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# Job strain and COPD exacerbations: an individual-participant meta-analysis

*To the Editor:*

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and disability worldwide [1]. The clinical course of COPD is characterised by exacerbations, which can be minor and manageable at home or in primary care, or severe, leading to hospitalisation or even death. Known causes of exacerbations include tobacco smoke, air pollution, dusts and fumes, and respiratory infections [1, 2]. One less well understood risk factor is stress, which could plausibly lead to COPD exacerbations as it can trigger inflammation [3, 4] and is associated with increased smoking [5], which are both implicated in COPD pathology [2]. Work is an important source of stress in the age groups in which COPD is typically diagnosed [1, 6]. However, we are not aware of previous investigations of work-related stress and the risk of COPD exacerbations.

In this study, we examined the associations between job strain (the most widely studied conceptualisation of work-related stress) and severe COPD exacerbations using individual-level data from 10 prospective cohort studies from the Individual Participant Data Meta-analysis in Working Populations (IPD-Work) Consortium [7]. Job strain is defined as a combination of high demands (excessive amounts of work) and low control (having little influence on what tasks to do and how to carry them out) at work.

We ascertained job strain from the participants' responses to questions on demands and control aspects of their work at study baseline. The responses were scored and for each participant, and mean scores were calculated for job-demand items and job-control items. Based on these, participants' job demands and job control were defined as high or low. A combination of high demands (a job demand score above the study-specific median) and low control (job control score below the study-specific median) was defined as high

strain and all other combinations as no strain. Job strain was validated and harmonised across the studies [7] and modelled as a binary exposure (high strain *versus* no strain).

Severe COPD exacerbations were ascertained from national hospitalisation and death registers and defined as International Classification of Diseases version 9 codes 491, 492 and 496, or version 10 codes J41, J42, J43 and J44. Our analyses were adjusted for harmonised age, sex, socioeconomic position, body mass index (BMI), tobacco smoking and alcohol intake.

We modelled the study-specific associations between job strain and COPD exacerbations using Cox regression. The Schoenfeld test suggested the proportional hazards assumption to be valid. Study-specific estimates were pooled in random effects meta-analyses and heterogeneity among these quantified using the  $I^2$ -statistic. All statistical analyses were conducted using Stata 11 (Stata Corporation Ltd, College Station, TX, USA), apart from study-specific analyses in the Danish studies, which were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Our analyses were based on 92 428 males and females (median age at baseline: 42 years), of whom 451 experienced a COPD exacerbation leading to hospitalisation (n=431) or death (n=20) during the follow-up (table 1). The median length of follow-up was 10 years, ranging from 2 to 23 years, and the mean  $\pm$  SD age at first severe COPD exacerbation was 60  $\pm$  9 years. Participants with job strain at baseline had a 32% higher risk of a severe COPD exacerbation (hazard ratio (HR) 1.32, 95% CI 1.04–1.68) than those with no strain in the age and sex-adjusted analyses (table 1). However, with additional adjustment for BMI, alcohol intake, smoking and socioeconomic position, this association attenuated to the null (HR 1.10, 95% CI 0.86–1.41).

When we stratified our analyses by baseline smoking status, there was no robust evidence for an association between job strain and the risk of COPD exacerbations among baseline smokers or baseline never-smokers after adjustment for potential confounders. Among baseline ex-smokers, job strain (compared with no strain) was associated with a 2.11-fold risk of a severe exacerbation (95% CI 1.03–4.31), independently of age, sex, socioeconomic position, BMI and alcohol intake (24 539 ex-smokers, including 63 cases of severe COPD exacerbation, 15 among participants with and 48 among those without job strain). All findings were similar in the analyses with the job strain model quadrants (passive job, active job and high strain compared with low strain) as the exposure as well as in sensitivity analyses with all asthma cases excluded.

In our meta-analyses, job strain was not associated with the risk of severe COPD exacerbations, independently of age, sex, socioeconomic position, BMI, smoking and alcohol intake. We found no association between job strain and severe COPD exacerbations among baseline never-smokers or baseline smokers but, among baseline ex-smokers, job strain was associated with an approximately two-fold increased risk of a severe exacerbation. The last finding should be interpreted as hypothesis generating, as it was based on small numbers and could be a chance finding. Baseline ex-smokers with COPD may have a more advanced disease than the COPD cases in the other smoking categories and our findings may also reflect the high risk of exacerbation at advanced stages of COPD (with the disease process causing both stress and exacerbations).

An important strength of our meta-analysis was that we used a large set of prospectively collected individual-level data. Of the 10 studies, five were population-based and another five were workplace-based but included participants from across the socioeconomic range (table 1). Thus, our findings are likely generalisable to the northern European workforce. We used a validated and harmonised exposure, job strain [7], and register-based COPD outcomes, which have good coverage and which are generally not prone to recall or other biases [8–10]. In addition to in-patient data, the hospitalisation registers covered outpatient appointments onwards from the mid-1990s in the Finnish and Danish studies [11] and from 2003 in the UK study [12].

