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## **Job Strain and the Risk of Severe Asthma Exacerbations: A Meta-analysis of Individual-participant Data from 100 000 European Men and Women**

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## **Abstract**

**Background** Many patients and health care professionals believe that work-related psychosocial stress, such as job strain, can make asthma worse but this is not corroborated by empirical evidence. We investigated the associations between job strain and the incidence of severe asthma exacerbations in working-age European men and women.

**Methods** We analysed individual-level data, collected between 1985 and 2010, from 102 175 working-age men and women in 11 prospective European studies. Job strain (a combination of high demands and low control at work) was self-reported at baseline. Incident severe asthma exacerbations were ascertained from national hospitalisation and death registries. Associations between job strain and asthma exacerbations were modelled using Cox regression and the study-specific findings combined using random effects meta-analyses.

**Results** During a median follow-up of 10 years, 1 109 individuals experienced a severe asthma exacerbation (430 with asthma as the primary diagnostic code). In the age and sex-adjusted analyses job strain was associated with an increased risk of severe asthma exacerbations defined using the primary diagnostic code (hazard ratio, HR: 1.27, 95% confidence interval, CI: 1.00, 1.61). This association attenuated towards the null after adjustment for potential confounders (HR: 1.22, 95% CI: 0.96, 1.55). No association was observed in the analyses with asthma defined using any diagnostic code (HR: 1.01, 95% CI: 0.86, 1.19).

**Conclusions** Our findings suggest that job strain is probably not an important risk factor for severe asthma exacerbations leading to hospitalisation or death.

## **Introduction**

Asthma, an intermittent inflammation of bronchioles and smooth muscle in the lungs, is among the most common chronic respiratory diseases (1, 2). Its prevalence in the working population varies by type of employment from 1.7% to 17% (3). Though rarely lethal (the estimated age-standardised death rate worldwide was 5.2 per 100 000 individuals in 2010), asthma is a major cause of disease burden, with the estimated years lived with disability amounting to 201 per 100 000 (4). Most patients manage their disease at home, with the help of their primary care physician. However, severe asthma exacerbations do happen, leading to hospitalisations and incurring costs to the individual and the health care system (1, 5, 6). In Western Europe, the age and sex-standardised hospital admission rates for asthma in adults vary (by country and demographics) from 19 to 76 per 100 000 (7).

Many triggers for asthma exacerbations, such as respiratory infections and allergens (e.g. dust, pollen and moulds) or airborne irritants (e.g. tobacco smoke, chemical fumes and pollution), are well known (1, 2, 6). The role of psychosocial factors in asthma exacerbations, however, is less well understood (1, 8-10). One psychosocial factor that may be implicated in asthma exacerbations is stress. Stress can make individuals prone to biological and behavioural triggers such as respiratory infections (11) and smoking (12) but the evidence for a direct link between stress and asthma exacerbations is unclear (1). Work is a common source of stress in adults and epidemiological research has shown that stress is associated with an increased risk of certain diseases (13, 14). However, a recent review identified no studies of work-related psychosocial stress and asthma exacerbations (8). To address this gap in the knowledge, we investigated the associations between job strain, an operationalisation of work-related psychosocial stress, and severe asthma exacerbations, defined as hospitalisations or deaths, in 100 000 European men and women.

## **Methods**

### *Studies*

We used individual-level data from 11 independent prospective cohort studies from Finland, Sweden, Denmark and the United Kingdom. All studies are part of the "Individual-participant-data Meta-analysis of Working Populations" (IPD-Work) Consortium. Studies included in the present analyses were Copenhagen Psychosocial Questionnaire I and II (COPSOQ-I and COPSOQ-II), Danish Work Environment Cohort Study (DWECS), Finnish Public Sector study (FPS), Health and Social Support (HeSSup), Intervention Project on Absence and Well-being (IPAW), Burnout, Motivation and Job Satisfaction study (Danish acronym PUMA), Still Working, Whitehall II and Work Lipids and Fibrinogen (WOLF) Norrland and WOLF Stockholm. Details of the IPD-Work Consortium and these studies have been published previously and are described in Appendix 1.

