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Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

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Abstract (294 words)

Objectives. To assess the association between job strain (JS) and the incidence of coronary heart disease (CHD) in North Italian employed men, adopting a stratified analysis by occupational class.

Methods. The study was conducted on 4103 working men, CHD-free at baseline, enrolled in population-based and factory-based cohorts. Risk factor measurements and follow-up procedures were carried out adopting the WHO MONICA standardised procedures. Occupational classes (OC) were derived from the Erikson-Goldthorpe-Portocarero classification. JS categories were defined based on overall sample medians of psychological job demand (PJD) and decision latitude (DL) derived from items of the Job Content Questionnaire, satisfying construct validity criteria. Age- and risk factors-adjusted CHD hazard ratios (HR) were estimated from Cox models, contrasting high strain (high PJD and low DL) vs non-high-strain categories.

Results. In a median follow-up of 14.6 years, 172 CHD events occurred, corresponding to a CHD incidence rate of 2.78 per 1,000 person-years. In the overall sample, high strain compared to non-high strain workers evidenced a 33% CHD excess risk, not statistically significant. No association was found among managers and proprietors. Conversely, the HR of high strain vs non-high strain was 1.79 (95%CI: 1.21-2.67) among non-manual and manual workers, with no substantial differences between them. The exclusion of the events occurred in the first three years of follow-up did not change the results. Adopting the quadrant-term JS groupings, among manual and non-manual workers, high strain and active (high PJD and high DL) categories in comparison to the low strain one (low PJD and high DL) showed HRs of 2.84 and 2.41, respectively.

Conclusions. Our findings support the association of job strain and CHD incidence among manual and non-manual workers. The non-high strain may not be the best reference category, when assessing the contribution of JS in determining CHD incidence.

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Strengths and limitations of this study

- A recently published meta-analysis and subsequent papers have drastically reduced the role of job strain (JS), measured by the Job Content Questionnaire (JCQ), as a primary risk factor for coronary heart disease (CHD), but some methodological shortcomings have been highlighted.
- In our pooled analysis with population- and factory-based cohorts and a wide range of job titles, we assessed the association between JS and CHD adopting some methodological refinements: we selected relevant JCQ items which showed satisfactory construct validity, and we performed a stratified analysis by occupational classes, motivated by the knowledge that stressors in salaried workers and other professional categories may have different contents.
- We explored the association using as the reference category low-JS, instead that the wider non-high JS category, which nullifies the separate effects of control and demands at work, focusing merely on the joint effect.
- Our findings showed that the CHD risks were higher among high JS manual and non-manual workers only, suggesting that JCQ better grasps job constrains in low-wage working categories; and the CHD risk increased substantially in high-JS when compared to low-strain only.
- The study did not include women due to the low incidence rate, and the small sample size anyhow deserves replications in different contexts to enhance confidence in results.

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Organizational constrains at the work place and sedentary activities are the two most common work-related cardiovascular disease (CVD) risk factors in post-industrialised societies [1]. The job demand-control model [2], developed by Karasek in the late 1970s is a widely used questionnaire to assess perceived work stress conditions. It is based on two major constructs: psychological job demand (PJD) and decision latitude (DL), defining high strain, active, passive and low-strain categories.

Belkic et al. [3] reviewing 17 prospective cohort, nine case-control and eight cross-sectional studies, concluded in favour of a positive association between job strain (JS) and cardiovascular disease in men. Kivimaki et al [4] in a meta-analysis of cohort studies estimated an overall age-adjusted 43% excess risk for high JS, assessed with the demand-control model. This report combined hazard ratios published by studies using different endpoints, some reporting combining estimates for men and women, and some adopting the approximate job-title imputed method to estimate exposures. This paper reported higher relative risks for the effort reword imbalance model [5] and injustice at work too. A more recent paper, based on a collaborative pooled analysis including mainly unpublished (10 out of 13) and published cohort studies, found an overall gender- and age-adjusted hazard ratio for high versus non-high JS of 1.23 (95%CI: 1.10–1.37). The non-high JS reference group combines active, passive and low strain original categories. Based on this low excess risk and an arguable estimate of the high JS prevalence, the authors calculated a small population attributable risk of 3-4% [6].

This publication stimulated an intense debate in the scientific community [7-13], and many scientists argued that some shortcomings had contributed to bias the results to the null association. Among them, it is noteworthy to mention the low participation rates and the predominance of white-collars in comparison to blue-collars. Both these selection biases may have produced a reduced recruitment of more stressed workers, which is a frequently reported problem in these studies. Another potential bias may be due to the misclassification of exposure as JS may change overtime, due to the predominance of different stressors in the work organisations in different time periods. A recent letter [14] highlighted some methodological and conceptual constrains related to the evaluation of

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JS. Some of them are arguable and some can only be addressed in future studies, as available data from most currently studies in psychosocial CHD epidemiology were not designed and did not collected the required information [14].

The aim of the present paper is to assess the association between JS and the incidence of CHD in pooled analysis of population-based and factory-based North Italian cohorts of employed men, in particular focusing on a stratified analysis based on occupational classes. If the JCQ model better describe constrains and strain conditions among salaried manual and non-manual workers only, also the relationship between JS and CHD incidence may vary between occupational classes. We reported hazard ratios for the entire follow-up period and after exclusion of the events occurred in the first three years, to investigate reverse causation.

Methods

Study cohorts

As a part of the WHO-MONICA Project, three surveys of the Brianza population (located North of Milan) took place over a ten-year period (1986-1987, 1989-1990 and 1993-1994) to estimate coronary risk factor changes over time [15]. In each survey a 10-year age and gender stratified random sample was drawn from municipality roles among 25 to 64-year-old residents in five area-representative towns. The participation rates were 70.1, 67.2 and 70.8% respectively. The PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study was another population survey, conducted in 1991-1992[16], with the sampling procedure applied to the 25 to 74-year old residents of the city of Monza, the largest town in Brianza. The participation rate was 66.9% among people up to 65 years of age. The overall sample size of currently employed people, free of CHD at baseline, were 2350 men and 1334 women.

The SEMM (Surveillance of Employees of the Municipality of Milan) study recruited employees of six departments of the Milan Municipality, screened for CVD risk factors between May 1991 and

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March 1996. The cohort contributed to the JACE Study [17]. The participation rates were 75.3% for men and 76.2% for women, respectively; and the overall sample size of the SEMM cohort, free of CHD at baseline, was of 2569 men and 5254 women. Women were not included in the analysis due to low number of CHD events (46 events in all the cohorts). The study approvals were obtained from the Ethical Committee of the University Hospital of Monza.

Occupational classes

As reported in a previous paper [15], we derived Erikson-Goldthorpe-Portocarero (EGP)-classes. To achieve sufficient statistical power, EGP classes were aggregated in three occupational classes, as follows: professionals, administrators, managers, proprietors and self-employers (EGP classes I, II and IV, called here briefly Managers&Proprietors), non-manual (EGP classes III and V) and manual (skilled and unskilled, EGP classes VI and VII) workers.

Job strain scales and scores

The Job Content Questionnaire (JCQ) was administered to all currently employed workers, using two different versions sharing the same core items. In the MONICA Brianza and PAMELA studies as well as for employees of the two first-recruited departments of the SEMM study, the short MONICA-MOPSY version [18] was used. The extended version of JCQ was instead adopted for the remaining four SEMM departments, when the study was included into the JACE Project [16]. In both questionnaires are present the same items assessing psychological job demand and decision latitude, each on a 4-point scale ranging from completely agree to completely disagree. A comparability analysis [19, 20] showed that equivalent PJD and DL scores and sub-scores can be calculated from both questionnaires.

We derived the conventional four JCQ categories based on the quadrant approach, with high strain defined as PJD values higher than the overall sample median and DL values lower than or equal to the median. The remaining three job strain categories, i.e. active, passive and low strain were also defined according to the standard criteria [2]. These three last strain categories were

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collapsed in a unique category, called non-high JS, to allow direct comparisons with the results reported by the pooled-cohort recent meta-analysis [6].

Measurements of other risk factors at baseline

In MONICA surveys, cardiovascular risk factors were collected at baseline strictly adhering to the standardized procedures and quality standards of the WHO-MONICA Project (http://www.ktl.fi/publications/monica/manual/index.htm). In the PAMELA and in the SEMM studies, risk factors were measured based on MONICA-like procedures. In brief, blood pressure was measured on sitting subjects at rest for at least 10 minutes, using a standard mercury sphygmomanometer equipped with larger cuff bladders if needed. The study variable for systolic blood pressure is the average of two measurements taken 5 min apart. Venous blood specimens were taken from the ante-cubital vein in fasting subjects (12h or more). Serum total cholesterol and HDL-cholesterol were measured by an enzymatic method. Blood glucose was determined on the same samples by an enzymatic method.

From standardized interviews information on cigarette smoking habits were available and a dichotomized study variable in current vs. past/never smokers was calculated. Diabetes mellitus was defined using self-reported diagnoses and information on insulin and oral hypoglycaemic treatments or based on a fasting blood glucose exceeding 126 mg/dl. Self-reported information on hospitalization for myocardial infarction, unstable angina pectoris, coronary revascularization was used to define a positive history of coronary event at baseline. Items on educational attainment were part of the standardized questionnaire, and it was dichotomized as “low” (less than high school) and “high” (high school or more).

