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ORIGINAL ARTICLE

Psychosocial Stressors at Work and Coronary Heart Disease Risk in Men and Women: 18-Year Prospective Cohort Study of Combined Exposures

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BACKGROUND. Psychosocial stressors at work, like job strain and effort-reward imbalance (ERI), can increase coronary heart disease (CHD) risk. ERI indicates an imbalance between the effort and received rewards. Evidence about the adverse effect of combined exposure to these work stressors on CHD risk is scarce. This study examines the separate and combined effect of job strain and ERI exposure on CHD incidence in a prospective cohort of white-collar workers in Quebec, Canada.

METHODS. Six thousand four hundred sixty-five white-collar workers without cardiovascular disease (mean age, 45.3±6.7) were followed for 18 years (from 2000 to 2018). Job strain and ERI were measured with validated questionnaires. CHD events were retrieved from medico-administrative databases using validated algorithms. Marginal Cox models were used to calculate hazard ratios (HR) stratified by sex. Multiple imputation and inverse probability weights were applied to minimize potential threats to internal validity.

RESULTS. Among 3118 men, 571 had a first CHD event. Exposure to either job strain or ERI was associated with an adjusted 49% CHD risk increase (HR, 1.49 [95% CI, 1.07–2.09]). Combined exposure to job strain and ERI was associated with an adjusted 103% CHD risk increase (HR, 2.03 [95% CI, 1.38–2.97]). Exclusion of early CHD cases and censoring at retirement did not alter these associations. Among 3347 women, 265 had a first CHD event. Findings were inconclusive (passive job HR, 1.24 [95% CI, 0.80–1.91]; active job HR, 1.16 [95% CI, 0.70–1.94]; job strain HR, 1.08 [95% CI, 0.66–1.77]; ERI HR, 1.02 [95% CI, 0.72–1.45]).

CONCLUSIONS. In this prospective cohort study, men exposed to job strain or ERI, separately and in combination, were at increased risk of CHD. Early interventions on these psychosocial stressors at work in men may be effective prevention strategies to reduce CHD burden. Among women, further investigation is required.

Key Words: cardiovascular disease ■ cohort studies ■ heart disease ■ men ■ occupational stress ■ women

Coronary heart diseases (CHD) are the most common type of cardiovascular diseases.[1] In 2017, CHD affected 126 million individuals representing 1.72% of the world's population. With 9 million deaths annually worldwide, CHD are the leading cause of death. Biological, biomedical, lifestyle and psychosocial risk factors are identified as relevant targets for CHD prevention.

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WHAT IS KNOWN

- Psychosocial stressors at work, from the job strain and effort-reward imbalance models, are associated with increased coronary heart disease risk.
- The combined effect of job strain and effort-reward imbalance may be especially harmful, however, evidence of their combined effect on coronary heart disease incidence is limited and inconsistent.

WHAT THE STUDY ADDS

- Men exposed to both job strain and effort-reward imbalance had twice the risk of incident coronary heart disease compared with those unexposed.
- The estimated effect of either job strain or effort-reward imbalance, in men, was of comparable amplitude to that of several biomedical and lifestyle coronary heart disease risk factors.
- Among women, results were inconclusive, and more studies are needed.

Nonstandard Abbreviations and Acronyms

CHD	Coronary heart disease
ERI	Effort-reward imbalance
HR	Hazard ratios
IPW	Inverse probability weights
PROQ	Prospective Quebec

Psychosocial stressors at work, from the job strain and effort-reward imbalance (ERI) models, were shown to increase CHD risk.[2,3] The job strain model categorizes exposure into 4 quadrants: job strain (high demands, low control), passive jobs (low demands, low control), active jobs (high demands, high control), and low job strain (low demands, high control).[4] The ERI model asserts that an imbalance between effort at work and rewards can be detrimental to health.[5] Both models cover different dimensions of the psychosocial environment at work. Job strain focuses on task characteristics,[4] whereas ERI focuses on broader socioeconomic conditions like salaries, promotion, and job stability.[5] Evidence support the separate[6,7] and independent[2] effects of these psychosocial stressors at work on CHD.

Combined exposure to job strain and ERI could be especially harmful.[3] However, evidence about the additive effect of both stressors on CHD risk is scarce and results are inconsistent.[3,8] Previous studies, conducted in Europe, have documented this effect using a binary definition of job strain exposure by grouping passive, and active jobs in the reference category[3,8] or assessed job strain exposure based on job titles,[8] which does not capture individual variations. Both methodological considerations could have led to nondifferential misclassification and effect underestimation.[8–10] Therefore, additional studies are needed, in other geographic settings. The present study aims to estimate the separate and combined effect of job strain and ERI on CHD incidence, using an 18-year Canadian prospective cohort of men and women, with special attention to internal validity.