It is a limitation of our study that a single baseline measurement of job strain may have been too imprecise an indicator of the exposure, which may have diluted our association estimates. Further research with repeated measurements of job strain over time would clarify this issue. Another limitation is that we had no data on disease severity or lung function at baseline. Other unmeasured confounders that might have influenced our estimates and should be controlled for in future studies include occupational exposures, concurrent illnesses, social support and physical activity. Finally, as our outcomes were severe COPD exacerbations, our findings are not necessarily generalisable to mild exacerbations.

We adjusted our analyses for smoking and alcohol intake but these could plausibly be on the causal pathway between job strain and COPD exacerbations. However, previous analyses of the IPD-Work Consortium data provided no conclusive evidence for longitudinal associations of job strain with smoking or alcohol intake, though job strain was associated with increasing smoking intensity. Further research would help to

TABLE 1 Participant characteristics and associations between job strain (compared with no strain) and the risk of severe chronic obstructive pulmonary disease (COPD) exacerbations

Study	Country	Baseline year	Participants with complete data <sup>#,†</sup>	Job strain at baseline	Females	Age at baseline years mean ± SD	Smokers at baseline	COPD exacerbations/ (hospitalisations/deaths)	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted <sup>‡</sup> HR (95% CI)
<b>COPSOQ-I</b>	Denmark	1997	1724	354 (20.5)	834 (48.4)	40.9 ± 10.6	634 (36.8)	24 (22/2)	0.55 (0.16–1.85)	0.53 (0.16–1.79)
<b>DWECS</b>	Denmark	2000	5410	1201 (22.2)	2514 (46.5)	41.9 ± 10.9	2000 (37.0)	47 (47/0)	1.94 (1.06–3.55)	1.76 (0.93–3.32)
<b>FPS</b>	Finland	2000	44064	7070 (16.0)	35537 (80.7)	44.5 ± 9.5	7874 (17.9)	90 (85/5)	1.39 (0.83–2.34)	1.03 (0.61–1.76)
<b>HeSSup</b>	Finland	1998	15016	2647 (17.6)	8469 (56.4)	39.6 ± 10.3	3936 (26.2)	10 (9/1)	2.03 (0.52–7.95)	1.43 (0.36–5.65)
<b>IPAW</b>	Denmark	1996–1997	1916	329 (17.2)	1272 (66.4)	41.2 ± 10.5	900 (47.0)	47 (46/1)	1.00 (0.47–2.14)	0.74 (0.34–1.62)
<b>PUMA</b>	Denmark	1999–2000	1730	260 (15.0)	1419 (82.0)	42.6 ± 10.2	679 (39.2)	16 (16/0)	0.81 (0.18–3.55)	0.75 (0.15–3.77)
<b>Still Working</b>	Finland	1986	8991	1399 (15.6)	2053 (22.8)	40.9 ± 9.1	2968 (33.0)	112 (107/5)	1.27 (0.78–2.09)	1.12 (0.68–1.85)
<b>Whitehall II</b>	UK	1997–1999	3500	329 (9.4)	905 (25.9)	41.7 ± 4.9	370 (10.6)	20 (18/2)	2.20 (0.64–7.58)	1.08 (0.28–4.11)
<b>WOLF Norrland</b>	Sweden	1996–1998	4580	582 (12.7)	752 (16.4)	44.0 ± 10.2	860 (18.8)	21 (20/1)	0.81 (0.19–3.52)	0.86 (0.19–3.88)
<b>WOLF Stockholm</b>	Sweden	1992–1995	5497	880 (16.0)	2376 (43.2)	41.5 ± 11.0	1378 (25.1)	64 (61/3)	1.26 (0.66–2.42)	1.21 (0.62–2.39)
<b>All</b>		<b>1986–2000</b>	<b>92428</b>	<b>15051 (16.3)</b>	<b>56131 (60.7)</b>	<b>41.9</b>	<b>21599 (23.4)</b>	<b>451 (431/20)</b>	<b>1.32 (1.04–1.68)<sup>§,¶,##</sup></b>	<b>1.10 (0.86, 1.41)<sup>§,¶,¶¶</sup></b>

Data are presented as n or n (%), unless otherwise stated. HR: hazard ratio; COPSOQ: Copenhagen Psychosocial Questionnaire; DWECS: Danish Work Environment Cohort Study; FPS: Finnish Public Sector study; HeSSup: Health and Social Support; IPAW: Intervention Project on Absence and Well-being; PUMA: Burnout, Motivation and Job Satisfaction study; WOLF: Work Lipids and Fibrinogen. <sup>#</sup>: our analyses were based on participants who were working at study baseline and had complete data on job strain, severe COPD exacerbations (hospitalisation or death) and covariates; we excluded individuals whose records could not be linked to hospitalisation or death registers, or who had missing data on job strain or potential confounders; in order to avoid previous severe exacerbations or concurrent worsening of symptoms causing individuals to report job strain individuals with a severe COPD exacerbation before the baseline (n=31) or during the first 30 days of follow-up (n=7) were also excluded. <sup>†</sup>: covariates in the multivariable-adjusted analyses of all participants were age, sex, socioeconomic position, body mass index (not available in Still Working), smoking and alcohol intake; one potentially eligible study (COPSOQ II) was excluded because in this study there were no COPD hospitalisations or deaths among the individuals exposed to job strain. <sup>‡</sup>: population-based studies: COPSOQ-I, DWECS, HeSSup and the two WOLF studies; workplace-based but included participants from across the socioeconomic range: FPS, IPAW, PUMA, Still Working and Whitehall II. <sup>§</sup>: random effects overall estimate. <sup>¶</sup>:  $I^2=0\%$ . <sup>##</sup>: p=0.7. <sup>¶¶</sup>: p=0.8.