Study endpoints and follow-up procedures

All subjects were followed from the baseline examination until first cardiovascular event, emigration, death, 80-th birthday or December 31st, 2008, whichever came first, based on locally adapted procedures, developed within the MORGAM Project

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[http://www.thl.fi/publications/morgam/manual/followup/fumethod.htm]. Vital status was actively investigated for all subjects, including those who moved to different towns in Italy, and death certificates were obtained from local health districts. Suspected fatal events were identified on the basis of selected underlying causes of death ICD-IX codes 410-414. Suspected non-fatal events were identified based on ICD-IX hospital discharge codes: 410-411 for acute coronary events, 36.0-9 for coronary revascularization. Acute events were further investigated and validated according to the MONICA diagnostic criteria. The study endpoint is the occurrence of a first major acute coronary event (myocardial infarction, acute coronary syndrome), fatal or non-fatal, or coronary revascularization. The follow-up was completed for 98.9% of them, with no differences across cohorts and occupational classes.

Statistical analysis

Of the 4839 male workers in the age range 25-64 years old, we excluded 736 subjects with missing values of JCQ items or CHD risk factors, and the final sample size was 4103. We calculated the age-adjusted mean (prevalence) of major CHD risk factors by occupational class and strain categories from generalized linear models, and tested differences among groups using Wald chi-square tests.

Factor Analysis with varimax rotation and Cronbach's α coefficients were used to assess the construct validity and internal consistency of JCQ items, respectively. These analyses were carried out on the population-based cohorts, characterized by wide job title variability.

Cox proportional hazards model with lifespan (attained age) on the time scale was adopted to study the associations between the risk of CHD event and job strain, dichotomized for most analyses in high strain versus non-high strain (reference category comprising passive, active and low-strain), adjusting for major risk factors. Stratified analyses were carried out by occupational classes. We also performed a separate analysis, using the four JCQ categories (with low strain as reference group). The analyses were performed using the Statistical Analysis System (Version 9.4,

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SAS Institute Inc, Cary, NC). The figure was drawn using the R software (R Foundation for Statistical Computing, Wien, Austria. http://www.R-project.org/).

Results

Among the 4103 25-64 years old employed men, CHD-free at baseline, in a median follow-up time of 14.6 years (interquartile range: 13.2-17.6 years), n. 172 incident major coronary events occurred, corresponding to a cumulative incidence rate of 2.78 per 1,000 p-y. Age-adjusted rates among Managers&Proprietors and Non-manual&Manual workers were 3.1 (95%CI 2.32-4.14) and 1.97 (1.60-2.41), respectively.

As shown in Table S1 in the Supplementary material, the results of the factor analysis carried out on the populations-based MONICA-PAMELA samples, evidenced a satisfactory construct validity of JCQ items, with the notable exception of one item of skill discretion (SD), i.e. "do not repeat things over and over" and two items of PJD, i.e. "work very fast" and "work very hard". Since these items did not contribute to the definition of the expected constructs, i.e. decision latitude and psychological job demand, they were excluded and the scores calculated with the residual available items. Cronbach's α coefficients were 0.70 and 0.75 for DL and 0.53 and 0.58 for PJD among Managers&Proprietors and Non-manual&Manual workers, respectively.

Table 1 shows the distributions of main socio-demographic variables, JS categories and cardiovascular risk factors in the entire sample and in the two OCs. Non-manual and manual workers were younger and less educated than managers and proprietors. In the entire sample, 26% are classified at high strain, as expected due to the quadrant-term approach based on medians and the orthogonality between the constructs (Pearson correlation coefficient between PJD and DL was -0.09). The highest prevalence of high strain was found among Non-manual&Manual workers, while active and low strain categories were prevalent among managers and proprietors. Managers&proprietors showed higher age-adjusted mean values of total cholesterol, but were less likely to smoke than Non-manual&Manual workers (all p-values <0.05). Conversely, the EGP-

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aggregated occupational classed did not differ for mean systolic blood pressure and HDL-cholesterol, nor for prevalence of diabetes (all p-values >0.2). As shown in Table S2 in the Supplementary material, none of the considered risk factors showed statistically significant differences between the four JCQ categories.

Table 2 shows the results of the analysis assessing the association between JS and CHD incidence, for the entire sample and by occupational classes. In the entire sample, high strain subjects evidenced an overall higher hazard ratio (HR) of 1.33 (95%CI 0.95-1.87) in comparison to non-high strain, which was confirmed even after the exclusion of the first three years of follow-up (HR=1.36, 0.94-1.96). No increased hazard of events for high vs. non-high strain was found among Managers&Proprietors, with HRs ranging from 0.71 to 0.61, both not statistically significant. Conversely, the hazard ratio for high vs non-high JS was 1.79 (1.21-2.67) among Non-manual&Manual workers, which again did not substantially change when events in the first three years were excluded [HR = 1.81 (1.18-2.77)]. When manual and non-manual workers were analysed separately, as Table 3 shows, the hazard ratios for the high strain *vs* non-high strain workers were 1.85 (95%CI 1.09-3.16) and 1.77 (95%CI 0.97-3.22) for manual and non-manual workers, respectively. To maximize the available number of events, this analysis were carried out including the entire follow-up period, but nevertheless, wide confidence intervals acknowledge the poor statistical power.

Table 4 shows the results of the association analysis between JS and CHD when the four JCQ quadrant-term categories are kept separated, and including all events occurred in the entire follow-up period, to maximize the available statistical power. Compared to the referent low-strain group, high strain Non-manual&Manual workers evidenced hazard ratio of 2.84 (95%CI 1.51-5.34), higher than when using the non-high strain group as the reference category. In addition, a risk excess was also found for active workers (2.41; 1.14-5.09), indicating that the demand dimension of JCQ in this workers is playing a major role in increasing the CHD risks. As shown in Figure 1, the survival curve of low strain in comparison to all the other job strain categories diverged already in the first years of

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follow-up, and persisted later on (panel A). This observation is in support of the detected small effect of reverse causation assessed with the exclusion of the events occurred during the first three years of follow-up. Moreover, the increase in cumulative risk over attained age (Figure 1, panel B) indicates that high strain men at the age of 50 years have the same cumulative risk of low strain men a decade older (Figure 1, panel B).

Discussion

In summary, in the investigated North Italian employed male pooled cohort we found a small increase in risk of CHD events in high job strain when compared to non-high job strain workers of 33% [HR=1.33 (95%CI 0.95-1.87)]. This estimate replicates the findings of recent meta-analyses, extending their results to a Southern European country with low CHD incidence rates. [6, 11] The novelty of our paper relates to results of the stratified analysis, which showed an excess risk of 79% [HR= 1.79 (95%CI 1.21-2.67)] among high strain Non-Manual&Manual workers. In this occupational class, when the four JCQ categories were separately analysed, the relative risk of CHD events of high strain *versus* low strain subjects increased to 2.84 (95%CI 1.51-5.34). It is noteworthy mentioning that the HR for active *versus* low strain workers was also elevated (HR=2.41; 1.14-5.09), indicating that the association can be biased towards the null hypothesis when active, low-strain and passive men are grouped in a unique non-high strain class.

The use of JCQ constructs based on the results of factor validity assessment have evidenced satisfactory internal consistency and reliability of the scores. The skill discretion item “do not repeat things over and over” may have different meanings in a variety of job profiles, working environments and countries; and it may not always connote monotony [21]. Two items of demand “work very fast” and “work very hard” assume minor importance in post-industrial work forces, while items describing pressure for having the work done or conflicting demands are constrains that still continue to characterise nowadays working conditions, as also reported by other authors [22]. This observation requires further investigations, as it points to the conclusion

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that the established JCQ questionnaire may be well suited to grasp the working constrains of salaried workers, in the low levels of the work organization only. The stressful aspects of job characteristics among people ranking at the higher level of the work organizations are probably related to prolonged working hours and excessive competitiveness, which are not adequately investigated by the actual formulation of the JCQ questionnaire [23].

We did not find relevant differences in the distribution of traditional cardiovascular risk factors, including systolic blood pressure, cholesterol as well as the prevalence of diabetes and cigarette smoking, among JCQ categories. In the population based sample we did find differences among JS categories in 24-hour systolic blood pressure means, but not when using clinical blood pressure measurements in the same age range [24]. This observation is in line with previous findings supporting the major importance of a direct, rather than an indirect, effect of strain on the cardiovascular system [21]. This direct effect is assumed to be attributable to the effect on psychobiological processes, as documented in a reduced heart rate variability [25] and in alterations of the hormonal or immune systems [26].