METHODS

The PROQ (Prospective Quebec) cohort is a longitudinal study for which details have been published elsewhere.[11] Briefly, the PROQ cohort recruited 9188 white-collar men and women, aged 18 to 65 years (mean, 40.2±8.7), from 19 public and semi-public enterprises in the Quebec region from 1991 to 1993. At recruitment, the participation proportion was 75%. The PROQ cohort–cardiovascular component consisted of 8895 participants, free of cardiovascular disease at recruitment. In-person data collection was performed from 1999 to 2001. Access to medico-administrative data to measure CHD incidence over 24 years was available up to December 31, 2018. All participants provided informed consent and the study was approved by the institutional review board of the Centre Hospitalier Universitaire de Québec-Université Laval Research Center. The data that supports the findings of this study are available from X.T. on reasonable request (xavier.trudel@crchudequebec.ulaval.ca).

This study includes 6465 working white-collar, without cardiovascular disease, from the PROQ cohort–cardiovascular component present at the 1999 to 2001 data collection. All were followed up to December 31, 2018 (Figure 1 details selection). Briefly, 8216, free of cardiovascular disease, participated from 1999 to 2001; 679 were lost to follow-up between 1991 and 1993 and 1999 and 2001 resulting in a participation proportion of 92%. From 1999 to 2001, 387 participants were identified with a prevalent cardiovascular pathology, and 959 participants were no longer exposed (ie, retired). For 405 participants, the outcome was not assessed as the medico-administrative databases could not be merged (ie, missing information, refusal, or failure to link with medico-administrative data). Therefore, the study comprises 3118 men and 3347 women followed for a median period of 18.7 years.

The validated French version of the Job Content Questionnaire was used to assess psychological demands and job control, using 18 items rated on a 4-point Likert-type scale.[12,13] The median of the general Quebec working population was used to classify high psychological demands (≥24) and low job control (≤72).[14] Job strain quadrant method (low job strain, passive jobs, active jobs, and job strain) was used to classify exposure.[4] Reward at work was measured by 9 original questions from the French version of the ERI scale.[5,15,16] Effort was measured by 9 items from the psychological demands scale.[12] The sum of both effort and reward was used to calculate the ERI ratio. Details can be found in Supplemental Material.[13,17–19]

Combined job strain and ERI exposure was defined as follows: the reference category comprised the participants with low job strain and unexposed to low rewards. Participants with low exposure refer to participants exposed to passive or active jobs or to ERI's low rewards (dichotomized at the study population median) but who were not in a state of imbalance. Intermediate exposure refers to participants with either job

