Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data

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Summary

Background Published work assessing psychosocial stress (job strain) as a risk factor for coronary heart disease is inconsistent and subject to publication bias and reverse causation bias. We analysed the relation between job strain and coronary heart disease with a meta-analysis of published and unpublished studies.

Methods We used individual records from 13 European cohort studies (1985–2006) of men and women without coronary heart disease who were employed at time of baseline assessment. We measured job strain with questions from validated job-content and demand-control questionnaires. We extracted data in two stages such that acquisition and harmonisation of job strain measure and covariables occurred before linkage to records for coronary heart disease. We defined incident coronary heart disease as the first non-fatal myocardial infarction or coronary death.

Findings 30 214 (15%) of 197 473 participants reported job strain. In 1·49 million person-years at risk (mean follow-up 7·5 years [SD 1·7]), we recorded 2358 events of incident coronary heart disease. After adjustment for sex and age, the hazard ratio for job strain versus no job strain was 1·23 (95% CI 1·10–1·37). This effect estimate was higher in published (1·43, 1·15–1·77) than unpublished (1·16, 1·02–1·32) studies. Hazard ratios were likewise raised in analyses addressing reverse causality by exclusion of events of coronary heart disease that occurred in the first 3 years (1·31, 1·15–1·48) and 5 years (1·30, 1·13–1·50) of follow-up. We noted an association between job strain and coronary heart disease for sex, age groups, socioeconomic strata, and region, and after adjustments for socioeconomic status, and lifestyle and conventional risk factors. The population attributable risk for job strain was 3·4%.

Interpretation Our findings suggest that prevention of workplace stress might decrease disease incidence; however, this strategy would have a much smaller effect than would tackling of standard risk factors, such as smoking.

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Introduction

Investigators have examined the role of psychological factors, such as personality type, cognition, and psychological stress, in the cause of coronary heart disease. Of these factors, psychosocial stress is the most commonly investigated.[1–3] Job strain—the combination of high job demands and low control at work—is one of the most widely studied definitions of psychosocial stress.[2] Although some studies[4–6] have shown that job strain is associated with a more than doubling in risk of coronary heart disease, findings from a meta-analysis[7] of cohort studies suggest that this excess risk is probably modest, at about 40%. Moreover, the importance of job strain as a risk factor for coronary heart disease continues to be debated because of several methodological shortcomings.

The first limitation is publication bias—ie, studies with significant results in the expected direction are more likely to be published and cited in scientific literature than are those with non-significant findings.[8] Second, in studies[9,10] of working hours (job demand), evidence shows that people spontaneously reduce their hours in the years before cardiac events, probably as a response to symptoms of advanced underlying disease. This action could result in perceptions of reduced job demands, which might contribute to reverse causation bias—ie, coronary heart disease affects levels of stress, rather than vice-versa. Exclusion from analysis of coronary heart disease events that occur in the first years of follow-up can reduce such bias, but few studies have been sufficiently powered to do this analysis.

We did a collaborative meta-analysis of individual participant data from published and unpublished studies of job strain and coronary heart disease to address the limitations of previous studies and the discordant evidence base.

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Methods

Study population

We used data from 13 independent cohort studies started between 1985 and 2006, in Finland, Sweden, Denmark, the Netherlands, Belgium, France, and the UK.[11–23] All studies were part of the individual-participant-data meta-analysis in working populations (IPD-Work) consortium, which was established at the Four Centres meeting in London, in 2008.[24] Details of the study design and participants have been previously published (appendix).

Our analyses were based on participants who were employed at baseline assessment between 1985 and 2006, dependent on the study (table). We excluded from analyses participants with missing data for age, sex, job strain, or incident events of coronary heart disease, and those with a diagnosis of coronary heart disease before the study baseline.

Each constituent study in the consortium was approved by the relevant local or national ethics committees and all participants gave informed consent to participate (appendix).