Among the strengths of the present study we mention the long follow-up period, the standardization of the methods to collect risk factors at baseline and to validate events, as they have been carried out adhering to the MONICA and MORGAM studies procedures. Among the limitations, we should acknowledge that our findings are on men only. We did not include women, due to the low number of events, which did not allow us to further stratify the analyses by occupational classes. We did not explore a dose-response relationship, but our findings support the major role of psychological job demand in determining the increased CHD risk, as both high strain and active worker showed the higher risks when compared to low strain subjects. We also did not explore the interaction effects with other work-related risk factors like social support and physical inactivity, as well as with behavioural risk factors [27, 28]. As we do have these baseline data for some of the cohorts, we will investigate these interactions in future reports, hoping to contribute to the current interest of the scientific community on these topics [29-33]. Finally, we did not collect data at

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baseline on other complementary theoretical models of stressful work, in particular the effort-reward imbalance model, which has shown remarkable associations with CVD and CHD outcomes [4, 5].

In conclusion, our findings support the association between job strain and CHD incidence in manual and non-manual workers, not among managers and proprietors. This can be attributable to the better chances of the present formulation of the JCQ questionnaire to grasp stressful job constrains in the low wage working categories. Moreover, to assess the effect of high strain on CHD, it is more accurate to use the low-strain instead of the wider non-high strain category, as the reference category. Again, the adoption of the latter category may also contribute to bias the results to the null. Our results require replications on larger and diversified samples.

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Author's contribution: MMF conceived the research question, drafted the manuscript and is the PI of the MONICA-Brianza and the SEMM study cohorts. GV, LB were responsible of the statistical analyses, contributed to interpretation of the data and revised the manuscript. GG and GC are the PIs of the PAMELA study and of the MONICA-Brianza cohorts, respectively; they both helped with data interpretation and contributed critically to introduction and discussion. All authors read and approved the final version of the paper, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests: none declared.

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Data sharing statement: statistical details are available upon request to the corresponding author

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Tables and figures

Table 1. Distribution of socio-demographic characteristics and age-adjusted mean and prevalence of major CVD risk factors at baseline, in the entire sample and by aggregated Erikson-Goldthorpe-Portocarero occupational classes. Men 25-64 years old and currently employed at baseline.

	Entire sample	Occupational class		p-value
		Managers& Proprietors	Non-Manual& Manual workers	
Subjects CHD-free at baseline, n	4103	819	3284	-
Age, years	40.9 (9.3)	44.0 (10.3)	40.1 (8.8)	<0.0001*
High School diploma or higher, %	39.4	45.8	37.8	<0.0001^
High Job Strain, %	26.0	12.9	29.2	<0.0001^
Active, %	14.8	23.6	12.6	
Passive, %	35.6	24.2	38.5	
Low Job Strain, %	23.7	39.3	19.8	
Systolic Blood Pressure, mm Hg	127.2 (16.2)	126.7	127.5	0.22§
Total Cholesterol, mg/dl	211.4 (41.3)	215.5	210.7	0.002§
HDL-cholesterol, mg/dl	49.5 (12.9)	49.4	49.6	0.79§
Current cigarette smokers,%	39.2	35.8	40.0	0.03§
Diabetes mellitus,%	2.6	2.8	2.3	0.3§
Median follow-up, years	14.6	17.2	14.0	-
CHD first fatal or non-fatal events, n	172	64	108	-

Unless, otherwise indicated, the numbers reported in the table are means and standard deviations (SD) *ANOVA F-test and ^ Chi-square test.
§Wald chi-square test (2df) from generalized linear model adjusted for age. Mean and prevalence of risk factors estimated at the sample age mean of 41 years.

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Table 2. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, for high job strain (HS) versus non-high job strain (no HS), as reference category. MONICA Brianza, PAMELA and SEMM cohorts. Men 25-64 years old and currently employed

		Entire sample				**Occupational class**							
						Managers&Proprietors				**Non-Manual&Manual workers**			
		N	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**
Job strain categories	*All events in the entire follow-up period included*												
	no HS	3038	126		REF	713	57		REF	2325	69		REF
	HS	1065	46	1.33	0.95 1.87	106	7	0.71	0.32 1.56	959	39	**1.79**	**1.21 2.67**
	Events occurred after the first three years of follow-up												
	no HS	3002	108		REF	697	47		REF	2305	61		REF
	HS	1049	39	1.36	0.94 1.96	102	5	0.61	0.24 1.55	947	34	**1.81**	**1.18 2.77**

Hazard Ratios (HRs) estimated from Cox regression models with age as the time scale, adjusted for systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. Job strain categories based on items of Psychological Job Demand and Decision Latititude.

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Table 3. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, for high job strain (HS) versus non-high job strain (no HS, reference category). Separate estimates for Non-manual and Manual workers. MONICA Brianza, PAMELA and SEMM cohorts.
Men 25-64 years old and currently employed at baseline.

		Non-manual workers					**Manual workers**				
		N	**#CHD**	**HR**	**95%CI**		**N**	**#CHD**	**HR**	**95%CI**	
	All events in the entire follow-up period										
Job strain categories	no HS	1067	32		REF		1258	37		REF	
	HS	399	17	1.77	0.97	3.22	560	22	**1.85**	**1.09**	**3.16**
	Events occurred after the first three years of follow-up										
	no HS	1058	27		REF		1247	34		REF	
	HS	394	14	1.76	0.91	3.40	553	20	**1.87**	**1.07**	**3.28**

Hazard Ratios (HRs) estimated from Cox regression models with age as the time scale, adjusted for systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. Job strain categories based on items of Psychological Job Demand and Decision Latititude.

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Table 4. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, according to job strain category. Low strain as reference category. MONICA Brianza, PAMELA and SEMM cohorts. Men 25-64 years old and currently employed at baseline.

Job strain categories	**Entire sample**				**Managers&Proprietors**				**Non-Manual& Manual workers**			
	N	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**
HIGH STRAIN	1065	46	1.48	0.96 2.28	106	7	0.69	0.29 1.62	959	39	**2.84**	**1.51 5.34**
ACTIVE	605	26	1.25	0.76 2.07	193	11	0.67	0.33 1.38	412	15	**2.41**	**1.14 5.09**
PASSIVE	1462	63	1.13	0.75 1.69	198	22	1.21	0.67 2.17	1264	41	1.67	0.90 3.13
LOW STRAIN	971	37	1.00	REF	322	24	1.00	REF	649	13	1.00	REF

Hazard Ratios (HRs) from Cox regression models with age as the time scale, adjusted for systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. CHD occurred during the entire follow-up period. Job strain categories based on items of Psychological Job Demand and Decision Latititude.

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Figure 1. Survival curves (panel A, left) and cumulative risk of coronary heart disease by attained age (panel B, right) in the four JCQ quadrant-term categories, among the occupational class of Non-manual&Manual workers. Men, 25-64 years old and currently employed at baseline

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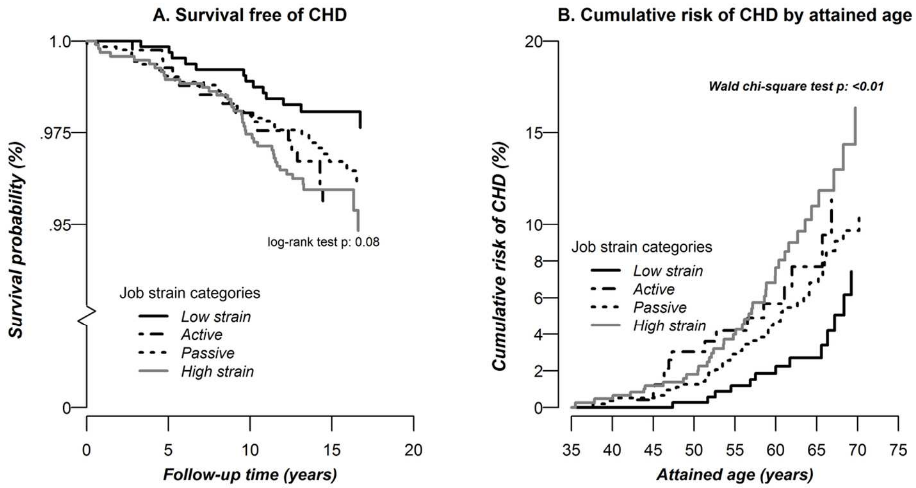

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Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

Supplementary tables.