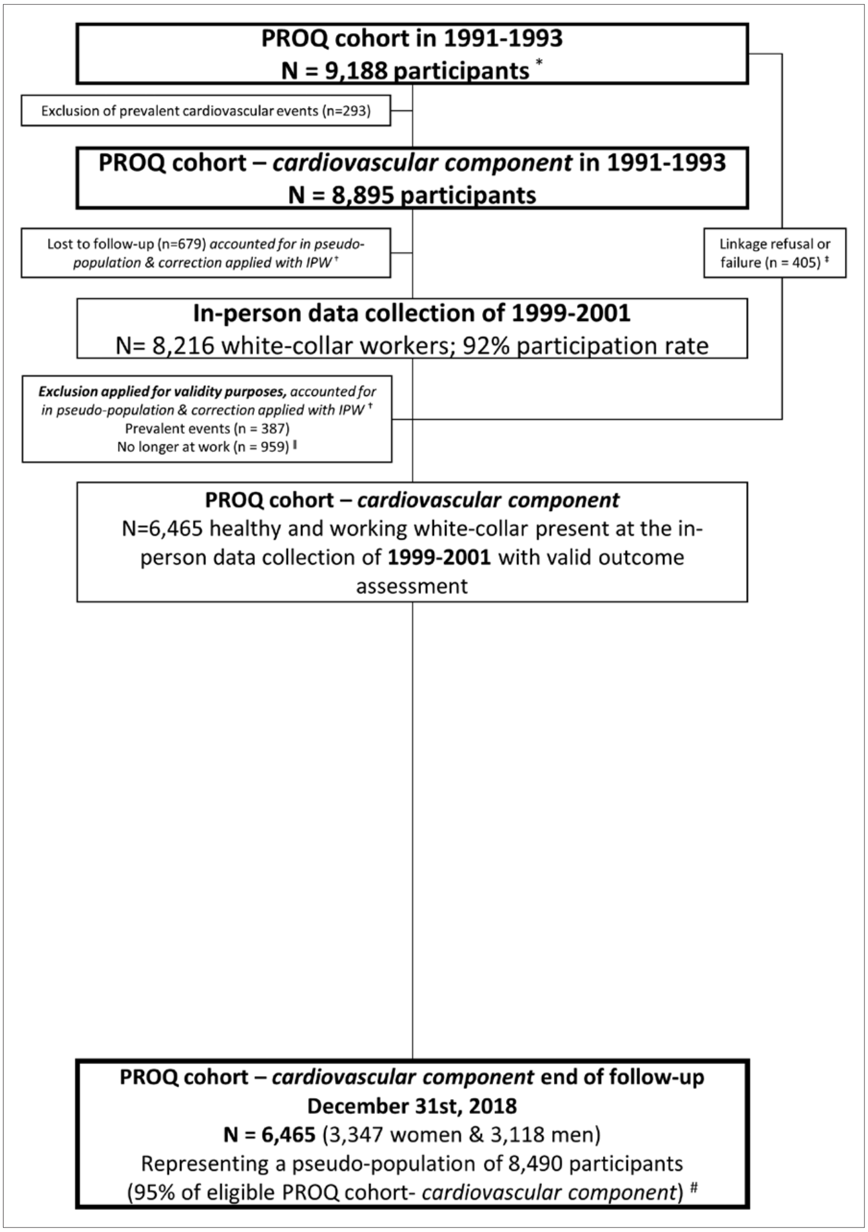

Figure 1. Flowchart of the cardiovascular component of the PROQ (Prospective Quebec) cohort on work and health.
*75% response rate. †Corrected for selection using inverse probability weighting (IPW) of selection. ‡Medico-administrative information not available for 405 participants. ||959 participants no longer at work. #Pseudo-population allows representation of 95% of eligible participants from PROQ cohort–cardiovascular component population (N=8895).

strain or ERI, but not both. Double exposure refers to participants exposed simultaneously to job strain and ERI (Figure S1).

CHD was assessed using medico-administrative databases and an algorithm validated by medical records (sensitivity, 77.0%; specificity, 97.5%; positive predictive value, 75.3%).[20] Diagnostic and procedure codes were extracted from Quebec public health insurance and hospitalization databases, as well as national death registry databases.[21] CHD codes included the *International Classification of Diseases, Ninth Revision*: 410–414, *International Classification of Diseases, Tenth Revision*: I20–I25, Canadian Classification of Diagnosis, Therapeutic and Surgical Procedures: 48.02, 48.03, 48.09, 481, and Canadian Classification of Health Interventions: 1.IJ.50, 1.IJ.57.GQ, and 1.IJ.76 (Figure S2). Participants with myocardial infarction, angina, acute and chronic coronary syndrome, and those who had a percutaneous coronary intervention, coronary artery bypass, or angioplasty were identified from 1991 to 2018 if they had at least one hospitalization with a diagnosis or procedure code for CHD or ≥2 physician claims within a year. The date of CHD was defined as the first date when one of these conditions was met.

Covariates were measured at the same time as exposure (T2). Details can be found elsewhere.[11] Height, weight, hips, waist circumferences, and blood pressure were measured by a trained-research nurse based on validated protocols and categorized according to current guidelines. Hypertension was defined by an average of 3 elevated blood pressure measurements, self-reported hypertension diagnosis, or antihypertensive medication use. Diabetes, hypercholesterolemia, and cardiovascular family history were self-reported. Smoking status, alcohol consumption, and physical activity were measured with validated questionnaires.[11] Self-reported weekly alcohol intake was classified as abstinent, low-risk (≤15 for men, ≤10 for women), or high-risk.[22] Physical activity was measured by frequency and duration of sessions to classify participants as low (<1 session/week), moderately active (1–2 sessions/week), or active (≥3 sessions/week).[23]

Statistical Analysis

There was a small number of missing data (Table 1). Nonetheless, a sequential approach to multiple imputation, with as many datasets as the percentage of missing data, was used.[24] Considering that the benefit of imputing the outcome is unclear, participants for whom medico-administrative data were unavailable (n=405) were not imputed, representing 4.5% of missing data for the entire PROQ cohort–cardiovascular component. To account for potential effect modification,[25,26] multiple imputations was performed by sex.

Associations were examined using marginal hazard ratios (HRs) and semiparametric Cox models, stratified by sex. Age as timescale with delayed entry (left truncation) at baseline age allowed to model the hazard as a function of the time-varying age of individuals, instead of a function of the arbitrary time since the start of the follow-up. People were followed for CHD events from the day of in-person visits at study baseline until CHD diagnosis, competing risk (ie, death), or end of follow-up, whichever came first. As recommended for etiologic studies, follow-up times were right censored at the time of competing risks.[27] This model assumes that censoring and truncation are independent of the event time conditional on the variables included in the model. The proportional hazards assumption of the Cox model was visually verified and was deemed satisfied. CIs were obtained using a robust sandwich covariance matrix[28] and were interpreted as a range of values compatible with the data.[29]

All Cox models only included exposure as an explanatory variable. Adjustment for potential confounders was performed using inverse probability weights (IPW) of confounding[30] and distinguishing between common confounders and potential mediators.[31] Cox models were sequentially adjusted for each subgroup of cofactors. First, a crude model was constructed, with sex stratification and age adjustment through timescale. Then sequential adjustment was performed for confounders (ie, spouse, education, out-of-work social support, hours of work per week, stressful life events, and personality) and potential mediators (ie, diabetes, cholesterol, hypertension, hip-waist ratio, family history of cardiovascular disease, smoking, alcohol, and leisure physical activity).