Assessment of job strain

Job strain was measured with questions from the validated job-content questionnaire and demand-control questionnaire, which were included in the baseline self-report questionnaire of all studies.[25] We have previously published a detailed description of the job-strain measure, including its validation and harmonisation, as part of this collaboration.[25] Briefly, participants were asked to answer questions about the psychosocial aspects of their job. For each participant, mean response scores were calculated for job-demand items (ie, questions about whether the participant had to work very hard, had excessive amounts of work, conflicting demands, or insufficient time) and job-control items (ie, questions about decision freedom and learning new things at work). The Pearson correlation coefficient between the harmonised scales used in this study and the complete versions was greater than 0.9 except for one study[25] in which it was 0.8.

We defined high job demands as having a job-demand score that was greater than the study-specific median score; similarly, we defined low job control as having a job control score that was lower than the study-specific median score. These categorisations are the original and most commonly used. We defined exposure as job strain (high demands and low control) versus no strain (all other combinations) according to the job-strain model.[1] To minimise investigator bias, we validated the job-strain measure before extracting data for coronary heart disease, with investigators masked to outcome information.[25]

Ascertainment of coronary heart disease

We obtained information about incident coronary heart disease during follow-up from national hospital admission and death registries in all studies. Two exceptions were the Belstress study[11] in which disease events were registered by the human resources department and occupational health service, and the Electricité De France-Gaz De France (GAZEL) cohort study[15] in which registry data for admission were not available and

	Country	Baseline	Number of participants	Number (%) of women	Number (%) of participants with job strain	Mean (SD) age at baseline (years)	Person-years	Number of CHD events (incidence per 10 000 person-years)
Whitehall II[21]	UK	1985–88	10 250	3398 (33%)	1437 (14%)	44·4 (6·1)	154 980	382 (24·6)
Still working[20]	Finland	1986	9129	2082 (23%)	1423 (16%)	40·9 (9·1)	193 809	729 (37·6)
WOLF-S[22]	Sweden	1992–95	5653	2447 (43%)	917 (16%)	41·5 (11·0)	81 516	106 (13·0)
Belstress[11]	Belgium	1994–98	14 226	0 (0%)	2190 (15%)	45·8 (6·0)	44 812	85 (19·0)
IPAW[17]	Denmark	1996–97	2022	1356 (67%)	355 (18%)	41·2 (10·5)	25 801	35 (13·6)
WOLF-N[23]	Sweden	1996–98	4678	780 (17%)	599 (13%)	44·0 (10·3)	53 891	122 (22·6)
COPSOQ-I[12]	Denmark	1997	1724	824 (48%)	354 (21%)	40·8 (10·5)	20 171	33 (16·4)
GAZEL[15]	France	1997	11 237	3132 (28%)	1630 (15%)	50·3 (3·0)	125 180	277 (22·1)
POLS[19]	Netherlands	1997–2002	24 473	10 093 (41%)	3904 (16%)	38·1 (11·1)	240 570	241 (10·0)
HeSSup[16]	Finland	1998	16 345	9102 (56%)	2866 (18%)	39·5 (10·2)	113 761	67 (5·9)
DWECS[13]	Denmark	2000	5463	2556 (47%)	1217 (22%)	41·8 (11·0)	48 074	55 (11·4)
FPS[14]	Finland	2000	47 373	38 317 (81%)	7728 (16%)	44·6 (9·4)	224 074	109 (4·9)
NWCS[18]	Netherlands	2005–06	44 900	23 085 (51%)	5594 (13%)	39·9 (11·8)	162 089	117 (7·2)
Total	..	1985–2006	197 473	97 172 (49%)	30 214 (15%)	42·3 (9·8)	1 488 728	2358 (15·8)

CHD=cardiovascular heart disease. WOLF-S=Work, Lipids, Fibrinogen-Stockholm. IPAW=Intervention Project on Absence and Well-being. WOLF-N=Work, Lipids, Fibrinogen-Norrland. COPSOQ-I=Copenhagen Psychosocial Questionnaire version I. GAZEL=Electricité De France-Gaz De France. POLS=Permanent Onderzoek Leefsituatie. HeSSup=Health and Social Support. DWECS=Danish Work Environment Cohort Study. FPS=Finnish Public Sector Study. NWCS=Netherlands Working Conditions Survey.

