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Allostatic Load as a mediator of the association between psychosocial risk factors and cardiovascular diseases. Recent evidence and indications for prevention

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ABSTRACT. Aims. ***Some categories of workers are more vulnerable to the detrimental effect of job strain on cardiovascular risk. We investigate allostatic load, the physiological "wear and tear" resulting from adaptation to chronic stress, as a candidate pathway to explain such vulnerability.***
Methods. ***We selected 25-64 years old salaried workers participants to three population-based cohorts. We defined allostatic load (AL) as the sum of z-scores of 9 selected biomarkers; occupational classes (OCs) from the Erikson-Goldthorpe-Portocarero schema; and job strain (JS) according to Karasek's demand-control model. We adopted the Oaxaca-Blinder decomposition to disentangle the OC gradient in AL into the differential exposure (attributable to different JS prevalence across OCs) and the differential vulnerability (attributable to a different effect of JS on AL across OCs) components.***
Results. ***In the n=2010 workers (62% men, 34% manuals), OCs, but not JS categories, were associated with AL, independently of age and gender (p-value: 0.02). In the overall sample, JS did not have an effect on the OC gradient in AL. Conversely, in workers with sleep impairment, depression, or not engaged into physical activity, JS had a positive differential vulnerability coefficient of 0.63 (95%CI 0.05 to 1.21).***
Conclusions. ***In manual workers with impaired capacity of response, job strain is associated with a disproportional allostatic load accumulation.***

Key words: *allostatic load, job strain, vulnerability, occupational class, Oaxaca-Blinder decomposition.*

RIASSUNTO. Ruolo di mediazione del carico allostatico nelle relazioni tra condizioni psico-sociali e malattie cardiovascolari. Quali evidenze e quali indicazioni per la prevenzione. ***Obiettivi.*** **Alcune categorie di lavoratori sono maggiormente vulnerabili agli effetti negativi dello stress lavoro-correlato sul rischio cardiovascolare. Vogliamo indagare l'accumulo di carico allostatico come possibile meccanismo d'azione.**
Metodi. **Lo studio comprende lavoratori salariati di età 25-64 anni reclutati in 3 coorti di popolazione. Abbiamo definito il carico allostatico (CA) come somma di z-score di 9 biomarcatori; le classi occupazionali (CO) secondo lo schema Erikson-Goldthorpe-Portocarero; ed il job strain (JS) con modello di Karasek. Tramite decomposizione di Oaxaca-Blinder, il gradiente occupazionale in CA è stato decomposto nella somma di due componenti:** ***differential exposure*** **(dovuta a diversa prevalenza di JS nelle CO) e** ***differential vulnerability*** **(diverso effetto di JS sul CA nelle diverse classi).**
Risultati. **Tra i 2010 lavoratori (62% uomini, 34% manuali), le classi occupazionali, ma non le categorie di JS, risultano**

Introduction

In the working population, perceived work stress is a well-known and independent risk factor for cardiovascular (CV) diseases, with an estimated increased risk between 32% and 45% as compared to a reference "no-stress" category (1). Recent literature allows identifying specific subgroups of workers in which job strain plays an even stronger role as CV risk factor. This is the case for routine non-manual and manual workers (2); for sedentary workers who are not engaged into any sport physical activity (3); and for hypertensive workers with impaired sleep (4). Once identified, these "frail" or "vulnerable" workers should constitute the preferred target for interventions at the workplace designed to reduce cardiovascular risk in the working as well as in the general population (5).

Two underlying mechanisms of action have been advocated to explain the association between work stress and CV disease. The first one is an indirect effect thought lifestyles and behavioral risk factors; and the second is a direct effect on the neuroendocrine stress pathway (6). The latter accounts for about two thirds of the total effect (7), and it involves the physiological response of the body to the external stressors and its ability to adapt to the surrounding environment. To this extent, the term "allostatic load" indicates the physiological "wear and tear" resulting from adaptation to chronic stressors (8). In the general population as well in the workforce, allostatic load has been conceptualized as a mediator of the pathway linking socio-economic status and psychosocial risk factors, including work stress, with chronic and CV diseases (6,9). As an exemplification, in the context of a multi-national collaborative study of prospective cohorts, our research group is investigating the complex interplay between education, allostatic load, and CV risk. In a two-step analyses plan, we will first estimate the educational class gradient in allostatic load and its major determinants; and then investigate the role of allostatic load as a mediator of the well-established educational gradient in cardiovascular disease incidence (10).

