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**Key terms:** cardiovascular mortality; cohort study; individual participant data; job demand–control model; job strain; occupational stress; premature death; psychosocial work environment; sex difference

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# Job strain and cardiovascular mortality over long-term follow-up: a harmonized multicohort individual participant data meta-analysis

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**Objective** We aimed to assess the long-term association between high job strain (JS) and cardiovascular disease (CVD) mortality in cohorts from Italy, Germany, and the United States.

**Methods** We harmonized data from four cohort studies (MONICA Brianza, SEMM, MONICA/KORA, MIDUS), selecting employed participants aged 30–60 years and CVD-free at baseline. High JS was operationalized as high job demands and low job control. CVD mortality was ascertained over a median follow-up of >23 years. We estimated Cox models within each cohort; the main model was adjusted for sex, age, education, and occupational class. Additional analyses examined JS categories (low JS, active, passive, high JS), subgroups by sex and occupational classes, and person-time < and ≥65 years. Results were pooled using random-effects meta-analysis. Relevant published studies were identified for synthesis with our results.

**Results** Over 444 767 person-years, 842 CVD deaths occurred. High JS was associated with CVD mortality [hazard ratio (HR) 1.14, 95% confidence interval (CI) 1.01–1.27], with no evidence of heterogeneity. Results were consistent across JS categories, by sex (men: HR 1.15, 95% CI 1.07–1.23; women: HR 1.11, 95% CI 0.88–1.39), and across person-time <65 years (HR 1.24, 95% CI 0.91–1.67) and ≥65 years (HR 1.10, 95% CI 0.80–1.50). The association was stronger among manual workers (HR 1.25, 95% CI 0.84–1.86). Job demands appeared to contribute more than job control. Four published studies with comparable follow-up but heterogeneous study designs reported estimates consistent with our findings.

**Conclusions** High JS is a long-term predictor of CVD mortality, consistently across sexes and during both working age and after retirement. Workplace redesign to reduce job demands, particularly among manual workers, is warranted within a comprehensive prevention strategy.

**Key terms** cohort study; job demand–control model; occupational stress; premature death; psychosocial work environment; sex difference.

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Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for 32% of global deaths and approximately 3 million deaths per year in Europe alone, with a substantial proportion of CVD deaths occurring prematurely (<65 years) (1–3). Importantly, CVD mortality is largely preventable, as it is linked to modifiable behavioral risk factors such as smoking, physical inactivity, and poor diet (2). High job strain (JS), defined as the combination of high job demands and low job control, has been proposed as a risk factor for CVD mortality, as it is associated with those risk factors as well as with adverse cardiovascular risk profiles, increased allostatic load, and neuroendocrine dysregulation leading to heightened inflammatory responses (4–7). While the association between high JS and CVD incidence is established (8–10), evidence regarding CVD mortality is mixed (11). Moreover, as most studies have followed participants for ≤10 years, long-term associations remain underexplored: such a window is too short to capture CVD mortality among workers who are young at baseline and to reveal whether the adverse impact of JS persists beyond retirement.

Analyses are therefore needed to disentangle the contribution of JS to premature versus later-life CVD mortality. Sex and occupational class differences also warrant closer examination. Men and women differ in both cardiovascular risk profiles and CVD outcomes, as well as in their exposure to and appraisal of JS. Prior studies suggest that the association between high JS and CVD incidence tends to be slightly stronger among men, though findings are inconsistent (12). Similarly, the association between JS and CVD outcomes may vary by occupational class, as previous research in Italian cohorts indicates that manual workers exhibit a stronger JS–coronary heart disease (CHD) incidence relationship (13). Whether this pattern extends to CVD mortality remains unclear.

Examining such long-term associations and performing subgroup analyses requires cohorts with sufficient follow-up (≥20 years), individual measurement of baseline JS and potential confounders, in particular education and occupational class, and adequate statistical power. Previous studies with long follow-up are sparse: some relied on job exposure matrices rather than direct assessments of JS (14), risking misclassification and precluding adjustment for individual characteristics; others were limited to single worker-based cohorts within specific industries (15), limiting generalizability and statistical power for subgroup analyses. Harmonizing data from multiple cohorts with comparable study designs and consistent measurement of exposure, outcomes, and covariates can address these limitations through individual participant data meta-analysis. Four cohort studies [the Italian MONICA Brianza and the Study of the Employees in the Municipality of Milan (SEMM), the German MONICA/KORA, and Midlife in the United States (MIDUS)] meet these requirements and have previously examined the effects of JS, albeit with different research aims (13, 16, 17).

The main objective of this study was to investigate the association between high JS and CVD mortality over long-term follow-up in harmonized population- and worker-based cohorts from Italy, Germany, and the US, also with separate analyses for premature and later-life mortality and by sex and occupational classes. In addition, we synthesized our findings with published literature on the long-term association between JS and CVD mortality.

## Methods

### Study population

This study is a two-stage individual participant data meta-analysis. Datasets from the aforementioned four cohort studies were harmonized and analyzed independently. Results were pooled using random-effects meta-analysis.