Table: **Characteristics of eligible participants**

non-fatal events were based on self-report questionnaires distributed yearly. Individuals were defined as having incident coronary heart disease according to the type and time of diagnosis of their first disease event. We used date of diagnosis, hospital admission due to myocardial infarction, or date of death from coronary heart disease to define disease incidence, which were recorded with MONICA categories, or codes from International Classification of Diseases ninth (ICD-9) or tenth (ICD-10) revision.[26–28] We used only main diagnosis from mortality and hospital records. We included all non-fatal myocardial infarctions that were recorded as I21–I22 (ICD-10) or 410 (ICD-9) and coronary deaths recorded as I20–I25 (ICD-10) and 410–414 (ICD-9).

Potential confounders and mediators

We defined all covariates before linkage to data for coronary heart disease.[24,29,30] In addition to age, sex, and socioeconomic status,[24] we used lifestyle factors and conventional coronary risk factors as covariates because they could be related to both job strain and coronary heart disease, and might therefore mediate or confound the association between job strain and disease. We defined socioeconomic status on the basis of an occupational title, which we obtained from employers or some registers (the Copenhagen Psychosocial Questionnaire [COPSOQ-1] study,[12] Danish Work Environment Cohort Study [DWECS],[13] Finnish Public Sector [FPS] study,[14] GAZEL,[15] Intervention Project on Absence and Well-being [IPAW] study,[17] Netherlands Working Conditions Survey [NWCS],[18] and the Still Working study[20]), or from questionnaires completed by participants (Belgian Job Stress Project [Belstress] study,[11] Permanent Onderzoek Leefsituatie [POLS],[19] Whitehall II study,[21] Work Lipids and Fibrinogen [WOLF]-Norrland,[23] and WOLF-Stockholm[22]). In the Health and Social Support study (HeSSup), socioeconomic status was defined on the basis of a participant's self-reported highest educational qualification. We categorised the harmonised socio-economic status into low, intermediate, and high.[24]

We extracted information about tobacco smoking,[30] alcohol intake, and physical activity[29] from questionnaires completed by participants in all studies. Individuals were classed as never, former, or current smokers. We used responses to questions about the total number of alcoholic drinks consumed per week to classify participants as non-drinkers, moderate drinkers (one to 14 drinks per week for women, one to 21 drinks per week for men), high to intermediate drinkers (15–20 drinks per week for women, 22–27 drinks per week for men), and heavy drinkers (≥21 drinks per week for women, ≥28 drinks per week for men). We calculated body-mass index (BMI) with data for height and weight, which were self-reported in three studies (FPS,[14] GAZEL,[15] and HeSSup[16]) and measured directly in Belstress,[11] Whitehall II,[21] WOLF-Norrland,[23] and WOLF-Stockholm.[22] We categorised BMI according to WHO recommendations:[31] less than 18·5 kg/m² (underweight), 18·5–24·9 kg/m² (normal weight), 25–29·9 kg/m² (overweight), and 30 kg/m² or more (obese). We grouped participants into three categories according to their level of leisure-time physical activity: sedentary (physically passive), highly active (at least 2·5 h of moderate, or at least 1 h 15 min of vigorous, physical activity per week), or moderately active (all other levels). With data from four studies (Belstress,[11] Whitehall II,[21] WOLF-Stockholm,[22] and WOLF-Norrland[23]), we constructed the Framingham cardiovascular disease risk score on the basis of age, total cholesterol, HDL cholesterol, systolic blood pressure, use of hypertensive drugs, smoking, and diabetes status.[32]
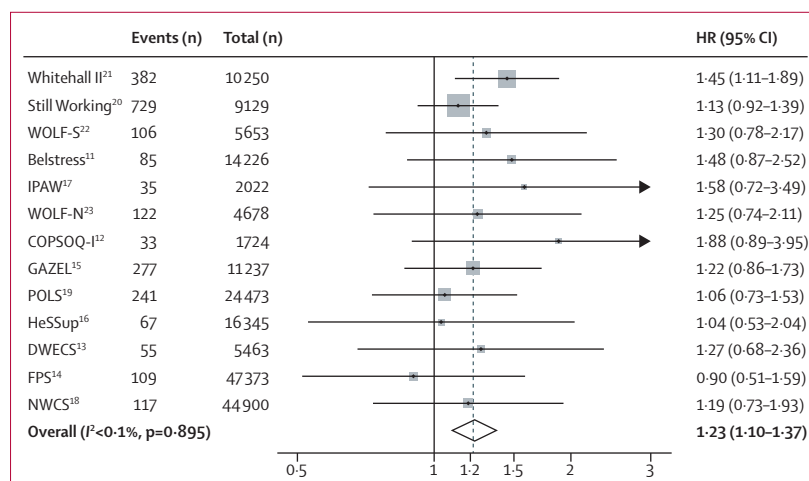
Statistical analysis