Participants at T2 differed from nonparticipants (Table S1). Therefore, IPW of selection,[30] were used to create a pseudo-population, representing 8490 PROQ–cardiovascular component participants. Sex-specific weights were assigned, representing the inverse of the probability of selection, to make participants comparable to those initially recruited. The IPW of selection model used the same set of covariates included in the fully adjusted IPW of confounding model but measured at T1. Selection and confounding IPW were truncated at the 99% percentile, to avoid extreme weight, and were multiplied.[32]

Several sensitivity analyses were performed. First, a period-at-risk exploration was performed to investigate reverse causation and a possible induction period by excluding early CHD cases within 3 and 5 years of exposure measurement. Right-censoring was also performed at retirement and 5-year postretirement, to investigate the role of exposure cessation. Second, complete case analyses were performed. Third, analyses were conducted without correction for selection bias. Fourth, conditional HRs were calculated, with standard statistical adjustment by including covariates in the Cox regression. Fifth, different categorizations for the combined exposure were considered allowing a comparison with previous studies.[3,8] Sixth, given the relative diagnostic subjectivity of angina, a

Table 1. Characteristics of Prospective Quebec Cohort Participants, 1999–2001

	Mean±SD, N(%)	
	Men (n=3118)	Women (n=3347)
Age at recruitment (1991–1993)	38.82±6.83	36.69±6.30
Age at baseline of the present study (1999–2001)	46.41±6.91	44.35±6.35
Age at end of follow-up*	63.89±7.20	62.70±6.53
Education		
High school or less	356 (11.42)	1321 (39.47)
College	797 (25.56)	976 (29.16)
University	1944 (62.35)	1027 (30.68)
Missing	21 (0.67)	23 (0.69)
Spouse (yes)	2506 (80.37)	2342 (69.97)
Missing	13 (0.42)	20 (0.60)
Low out-of-work social support	2318 (74.34)	1752 (52.35)
Missing	83 (2.66)	85 (2.54)
Hours of work/wk	36.62±5.32	34.75±4.70
Missing	29 (0.93)	38 (1.14)
Stressful life events	1179 (37.81)	1563 (46.70)
Missing	21 (0.67)	29 (0.87)
Angry, hostile, or cynical personality	726 (23.28)	765 (22.86)
Missing	27 (0.87)	30 (0.90)
Job strain model		
Low job strain	665 (21.33)	465 (13.89)
Passive job	889 (28.51)	1435 (42.87)
Active job	1068 (34.25)	717 (21.42)
Job strain	472 (15.14)	681 (20.35)
Missing	24 (0.77)	49 (1.46)
Effort-reward imbalance	769 (24.66)	778 (23.24)
Missing	104 (3.34)	154 (4.60)
Combined exposure to job strain and effort-reward imbalance†		
Unexposed	422 (13.53)	313 (9.35)
Low exposure	1617 (51.86)	1770 (52.88)
Intermediary exposure	704 (22.58)	743 (22.20)
Double exposure	260 (8.34)	344 (10.28)
Missing	115 (3.69)	177 (5.29)
Diabetes	86 (2.76)	95 (2.85)
Missing	5 (0.16)	13 (0.39)
Hypercholesterolemia	1126 (36.11)	585 (17.48)
Missing	11 (0.35)	12 (0.36)
Hypertension	890 (28.54)	555 (16.58)
Missing	15 (0.48)	13 (0.39)
Family cardiovascular disease history	1225 (39.29)	1482 (44.28)
Missing	70 (2.25)	73 (2.18)
Hip-waist ratio‡		
Low-risk	2650 (84.99)	2765 (82.61)
High-risk	352 (11.29)	373 (11.14)
Missing	116 (3.72)	209 (6.24)

(*Continued*)

Table 1. Continued

	Mean±SD, N(%)	
	Men (n=3118)	Women (n=3347)
Body mass index		
Healthy (<25.0 kg/m²)	1162 (37.27)	1996 (59.64)
Overweight (25.0–30.0 kg/m²)	1461 (46.86)	896 (26.77)
Obesity (≥30.0 kg/m²)	436 (13.98)	372 (11.11)
Missing	59 (1.89)	83 (2.48)
Current smoker	485 (15.55)	645 (19.27)
Missing	6 (0.19)	17 (0.51)
Alcohol consumption§		
Abstinent	158 (5.07)	249 (7.44)
Low-risk consumption	2724 (87.36)	2917 (87.15)
High-risk consumption	230 (7.38)	173 (5.17)
Missing	6 (0.19)	8 (0.24)
Leisure physical activity level‖		
Low	971 (31.14)	1270 (37.94)
Moderate	1161 (37.24)	1244 (37.17)
Active	971 (31.14)	825 (24.65)
Missing	15 (0.48)	8 (0.24)

N (number of participants); kg/m² (kilogram/ meter²). CHD indicates coronary heart disease

*Age at the end of follow-up defined as the age of participant at CHD diagnosis, competing risk, or end of the study (December 31, 2018).

†Double exposure: job strain and effort-reward imbalance; intermediary exposure: job strain or effort-reward imbalance, but not both; low exposure: passive or active job or unexposed to low rewards; unexposed: low job strain and unexposed to low rewards.