Table S1. Factor matrix after Varimax rotation of JCQ scores and subscores. The MONICA-Brianza and PAMELA cohorts

JCQ Items - scales	All occupational classes (n=1943)		Managers&Proprietors (n=745)		Non-manual&Manual workers (n=1198)	
Learn new things - SK	**0.5511**	0.0221	**0.4659**	0.0156	**0.5835**	-0.010
High level of skill - SK	**0.6712**	0.0091	**0.6413**	-0.0711	**0.7018**	0.004
Be creative - SK	**0.7078**	-0.0521	**0.6333**	-0.0621	**0.7123**	-0.09787
Not repeat things over and over - SK	0.0293	0.1373	-0.0999	0.2360	0.0520	0.0766
I decide how much work I have to do - DA	**0.6008**	-0.2095	**0.5043**	-0.1816	**0.5065**	-0.3065
Freedom to decide what do at job - DA	**0.6094**	-0.2089	**0.5130**	-0.1496	**0.5332**	-0.31683
Working very fast - PJD	0.2606	0.0989	0.2877	0.0521	0.2280	0.1125
Working very hard - PJD	0.2451	0.1317	0.2842	0.0545	0.1858	0.1532
Excessive amount of work required - PJD	-0.0055	**0.5462**	0.1094	**0.4995**	-0.08407	**0.5582**
Not enough time to get the job done - PJD	0.0342	**0.6965**	0.1071	**0.7922**	-0.011	**0.6372**
Conflicting demands - PJD	-0.1869	**0.4336**	-0.0834	**0.3538**	-0.142	**0.5099**

Abbreviations: SK = skill discretion, DA = decision authority; PJD = psychological job demand; DL = decision latitude; JCQ= Job Content Questionnaire

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Table S2. Distribution of socio-demographic characteristics and age-adjusted mean and prevalence of major CVD risk factors at baseline, by job strain categories. Men 25-64 years old and currently employed at baseline

	ACTIVE	HIGH STRAIN	LOW STRAIN	PASSIVE	p-value
Subjects CHD-free at baseline, n	605	1065	971	1462	-
Age, years	40.3 (9.4)	39.4 (8.8)	42.1 (9.5)	41.3 (9.2)	<0.0001*
High School diploma or higher, %	50.4	42.4	40.7	31.7	<0.0001^
Systolic Blood Pressure, mm Hg	127.0	126.5	127.2	128.1	0.06§
Total Cholesterol, mg/dl	213.1	211.3	211.9	211.2	0.8§
HDL-cholesterol,mg/dl	48.6	49.4	50.1	49.7	0.2§
Current cigarette smokers, %	39.7	41.2	37.1	38.8	0.3§
Diabetes mellitus, %	2.4	1.8	2.3	2.9	0.4§
Median follow-up, years	14.6	13.9	15.0	14.6	-
CHD first fatal or non-fatal events, n	26	46	37	63	-

Unless, otherwise indicated, the numbers reported in the table are means and standard deviations (SD)
*ANOVA F-test (3df). ^ Chi-square test (3df).
§Wald chi-square test (3df) from generalized linear model adjusted for age
Mean and prevalence of risk factors estimated at the sample age mean of 41 years

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Supplementary material for the paper:

Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Actions
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	The study design is stated both in the title and in the abstract (page 2).
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	See abstracts conclusions (page 2).
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	The recent debate about job strain, and the methodological issues in defying the association between coronary heart disease and strain, are summarized in the introduction section (pages 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses	See at page 5, end of introduction section
Methods			
Study design	4	Present key elements of study design early in the paper	The Methods section (pages 5-7) is articulated in the following sub-headings: Study cohorts; Occupational classes; Job strain scales and scores; Measurement of other risk factors at baseline; Study endpoint and follow-up procedures; Statistical analysis
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	See the following sub-headings: "Study cohorts" (page 5); "Study endpoint and follow-up procedures" (page 8).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	See the paragraphs "Study cohorts" (page 5) and "Study endpoint and follow-up procedures" (page 8). The former also contains information on participation rates
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	See the paragraph "Statistical analysis" on page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See paragraphs "Occupational classes", "Job strain scales and scores" and "Measurement of other risk factors at baseline" in the study methods section (pages 6-7).

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Bias	9	Describe any efforts to address potential sources of bias	Participation rates are disclosed in the methods section ("study cohorts", page 5). A sensitivity analysis excluding the first three years of follow-up was performed to address reverse causation. Information on follow-up quality, including its completeness, is available at page 8 ("Study endpoint and follow-up procedures").
Study size	10	Explain how the study size was arrived at	See the first period in the "statistical analysis" sub-heading in the Methods section (page 8)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See the "Statistical Analysis" paragraph (page 8)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See the "Statistical Analysis" paragraph (page 8-9)
		(*b*) Describe any methods used to examine subgroups and interactions	Stratified analyses by occupational classes are described in the "Statistical Analysis" paragraph (page 8-9).
		(*c*) Explain how missing data were addressed	See the first line in the "Statistical analysis " paragraph (page 8)
		(*d*) If applicable, explain how loss to follow-up was addressed	See the "Statistical Analysis" paragraph (page 8-9) for details on the survival analysis techniques
		(*e*) Describe any sensitivity analyses	See the statistical analysis paragraph, page 8, for the sensitivity analysis after excluding subjects with less than 3 years of follow-up.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Participation rates are reported in the paragraph "Study cohorts" (page 5).
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Table 1 in the main text (page 18) and Table S2 in the supplementary material (page 2).
		(b) Indicate number of participants with missing data for each variable of interest	See the first sentence in the "Statistical analysis" paragraph (page 8).
		(c) Summarise follow-up time (eg, average and total amount)	See Table 1 and the first sentence in the "Results" section (page 9).
Outcome data	15*	Report numbers of outcome events or summary measures over time	See Table 1 and the first sentence in the "Results" section (page 9).

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	We provide age-adjusted estimates for cardiovascular disease risk factors distribution in Table 1 (page 18) and Table S2 (supplementary material page 2). Table 2-4 (pages 19-21) report the confounder-adjusted estimates of hazard ratios; the list of confounders, which are represented by major cardiovascular disease risk factors, is reported among the table footnotes. For a discussion on cardiovascular disease risk factors as potential confounders see the discussion section at page 12 ("We did not find…immune system").
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The results of the stratified analyses by occupational classes are reported in tables 2-4 (pages 19-21). The results of the sensitivity analysis excluding the first three years of follow-up are reported in tables 2 and 3 (pages 19 and 20).
Discussion			
Key results	18	Summarise key results with reference to study objectives	See the first paragraph in the Discussion section, page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Study limitations are reported and discussed at pages 12-13.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	See study limitations, on page 12, and the final sentence in the conclusion, on page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source of funding is reported in the dedicated section of the paper (page 14).

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

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http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts

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Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, job strain, occupational class

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Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

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Key words: job strain, coronary heart disease, occupational class

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Abstract (294 words)

Objectives. To assess the association between job strain (JS) and the incidence of coronary heart disease (CHD) in North Italian employed men, adopting a stratified analysis by occupational class.

Methods. The study was conducted on 4103 working men, CHD-free at baseline, enrolled in population-based and factory-based cohorts. Risk factor measurements and follow-up procedures were carried out adopting the WHO MONICA standardised procedures. Occupational classes (OC) were derived from the Erikson-Goldthorpe-Portocarero classification. JS categories were defined based on overall sample medians of psychological job demand (PJD) and decision latitude (DL) derived from items of the Job Content Questionnaire, satisfying construct validity criteria. Age- and risk factors-adjusted CHD hazard ratios (HR) were estimated from Cox models, contrasting high strain (high PJD and low DL) vs non-high-strain categories.

Results. In a median follow-up of 14.6 years, 172 CHD events occurred, corresponding to a CHD incidence rate of 2.78 per 1,000 person-years. In the overall sample, high strain compared to non-high strain workers evidenced a 39% CHD excess risk, not statistically significant. No association was found among managers and proprietors. Conversely, the HR of high strain vs non-high strain was 1.78 (95%CI: 1.20-2.66) among non-manual and manual workers, with no substantial differences between them. The exclusion of the events occurring in the first three years of follow-up did not change the results. Adopting the quadrant-term JS groupings, among manual and non-manual workers, high strain and active (high PJD and high DL) categories in comparison to the low strain one (low PJD and high DL) showed HRs of 2.92 and 2.47, respectively.

Conclusions. Our findings support the association of job strain and CHD incidence among manual and non-manual workers. The non-high strain may not be the best reference category, when assessing the contribution of JS in determining CHD incidence.

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Strenghts and limitations of this study

- A recently published meta-analysis and subsequent papers have drastically reduced the role of job strain (JS), measured by the Job Content Questionnaire (JCQ), as a primary risk factor for coronary heart disease (CHD), but some methodological shortcomings have been highlighted.
- In our pooled analysis with population- and factory-based cohorts and a wide range of job titles, we assessed the association between JS and CHD adopting some methodological refinements: we selected relevant JCQ items which showed satisfactory construct validity, and we performed a stratified analysis by occupational classes, motivated by the knowledge that stressors in salaried workers and other professional categories may have different contents.
- We explored the association using as the reference category low-JS, instead that the wider non-high JS category, which nullifies the separate effects of control and demands at work, focusing merely on the joint effect.
- Our findings showed that the CHD risks were higher among high JS manual and non-manual workers only, suggesting that JCQ better grasps job strains in low-wage working categories; and the CHD risk increased substantially in high-JS when compared to low-strain only.
- The study did not include women due to the low incidence rate, and the small sample size anyhow deserves replications in different contexts to enhance confidence in results.

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Organizational stressors at the work place and sedentary activities are the two most common work-related cardiovascular disease (CVD) risk factors in post-industrialised societies [1]. The job demand-control model [2], developed by Karasek in the late 1970s is a widely used questionnaire to assess perceived work stress conditions. It is based on two major constructs: psychological job demand (PJD) and decision latitude (DL), defining high strain, active, passive and low-strain categories.