We modelled job strain as a binary exposure (strain vs no strain). Having ascertained that the proportional hazards assumption was not violated, we analysed data for each study with Cox proportional hazards regression models. Each participant was followed up from the date of their baseline assessment to the earliest of coronary heart disease event, death, or the end of follow-up. The minimally adjusted models included age and sex. We further adjusted these models for socioeconomic status, lifestyle factors (physical activity, smoking, alcohol intake, and BMI) and the Framingham risk score.[32]

We pooled the study-specific effect estimates and their standard errors in fixed-effects and random-effects meta-analyses; however, we present findings from only the random-effects analyses, the more conservative approach. We assessed heterogeneity with the I^2 statistic. We calculated population attributable risk (PAR) for job strain with accompanying 95% CIs. This risk is the proportion of all cases of coronary heart disease that are

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See Online for appendix

	Events (n)	Total (n)		HR (95% CI)
Whitehall II[21]	382	10250		1·45 (1·11–1·89)
Still Working[20]	729	9129		1·13 (0·92–1·39)
WOLF-S[22]	106	5653		1·30 (0·78–2·17)
Belstress[11]	85	14226		1·48 (0·87–2·52)
IPAW[17]	35	2022		1·58 (0·72–3·49)
WOLF-N[23]	122	4678		1·25 (0·74–2·11)
COPSOQ-I[12]	33	1724		1·88 (0·89–3·95)
GAZEL[15]	277	11237		1·22 (0·86–1·73)
POLS[19]	241	24473		1·06 (0·73–1·53)
HeSSup[16]	67	16345		1·04 (0·53–2·04)
DWECS[13]	55	5463		1·27 (0·68–2·36)
FPS[14]	109	47373		0·90 (0·51–1·59)
NWCS[18]	117	44900		1·19 (0·73–1·93)
Overall (I^2<0·1%, p=0·895)				1·23 (1·10–1·37)

Figure 1: **Random-effects meta-analysis of the association between job strain and incident coronary heart disease**
Estimates are adjusted for age and sex. WOLF-S=Work, Lipids, Fibrinogen-Stockholm. IPAW=Intervention Project on Absence and Well-being. WOLF-N=Work, Lipids, Fibrinogen-Norrland. COPSOQ-I=Copenhagen Psychosocial Questionnaire version I. GAZEL=Electricité De France-Gaz De France. POLS=Permanent Onderzoek Leefsituatie. HeSSup=Health and Social Support. DWECS=Danish Work Environment Cohort Study. FPS=Finnish Public Sector Study. NWCS=Netherlands Working Conditions Survey.

attributable to job strain, with the assumption of a causal association. We calculated as: f(HR–1)/[1+f(HR–1)], in which f is the frequency of job strain in the total population at baseline and HR is the hazard ratio for incident coronary heart disease for job strain versus no job strain. We adjusted the PAR estimates for covariates in a similar way to the corresponding Cox models for HRs.