understand the direction of these associations, for if smoking and alcohol were mediators, job strain might be associated with COPD exacerbations *via* these risk factors.

In conclusion, our meta-analyses suggest that job strain is not associated with severe COPD exacerbations, though imprecise exposure or residual confounding may have influenced our results. This investigation should therefore be considered a hypothesis-generating study to encourage further research in this area. Importantly, associations between repeated measurements of job strain and indicators of COPD severity (e.g. lung function tests) would merit further study.



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Multiple cohort studies do not support job strain being a major independent risk factor for severe COPD exacerbations <http://ow.ly/tAyq2>

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## HIV and multidrug-resistant tuberculosis: overlapping epidemics

*To the Editor:*

People infected with *Mycobacterium tuberculosis* and HIV are much more likely to develop active tuberculosis (TB) than people with *M. tuberculosis* but without HIV [1]. Patients infected with multidrug-resistant (MDR)-TB (defined as resistance to at least rifampicin and isoniazid, the two most powerful anti-TB drugs) require longer, more expensive treatment regimens than drug-susceptible TB, with poorer treatment success [2, 3]. Therefore, MDR-TB poses a major challenge to the control of TB, with an estimated global disease incidence in 2012 of ~450 000 cases (95% CI 300 000–600 000) [4]. Although HIV is a powerful risk factor for all forms of TB and institutional outbreaks of MDR-TB among people living with HIV have been reported [5], population-level data on the association between HIV infection and MDR-TB are limited.

We explored the relationship between HIV infection and MDR-TB disease using data reported by member states to the World Health Organization (WHO) within the context of the Global Project on Anti-TB Drug Resistance Surveillance. The data were aggregated numbers of cases reported from either drug resistance surveys or continuous surveillance systems. Such surveys are epidemiological studies designed to measure drug resistance among a representative sample of notified pulmonary TB patients. Continuous surveillance is based on routine drug susceptibility testing of all bacteriologically confirmed TB patients. Subnational level data that were not representative of the entire country were excluded from the analysis, except for the Russian Federation and Ukraine, which are high MDR-TB burden countries for which high quality national level data were not available. The data included in the analysis met the criteria for data quality and national representativeness provided in detail elsewhere [4, 6]. The laboratory methods used for diagnosis were endorsed by WHO.

For each country, the relationship between HIV infection and MDR-TB disease was investigated by logistic regression to calculate odds ratios and 95% confidence intervals, using Stata (version 12; StataCorp, College Station, TX, USA). For countries with data from multiple years, robust standard errors accounted for within-country time dependencies. In order to minimise bias, data for a given year were excluded if  $\leq 25\%$  of reported TB patients had a documented HIV test result. 41 countries, accounting for 25% of the estimated global MDR-TB burden in 2012, met the inclusion criteria for  $\geq 1$  year. Most were high-income countries and/or in the European Region. Only four countries were in the African region, which accounted for 75% of the global number of HIV-positive TB cases in 2012 [4]. Of these 41 countries, odds ratios could be calculated for 24 countries; the other 17 countries reported no HIV-positive MDR-TB cases (table 1). Complete HIV and MDR-TB data were available for 104 781 TB patients from 1997–2012.

For 11 of the 24 countries for which the analysis was performed, HIV-positive TB patients had a significantly higher odds ( $p < 0.05$ ) of MDR-TB disease than HIV-negative TB patients (table 1). Seven of these countries were in eastern Europe and central Asia: Estonia, Kazakhstan, Latvia, the Republic of Moldova, the Russian Federation, the Ukraine and Uzbekistan. For almost all of these 11 countries, the prevalence of MDR-TB among newly diagnosed TB cases (table 1) was higher than the estimated global average of 3.6% (95% CI 2.1–5.1%) in 2012 [4]. Although the odds ratio was highest in Kuwait, only low numbers of HIV-positive cases were reported. HIV-positive TB patients in the USA had a lower odds of MDR-TB disease than HIV-negative patients.

As data were included if  $\geq 75\%$  of reported TB patients had a documented HIV test, the possibility of bias due to missing data cannot be ruled out. Although a positive association between HIV infection and MDR-TB disease was demonstrated in less than half of the countries, a recent systematic review and meta-analysis found an odds of MDR-TB in HIV-positive patients that was 1.24 times (95% CI 1.04–1.43) higher than in