Belkic et al. [3] reviewing 17 prospective cohort, nine case-control and eight cross-sectional studies, concluded in favour of a positive association between job strain (JS) and cardiovascular disease in men. Kivimaki et al [4] in a meta-analysis of cohort studies estimated an overall age-adjusted 43% excess risk for high JS, assessed with the demand-control model. This report combined hazard ratios published by studies using different endpoints, some reporting combining estimates for men and women, and some adopting the approximate job-title imputed method to estimate exposures. This paper reported higher relative risks for the effort reword imbalance model [5] and injustice at work too. A more recent paper, based on a collaborative pooled analysis including mainly unpublished (10 out of 13) and published cohort studies, found an overall gender- and age-adjusted hazard ratio for high versus non-high JS of 1.23 (95%CI: 1.10–1.37). The non-high JS reference group combines active, passive and low strain original categories. Based on this low excess risk and an arguable estimate of the high JS prevalence, the authors calculated a small population attributable risk of 3-4% [6].

This publication stimulated an intense debate in the scientific community [7-13], and many scientists argued that some shortcomings had contributed to bias the results to the null association. Among them, it is noteworthy to mention the low participation rates and the predominance of white-collars in comparison to blue-collars. Both these selection biases may have produced a reduced recruitment of more stressed workers, which is a frequently reported problem in these studies. Another potential bias may be due to the misclassification of exposure as JS may change overtime, due to the predominance of different stressors in the work organisations in different time periods. A recent letter [14] highlighted some methodological and conceptual limitations related to the evaluation of

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JS. Some of them are arguable and some can only be addressed in future studies, as available data from most recent studies in psychosocial CHD epidemiology were not designed and did not collected the required information [14].

The aim of the present paper is to assess the association between JS and the incidence of CHD in pooled analysis of population-based and factory-based North Italian cohorts of employed men, in particular focusing on a stratified analysis based on occupational classes. In a previous paper (15) we found that JS contributes to explain the CHD risk excess in manual compared to non-manual workers, but not the one observed in managers and self-employers. This finding may implies that the JCQ model better describe strain conditions among salaried manual and non-manual workers only. We reported hazard ratios for the entire follow-up period and after exclusion of the events occurred in the first three years, to investigate reverse causation.

Methods

Study cohorts

As a part of the WHO-MONICA Project, three surveys of the Brianza population (located North of Milan) took place over a ten-year period (1986-1987, 1989-1990 and 1993-1994) to estimate coronary risk factor changes over time [15]. In each survey a 10-year age and gender stratified random sample was drawn from municipality roles among 25 to 64-year-old residents in five area-representative towns. The participation rates were 70.1, 67.2 and 70.8% respectively. The PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study was another population survey, conducted in 1991-1992[16], with the sampling procedure applied to the 25 to 74-year old residents of the city of Monza, the largest town in Brianza. The participation rate was 66.9% among people up to 65 years of age. The overall sample size of individuals who were free of CHD and employed at the time of recruitment was 2350 men and 1334 women.

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The SEMM (Surveillance of Employees of the Municipality of Milan) study recruited employees of six departments of the Milan Municipality, screened for CVD risk factors between May 1991 and March 1996. The cohort contributed to the JACE Study [17]. The participation rates were 75.3% for men and 76.2% for women, respectively; and the overall sample size of the SEMM cohort, free of CHD at baseline, was of 2569 men and 5254 women. Women were not included in the analysis due to low number of CHD events (46 events in all the cohorts). The study approvals were obtained from the Ethical Committee of the University Hospital of Monza.

Occupational classes

As reported in a previous paper [15], we derived Erikson-Goldthorpe-Portocarero (EGP)-classes. To achieve sufficient statistical power, EGP classes were aggregated in three occupational classes, as follows: professionals, administrators, managers, proprietors and self-employers (EGP classes I, II and IV, called here briefly Managers&Proprietors), non-manual (EGP classes III and V) and manual (skilled and unskilled, EGP classes VI and VII) workers.

Job strain scales and scores

The Job Content Questionnaire (JCQ) was administered to all employed workers, using two different versions sharing the same core items. In the MONICA Brianza and PAMELA studies as well as for employees of the two first-recruited departments of the SEMM study, the short MONICA-MOPSY version [18] was used. The extended version of JCQ was instead adopted for the remaining four SEMM departments, when the study was included into the JACE Project [16]. In Table S1 of supplementary material the original items for demand and control are reported for both questionnaires. The common items assessing psychological job demand and decision latitude, each on a 4-point scale ranging from completely agree to completely disagree, were used. A comparability analysis [19, 20] showed that equivalent PJD and DL scores and sub-scores can be calculated from both questionnaires.

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We derived the conventional four JCQ categories based on the quadrant approach, with high strain defined as PJD values higher than the overall sample median and DL values lower than or equal to the median. The remaining three job strain categories, i.e. active, passive and low strain were also defined according to the standard criteria [2]. These three last strain categories were collapsed in a unique category, called non-high JS, to allow direct comparisons with the results reported by the recent pooled-cohort meta-analysis [6].

Measurements of other risk factors at baseline

In MONICA surveys, cardiovascular risk factors were collected at baseline strictly adhering to the standardized procedures and quality standards of the WHO-MONICA Project (http://www.ktl.fi/publications/monica/manual/index.htm). In the PAMELA and in the SEMM studies, risk factors were measured based on MONICA-like procedures. In brief, blood pressure was measured on sitting subjects at rest for at least 10 minutes, using a standard mercury sphygmomanometer equipped with larger cuff bladders if needed. The study variable for systolic blood pressure is the average of two measurements taken 5 min apart. Venous blood specimens were taken from the ante-cubital vein in fasting subjects (12h or more). Serum total cholesterol and HDL-cholesterol were measured by an enzymatic method. Blood glucose was determined on the same samples by an enzymatic method.

From standardized interview information on cigarette smoking habits was available and dichotomized as current vs. past/never smokers in this analysis. Diabetes mellitus was defined using self-reported diagnoses and information on insulin and oral hypoglycaemic treatments or based on a fasting blood glucose exceeding 126 mg/dl. Self-reported information on hospitalization for myocardial infarction, unstable angina pectoris, coronary revascularization was used to define a positive history of coronary event at baseline. Items on educational attainment were part of the standardized questionnaire, and it was dichotomized as “low” (less than high school) and “high” (high school or more).

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Study endpoints and follow-up procedures

All subjects were followed from the baseline examination until first cardiovascular event, emigration, death, 80-th birthday or December 31st, 2008, whichever came first, based on locally adapted procedures, developed within the MORGAM Project [http://www.thl.fi/publications/morgam/manual/followup/fumethod.htm]. Vital status was actively investigated for all subjects, including those who moved to different towns in Italy, and death certificates were obtained from local health districts. Suspected fatal events were identified on the basis of selected underlying causes of death ICD-IX codes 410-414. Suspected non-fatal events were identified based on ICD-IX hospital discharge codes: 410-411 for acute coronary events, 36.0-9 for coronary revascularization. Acute events were further investigated and validated according to the MONICA diagnostic criteria. The study endpoint is the occurrence of a first major acute coronary event (myocardial infarction, acute coronary syndrome), fatal or non-fatal, or coronary revascularization. The follow-up was completed for 98.9% of them, with no differences across cohorts and occupational classes.

Statistical analysis

Of the 4827 male workers in the age range 25-64 years old, we excluded 724 subjects with missing values of JCQ items or CHD risk factors, and the final sample size was 4103. We calculated the age-adjusted mean (prevalence) of major CHD risk factors by occupational class and strain categories from generalized linear models, and tested differences among groups using Wald chi-square tests.

Factor Analysis with varimax rotation and Cronbach's α coefficients were used to assess the construct validity and internal consistency of JCQ items, respectively. These analyses were carried out on the population-based cohorts, characterized by wide job title variability.

Cox proportional hazards model with lifespan (attained age) on the time scale was adopted to study the associations between the risk of CHD event and job strain, dichotomized for most

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analyses in high strain versus non-high strain (reference category comprising passive, active and low-strain), adjusting for major risk factors and a dummy variable to indicate the study type (population- vs. factory-based). Stratified analyses were carried out adding a job strain*occupational class interaction term in the models; the p-value for the interaction term represented the formal test for the hypothesis of no change in the association between job strain and CHD in different occupational classes (Wald chi-square test). We also performed a separate analysis, using the four JCQ categories (with low strain as reference group). The analyses were performed using the Statistical Analysis System (Version 9.4, SAS Institute Inc, Cary, NC). The figure was drawn using the R software (R Foundation for Statistical Computing, Wien, Austria. http://www.R-project.org/).

Results

In a median follow-up time of 14.6 years (interquartile range: 13.2-17.6 years), 172 incident major coronary events occurred in our study sample, corresponding to a cumulative incidence rate of 2.78 per 1,000 p-y. Age-adjusted rates among Managers&Proprietors and Non-manual&Manual workers were 3.1 (95%CI 2.32-4.14) and 1.97 (1.60-2.41), respectively. The exclusion of individuals with missing data did not alter the excess risk in Managers&Proprietors with respect to the Non-manual&Manual workers (Supplementary Table S5).