We used SAS (version 9.2) to analyse study-specific data, except for NWCS and POLS, for which we used SPSS (version 16.0). We did meta-analyses with Stata-MP (version 11.1).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Events (n)	Total (n)		HR (95% CI)
Follow-up				
First 3 years excluded (13 studies)[11–23]	1824	196 939		1·31 (1·15–1·48)
First 5 years excluded (9 studies)[12, 13, 15–17, 20–23]	1411	80 247		1·30 (1·13–1·50)
Adjustments				
SES (13 studies)[11–23]	2358	197 473		1·17 (1·05–1·31)
SES—health behaviours (7 studies)[11, 14–16, 21–23]	1068	102 586		1·21 (1·03–1·44)
SES—Framingham score (4 studies)[11, 21–23]	684	34 115		1·42 (1·16–1·74)
Publication status				
Published (3 studies)[11, 21, 22]	573	30 129		1·43 (1·15–1·77)
Unpublished (10 studies)[12–20, 23]	1785	167 344		1·16 (1·02–1·32)
Region				
Nordic countries (8 studies)[12–14, 16, 17, 20, 22, 23]	1256	92 387		1·18 (1·01–1·37)
Continental Europe (4 studies)[11, 15, 18, 19]	720	94 836		1·19 (0·97–1·47)
UK (1 study)[21]	382	10 250		1·45 (1·11–1·89)
All (13 studies)	2358	197 473		**1·23 (1·10–1·37)**

Figure 2: **Association of job strain with incident coronary heart disease in relation to study follow-up periods, adjustments, publication status for data, and geographical region**
Estimates are adjusted for age and sex unless otherwise stated. Some estimates are further adjusted for SES, health behaviours, and the Framingham score. SES=socioeconomic status.

	Events (n)	Total (n)		HR (95% CI)
Sex				
Men	1595	99 822		1·29 (1·13–1·48)
Women	229	97 117		1·46 (1·07–1·99)
Age group				
<50 years	873	138 918		1·29 (1·08–1·54)
≥50 years	951	58 021		1·36 (1·14–1·62)
Socioeconomic status				
High	320	43 450		1·65 (1·08–2·52)
Intermediate	612	84 184		1·31 (1·05–1·64)
Low	864	64 431		1·24 (1·05–1·47)

Figure 3: **Association of job strain with incident coronary heart disease in subgroups**
Estimates are adjusted, when appropriate, for age and sex. We excluded events that occurred in the first 3 years of follow-up.