‡High-risk hip-waist ratio defined as ≥1.0 in men and ≥0.85 in women.

§Low-risk weekly alcohol consumption defined as ≤15 for men and ≤10 for women.

‖Leisure physical activity levels defined as low (less than one 20–30-minute session per week), moderate (1 or 2 sessions per week), and active is ≥3 sessions per week.

sensitivity analysis was conducted by excluding angina cases (*International Classification of Diseases, Ninth Revision*: 413 or *International Classification of Diseases, Tenth Revision*: I20) to test the robustness of the findings. Finally, a possible cohort effect was tested with further adjustment for age at baseline.

RESULTS

Table 1 presents descriptive statistics for the 3118 men and 3347 women from the PROQ cohort. From 1999 to 2001, men were, on average, 46 years old, and most had completed a university degree. Women were, on average, 44 years old, and most had completed a high school degree. Men had a higher prevalence of comorbidities (ie, diabetes, hypertension, and hypercholesterolemia) than women. Low exposure to psychosocial stressors at work (ie, either passive, active job or low reward), was observed in about half of men and women. Twenty-two percent of men and women had either exposure to job strain or ERI. Combined exposure to job strain and ERI was found in 8.34% of men and 10.28% of women. The remaining 13.53% of men and 9.35% of women were unexposed (ie, low job strain or unexposed to low rewards). Cumulative CHD incidence differed by sex. A total of 571 and 265 incident CHD cases were recorded among men and women, respectively. Men contributed to 52 992 person-years and women to 59 787 person-years resulting in crude cumulative CHD incidences of 10.78‰ and 4.43‰ person-years, respectively. Expected associations between traditional risk factors and CHD incidence were observed among both men and women (Table 2; Table S2). Biomedical and anthropometric factors were associated with increased CHD risk ranging from 23% to 98% among men and 25% to 151% among women.

Men with low exposure to psychosocial stressors at work had a 15% CHD risk increase (HR, 1.15 [95% CI, 0.85–1.56]) compared with their unexposed counterparts (Table 3). Men with either job strain or ERI exposure had a 49% CHD risk increase (HR, 1.49 [95% CI, 1.07–2.09]); whereas workers exposed to both had a 103% CHD risk increase (HR, 2.03 [95% CI, 1.38–2.97]). Associations were robust to adjustment for demographic, socioeconomic, psychosocial, personality, stressful life events, biomedical, and lifestyle factors. Among women, intermediaries, and combined exposures to job strain and ERI resulted in HRs close to 1 and wide CI including the null value. The HRs for passive and active jobs, from the job strain model, were 1.24 (95% CI, 0.80–1.91) and 1.16 (95% CI, 0.70–1.94), respectively.

Kaplan-Meier curves, displaying the time-to-event progression of CHD cases for men and women, with stratification by exposure categories for job strain, ERI, separately and in combination are presented in Figure 2, Figures S3 and S4.

Among men, 110 (19%) early CHD cases occurred within 5 years of exposure measurement and 399 (70%) CHD cases occurred within 5 years of retirement. After exclusion of these early CHD cases and after right-censoring postretirement, low, intermediaries, and double exposure, were associated with increased CHD risk. Further details can be found in the Supplemental Material (Tables S3 and S4). HRs were marginally higher in complete case analyses (Tables S5 and S6). Conditional HRs were generally further from the null value when compared with marginal HRs (Table S7). In analysis with multiple imputation, associations were comparable in analysis with and without IPW of selection (Table S8). Associations remained but were weakened when using alternate definitions of combined exposure (Table S9). The removal of angina codes yielded similar results (Table S10). No change was observed after adjustment for age at baseline (Table S11).

DISCUSSION

In the present study, men exposed to combined job strain and ERI had a 2-fold CHD risk increase when compared with those unexposed. Men exposed to either job strain

Table 2. Marginal HR of Traditional Coronary Heart Disease Risk Factors

	Men ($n_{participants}$=3,118; n_{events}=571)			Women ($n_{participants}$=3,347; n_{events}=265)		
	$n_{exposed}$	n_{events}	HR (95% CI)*	$n_{exposed}$	n_{events}	HR (95% CI)*
Diabetes	86	23	1.23 (0.76–1.97)	97	17	2.51 (1.42–4.43)†
Hypertension	890	232	1.62 (1.35–1.94)†	555	81	1.72 (1.28–2.31)†
Hypercholesterolemia	1131	278	1.42 (1.18–1.70)†	586	59	1.25 (0.92–1.71)
Family cardiovascular disease history	1871	277	1.52 (1.27–1.82)†	1839	113	1.63 (1.25–2.11)†
Hip-waist ratio						
High risk (≥1.00 in men and ≥0.85 in women)	360	113	1.69 (1.32–2.17)†	393	56	1.78 (1.27–2.49)†
Body mass index						
Overweight (25.0–30.0 kg/m²)	1491	294	1.59 (1.29–1.96)†	922	82	1.25 (0.93–1.68)
Obesity (≥30.0 kg/m²)	442	121	1.98 (1.53–2.55)†	382	53	1.85 (1.33–2.58)†
Current smoker	487	114	1.35 (1.07–1.69)†	648	64	1.48 (1.09–2.01)†
Alcohol consumption						
Abstinent	159	37	1.30 (0.91–1.86)	249	28	1.28 (0.83–1.98)
High-risk consumption (>15/wk for men and >10/wk for women)	230	46	1.11 (0.81–1.52)	173	11	0.89 (0.48–1.65)
Leisure physical activity level						
Moderate (1 or 2 weekly)	1167	194	0.85 (0.69–1.06)	1246	105	0.88 (0.67–1.17)
Active (≥3 weekly)	974	179	0.85 (0.68–1.05)	827	44	0.50 (0.35–0.72)†