### *Participants*

Our analyses were based on participants worked at study baseline and had complete data on job strain, age, sex, socioeconomic position, body mass index (BMI), smoking, alcohol intake and asthma, and no history of asthma hospitalisation before the study baseline or during the first 30 days of follow-up (Table 1). We excluded individuals with missing data on job strain or covariates (in the analyses with primary asthma diagnosis as the outcome: n=8 752, 7.9%, and in the analyses with any asthma diagnosis as the outcome: n=9 214, 8.3%).

### *Job strain exposures*

Job strain was ascertained using questions from the validated Job Content and Demand-Control Questionnaires (15, 16). A detailed description of the job strain measure has been published previously (17). Briefly, participants answered questions on the psychosocial aspects of their job at study baseline. For each participant, mean response scores were calculated for job demands items and job control items. High demands were defined as a score higher than the study-specific median

score; low control was defined as a score lower than the study-specific median score. Job strain was categorised as high strain (high demands and low control), active job (high demands and high control), passive job (low demands and low control) and low strain job (low demands and high control). Binary job strain was defined as job strain (high demands and low control) versus no strain (all other categories combined).

### *Asthma exacerbations*

Severe asthma exacerbations were ascertained from national hospitalisation and death registries in all studies. Asthma was defined as the International Classification of Diseases (ICD) version 9 code 493 or version 10 codes J45 or J46. (18-20) We investigated asthma as the primary diagnostic code and asthma as any diagnostic code. The date of the asthma exacerbation was defined as the date of hospital admission or the date of death to which asthma contributed. Hospital records were available since the 1960s in WOLF studies, 1970s in FPS, Still Working and the Danish studies, and 1997 in HeSSup.

### *Potential confounders*

We adjusted our analyses for age, sex, socioeconomic position, BMI, tobacco smoking and alcohol intake. Details of the ascertainment, harmonisation and modelling of these are provided in Appendix 2. Briefly, information on sex and age was obtained from population registries or interview. Socioeconomic position was based on occupation ascertained from the employers' or other registers or participant-completed questionnaires. Smoking and alcohol intake were participant-reported. BMI (weight in kilograms divided by height in meters squared) was calculated from height and weight, which were participant-reported or measured at baseline examination.

### *Statistical analyses*

We modelled job strain as binary (strain vs. no strain) and categorical (high strain, active job and passive job vs. low strain). Asthma exacerbations (hospitalisations or deaths, with asthma as the primary diagnostic code or as any diagnostic code) were modelled as binary outcomes. We modelled the associations between job strain and asthma exacerbations in each study using Cox regression, with the participant's age as the time-scale. Each participant was followed from the date of their baseline assessment to the first asthma hospitalisation, death or the end of the registry follow-up, whichever occurred first. We ran age and sex-adjusted models and multivariable-adjusted models, which were further adjusted for socioeconomic position, BMI, smoking and alcohol intake. We checked the proportional hazards assumption using the Schoenfeld-test. The study-specific effect estimates were pooled using fixed effect and random effects meta-analyses and heterogeneity was quantified using the  $I^2$  statistic. (21) Both fixed and random effects meta-analyses are shown in the figures for comparison but results from random effects meta-analyses are reported in the text. Meta-regression was used to examine the impact of study-level characteristics. Data on pre-baseline hospitalisations were unavailable in Whitehall II but we conducted sensitivity analyses to explore the impact of this (Appendix 3). All statistical analyses were conducted using Stata 11 (Stata Corporation Ltd., College Station, Texas, US) apart from study-specific analyses in the Danish studies, which were conducted using SAS 9.2 (SAS Institute Inc., Cary, North Carolina, US).

## **Results**

The characteristics of the studies and participants are shown in Table 1 and Appendix 3, Table S1. Of the 102 207 participants, 56% were women. The proportion of participants who reported job strain at baseline varied by study, from 13% to 22%. During a median follow-up of 10 years (range: 1 to 24 years), 430 individuals had a severe asthma exacerbation as a primary diagnostic code and 1 109 individuals had a severe asthma exacerbation as any diagnostic code (Table 1).