As shown in Table S2 in the Supplementary material, the results of the factor analysis carried out on the populations-based MONICA-PAMELA samples, evidenced a satisfactory construct validity of JCQ items, with the notable exception of one item of skill discretion (SD), i.e. “do not repeat things over and over” and two items of PJD, i.e. “work very fast” and “work very hard”. Since these items did not contribute to the definition of the expected constructs, i.e. decision latitude and psychological job demand, they were excluded and the scores calculated with the residual available items. Cronbach’s α coefficients were 0.70 and 0.75 for DL and 0.53 and 0.58 for PJD among Managers&Proprietors and Non-manual&Manual workers, respectively.

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Table 1 shows the distributions of main socio-demographic variables, JS categories and cardiovascular risk factors in the entire sample and in the two OCs. Non-manual and manual workers were younger and less educated than managers and proprietors. In the entire sample, 26% were classified at high strain, as expected due to the quadrant-term approach based on medians and the orthogonality between the constructs (Pearson correlation coefficient between PJD and DL was -0.09). The highest prevalence of high strain was found among Non-manual&Manual workers, while active and low strain categories were prevalent among managers and proprietors. Managers&proprietors showed higher age-adjusted mean values of total cholesterol, but were less likely to smoke than Non-manual&Manual workers (all p-values <0.05). Conversely, the EGP-aggregated occupational classed did not differ for mean systolic blood pressure and HDL-cholesterol, nor for prevalence of diabetes (all p-values >0.2). As shown in Table S3 in the Supplementary material, none of the considered risk factors showed statistically significant differences between the four JCQ categories.

Table 2 shows the results of the analysis assessing the association between JS and CHD incidence, for the entire sample and by occupational classes. In the entire sample, high strain subjects evidenced an overall higher hazard ratio (HR) of 1.39 (95%CI 0.99-1.97) in comparison to non-high strain, which was confirmed even after the exclusion of the first three years of follow-up (HR=1.39, 0.96-2.03). No increased hazard of events for high vs. non-high strain was found among Managers&Proprietors, with HRs ranging from 0.71 to 0.61, both not statistically significant. Conversely, the hazard ratio for high vs non-high JS was 1.78 (1.20-2.66) among Non-manual&Manual workers, which again did not substantially change when events in the first three years were excluded [HR = 1.80 (1.17-2.76)]. The job strain*occupational class interaction term was statistically significant (p=0.04), suggesting the presence of heterogeneity by occupational class in the association between job strain and CHD. Finally, these findings were confirmed when population- and factory-based cohorts were analysed separately (Supplementary material Table S4). When manual and non-manual workers were analysed separately, as Table 3 shows, the hazard ratios for the high strain *vs* non-high strain

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workers were 1.94 (95%CI 1.13-3.32) and 1.70 (95%CI 0.94-3.08) for manual and non-manual workers, respectively. There was no evidence of occupation*job strain interaction (p-value = 0.7). To maximize the available number of events, this analysis were carried out including the entire follow-up period, but nevertheless, wide confidence intervals acknowledge the poor statistical power.

Table 4 shows the results of the association analysis between JS and CHD when the four JCQ quadrant-term categories are kept separated, and including all events occurred in the entire follow-up period, to maximize the available statistical power. Compared to the low-strain group, high strain Non-manual&Manual workers evidenced hazard ratio of 2.92 (95%CI 1.54-5.51), higher than when using the non-high strain group as the reference category. In addition, a risk excess was also found for active workers (2.47; 1.17-5.23), indicating that the demand dimension of JCQ in this workers is playing a major role in increasing the CHD risks. As shown in Figure 1, the survival curve of low strain in comparison to all the other job strain categories diverged already in the first years of follow-up, and persisted later on (panel A). This observation is in support of the detected small effect of reverse causation assessed with the exclusion of the events occurred during the first three years of follow-up. Moreover, the increase in cumulative risk over attained age (Figure 1, panel B) indicates that high strain men at the age of 50 years have the same cumulative risk of low strain men a decade older (Figure 1, panel B).

Discussion

In summary, in the investigated North Italian employed male pooled cohort we found a small increase in risk of CHD events in high job strain when compared to non-high job strain workers of 39%, not statistically significant. This estimate replicates the findings of recent meta-analyses, extending their results to a Southern European country with low CHD incidence rates. [6, 11] The novelty of our paper relates to results of the stratified analysis, which showed an excess risk of 78% [HR= 1.78 (95%CI 1.20-2.66)] among high strain Non-Manual&Manual workers. In this occupational class, when the four JCQ categories were separately analysed, the relative risk of CHD events of high

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strain *versus* low strain subjects increased to 2.92 (95%CI 1.54-5.51). It is noteworthy mentioning that the HR for active *versus* low strain workers was also elevated (HR=2.47; 1.17-5.23), indicating that the association can be biased towards the null hypothesis when active, low-strain and passive men are grouped in a unique non-high strain class.

The use of JCQ constructs based on the results of factor validity assessment have evidenced satisfactory internal consistency and reliability of the scores. The skill discretion item "do not repeat things over and over" may have different meanings in a variety of job profiles, working environments and countries; and it may not always connote monotony [21]. Two items of demand "work very fast" and "work very hard" assume minor importance in post-industrial work forces, while items describing pressure for having the work done or conflicting demands are stressors that still continue to characterise nowadays working conditions, as also reported by other authors [22]. This observation requires further investigations, as it points to the conclusion that the established JCQ questionnaire may be well suited to grasp the working strains of salaried workers, in the low levels of the work organization only. The stressful aspects of job characteristics among people ranking at the higher level of the work organizations are probably related to prolonged working hours and excessive competitiveness, which are not adequately investigated by the actual formulation of the JCQ questionnaire [23].

We did not find relevant differences in the distribution of traditional cardiovascular risk factors, including systolic blood pressure, cholesterol as well as the prevalence of diabetes and cigarette smoking, among JCQ categories. In the population based sample we did find differences among JS categories in 24-hour systolic blood pressure means, but not when using clinical blood pressure measurements in the same age range [24]. This observation is in line with previous findings supporting the major importance of a direct, rather than an indirect, effect of job strain on the cardiovascular system [21]. This direct effect is assumed to be attributable to the effect on

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psychobiological processes, as documented in a reduced heart rate variability [25] and in alterations of the hormonal or immune systems [26].

Among the strengths of the present study we mention the long follow-up period, the standardization of the methods to collect risk factors at baseline and to validate events, as they have been carried out adhering to the MONICA and MORGAM studies procedures. Among the limitations, we should acknowledge that our findings are on men only. We did not include women, due to the low number of events, which did not allow us to further stratify the analyses by occupational classes. We did not explore a dose-response relationship, but our findings support the major role of psychological job demand in determining the increased CHD risk, as both high strain and active worker showed the higher risks when compared to low strain subjects. We also did not explore the interaction effects with other work-related risk factors like social support and physical inactivity, as well as with behavioural risk factors [27, 28]. As we do have these baseline data for some of the cohorts, we will investigate these interactions in future reports, hoping to contribute to the current interest of the scientific community on these topics [29-33]. Finally, we did not collect data at baseline on other complementary theoretical models of stressful work, in particular the effort-reward imbalance model, which has shown remarkable associations with CVD and CHD outcomes [4, 5].

In conclusion, our findings support the association between job strain and CHD incidence in manual and non-manual workers, not among managers and proprietors. This can be attributable to the better chances of the present formulation of the JCQ questionnaire to grasp job stressors in the low wage working categories. Moreover, to assess the effect of high strain on CHD, it is more accurate to use the low-strain instead of the wider non-high strain as the reference category, since the adoption of the latter may contribute to bias the association to the null. Our results require replications on larger and diversified samples.

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Author's contribution: MMF conceived the research question, drafted the manuscript and is the PI of the MONICA-Brianza and the SEMM study cohorts. GV, LB were responsible of the statistical analyses, contributed to interpretation of the data and revised the manuscript. GG and GC are the PIs of the PAMELA study and of the MONICA-Brianza cohorts, respectively; they both helped with data interpretation and contributed critically to introduction and discussion. All authors read and approved the final version of the paper, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement: statistical details are available upon request to the corresponding author

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Tables and figures

Table 1. Distribution of socio-demographic characteristics and age-adjusted mean and prevalence of major CVD risk factors at baseline, in the entire sample and by aggregated Erikson-Goldthorpe-Portocarero occupational classes. Men 25-64 years old and employed at time of recruitment.

	Entire sample	Occupational class		p-value
		Managers& Proprietors	Non-Manual& Manual workers	
Subjects CHD-free at baseline, n	4103	819	3284	-
Age, years	40.9 (9.3)	44.0 (10.3)	40.1 (8.8)	<0.0001*
High School diploma or higher, %	39.4	45.8	37.8	<0.0001^
High Job Strain, %	26.0	12.9	29.2	<0.0001^
Active, %	14.8	23.6	12.6	
Passive, %	35.6	24.2	38.5	
Low Job Strain, %	23.7	39.3	19.8	
Systolic Blood Pressure, mm Hg	127.2 (16.2)	126.7	127.5	0.22§
Total Cholesterol, mg/dl	211.4 (41.3)	215.5	210.7	0.002§
HDL-cholesterol, mg/dl	49.5 (12.9)	49.4	49.6	0.79§
Current cigarette smokers,%	39.2	35.8	40.0	0.03§
Diabetes mellitus,%	2.6	2.8	2.3	0.3§
Median follow-up, years	14.6	17.2	14.0	-
CHD first fatal or non-fatal events, n	172	64	108	-

Unless, otherwise indicated, the numbers reported in the table are means and standard deviations (SD) *ANOVA F-test and ^ Chi-square test.
§Wald chi-square test (2df) from generalized linear model adjusted for age. Mean and prevalence of risk factors estimated at the sample age mean of 41 years.