Results

We excluded from analyses 5124 (3%) of 203 816 participants who had missing data for age, sex, job strain, or incident coronary heart disease events, and 1219 (1%) with a diagnosis of coronary heart disease before the study baseline. Thus, 197 473 participants were included in the analysis (table). Mean age at study entry was 42·3 years (SD 9·8) and half of participants were women. Dependent on the study, between 13% and 22% of participants had job strain (table).
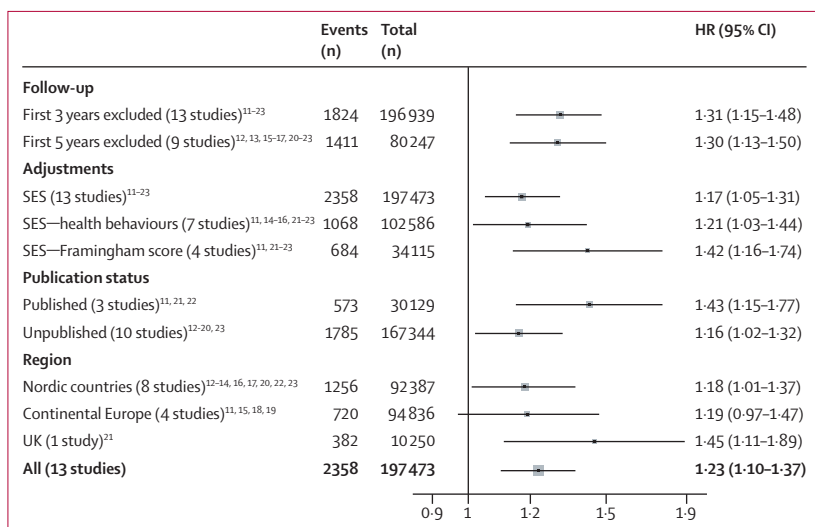
During 1 488 728 person-years at risk (mean follow-up 7·5 years [SD 1·7]), we recorded 2358 incident coronary heart disease events. Heterogeneity in study-specific estimates was small (figure 1). In analysis adjusted for age and sex only, job strain was associated with a significant increase in risk of incident coronary heart disease (figure 1). The corresponding PAR for job strain was 3·4% (95% CI 1·5–5·4). The age-adjusted and sex-adjusted HR attenuated to 1·17 (1·05–1·31) after further adjustment for socioeconomic status. The appendix shows results based on alternative definitions of job strain.

We noted a substantial difference in the association between job strain and coronary heart disease between published[11,33,34] and unpublished studies (figure 2). Although data from unpublished studies suggested a weaker association than did those from published studies (figure 2), the association was significant. Exclusion of coronary heart disease cases at the first 3 years and 5 years of follow-up to minimise reverse causality slightly strengthened the association (figure 2). Adjustment for lifestyle factors (BMI, physical activity, smoking, and alcohol intake) or conventional risk factors (the Framingham score), in addition to age, sex, and socioeconomic status, did not substantially change the magnitude of association between job strain and coronary heart disease (figure 2). Similarly, we noted few differences in the effect of job strain on coronary heart disease between studies from Nordic countries, continental Europe, and the UK (figure 2).
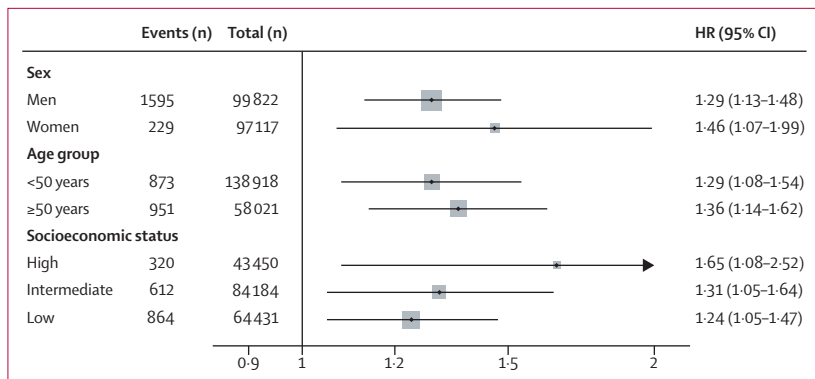
Figure 3 shows analysis of the association between job strain and coronary heart disease by demographic characteristics, with exclusion of disease events in the first 3 years of follow-up. The association was significant and broadly similar for men and women, those younger and older than 50 years, and at all levels of socioeconomic status (figure 3).

Discussion

The pooling of published and unpublished studies allowed us to investigate the association between coronary heart disease and exposure to job strain with greater precision than has previously been possible. Our findings suggest that job strain is associated with a small, but consistent, increased risk of an incident event of cardiovascular heart disease. Adjustment for lifestyle and conventional risk factors, and for age, sex, and

socioeconomic status, did not substantially change the magnitude of this association.