Job strain at baseline was associated with an increased risk of severe asthma exacerbations in the age and sex-adjusted analyses with the outcome definition based on the primary diagnostic code (HR: 1.27, 95% CI: 1.00, 1.61) (Figure 1) However, with additional adjustment for socioeconomic position, BMI, smoking and alcohol intake, this association attenuated towards the null (HR: 1.22, 95% CI: 0.96, 1.55) (Figure 2). Job strain was not associated with severe asthma exacerbations defined as any diagnostic code in the age and sex-adjusted analyses (HR: 1.07, 95% CI: 0.91, 1.25) or multivariable-adjusted analyses (HR: 1.01, 95% CI: 0.86, 1.19) (Figures 1 and 2). There was little heterogeneity among the study-specific estimates.

We found no clear evidence for an association of passive job or high strain with severe asthma exacerbations (Figure 3). The findings were similar in the analyses with asthma exacerbations defined based on primary or any diagnostic code. There was some indication of active job (high demands and high control over work) being associated with a slightly increased risk of a severe asthma exacerbation (multivariable-adjusted HRs: asthma as primary diagnostic code: 1.28, 95% CI: 0.98, 1.57; asthma as any diagnostic code: 1.24, 95% CI: 1.05, 1.47) (Figure 3). The study-specific results, on which these summary estimates are based, are shown in Appendix 3 (Figures S1-S4).

As smoking is a strong confounder to any association between work-related stress and asthma exacerbations, we also fitted all the models stratified by baseline smoking. We found no clear evidence of job strain being associated with severe asthma exacerbations in baseline smokers or baseline non-smokers (Appendix 3, Table S2). Results from these and other sensitivity analyses (described in Appendix 3) suggest that our findings are robust.

## **Discussion**

### *Main findings*

In our meta-analyses of individual-level data from over 100 000 participants from four European countries, we found no clear evidence for an association between job strain (a combination of high demands and low control over work) and the risk of severe asthma exacerbations, regardless of whether asthma was ascertained from the primary diagnostic code (HR: 1.22, 95% CI: 0.96, 1.55) or any diagnostic code (HR: 1.01, 95% CI: 0.86, 1.19). These findings suggest that job strain is probably not an important risk factor of severe asthma exacerbations leading to hospitalisation or death. However, active job (high demands and high control over work), was associated with an up to 1.28-fold increase in the risk of severe asthma exacerbations. These estimates were robust to adjustment for age, sex, socioeconomic position, smoking, alcohol intake and BMI, which suggests that they are not explained by unhealthy lifestyle among individuals reporting job strain

#### *Our findings in context*

Work-related psychosocial stress has been reported being associated with an increased risk of depression (14) as well as some, though not all, somatic diseases (13, 22, 23). Results of animal and *in vitro* studies suggests that the physiological stress response, characterised by inflammation and other changes in the immune system functions, may have an aetiological role in asthma (24). There is some evidence that stressful life-events increase the risk of asthma exacerbations in children (25) and adults (26). Stress is also associated with asthma triggers, such as respiratory infections (11, 27) and smoking (12). However, we found no association between job strain and severe asthma exacerbations, which could suggest that at population-level, job strain specifically or without other life-stressors does not make asthma worse.

In our analyses having an active job (high demands combined with high control over work) was associated with a slight increase in the risk of severe asthma exacerbations. This association was not hypothesised. However, similar findings in relation to other diseases have been reported. An active job was associated with a 38% increase in the risk of myocardial infarction or stroke (95% CI: 1.07,

1.77) in the United States Women's Health Survey (n=22 086) (28). Among 48 361 women in the Finnish Public Sector study, those with active jobs were more likely to have cerebrovascular disease than those with low strain jobs (odds ratio: 2.32, 95% CI: 1.30, 4.10) (29). High decision authority, a feature of active jobs, was associated with an increase in mortality among Finnish industrial employees (30) . Despite the similar associations between active job and other outcomes, we believe that the association between an active job and an increased risk of a severe asthma exacerbation requires cautious interpretation. This finding may relate to job strain (high demands and low control) and active job (high demands and high control) measuring different aspects of work-related stress. In the original job strain theory, job strain is proposed to be detrimental to health, whereas high control over work is proposed to buffer against the adverse health effects of high demands. However, it may be that job strain captures the stressful aspects of routine work and that active job captures stress resulting from decision authority, control and responsibility, not only over one's own but also over others' work, which are more typical to managerial-level jobs.