The MONICA Brianza study consists of three independent cohorts recruited from the general population aged 25–64 years in the Brianza area (Lombardy, Italy) in 1986–1987, 1989–1990, and 1993–1994 (18). SEMM includes individuals aged 18–65 years old recruited through random sampling between 1993 and 1996 among civil servants of the city of Milan (nursery workers, kindergarten personnel, social service workers, office clerks, and local police) (19). The same research group performed both studies, with harmonized methodologies for data collection and follow-up procedures. The MONICA/KORA study consists of three independent cohorts recruited from the general population in three waves (1984/85, 1989/90, 1994/95) via two-stage cluster sampling in Augsburg and a random selection of 16 communities from adjacent districts (20, 21). The MIDUS study includes non-institutionalized, English-speaking adults aged 25–74 years in the coterminous US, with a baseline sample comprising a national sample recruited through random-digit dialing (RDD) in 1995–1996, oversamples from five metropolitan areas in the US, siblings of individuals from the RDD sample, and a national RDD sample of twin pairs (22). Data collection was conducted through telephone interviews and self-administered questionnaires. Participation was 68–79% across cohorts (supplementary material, https://www.sjweh.fi/article/4325, table S1).

For this study, we selected individuals who were employed and free of CVD (self-reported through questionnaires) at baseline. We restricted the sample to those aged 30–60 years as participants <30 have limited relevance for CVD mortality, while those >60 represented a negligible fraction of most cohorts (MONICA Brianza:

3%; SEMM: 0.2%; MONICA/KORA: 3%), and their exclusion improved age comparability across studies. The flow of participants is reported in supplementary figure S1.

### Definition and harmonization of the exposure

The exposure of interest was high JS, defined according to the Job Demand–Control Model as the combination of high job demands and low job control (23). Job demands and job control were assessed using MONICA-Optional Psychosocial Substudy versions of the Job Content Questionnaire in MONICA Brianza, SEMM, and MONICA/KORA (24) and with items based on the Job Demand–Control Model in MIDUS. Supplementary table S2 reports the questionnaire versions, scoring methods, and labels of the items used to assess job demands and job control across cohorts. High JS (reference: non-high JS) was defined based on cohort-specific median values. For MONICA Brianza and SEMM, due to different medians across men and women, sex-specific medians were used. For secondary analyses, the four JS categories according to the Job Demand–Control Model (low JS, active, passive, and high JS) were derived using the same cohort-specific medians.

### Definition and harmonization of the outcome

The outcome was CVD mortality, defined as death with an underlying cause coded ICD-9 390-459 (and 798 for sudden death in MONICA/KORA) or ICD-10 I00-I99. Secondary outcomes were CHD mortality (ICD-9 410-414, plus 798 in MONICA/KORA; ICD-10 I20-I25) and all-cause mortality. For MONICA Brianza and SEMM, vital status was actively ascertained through the municipality of residence at fixed time points after baseline (latest update: 31/12/2017); the cause of death was determined from death certificates. For MONICA/KORA, vital status was regularly checked by mailing follow-up questionnaires to all participants and through population registries both inside and outside the study area, with deaths ascertained up to 2021; cause of death was identified from death certificates. For MIDUS, CVD mortality data through 2023 were accessed via a separate dataset linked to the National Death Index with variables specifying decedent status, source of decedent information, month and year of death, and ICD codes. Median follow-up by cohort was 23.1–28.5 years (supplementary table S1).

### Definition and harmonization of the covariates

Occupation at baseline was classified using the ISCO-88 standard in the MONICA Brianza and SEMM studies and subsequently mapped to the Erikson-Goldthorpe-Portocarero class scheme using established procedures (25), using an ad-hoc, nine-categories classification in MONICA/KORA, and using the first-digit major groups of the 1980 US Census classification in MIDUS. These classifications were harmonized into a common occupational class variable with three categories: "managers, professionals and self-employed", "non-manual workers", and "manual workers". The mapping of original classifications to the harmonized categories is reported in supplementary table S3.

Educational attainment was harmonized into three categories: low (primary or middle school), intermediate (high school or vocational school), and high (university or higher). The mapping to the harmonized categories is reported in supplementary table S4.

Cigarette smoking (current versus former or never), hypertension, and type 2 diabetes were harmonized as dichotomous variables. Body mass index (BMI) was calculated from measured (MONICA Brianza, SEMM, and MONICA/KORA) or self-reported (MIDUS) weight and height, and then categorized as <25, ≥25 and <30, ≥30 kg/m$^2$. Details about the harmonization of these variables are reported in supplementary table S5.

Total and HDL serum cholesterol were available for MONICA Brianza, SEMM, and MONICA/KORA and presented only for descriptive purposes.

### Statistical analysis

Categorical variables were summarized using frequencies and percentages, numerical variables using means and standard deviations. Within each cohort, differences in socio-demographic, occupational and CVD risk factors between workers with high JS and those without were evaluated using sex- and age-adjusted logistic regression models. Missing values were treated as a separate category for these descriptive analyses and then handled through multiple imputation in the subsequent models.

Within each cohort, the association between baseline high JS (reference: non-high JS) and CVD mortality was examined using Cox models with attained age as the time scale, adjusting covariates incrementally across models. Model 1 adjusted for sex and, in MIDUS only, race. Model 2, the main model for subsequent analyses, additionally adjusted for educational attainment and occupational class, with low and intermediate education collapsed in MIDUS due to small numbers. Model 3 additionally adjusted for CVD risk factors; given that these variables may lie on the causal pathway between high JS and CVD mortality (4, 26–28), this model was estimated to descriptively approximate the direct effect of high JS on CVD mortality net of these risk factors. The proportional hazards assumption was assessed for model 2 via scaled Schoenfeld residuals across imputed datasets within each cohort.