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Table 2. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, for high job strain (HS) versus non-high job strain (no HS), as reference category. MONICA Brianza, PAMELA and SEMM cohorts. Men 25-64 years old and employed at time of recruitment

		Entire sample				**Occupational class**								**p-value^**
						Managers & Proprietors				**Manual and Non-manual Workers**				
		N	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**	**N**	**#CHD**	**HR**	**95%CI**	
Job strain categories	*All events in the entire follow-up period included*													
	no HS	3038	126		REF	713	57		REF	2325	69		REF	**0.04**
	HS	1065	46	1.39	0.99 1.97	106	7	0.71	0.32 1.56	959	39	**1.78**	**1.20 2.66**	
	Events occurred after the first three years of follow-up													
	no HS	3002	108		REF	697	47		REF	2305	61		REF	**0.04**
	HS	1049	39	1.39	0.96 2.03	102	5	0.61	0.24 1.55	947	34	**1.80**	**1.173 2.762**	

Hazard Ratios (HRs) estimated from Cox regression models with age as the time scale, adjusted for study type (population-based vs. factory-based), systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. Job strain categories based on items of Psychological Job Demand and Decision Latitude.

^: p-value for interaction test between occupational class and high-strain (1 df Wald chi-square test)

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Table 3. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, for high job strain (HS) versus non-high job strain (no HS, reference category). Separate estimates for Non-manual and Manual workers. MONICA Brianza, PAMELA and SEMM cohorts.
Men 25-64 years old and employed at time of recruitment.

		Non-manual workers					Manual workers					p-value^
		N	#CHD	HR	95%CI		N	#CHD	HR	95%CI		
Job strain categories	*All events in the entire follow-up period*											
	no HS	1067	32		REF		1258	37		REF		0.7
	HS	399	17	1.70	0.94	3.08	560	22	**1.94**	**1.13**	**3.32**	
	Events occurred after the first three years of follow-up											
	no HS	1058	27		REF		1247	34		REF		0.7
	HS	394	14	1.68	0.88	3.23	553	20	**1.95**	**1.11**	**3.43**	

Hazard Ratios (HRs) estimated from Cox regression models with age as the time scale, adjusted for study type (population-based vs. factory-based), systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. Job strain categories based on items of Psychological Job Demand and Decision Latitude.
^: p-value for interaction test between occupational class and high-strain (1 df Wald chi-square test)

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Table 4. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, according to job strain category. Low strain as reference category. MONICA Brianza, PAMELA and SEMM cohorts. Men 25-64 years old and employed at time of recruitment.

Job strain categories	Entire sample					Managers & Proprietors					Manual and Non-manual Workers				
	N	#CHD	HR	95%CI		N	#CHD	HR	95%CI		N	#CHD	HR	95%CI	
HIGH STRAIN	1065	46	1.57	1.01	2.44	106	7	0.60	0.25	1.47	959	39	**2.92**	**1.54**	**5.51**
ACTIVE	605	26	1.28	0.77	2.12	193	11	0.64	0.31	1.32	412	15	**2.47**	**1.17**	**5.23**
PASSIVE	1462	63	1.14	0.76	1.72	198	22	1.16	0.64	2.1	1264	41	1.67	0.89	3.12
LOW STRAIN	971	37	1.00	REF		322	24	1.00	REF		649	13	1.00	REF	

Hazard Ratios (HRs) from Cox regression models with age as the time scale, adjusted for study type (population-based vs. factory-based), systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. CHD occurred during the entire follow-up period. Job strain categories based on items of Psychological Job Demand and Decision Latitude.

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Figure 1. Survival curves (panel A, left) and cumulative risk of coronary heart disease by attained age (panel B, right) in the four JCQ quadrant-term categories, among the occupational class of Non-manual&Manual workers. Men, 25-64 years old and employed at time of recruitment

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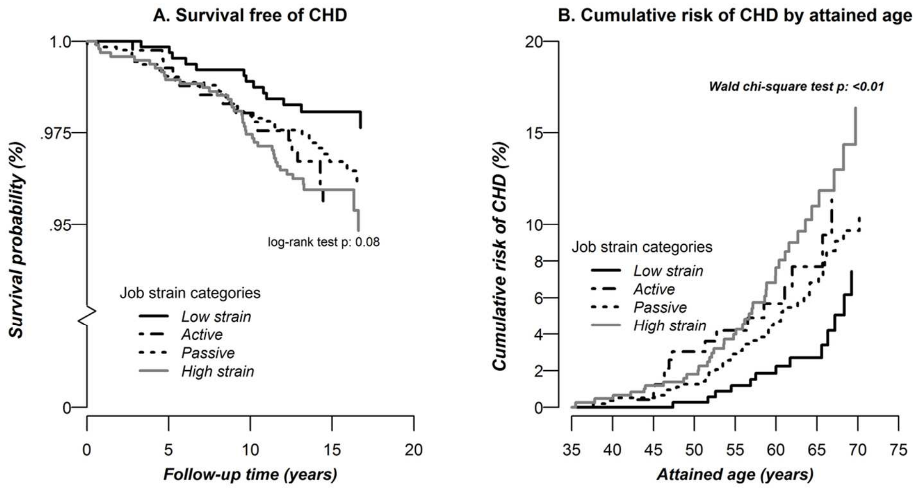

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Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

Supplementary tables.

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Table S1: Original items for demand and control in the two versions of the Job Content Questionnaire used in the paper.

JCQ version	MONICA-MOPSY [1]		JACE [2]	
Number of items	11		34	
Study cohorts	MONICA-Brianza, PAMELA, SEMM (first 2 departments)		SEMM (departments from 3 to 6)	
JCQ scale	**Item name**	**Item question**	**Item name**	**Item question**
Decision Latitude	LEARN	My job requires that I learn new things	JOBLEARN	My job requires that I learn new things
	SKILL	My job requires a high level of skill	JOBHISKI	My job requires a high level of skill
	CREATIV	My job requires that I be creative	JOBCREAT	My job requires me to be creative
	OVER	My job requires that I do things over and over	JOBREPET	My job involves a lot of repetitive work
	DECIS	I have freedom to decide what I do on my job	JOBDECIS	My job allows me to make a lot of decisions of my own
	RESPONS	It is my responsibility to decide how much work I get done	JOBFREED	On my job, I have very little freedom to decide how I do my work
			JOBVARIE	I get do a variety of different things on my job
			JOBINFLU	I have a lot of say about what happens on my job
			JOBDEVEL	I have an opportunity to develop my own special abilities
Psychological Job Demand	FASTWORK	My job requires working very fast	JOBFAST	My job requires working very fast
	HARDWORK	My job requires working very hard	JOBHARD	My job requires working very hard
	EXCWORK	I am not asked to do an excessive amount of work	JOBEXCES	I am not asked to do an excessive amount of work
	TIME	I have enough time to get the job done	JOBEXTM	I have enough time to get the job done
	FREECON	I am free from conflicting demands others make	JOBCONFL	I am free from conflicting demands that others make

References: 1. World Health Organization: MONICA Psychosocial Optional Study Manual: Suggested Measurement Instruments. Copenhagen: WHO Regional Office for Europe, 1989. 2. Houtman I et al. Eur J Public Health. 1999;9(1):52–7

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Table S2. Factor matrix after Varimax rotation of JCQ scores and subscores. The MONICA-Brianza and PAMELA cohorts

JCQ Items - scales	All occupational classes (n=1943)		Managers&Proprietors (n=745)		Non-manual&Manual workers (n=1198)	
Learn new things - SK	**0.5511**	0.0221	**0.4659**	0.0156	**0.5835**	-0.010
High level of skill - SK	**0.6712**	0.0091	**0.6413**	-0.0711	**0.7018**	0.004
Be creative - SK	**0.7078**	-0.0521	**0.6333**	-0.0621	**0.7123**	-0.09787
Not repeat things over and over - SK	0.0293	0.1373	-0.0999	0.2360	0.0520	0.0766
I decide how much work I have to do - DA	**0.6008**	-0.2095	**0.5043**	-0.1816	**0.5065**	-0.3065
Freedom to decide what do at job - DA	**0.6094**	-0.2089	**0.5130**	-0.1496	**0.5332**	-0.31683
Working very fast - PJD	0.2606	0.0989	0.2877	0.0521	0.2280	0.1125
Working very hard - PJD	0.2451	0.1317	0.2842	0.0545	0.1858	0.1532
Excessive amount of work required - PJD	-0.0055	**0.5462**	0.1094	**0.4995**	-0.08407	**0.5582**
Not enough time to get the job done - PJD	0.0342	**0.6965**	0.1071	**0.7922**	-0.011	**0.6372**
Conflicting demands - PJD	-0.1869	**0.4336**	-0.0834	**0.3538**	-0.142	**0.5099**