However, despite the clear conceptual framework, so far only a few studies have actually investigated the association between work stress and allostatic load in the

associate con il CA, indipendentemente da età e sesso (p-value: 0.02). Nel campione complessivo, JS non ha alcun effetto sul gradiente occupazionale nel CA. Tuttavia, nel sotto-gruppo di lavoratori con disturbi del sonno, disturbi depressivi e che non praticano attività fisica, la componente di *differential vulnerability* legata al JS è positiva (0.63; CI95%: 0.05-1.21).
***Conclusioni*. I lavoratori manuali con ridotta capacità di risposta sono più vulnerabili ad accumulo di carico allostatico legato a job strain.**

Parole chiave: carico allostatico, stress lavoro-correlato, fragilità, classi occupazionali, decomposizione di Oaxaca-Blinder.

working population, with heterogeneous study settings and inconsistent findings (see Table I). In addition, the evidence reported above (2-4) suggest that specific subgroups of workers may be more vulnerable to the effect of work stress on allostatic load; i.e. as compared to other workers, they may fail to adapt in presence of the same amount of external stress conditions. According to this hypothesis, the difference in allostatic load between two groups of workers is the resultant of two distinct mechanisms, namely: *differential exposure,* due to a different work stress distribution; and *differential vulnerability,* due to an increased susceptibility to work stress and to a lower capacity of response (11). To this extent, the Oaxaca-Blinder decomposition has been recently applied to the epidemiology field as a method to estimate the two components (12).

In the current analysis, we aimed at estimating the gradient in allostatic load between manual and non-manual workers, in a sample of salaried employees aged 25-64 years old at recruitment in population-based cohorts conducted in the Brianza area (Northern Italy). Furthermore, we assessed the contribution to the occupational class gradient in allostatic load of job strain in terms of *differential exposure* and *differential vulnerability*, estimated with the Oaxaca-Blinder method. Finally, we hypothesized that the differential vulnerability effect of job strain was larger among workers with impaired capacity of response, as represented by the presence of moderate or critical depression symptoms, sleep impairment, and no sport physical activity.

Materials and methods

The study sample comprises three large population-based cohorts with baseline visit between 1989 and 1994 as part of the MONICA-Brianza and the PAMELA Study (2,3). From the original cohorts, we selected individuals aged 25 to 64 years old and employed as salaried workers at baseline (n=2476). At baseline, participants underwent a full physical examination, and a fasting blood sample was drawn. The Allostatic Load score was computed as the sum of z-scores for 9 different markers from the metabolic (blood glucose, total and HDL-Cholesterol, triglycerides and body mass index), the cardiovascular (systolic and diastolic blood pressure), the inflammatory (white blood cell count) and the organ damage (estimated Glomerular Filtration Rate (13)) systems, according to standard literature in the field (14). Furthermore, as extensively reported in previous papers (2,3,15), study participants fulfilled the following validated and standardized questionnaires: the Job Content Questionnaire for perceived job strain; the Baecke Questionnaire for physical activity at work and during sport; the Jenkins Questionnaire for sleep disturbances and duration over the past month; and the Maastricht questionnaire for vital exhaustion. Anamnestic information on diabetes and cardiovascular disease was also recorded from questionnaire, together with lifestyles (alcohol intake and smoking habits), marital status and the number of children. The combination of the latter two defined family responsibility as single/ever married with no children *vs*. ever married with children. Finally, we defined three occupational classes (OCs) from the original Erikson-Goldthorpe-Portocarero classification as managers; routine non-manuals; and

Table I. ***Summary of studies investigating the association between perceived work stress and allostatic load***

#	First Author	Full reference	Country	Study design	Setting	Sample size	Age range	Gender	Work stress	Number of AL markers	Summary of findings
1	Mauss D	Stress 2015;18(4);475-83	GER	Cross-sectional	Industrial workers	3797	15-64	M, W	ERI model	15	High ERI associated with increased AL mean score
2	Juster R	Stress 2013;16(6):616-29	CAN	Cross-sectional	Healthy volunteers	199	20-64	M, W	JCQ model	15	No association in men. Negative association between Job Demand al AL in women
3	Westerlund, H.	PLoS One, 7(4), e35967	SWE	Cross-sectional	Population-based cohort	673	43	M, W	JCQ model	12	JS associated with increased AL only among participants with adversity in adolescence. JS associated with lower AL in men
4	Cuitún Coronado, J.	Int J Environ Res Public Health 2018 Jan 24;15(2)	UK	Longitudinal	Population-based cohort	1020	50+	M, W	ERI model	15	Higher ERI associated with higher AL. Employees had higher AL when they had recently been exposed to ERI