These models were also estimated using as predictors JS categories (reference: low JS) and job demands and job control dichotomized at the median. In addition, subgroup analyses by sex and occupational class (with "managers, professionals, self-employed" and "non-manual workers" collapsed to increase statistical power and improve comparability with other studies) were conducted. Hazard ratios (HR) for premature versus later-life CVD deaths were estimated separately for person-time <65 and ≥65 years. Complete-case analysis was run as a sensitivity check for model 2, and all models were repeated for CHD and all-cause mortality.

The log(HR) and standard errors from these models were then pooled using a random-effect model estimator with Knapp-Hartung adjustment. For the subgroup analyses, subgroup-specific estimates from each cohort were pooled using meta-regression with the subgroup variable as a moderator. For the analysis by attained age, separate models were fitted for person-time <65 and ≥65 years, and the pooled estimates were compared using a Welch's t-test with Satterthwaite degrees of freedom. Heterogeneity was assessed using Cochran's Q (P<0.10) and the $I^2$ statistic. The meta-analysis was performed using R (version 4.5.1).

### Synthesis with published literature

We conducted a literature search for published cohort studies on JS and CVD mortality in subjects free of CVD at baseline and with median follow-up duration ≥20 years. Since a prior systematic review had already covered work stressors, including JS, and mortality outcomes through 2019 (11), we extracted relevant studies from it and searched separately for publications from 2019 to 2026 (details in the supplementary material). Study characteristics and JS operationalization were tabulated. Estimates of the association between high JS and CVD mortality were evaluated for inclusion in the corresponding meta-analyses or, where heterogeneity in study design precluded pooling, tabulated.

## Results

Table 1 summarizes the characteristics of the four cohorts (see supplementary table S6 for characteristics by sex). SEMM had a higher proportion of women and included slightly younger participants compared with

**Table 1.** Socio-demographic, occupational and cardiovascular risk factors and job strain characteristics of the four study cohorts. [SD=standard deviation.]

| Variable | Value | MONICA Brianza (N=2263) | | SEMM (N=6449) | | MONICA/KORA (N=6370) | | MIDUS (N=3381) | |
|---|---|---|---|---|---|---|---|---|---|
| | | N (%) | Mean (SD) | N (%) | Mean (SD) | N (%) | Mean (SD) | N (%) | Mean (SD) |
| Female sex | | 781 (34.5) | | 4195 (65.0) | | 2449 (38.4) | | 1632 (48.3) | |
| Age | | | 42.8 (8.0) | | 40.5 (7.2) | | 44.6 (8.5) | | 43.8 (8.3) |
| Educational attainment | Low | 1447 (64.0) | | 3241 (50.7) | | 3451 (54.2) | | 179 (5.3) | |
| | Intermediate | 650 (28.7) | | 2830 (44.3) | | 2009 (31.6) | | 1959 (58.0) | |
| | High | 165 (7.3) | | 322 (5.0) | | 907 (14.2) | | 1238 (36.7) | |
| | Missing | 1 | | 56 | | 3 | | 5 | |
| Occupation | Managers, professionals & self-employed | 815 (36.3) | | 1856 (28.8) | | 1576 (25.5) | | 1685 (50.1) | |
| | Non-manual workers | 887 (39.5) | | 2303 (35.7) | | 2087 (33.8) | | 867 (25.8) | |
| | Manual workers | 542 (24.2) | | 2290 (35.5) | | 2514 (40.7) | | 813 (24.2) | |
| | Missing | 19 | | 0 | | 193 | | 16 | |
| Body mass index (kg/m$^2$) | <25 | 1153 (51.4) | | 3207 (51.6) | | 2373 (37.5) | | 1315 (40.5) | |
| | ≥25–<30 | 864 (38.5) | | 2137 (34.4) | | 2886 (45.6) | | 1231 (37.9) | |
| | ≥30 | 226 (10.1) | | 873 (14.0) | | 1064 (16.8) | | 700 (21.6) | |
| | Missing | 20 | | 232 | | 47 | | 135 | |
| Current cigarette smoking | | 797 (35.2) | | 2254 (35.8) | | 2021 (31.7) | | 768 (29.8) | |
| | Missing | 1 | | 153 | | 0 | | 801 | |
| Hypertension | | 553 (24.4) | | 1198 (19.0) | | 2127 (33.4) | | 437 (12.9) | |
| | Missing | 1 | | 140 | | 0 | | 7 | |
| Type 2 diabetes | | 76 (3.4) | | 65 (1.0) | | 98 (1.5) | | 109 (3.2) | |
| | Missing | 1 | | 0 | | 1 | | 8 | |
| Total cholesterol | | | 212.0 (42.2) | | 205.0 (38.8) | | 233.2 (45.7) | | n\a |
| | Missing | 15 | | 63 | | 116 | | | |
| HDL cholesterol | | | 54.3 (14.4) | | 55.6 (15.3) | | 55.5 (17.0) | | n\a |
| | Missing | 13 | | 106 | | 130 | | | |
| Job strain categories | Low job strain | 384 (21.2) | | 1211 (23.5) | | 1414 (25.5) | | 515 (15.4) | |
| | Passive | 418 (23.1) | | 1539 (29.8) | | 1571 (28.4) | | 736 (21.9) | |
| | Active | 418 (23.1) | | 1026 (19.9) | | 1493 (26.9) | | 1196 (35.7) | |
| | High job strain | 590 (32.6) | | 1380 (26.8) | | 1062 (19.2) | | 907 (27.0) | |
| | Missing | 453 | | 1293 | | 830 | | 27 | |
| High job strain | Non-high | 1220 (67.4) | | 3776 (73.2) | | 4478 (80.8) | | 2447 (73.0) | |
| | High | 590 (32.6) | | 1380 (26.8) | | 1062 (19.2) | | 907 (27.0) | |
| | Missing | 453 | | 1293 | | 830 | | 27 | |

