high job demand had a multivariate-adjusted RR of 2.63 for cardiovascular events, including stroke, compared with those with low job demand. However, there was no significant association between job control and cardiovascular events.[14] Conversely, a large-scale study of 2,991,973 individuals in Sweden reported that the risk of stroke was higher in low job control occupations.[12] In our study, the risk of stroke was increased in those with high job strain (a combination of low control and high demand jobs) but not in those with low control or high demand jobs, respectively, or in other combinations of job control and job demand categories, such as passive or active jobs. Although the Swedish study used a larger sample to detect the mildly elevated risk of stroke (HR = 1.07 and 1.08 in women and men, respectively),[12] our study found that individuals exposed to high job strain had 22% higher risk of stroke and 58% higher risk of ischemic stroke. These findings demonstrate that the combination of low control and high demand job characteristics is more important for identifying those at higher risk of stroke. Furthermore, cultural differences may have an important effect on perceive job strain. For example, it was reported that German physicians perceived higher job stress than Australian physicians and coping behavior was significantly different between them.[31] Of note, although the included studies in our meta-analysis were from different countries, there was no significant heterogeneity for risk of stroke among the studies. These results highlight the importance of defining job stress on the basis of the DCM. An expanded version of the job strain model, combining low control, high demand, and low social support, also known as "iso-strain," was assumed to confer the highest risk of illness.[32] The Whitehall II Study demonstrated that iso-strain jobs were significantly associated with incidence of CHD.[33] However, a study from Sweden reported that, while social support at work was an independent predictor of myocardial infarction and stroke among women, there was no evidence to support the iso-strain model.[21] Other potential sources of stress, including job injustice[34,35] and effort–reward imbalance[1,36] exist, which may also be associated with the risk of CVD. We did not review these models in our study because few articles reported the association between them and the risk of stroke. Future prospective cohort studies are needed to test other job stress models and risk of stroke.

Because of the robust association between high strain jobs and stroke demonstrated in our study, successful interventions could have a major public health impact. Possible interventions can be categorized into different aspects. One is aiming to change the occupational context, such as organizational development and job redesign.[37] Another is aiming to increase individual psychological resources and responses. Some psychotherapy methods, such as cognitive behavioral therapy, relaxation therapy, and multimodal interventions, have been shown to be helpful for coping with stress.[38] A high rating pathway was considered as both organizationally and individually focused.[39] Furthermore, lifestyle modifications such as smoking cessation, a balanced diet, and exercise are essential for reducing the risk of stroke.

There are several limitations in this meta-analysis. First, the association between high strain jobs and the increased risk of stroke in men was not significant, which may be because of the limited number of included studies. Furthermore, the difference in stroke risk between men and women was not significant, so this finding should be interpreted with caution. Further studies are needed to clarify the association between job strain and stroke in men. Second, in most of the studies, job strain was measured at a single time point. Data from the Whitehall II Study suggest that the association of job strain and risk of CHD may be underestimated by single-time assessment of work stress.[40] Furthermore, some studies also suggest that individuals with high strain jobs might leave work during follow-up in an attempt to reduce stress. This would dilute the positive results of the baseline state and underestimate the risk of high strain.[12,30] Nevertheless, our study indicates that high strain is a strong risk factor for stroke. Third, although the results remained significant when sensitivity analyses were conducted by omitting studies unadjusted for confounders or only age-adjusted, most of the included studies were not adequately adjusted for other risk factors. Further studies are needed to evaluate whether job stress directly increases the risk of stroke or whether other concurrent risk factors are responsible for the increased risk observed.

Because this meta-analysis revealed that exposure to high strain jobs was associated with an increased risk of stroke, especially in women, it is of vital importance for individuals with high strain occupations to address lifestyle issues. High-risk subpopulations with high strain occupations combined with other cardiovascular risk factors should also be considered in controlled trials of interventions to prevent stroke.

AUTHOR CONTRIBUTIONS

Y. Huang, S.X., T.L., and D.X. were responsible for the initial plan, study design, conducting the study, data interpretation, and manuscript drafting. Y. Huang and S.X. were responsible for statistical analysis. Y. Huang, S.X., J.H., D.Z., and C.L. were responsible for data collection, data extraction, and data interpretation. Y. Huang, S.X., and Y. Hu were responsible for data interpretation and manuscript drafting. T.L. and D.X. are guarantors.

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DISCLOSURE

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