HR; 95% CI; N (number of participants, exposed, or events); kg/m² (kilogram/ meter²). Survival models are weighted using selection weights (inverse probability weighting) and statistical adjustment using confounding weights. Selection and confounding weights are multiplied. CIs were estimated with a robust sandwich estimate for the covariance matrix.

*Age adjusted through timescale and stratified for sex.

†CI excluding the null value.

or ERI had a 1.5-fold CHD risk increase. These risks were obtained using an 18-year prospective cohort, with correction for selection bias and with multiple imputation to account for missing data. The observed associations were robust to adjustment for major CHD risk factors. Among women, results were inconclusive.

Previous studies showed inconsistent results. Sørensen et al[8] reported that combined exposure to job strain and ERI was associated with a modest CHD risk increase, among men (HR, 1.15) and women (HR, 1.11). These estimates were similar or only slightly higher than those observed for exposure to either stressor. Dragano et al[3] reported that combined exposure to job strain and ERI was associated with a higher CHD risk increase (HR, 1.41) when compared with exposure to either stressor (HR, 1.16), among men and women combined. In both studies, a binary job strain definition was used. This definition could have led to misclassification and effect underestimation given the grouping of passive and active exposures with low strain in the reference category. In the present study, the quadrant measure of job strain was used, which considers all job strain components. This allowed the reference category to be compatible with the theoretical minimum risk level, for example, the risk level that would result in the lowest population risk.[33] As expected, when using a binary job strain definition, our results showed weaker associations for combined exposure (Table S8). Previous studies also used exposure definition based on job titles,[8] or had a shorter follow-up.[3] Since removing individual variations of exposure and restricting the optimal period at risk can both lead to effect underestimation, these limitations, avoided in the present study, may also contribute to explain the higher CHD risk increase that we observed, among men.

The estimated effect of either job strain or ERI on CHD incidence, in men, was of comparable amplitude to that of several biomedical and lifestyle CHD risk factors. Whereas job strain and ERI in combination were associated with an increased CHD risk of comparable magnitude to that of obesity.

Results from the present study are consistent with the current understanding of pathophysiological mechanisms. Over the course of professional life, exposure to psychosocial stressors at work in combination with more traditional risk factors can promote the occurrence and progression of coronary atherosclerosis with the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the hypothalamo-pituitary-adrenal axis.[34] Psychosocial stressors at work can also precipitate a cardiovascular event through sympathetic nervous system activation. Atherosclerotic plaque disruption and platelet activation are triggered by increased heart rate, blood pressure, and coronary vasoconstriction.

It has been suggested that early CHD cases may introduce reverse causation or effect underestimation given a possible induction period.[3,33,35] Our results

Table 3. Marginal HR of the Separate and Combined Effect of Job Strain and Effort-Reward Imbalance on Incident Coronary Heart Disease

Men ($n_{participants}$=3 118; n_{events}=571)	$n_{exposed}$	n_{events}	HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡
Combined exposure to job strain and ERI§					
Unexposed	436	62	Reference (1.00)		
Low exposure	1675	288	1.10 (0.77–1.57)	1.15 (0.85–1.56)	1.15 (0.85–1.57)
Intermediary exposure	741	149	1.31 (0.88–1.95)	1.49 (1.07–2.09)‖	1.41 (1.01–1.99)‖
Double exposure	266	72	2.08 (1.40–3.11)‖	2.03 (1.38–2.97)‖	1.95 (1.32–2.87)‖
Job strain model					
Low job strain	669	111	Reference (1.00)		
Passive job	899	167	1.10 (0.82–1.47)	1.06 (0.80–1.39)	1.08 (0.82–1.42)
Active job	1075	185	1.04 (0.79–1.39)	1.07 (0.81–1.41)	1.04 (0.79–1.38)
Job strain	475	108	1.45 (1.01–2.10)‖	1.51 (1.12–2.04)‖	1.47 (1.09–1.99)‖
ERI model					
Unexposed	2 320	386	Reference (1.00)		
Imbalance state	798	185	1.50 (1.23–1.81)‖	1.55 (1.26–1.89)‖	1.55 (1.26–1.90)‖
Women ($n_{participants}$=3 347; n_{events} =26)	**$n_{exposed}$**	**n_{events}**	**HR (95% CI)***	**HR (95% CI)†**	**HR (95% CI)‡**
Combined exposure to job strain and ERI§					
Unexposed	326	24	Reference (1.00)		
Low exposure	1871	152	0.92 (0.57–1.49)	0.99 (0.62–1.57)	1.00 (0.62–1.61)
Intermediary exposure	790	64	1.00 (0.59–1.69)	1.03 (0.61–1.72)	1.02 (0.60–1.73)
Double exposure	360	25	0.89 (0.48–1.65)	0.86 (0.46–1.61)	0.85 (0.45–1.62)
Job strain model					
Low job strain	471	29	Reference (1.00)		
Passive job	1469	132	1.25 (0.80–1.95)	1.24 (0.80–1.91)	1.23 (0.79–1.90)
Active job	721	55	1.07 (0.65–1.76)	1.16 (0.70–1.94)	1.13 (0.67–1.89)
Job strain	686	49	1.08 (0.65–1.78)	1.08 (0.66–1.77)	1.02 (0.62–1.67)
ERI model					
Unexposed	2523	200	Reference (1.00)		
Imbalance state	824	65	1.08 (0.78–1.48)	1.02 (0.72–1.45)	1.02 (0.72–1.44)