the other cohorts. Over a third of MIDUS participants held a university degree or higher, compared with 14% in MONICA/KORA and 5–7% in MONICA Brianza and SEMM. Only 5% of MIDUS participants had low educational attainment, compared with over half in the European cohorts. Occupational composition also differed, with MIDUS being roughly equally split between the "managers, professionals and self-employed" class and the remaining occupational categories, while the other three cohorts had a larger share of non-manual and manual workers. MONICA/KORA showed the highest prevalence of hypertension and highest total cholesterol levels, MONICA Brianza and SEMM had the most current smokers, and obesity (BMI ≥30 kg/m$^2$) was most common in MIDUS, which together with MONICA Brianza also had the highest prevalence of type 2 diabetes.

Comparisons by high JS status regarding sociodemographic, occupational and CVD risk factors are reported in supplementary table S7. High JS was more prevalent among those with lower educational attainment and manual workers. In MONICA Brianza, workers with high JS were less likely to be obese, whereas the opposite was observed in SEMM and MONICA/KORA. Cigarette smoking was associated with high JS in SEMM and MONICA/KORA, diabetes in MONICA/KORA, and higher total and HDL cholesterol levels in MONICA/KORA.

Across the cohorts, 842 CVD deaths (391 CHD, 2831 all-cause) occurred over 444 767 person-years, among 18 463 individuals. At the end of follow-up, the mean age was 68.5 years in MONICA Brianza (64.2% were ≥65 years old), 62.9 in SEMM (37.7%), 68.5 in MONICA/KORA (61.7%), and 70.5 in MIDUS (70.5%). Number of CVD deaths and sex-specific, age-adjusted CVD mortality rates by cohort are reported in supplementary table S8.

### Results of the meta-analysis

Table 2 reports the meta-analytic results. In the age- and sex-adjusted model, high JS was associated with a 24% higher CVD mortality risk. The association attenuated after adjustment for educational attainment and occupational class, but remained statistically significant (HR 1.14, 95% CI 1.01–1.27). The forest plot for this model is reported in figure 1. No violation of the proportional hazards assumption was detected across all imputed datasets in each cohort. Further adjustment for CVD risk factors rendered the association non-significant. Across all these meta-analytic models, there was no evidence of heterogeneity (supplementary table S9). The sensitivity analysis performed using complete data showed comparable results (HR 1.14; 95% CI 1.01–1.31).

JS categories showed a similar attenuation pattern: the HR of high JS (reference: low JS) was reduced to 1.13 after adjustment for educational attainment and occupational class and further diminished with CVD risk factor adjustment. The forest plot of the main model is reported in supplementary figure S2. All these estimates were non-significant, with no heterogeneity.

When JS components were analyzed separately, the pooled HR from model 2 were 1.14 and 1.02 for job demands and job control, respectively, both non-statisti-

**Table 2.** Hazard ratios (HR) for CVD mortality resulting from the meta-analyses, with progressive adjustment for sex, educational attainment, occupational class and CVD risk factors. [CI=confidence interval; Ref=reference.]

| Predictor | Model 1 [a] | | Model 2 [b] | | Model 3 [c] | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| High job strain | | | | | | |
| Non-high | Ref | | Ref | | Ref | |
| High | 1.24 | 1.05–1.48 | 1.14 | 1.01–1.27 | 1.09 | 0.93–1.27 |
| Job strain categories | | | | | | |
| Low job strain | Ref | | Ref | | Ref | |
| Active | 1.04 | 0.89–1.22 | 1.06 | 0.89–1.26 | 1.06 | 0.93–1.21 |
| Passive | 1.02 | 0.61–1.70 | 0.90 | 0.56–1.45 | 0.87 | 0.48–1.57 |
| High job strain | 1.30 | 0.96–1.76 | 1.13 | 0.90–1.42 | 1.07 | 0.80–1.44 |
| Job demands | | | | | | |
| Low | Ref | | Ref | | Ref | |
| High | 1.09 | 0.89–1.34 | 1.14 | 0.88–1.48 | 1.14 | 0.85–1.55 |
| Job control | | | | | | |
| Low | Ref | | Ref | | Ref | |
| High | 0.90 | 0.61–1.31 | 1.02 | 0.72–1.45 | 1.06 | 0.70–1.61 |
| High job strain, attained age <65 years | | | | | | |
| Non-high | Ref | | Ref | | Ref | |
| High | 1.33 | 1.13–1.57 | 1.24 | 0.91–1.67 | 1.17 | 0.82–1.67 |
| High job strain, attained age ≥65 years | | | | | | |
| Non-high | Ref | | Ref | | Ref | |
| High job | 1.19 | 0.80–1.77 | 1.10 | 0.80–1.50 | 1.05 | 0.75–1.48 |

[a] Adjusted for sex and age.
[b] Adjusted for sex, age, educational attainment and occupational class.
[c] Adjusted for sex, age, educational attainment, occupational class cigarette smoking, hypertension, type 2 diabetes, and body mass index.