Abbreviations: SK = skill discretion, DA = decision authority; PJD = psychological job demand; DL = decision latitude; JCQ= Job Content Questionnaire

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Table S3. Distribution of socio-demographic characteristics and age-adjusted mean and prevalence of major CVD risk factors at baseline, by job strain categories. Men 25-64 years old and currently employed at baseline

	ACTIVE	HIGH STRAIN	LOW STRAIN	PASSIVE	p-value
Subjects CHD-free at baseline, n	605	1065	971	1462	-
Age, years	40.3 (9.4)	39.4 (8.8)	42.1 (9.5)	41.3 (9.2)	<0.0001*
High School diploma or higher, %	50.4	42.4	40.7	31.7	<0.0001^
Systolic Blood Pressure, mm Hg	127.0	126.5	127.2	128.1	0.06§
Total Cholesterol, mg/dl	213.1	211.3	211.9	211.2	0.8§
HDL-cholesterol,mg/dl	48.6	49.4	50.1	49.7	0.2§
Current cigarette smokers, %	39.7	41.2	37.1	38.8	0.3§
Diabetes mellitus, %	2.4	1.8	2.3	2.9	0.4§
Median follow-up, years	14.6	13.9	15.0	14.6	-
CHD first fatal or non-fatal events, n	26	46	37	63	-

Unless, otherwise indicated, the numbers reported in the table are means and standard deviations (SD)
*ANOVA F-test (3df). ^ Chi-square test (3df).
§Wald chi-square test (3df) from generalized linear model adjusted for age
Mean and prevalence of risk factors estimated at the sample age mean of 41 years

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Table S4. Multivariate-adjusted Hazard Ratios (HR) and 95% confidence intervals (95%CI) of first CHD event, for high job strain (HS) versus non-high job strain (no HS) as reference category, separately in population-based (MONICA Brianza and PAMELA) and factory-based (SEMM study) cohorts.
Men 25-64 years old and employed at time of recruitment.

		Entire sample					Occupational class										
							Managers & Proprietors					**Manual and Non-manual Workers**					**p-value^**
		N	**#CHD**	**HR**	**95%CI**		**N**	**#CHD**	**HR**	**95%CI**		**N**	**#CHD**	**HR**	**95%CI**		
Job strain categories	*Population-based cohorts (MONICA-Brianza and PAMELA)*																
	no HS	1601	88		REF		667	51		REF		934	37		REF		0.05
	HS	342	19	1.24	0.75	2.03	78	4	0.60	0.216	1.67	264	15	**1.94**	**1.06**	**3.55**	
	Factory-based cohorts (SEMM Study)																
	no HS	1437	38		REF		46	6		REF		1391	32		REF		0.3
	HS	723	27	1.55	0.95	2.55	28	3	0.70	0.173	2.83	695	24	1.68	0.985	2.87	

HR estimated from Cox regression models with age as the time scale, adjusted for study type (population-based vs. factory-based), systolic blood pressure, total cholesterol, HDL cholesterol, diabetes and current smokers. Job strain categories based on items of Psychological Job Demand and Decision Latitude.
^: p-value for interaction test between occupational class and high-strain (1 df Wald chi-square test)

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Table S5. Distribution of socio-demographic characteristics and age-adjusted mean and prevalence of major CVD risk factors at baseline, according to the presence of missing values in the JCQ and/or major CVD risk factors. Men 25-64 years old and employed at time of recruitment.

	Missing data	Complete data	p-value
Subjects CHD-free at baseline, n	724	4103	-
Age, years	43.8 (9.6)	40.9 (9.3)	<0.0001*
High School diploma or higher, %	27.0	39.4	<0.0001^
Men from population-based cohorts, %	51.5	47.4	0.04^
Managers&Proprietors, %	24.2	20.0	0.01^
Systolic Blood Pressure, mm Hg	130.8 (18.4)	127.2 (16.2)	0.04§
Total Cholesterol, mg/dl	212.3 (45.3)	211.4 (41.3)	0.05§
HDL-cholesterol, mg/dl	49.3 (12.6)	49.5 (12.9)	0.63§
Current cigarette smokers, %	41.0	39.2	0.2§
Diabetes mellitus, %	3.4	2.6	0.9§
Median follow-up, years	14.1	14.6	-
CHD first fatal or non-fatal events, n	51	172	-
Age-adjusted CHD rate, per 1,000 p-y#			
Overall	3.0 (2.2-4.1)	2.2 (1.9-2.7)	0.07§§
Managers&Proprietors	5.1 (3.0-8.5)	3.1 (2.3-4.1)	0.16§§
Non-manual&manual workers	2.8 (1.8-4.2)	2.0 (1.6-2.4)	0.26§§

Unless, otherwise indicated, the numbers reported in the table are means and standard deviations (SD). Missing data: JCQ n = 594; risk factors n = 75; both n=55.#: Estimated at the age of 41 years. *ANOVA F-test and ^ Chi-square test. §Wald chi-square test from generalized linear model adjusted for age §§Wald chi-square test from Poisson model adjusted for age

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Supplementary material for the paper:

Job strain and the incidence of coronary heart diseases: does the association differ among occupational classes? A contribution from a pooled analysis of Northern Italian cohorts.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Actions
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	The study design is stated both in the title and in the abstract (page 2).
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	See abstracts conclusions (page 2).
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	The recent debate about job strain, and the methodological issues in defying the association between coronary heart disease and strain, are summarized in the introduction section (pages 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses	See at page 5, end of introduction section
Methods			
Study design	4	Present key elements of study design early in the paper	The Methods section (pages 5-9) is articulated in the following sub-headings: Study cohorts; Occupational classes; Job strain scales and scores; Measurement of other risk factors at baseline; Study endpoint and follow-up procedures; Statistical analysis
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	See the following sub-headings: "Study cohorts" (page 5); "Study endpoint and follow-up procedures" (page 8).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	See the paragraphs "Study cohorts" (page 5) and "Study endpoint and follow-up procedures" (page 8). The former also contains information on participation rates
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	See the paragraph "Statistical analysis" on pages 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See paragraphs "Occupational classes", "Job strain scales and scores" and "Measurement of other risk factors at baseline" in the study methods section (pages 6-7).

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Bias	9	Describe any efforts to address potential sources of bias	Participation rates are disclosed in the methods section ("study cohorts", pages 5-6). A sensitivity analysis excluding the first three years of follow-up was performed to address reverse causation. Information on follow-up quality, including its completeness, is available at page 8 ("Study endpoint and follow-up procedures").
Study size	10	Explain how the study size was arrived at	See the first period in the "statistical analysis" sub-heading in the Methods section (page 8)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See the "Statistical Analysis" paragraph (page 8)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See the "Statistical Analysis" paragraph (page 8-9)
		(*b*) Describe any methods used to examine subgroups and interactions	Stratified analyses by occupational classes are described in the "Statistical Analysis" paragraph (page 8-9).
		(*c*) Explain how missing data were addressed	See the first line in the "Statistical analysis " paragraph (page 8)
		(*d*) If applicable, explain how loss to follow-up was addressed	See the "Statistical Analysis" paragraph (page 8-9) for details on the survival analysis techniques
		(*e*) Describe any sensitivity analyses	See the statistical analysis paragraph, page 8, for the sensitivity analysis after excluding subjects with less than 3 years of follow-up.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Participation rates are reported in the paragraph "Study cohorts" (page 5-6).
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Table 1 in the main text and Table S3 in the supplementary material
		(b) Indicate number of participants with missing data for each variable of interest	See the first sentence in the "Statistical analysis" paragraph (page 8) and Table S5 in the Supplementary Material.
		(c) Summarise follow-up time (eg, average and total amount)	See Table 1 and the first sentence in the "Results" section (page 9).
Outcome data	15*	Report numbers of outcome events or	See Table 1 and the first sentence in the

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		summary measures over time	"Results" section (page 9).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	We provide age-adjusted estimates for cardiovascular disease risk factors distribution in Table 1and Table S3. Table 2-4 report the confounder-adjusted estimates of hazard ratios; the list of confounders, which are represented by major cardiovascular disease risk factors, is reported among the table footnotes. For a discussion on cardiovascular disease risk factors as potential confounders see the discussion section at page 12-13 ("We did not find…immune system").
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The results of the stratified analyses by occupational classes are reported in tables 2-4. The results of the sensitivity analysis excluding the first three years of follow-up are reported in tables 2 and 3. Table S4 in the Supplementary Material reports the association between job strain and CHD separately for the population-based and the factory-based cohorts.
Discussion			
Key results	18	Summarise key results with reference to study objectives	See the first paragraph in the Discussion section, page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Study limitations are reported and discussed at page 13.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	See study limitations, on page 13, and the final sentence in the conclusion, on page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source of funding is reported in the dedicated section of the paper (page 14).

*Give information separately for exposed and unexposed groups.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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