HR; 95% CI; N (number of participants, exposed, or events); ERI model. Survival models are weighted using selection weights (inverse probability weighting) and statistical adjustment using confounding weights. Selection and confounding weights are multiplied. CIs were estimated with a robust sandwich estimate for the covariance matrix. ERI, effort-reward imbalance; HR, hazard ratio

*Age adjusted through timescale and stratified for sex.

†Further adjusted for living with spouse (yes/no), education (categorical), low out-of-work social support (yes/no), hours of work per week (continuous), personality (dichotomic scale) and stressful life events (yes/no).

‡Further adjusted for diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), family history of cardiovascular disease (yes/ no), hip-waist ratio (categorical), smoking status (categorical), alcohol consumption profile (categorical) and leisure physical activity levels (categorical).

§Double exposure: job strain and effort-reward imbalance; Intermediary exposure: job strain or effort-reward imbalance, but not both; Low exposure: passive or active job or ERI's unexposed to low rewards; Unexposed: low job strain and unexposed to low reward.

‖CI excluding the null value.

showed marginally strengthened deleterious associations after the removal of early CHD cases. Moreover, psychosocial stressors at work effects could persist after the end of exposure,[36] as illustrated by associations over the whole period and using different censoring windows around retirement age. These findings are consistent with previous literature,[3,6,35] and the natural disease history, as the progression of atherosclerosis, is not linear and occurs silently over many decades.[37]

The results among women are inconclusive. The CIs, that can be interpreted as the interval compatible with the observed data, were wide enough to encompass both protective and detrimental effects.[38] Important differences between men and women are known in terms of CHD pathophysiology; lower number of CHD cases, and delayed onset of the disease are expected among women. This can be, in part, explained by the protective effect of estrogens.[1] In the present study, half as less CHD cases were observed in women. Women could have been more likely to experience a cardiovascular event long after the end of exposure, which render the observation of an exposure-effect relationship