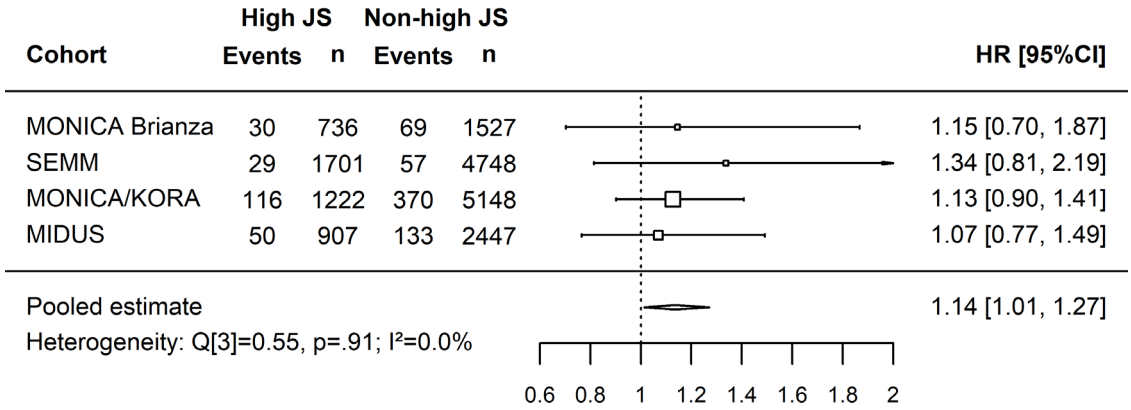


**Figure 1.** Forest plot of the meta-analytical results for the association between high job strain (JS) (reference: non-high JS) and cardiovascular disease mortality, adjusted for age, sex, educational attainment, and occupational class. Note: Sample sizes and number of events for each cohort represent means across multiply imputed datasets. For MONICA/KORA, 32 subjects had unknown cause of death. These missing data were handled through multiple imputation, which may affect reported event counts. [HR hazard ratio.]

cally significant (supplementary figures S3 and S4). The heterogeneity test was non-significant for box exposures. However, for job control, point estimates were below unity in MONICA Brianza, SEMM and MONICA/KORA, whereas in MIDUS the HR was 1.40 (95% CI 1.02–1.91).

Subgroup analyses by sex and occupational class based on model 2 revealed no statistically significant moderating effects (meta-regression P=0.60 and P=0.32, respectively). For sex, point estimates were similar among men and women, though the association reached statistical significance only among men (HR 1.15, 95% CI 1.07–1.23 versus women: HR 1.11, 95% CI 0.88–1.39), with no evidence of heterogeneity in either subgroup. For occupational class, point estimates were higher among manual (HR 1.25, 95% CI 0.84–1.86) than non-manual (HR 1.05, 95% CI 0.72–1.54) workers, again with no evidence of heterogeneity. Forest plots for both analyses are presented in figure 2.

In the analysis by attained age, the pooled HR for high JS in model 1 was significant for <65 years (HR 1.33, 95% CI 1.13–1.57) only. In model 2, the HR was 1.24 (95% CI 0.91–1.67) for <65 years and 1.10 (95% CI 0.80–1.50) for ≥65 years, with no within-subgroup heterogeneity. The two pooled estimates using this model did not differ significantly (Welch's t-test P=0.84).

The results of the analyses of CHD mortality are reported in supplementary tables S10–S11, and the forest plot for the main model in supplementary figure S5. Overall, point estimates in model 2 were attenuated compared to CVD mortality, but the analysis suffered from low statistical power. No associations were found between JS, JS categories, job demands, or job control and all-cause mortality (supplementary tables S12–S13).

### Synthesis with published literature

Two studies were identified from the previous systematic literature review (15, 29), and the update of the literature search yielded two additional studies (search results: 212) (14, 17). The characteristics of these studies and their reported estimates are summarized in table 3. Two studies employed job exposure matrices to assess JS (14, 29) and two used self-report questionnaires (15, 17). Overall, the reported estimates for the association between JS and CVD mortality were above unity. However, substantial heterogeneity in study design precluded a formal meta-analysis of these estimates. Specifically, Alterman et al (29) included only men, presented analyses only for CHD mortality and employed a different adjustment set compared with our study; Kivimäki et al (15) operationalized JS using three categories (low, intermediate, high); Niedhammer et al (14) examined mortality "on the job" (ie, until retirement or death/censoring) for the last job held or operationalized JS by dichotomizing the means of job control and job demands over time; and Matthews et al (17) analyzed a subgroup of MIDUS participants who completed both the first and second waves of the study.