Abbreviations: AL = Allostatic Load; JCQ = Job Content Questionnaire; ERI = Effort Reward Imbalance; GER = Germany; CAN = Canada; SWE = Sweden; UK = United Kingdom; M = Men; W = Women manual workers (including skilled and unskilled). From the selected n=2476 men and women, we excluded individuals with missing data on allostatic load (n=100), psychosocial variables and physical activity scores (n=356) or on lifestyles (n=10), leaving a final sample for the analyses of 2010 workers (1242 men). We estimated the age and gender-adjusted association between occupational class, job strain categories, and occupational physical activity classes (low, intermediate, and high) with allostatic load using linear regression models. The same approach was repeated on the four allostatic load components mentioned above. To estimate the *differential exposure* and the *differential vulnerability* components in the occupational class gradient in allostatic load, we adopted the Oaxaca-Blinder decomposition method (12), including age, gender, job strain, family responsibility, current cigarette smoking, alcohol intake, and sport physical activity. Briefly, the *differential exposure* is the amount of occupational class gradient in allostatic load that is attributable to a different distribution of the considered factors across OCs. The *differential vulnerability* is the amount of occupational gradient in allostatic load that is attributable to a different effect of the considered factors on the allostatic load across the OCs (12). The decomposition was applied in the overall sample, as well as in sub-groups of workers with impaired capacity of response, defined as: no sport physical activity (n=1350); moderate or critical depression symptoms (Maastricht questionnaire score≥5; n=795); sleep disturbances (either Jenkins Questionnaire Score≥10 or sleep duration≤6 hours or ≥9 hours/night; n=638); presence of the three conditions at the same time (n=283). The statistical analyses were performed with the SAS software release 9.4, while the Oaxaca-Blinder decomposition was estimated using the oaxaca command in STATA (16).

Results

The study sample was characterized by a mean age of 40.2±9.4 years old; 20% were managers, 46% routine non-manuals, and 34% manual workers. After adjustment for age and gender, allostatic load score was associated with occupational class (p-value=0.02), being higher in manual workers (0.312) as compared to managers (-0.166) and routine non-manuals (-0.246). Conversely, there was no association of allostatic load with physical activity at work (p-value = 0.59) nor with job strain (p-value = 0.16). However, a sub-score analyses revealed that high demand was associated with increased metabolic system score (p-value = 0.03) and a decreased organ damage score (p-value = 0.002). The Oaxaca-Blinder decomposition indicated that the occupational class gradient in allostatic load was mainly attributed to a *differential exposure* of age (0.23; 95%CI 0.11 to 0.35), family responsibility (0.12; 0.03 to 0.21) and sport physical activity (0.27; 0.10 to 0.44). We observed no *differential vulnerability* except for male gender (-0.59; -1.12 to -0.06): the negative coefficient indicates that women engaged in manual occupations accumulate more allostatic load that men in the same class. In the overall sample, job strain did not play any role in the occupational class gradient. However, in stratified analyses on workers with impaired capacity of response, it emerged a positive *differential vulnerability* coefficient for job strain. In particular, in the subsample of workers with sleep disturbances, the differential vulnerability coefficient for job strain was 0.39 (95%CI: 0.05 to 0.73), increasing to 0.63 (0.05 to 1.21) when sleep disturbances were observed together with no sport physical activity and moderate to critical depression symptoms.

Discussion and conclusions

In the current cross-sectional analysis on a large sample of salaried workers from Northern Italy, allostatic load was associated with occupational classes, but not with job strain categories. This is in agreement with inconsistent literature results for the demand-control model reported in Table 1. However, the Oaxaca-Blinder decomposition revealed that among workers with impaired capacity of response, exposure to job strain led to a disproportional allostatic load accumulation in manuals as compared to non-manual workers. This finding constitutes a plausible pathway for the interaction between job strain and occupation, physical activity and sleep disturbances on cardiovascular disease risk observed in literature (2-4), and therefore it deserves replication in other contexts. Due to their increased susceptibility to job strain, occupational health interventions should specifically target manual workers in a frailty condition. Our findings suggest that within the allostatic load approach, a few risk factors that may be collected in total worker health programs can help identifying more vulnerable subgroups of employees and to apply strategies to protect them from job strain and other work-related and behavioral risk factors.

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