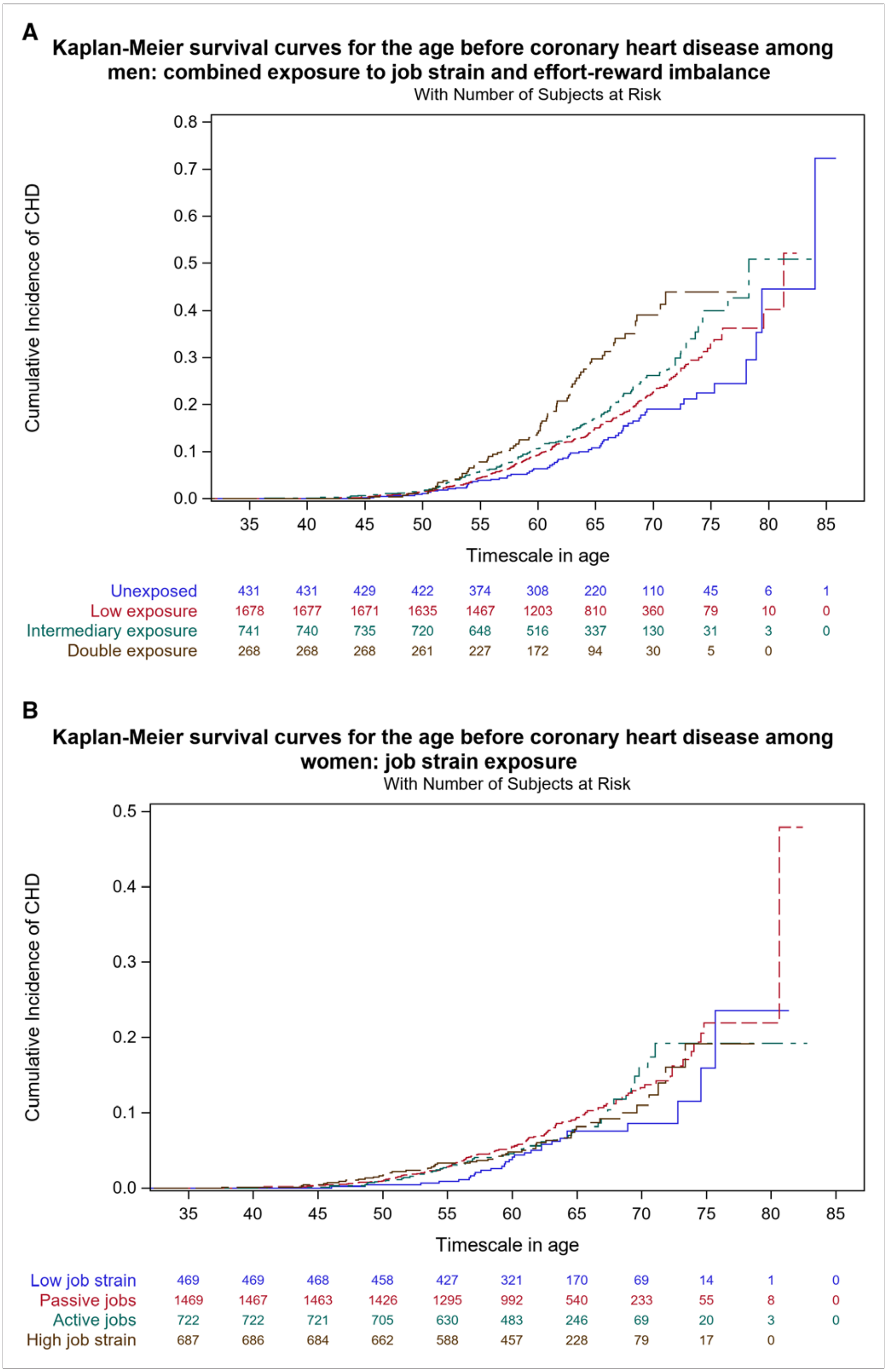

Figure 2. Kaplan-Meier survival curves for time to first coronary heart disease (CHD) event by combined and separate exposure to job strain and effort-reward imbalance, by sex.
Cumulative incidence in presence of competing risks (ie, deaths) was estimated using a non-parametric estimator. CHD indicates coronary heart disease.

more difficult. Nonetheless, sex investigations are of great importance to increase our current understanding of the role of psychosocial stressors at work in CHD cause among women. Future meta-analysis, pooling results specifically among women, could contribute to clarifying this role.

Strengths and Limitations

Our study relied on an 18-year prospective cohort and a large sample of white-collar workers, holding a variety of jobs. Efforts were made to reduce selection bias. Response proportion (75%) and access to medico-administrative data for CHD assessment (95%) were high, and loss to follow-up (8%) was low. Statistical methods were used to account for different sources of selection. Adjustment was performed sequentially to avoid effect underestimation due to statistical control for potential mediators.[31] Validated instruments were used to assess job strain and ERI while combined exposure allowed for a precise differentiation of risk levels. Finally, marginal effect measures were estimated, representing the average effect on the population, facilitating the public health interpretation of our results.

Limitations must be acknowledged. There is a risk of fortuitous associations due to multiple testing. However, analyses were planned a priori, and hypothesis driven. The exposure may have changed over the course of the study. Therefore, the 1-point exposure assessment used in the present study could lead to an underestimation of the true effect.[9] Future studies should consider exposure chronicity and persistence over time. CHD event definition using medical databases had a sensitivity of 77% when compared with medical records.[20] Potential misclassification of the outcome would be nondifferential regarding exposure and would have led to effect underestimation.[9] Finally, the study population is limited to white-collar. However, the prevalence of exposure to psychosocial stressors at work in the PROQ was comparable to that of the Quebec general working population, supporting external validity. It was also suggested that associations between risk factors and CHD incidence among white-collar are of comparable magnitude to those observed in the general population.[39]

Clinical and Public Health Implications

Psychosocial stressors at work are modifiable, frequent, and long-term exposures.[40] In the present study, CHD risk increases of 50% to 100% were observed among men exposed to job strain and ERI. A substantial proportion of men were exposed to one (23.8%) or both (8.5%) work stressors. There is a need for improved recognition of psychosocial stressors at work as important CHD contributors. Integrative and interdisciplinary approaches should be used to tackle psychosocial stressors at work. This involves going beyond traditional modifiable individual behaviors but rather including population-based prevention strategies taking into consideration both the individual and their work environment.

Intervention studies are needed to quantify the benefits of targeting psychosocial work stressors for CHD prevention. The present study suggests that interventions should aim to reduce stressors from both job strain and ERI models and may be more effective in men. However, reducing these stressors could also benefit women, as they are related to other prevalent health problems such as depression.[41]

Conclusions

In the present study, men exposed to job strain or ERI, separately and in combination, were at increased risk of CHD. Both types of psychosocial stressors at work contribute to CHD burden among men. Psychosocial stressors of both models should be considered in CHD prevention strategies.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S11
Figures S1–S4

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