## Discussion

The main result of this harmonized multicohort study comprising both population-based and occupational cohorts is that high JS is associated with CVD mortality over a long-term follow-up. This association persisted after adjusting for occupational class and education, and was consistent across sexes, occupational classes, JS cat-

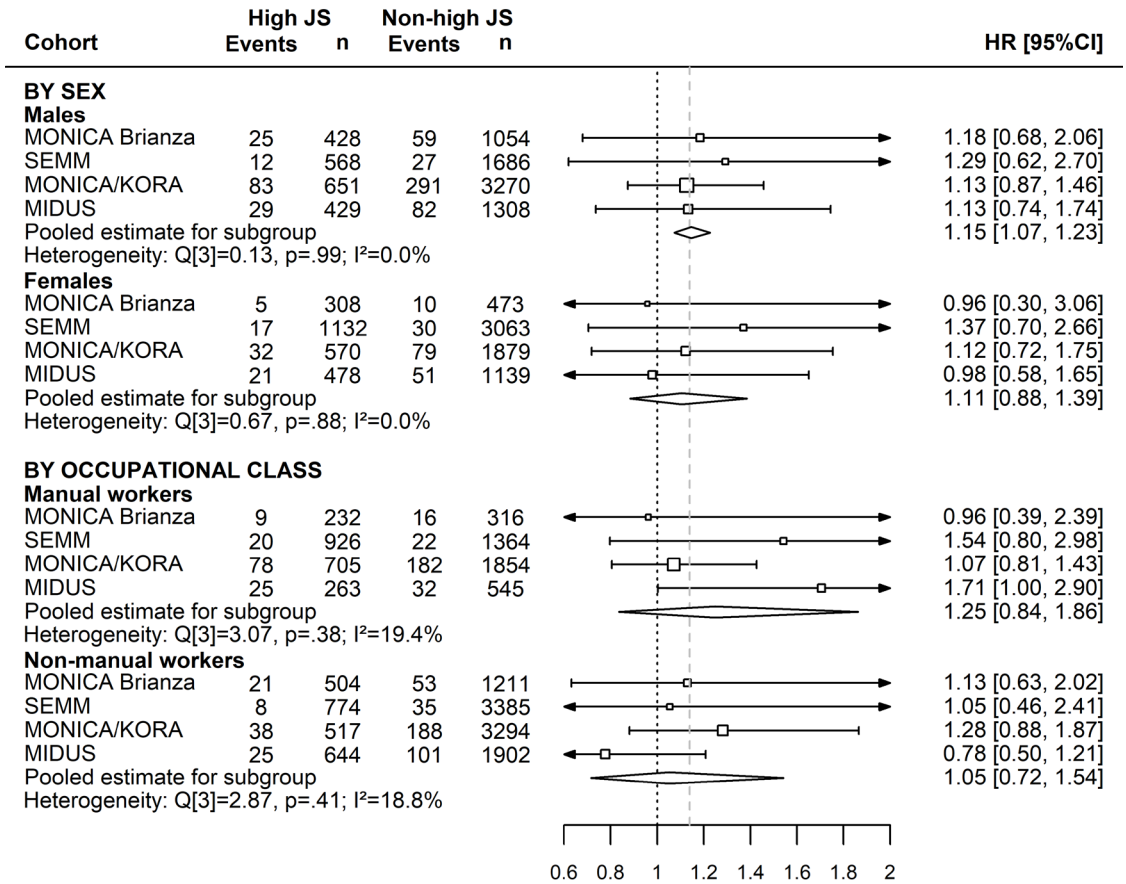


**Figure 2.** Forest plot of the meta-analytical results for the association between high job strain (JS) (reference: non-high JS) and cardiovascular disease mortality stratified by sex and occupational class. Note: The dashed grey line corresponds to the pooled estimate from the overall model. Subgroup analyses by sex were adjusted for age, educational attainment, and occupational class. Subgroup analyses by occupational class were adjusted for sex, age, and educational attainment. Sample sizes and number of events for each cohort represent means across multiply imputed datasets. For MONICA/KORA, 32 subjects had unknown cause of death. These missing data were handled through multiple imputation, which may affect reported event counts. [HR hazard ratio.]

egories, and person-time before and after retirement age.

Whether JS is associated with long-term CVD mortality has remained uncertain as the few studies with extended follow-up lacked adjustment for individual characteristics, relied on job exposure matrices, or were limited to single occupational cohorts using non-standard operationalizations of high JS. A previous review of shorter follow-up studies reported a non-significant association between high JS and CHD mortality (HR 1.30 in multivariable-adjusted analysis), though heterogeneity in JS definitions, operationalizations, and modeling approaches contributed to substantial between-study variability (11). By using harmonized procedures and a consistent operationalization of high JS, our study addresses these limitations. The association holds for premature CVD deaths occurring during working life, indicating that a substantial share of the burden might be preventable through workplace interventions. Although our results cannot be interpreted as causal because effect sizes were relatively small and an exposure–response relationship could not be assessed (30), the persistence of the association after adjustment for socioeconomic variables, its biological plausibility (4–7) and relevance to working-age mortality strengthen the epidemiological case for high JS as a contributor to CVD mortality.