Our study is twice as large as the most recent meta-analysis of this topic (n=83 000), which uses only published data.[7] The effect estimate in our study is substantially lower. We assume that our estimate is less biased than those reported previously for two reasons. First, by contrast with literature reviews, we included unpublished data. The summary estimate that we obtained from published studies[11,33,34] was the same as that reported in previous reviews,[7] whereas the estimate from unpublished data was much lower, indicating publication bias. Second, previous reviews were based on prospective studies with follow-up for coronary heart disease starting immediately after the assessment of job strain. This method raises concerns about reverse causation because the assessment of self-reported job strain could have been affected by subclinical vascular disease, which manifests in the first years of follow-up. Indeed, reduced working hours, related to reduced risk of job strain, are more common in employees with advanced undiagnosed disease than in their healthy counterparts.[9,10] In our study, the magnitude of the relation between job strain and incident coronary heart disease was slightly strengthened in models that excluded disease events that occurred in the first 3 years or 5 years of follow-up. We believe these estimates to be less biased by reverse causation than are those from previous analyses, which included early events.

Previous studies have reported differences in findings for the association between job strain and coronary heart disease between sexes, with some showing increased HRs in women[35] and others in men.[33,36] In the INTERHEART case-control study,[37] which was based on a more generalised measure of work stress than our study, job strain was associated with a greater risk of myocardial infarction in men than in women. However, as in our analysis, many other studies have reported similar effect estimates between sexes.[38–41] Some studies have suggested that the effect of job strain might be weaker in employees older than 50 years than in those who are younger.[34,42] Our findings suggest that such differences between age groups are likely to be small if reverse causation bias (which is especially common in old age groups in whom disease is more prevalent) is minimised by exclusion of disease events in the first years of follow-up.

A limitation of our study is that it is not based on a systematic review. Because we used non-randomised observational data, we could not make conclusions about causality, and we cannot exclude residual confounding as an alternative explanation for our findings. We did not assess underlying mechanisms linking job strain to coronary heart disease. These mechanisms might include dysregulation of the hypothalamus-pituitary-adrenal cortex axis and autonomic nervous system,[3,43] a conversion of temporary increases in blood pressure to chronic high blood pressure in relation to long-term stress,[2,44] and deteriorations in health habits (eg, reduced physical activity).[29,42] We noted some heterogeneity in the measurement of job strain, risk factors, and incident coronary heart disease between studies, which, despite data harmonisation, might have contributed to imprecision in our estimates. However, I^2 heterogeneity in associations of job strain and disease between studies was not substantial.

We measured exposure to job strain on the basis of one baseline assessment; however, some studies have suggested that cumulative exposure to job strain, ascertained by several assessments repeated in time, could be a stronger predictor of coronary heart disease.[42] Measurement of job strain and health behaviours was based on self-reports; thus, reporting bias might have overestimated or underestimated associations. Never-theless, studies that focus on external sources of stress, such as organisational downsizing, death of a child, and caring for a sick spouse at home, have confirmed that stress at work and in private life might be associated with an increased risk of coronary heart disease.[45–47]

Primary-care practitioners need evidence-based in-formation to advise patients with work-related stress. Stress is a recognised health hazard[2,3,48] and European guidelines for prevention of coronary heart disease recommend stress management for high-risk indi-viduals.[49] The INTERHEART study[50] of 15 000 patients with myocardial infarction and 15 000 healthy controls, the largest case-control study in this domain, showed that work stress doubled risk of coronary heart disease,[37] whereas prospective data from published cohort studies suggest a 1·4 times increased risk.[7] From our col-laborative analysis, we noted that this increase was smaller at 1·2–1·3 times. The population attributable risk in our study suggests that if the recorded association were causal, then job strain would account for a notable proportion of coronary heart disease events in working populations. However, the PAR is substantially less than that for standard risk factors, such as smoking (36% in INTERHEART), abdominal obesity (20%), and physical inactivity (12%).[50]

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