Our main analysis compared high JS versus non-high JS, and is therefore based on the original conceptualization of JS as a combination of high job demands and low job control, consistent with psychological theory positing that stress arises when external demands are perceived to exceed an individual's coping capacity (23). The analyses by JS categories and components instead conceptualize independent effects of job demands and control (active: high demands without low control, passive: low demands with low control), with high JS representing their interaction (31). Point estimates were similar for high JS versus non-high JS or versus low JS, although the analysis by JS categories was less

**Table 3.** Characteristics and results of studies from the literature search assessing the association between job strain (JS) and cardiovascular disease (CVD) mortality with ≥20 years of follow–up. [CHD=coronary heart disease; CI=confidence interval; HR hazard ratio; NP=not performed; PA=physical activity; SBP=systolic blood pressure].

| Authors, year | Study sample | Age (years) | Sex | Occupational classes | Job characteristics measurement | JS operationalization | Follow–up duration | Model adjustment | JS–CVD mortality association estimate HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Kivimäki et al, 2002 (15) | Employees from Valmet Industries (N=812) | ≤27 (N=251) 28–47 (N=330) >47 (N=231) | Men (N=545) Women (N=267) | Managers (N=94) Other office staff (N=267) Skilled workers (N=165) Semi-skilled workers (N=284) | Self–reported questionnaire with four items assessing job demands and twelve items assessing job control | High JS (high or intermediate job demands; low job control), low JS (low job demands; high or intermediate job control), intermediate JS (all other combinations) | Median: 27 years | Age and sex | Int. vs low: 1.53 (0.83–2.82); High vs low: 2.20 (1.16–4.17) |
| | | | | | | | | Age, sex, occupation | Int. vs low: 1.36 (0.72–2.57); High vs low: 1.89 (0.93–3.81) |
| | | | | | | | | Age, sex, smoking, PA | Int. vs low: 1.71 (0.92–3.17); High vs low: 2.20 (1.12–4.32) |
| | | | | | | | | Age, sex, SBP, cholesterol, BMI | Int. vs low: 1.58 (0.84–2.95); High vs low: 2.35 (1.22–4.52) |
| | | | | | | | | Age, sex, occupation, smoking, PA, SBP, cholesterol, BMI | Int. vs low: 1.64 (0.85–3.19); High vs low: 2.22 (1.04–4.73) |
| Alterman et al, 1994 (29) | Employees from Hawthorne works (N=1683) | 38–56 | Only men | White collars (N=445) Blue collars (N=1238) | Scores for job control and job demands were linked to 1960 US Census occupation codes of the participants | Job demands and job control scores were categorized in tertiles. High JS was defined as job control in the lower tertile and job demands in the highest tertile | Median: 25 years | Age | High JS–CHD mortality association estimate: 1.48 (0.98–2.24) |
| | | | | | | | | Age, SBP, cholesterol, cigarettes smoked/day, alcohol, family history of CVD | High JS–CHD mortality association estimate:1.43 (0.94–2.16) |
| | | | | | | | | Previous model + education | High JS–CHD mortality association estimate: 1.40 (0.92–2.14) |
| | | | | | | | | Previous model + occupational class | High JS–CHD mortality association estimates: All subjects: 1.03 (0.75–1.41) White collars: NP Blue–collars: 1.03 (0.75–1.42) |
| Niedhammer et al, 2020 (14) | Workers from national employment registry (INSEE DADS panel data, 1976–2002) (N=1 496 332) | Mean age at entrance: 28 for men; 27 for women | Men (N=798 547) Women (N=697 785) | Occupational class was not categorized | Job exposure matrix. Job demands and job control scores were assigned to each occupation held during follow–up period | Current exposure (time–varying): high job demands and low job control assigned to the occupation held at CVD death or censoring. | "On–the–job" [a] | Age, calendar time, biomechanical, physical, chemical and biological exposures | Men: 1.30 (1.16–1.46) Women 1.24 (0.97–1.58) |
| | | | | | | Cumulative exposure: average JS across jobs held until censoring or CVD death | "On–the–job" [a] | | Men: 1.33 (1.18–1.50) Women: 1.26 (1.02–1.56) |
| | | | | | | | 1976–2002 | | Men: 1.19 (1.13–1.24) Women: 1.06 (0.99–1.13) |
| | | | | | | Recency–weighted cumulative exposure: same, with higher weights assigned to more recent jobs | "On–the–job" [a] | | Men: 1.26 (1.12–1.42) Women: 1.41 (1.13–1.76) |
| | | | | | | | 1976–2002 | | Men: 1.26 (1.17–1.36) Women: 1.16 (1.01–1.33) |
| Matthews et al, 2023 (17) | Workers who participated in MIDUS I and MIDUS II (N=1870) | <46 years (N=1157), 46–55 (N=514), ≥56 years (N=199) | Men (N=933), Women (N=937) | Not reported | Self–reported questionnaire with five items assessing job demands and nine items assessing job control | Job demands and job control scores were dichotomized based on sample medians at baseline (MIDUS I). High JS was defined as high job demands and low job control | 1995 / 1996–2018 | Age, sex | 1.37 (0.51–3.65) |
| | | | | | | | | Age, sex, race, marital status, education, household income | 1.29 (0.48–3.49) |

[a] Until the end of last job, censoring or death within 1976–2002 period.

powered. When examining the other JS categories or the individual components, the effects of job demands and control were weaker. This suggests that the interaction between job demands and control captures risk more effectively than either dimension alone, consistent with previous studies on CHD incidence (31, 32).

Regarding the components, the review by Taouk et al (11) found that job control, but not demands, was significantly associated with CHD mortality. Direct comparisons with our data are difficult: pooled estimates for both components were non-significant, and cohort-specific point estimates diverged as in MIDUS higher job control was associated with higher mortality. This detrimental pattern echoes findings from other US cohorts among women, including the Framingham Offspring Study (33) and the Women's Health Study (34), often attributed to added strain among women in traditionally male-dominated roles. In the MIDUS cohort, however, the association between job control and CVD mortality was consistent across sexes (data not shown), possibly reflecting broader cultural or labor-market factors or that its job control items capture roles with greater responsibility and burden. As the MIDUS sample is not fully representative of the US population, in particular due to oversampling in metropolitan areas, results from this cohort should be interpreted with caution.

High JS was significantly associated with CVD mortality among men, with a slightly lower point estimate and greater uncertainty among women. This pattern, also reported by Niedhammer et al using job exposure matrices (14) and for CHD incidence (10), may partly reflect limited statistical power among women, though its consistency across studies suggests the association could be inherently more variable in this group, possibly due to additional work and non-work factors not captured by the Demand–Control Model.

In the analysis by occupational class, manual workers had a higher point estimate, although the moderating effect of occupational class was not significant and the CI were wide for both classes. This aligns with evidence that manual workers face higher mortality and more unfavorable working conditions (35), suggesting that the impact of JS may be particularly pronounced in this group. Improving psychosocial working conditions for manual workers is therefore expected to reduce CVD mortality (36). Although evaluating interventions is beyond the scope of this study, evidence supports work reorganization approaches, at the organizational level (eg, job redesign, psychosocial safety climate, leadership development) and individual level (eg, job crafting) (37, 38). Given that JS reflects structural work features, our findings align more closely with this approach (37) than with those using individual-level interventions at the workplace (39).

The association between high JS and CHD mortality appeared weaker than for CVD mortality, though power for our analysis was low. No association was found with all-cause mortality; findings in the literature are mixed (11, 40) but an effect of high JS is more plausible for CVD-specific than for all-cause mortality.

The association between high JS and CVD mortality attenuated after adjusting for CVD risk factors. The role of CVD risk factors as confounders or mediators in the association between high JS and CVD outcomes remains debated (26). Nonetheless, theoretical models posit that JS influences lifestyle habits, leading to unfavorable health conditions such as diabetes and hypertension, which in turn increase CVD risk; the associations between high JS and adverse lifestyle behaviors and metabolic risk factors support this mediation hypothesis (4, 27, 28). Accordingly, our model 2 estimates can be interpreted as the total effect and the adjusted for CVD risk factors as approximating the direct effect.

Two methodological aspects may have biased the observed associations toward the null. Because the prevalence of JS varies across countries (41), the established median-based operationalization fixes high JS at roughly a quarter of each cohort, so a genuinely stressed individual in a high-JS country could be classified as non-exposed, and vice versa. Additionally, JS was assessed only at baseline, raising the likely possibility of exposure misclassification, as individuals classified as exposed at baseline may plausibly have moved to lower-strain occupations over time.

This study has several strengths. Harmonized analytical procedures applied across independent cohorts from different countries, both population-based and occupational, enhanced the comparability and robustness of the findings. Additionally, we were able to examine the association between high JS and CVD mortality over a timeframe that extends well beyond the typical follow-up in occupational health studies. Nonetheless, despite pooling data from four cohorts, statistical power remained insufficient for more granular analyses. Additionally, despite harmonization, some heterogeneity across cohorts in recruitment, measurement, and populations was present; with only four cohorts, heterogeneity tests have limited power, so pooled estimates should be interpreted with this caveat.

The use of occupational and population-based cohorts from Europe and the US supports the generalizability of our findings across different worker types and Western high-income country contexts. However, results may not be generalizable to settings where the nature and organization of work differ substantially from those represented in this study.

### Concluding remarks

High JS is already recognized as an occupational hazard by major international bodies (42). Our findings show it is associated with CVD mortality over long-term follow-up, including premature deaths and deaths after retirement. This underscores the importance of addressing psychosocial working conditions as part of cardiovascular prevention strategies, as the health consequences of sustained exposure to high JS may manifest decades after the exposure itself.

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### Conflict of interest and funding

All authors declare no conflicts of interest.

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### Ethical approval and informed consent statements

The study was performed in accordance with the Declaration of Helsinki, and all study participants provided written informed consent. The MONICA-Brianza received ethical approval from the Ethics Committee of the University Hospital of Monza, Monza, Italy (approval ID: 192/2005). The Ethics Committee of ASST Sette Laghi, Varese, Italy approved the SEMM study on 5 September 2017. The MONICA-Augsburg study was approved by the local authorities. The follow-up in the KORA framework was approved by the Ethics Committee of the Bavarian Chamber of Physicians (08094). This analytic project was approved as exempt research by the University of California, Los Angeles Institutional Review Board (IRB#22–000604).

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