### *Strengths and limitations*

Our analyses were based on a large set of data from European men and women from a range of work settings and socioeconomic backgrounds, making the findings widely generalisable to working people in Northern and Western Europe. We investigated a validated measure of work-related psychosocial stress, job strain, which was harmonised across the studies, thus making it reasonable to combine the study-specific results in meta-analyses (15, 17). Also, by using an exposure that was defined and harmonised before the acquisition of outcome data, we avoided bias arising from *post-hoc* modifications of the exposure measure (17).

Our register-based outcomes are strength as well as a limitation. Asthma exacerbations ascertained from hospitalisation and death registers were based on clinical diagnoses. The specificity of the asthma diagnoses in the Danish hospitalisation register is 98% (31). The specificity and positive

predictive values for the majority of diseases are also reasonable in the Finnish (95%) and Swedish (85-95%) hospitalisation registers (32, 33). Prospectively collected, register-based outcome data cannot have been influenced by recall bias from the participants or the diagnosing physicians. However, as our analyses focused on severe asthma exacerbations, the findings cannot be extrapolated to associations between job strain and mild asthma exacerbations, which the patients can manage at home or in primary care. Also, the number of incident asthma exacerbations in the analyses using primary diagnostic codes to define asthma outcomes was smaller (n=430) than in the analyses using any diagnostic code for asthma in the outcome definition (n=1 109), which limited the statistical power in the first set of analyses.

Similarly, our study design has strengths as well as limitations. On one hand, our individual-participant meta-analyses of unpublished data were not prone to publication, reporting or citation biases, but on the other, our data were obtained from a collaborative research project and thus not based on a search of all potentially existing unpublished data. Another limitation is that we had no harmonised data on changes in job strain, occupation or working environments, exposure to air pollution, or the asthmatics' control of their disease, and were thus unable to investigate whether these influenced our findings. Finally, though we adjusted our analyses for a number of potential confounders, it is possible that residual confounding from other unknown or unmeasured confounders has influenced our estimates, or that they occurred due to chance.

### *Clinical relevance*

Our findings would be useful to clinicians, particularly in occupational healthcare, who need evidence-based information on work-related factors that impact on the management of asthma in adults. This information would also benefit patients, who may be concerned about the impact of stressful work on asthma. The association between active jobs and an increased risk of severe asthma exacerbations, however, would merit further research and it would be premature to propose

changes to clinical practice based on this observation. Also, further studies would help to ascertain whether other aspects of work-related stress, such as low remuneration for demanding work or long working hours, might have an impact on asthma exacerbations.

### *Conclusions*

Our findings suggest that job strain is unlikely to be an important risk factor for severe asthma exacerbations. The observed association between active job and an increased risk of severe asthma exacerbations should, at this stage, be treated as a hypothesis-generating finding.

## **Author contributions**

All authors participated in designing the investigation, generating hypotheses, interpreting the data and writing and critically reviewing the paper. Some authors participated in collecting the data. Katriina Heikkila analysed the data from FPS, HeSSup, Still Working, Whitehall II and WOLF Norrland and WOLF Stockholm. Ida E.H. Madsen analysed data from COPSOQ-I, DWECS, IPAW and PUMA. Katriina Heikkila wrote the first draft of the paper with help from Mika Kivimäki.

## **Ethical approval**

Each constituent study in the IPD-Work consortium was approved by the relevant local or national ethics committees and all participants gave informed consent to take part. Details of the ethical approval are provided in Appendix 1.

## **Data access**

Katriina Heikkila and Mika Kivimäki had full access to anonymised data from FPS, HeSSup, Still Working, Whitehall II and WOLF Norrland and WOLF Stockholm. Ida E.H. Madsen had full access to anonymised data from COPSOQ-I, COPSOQ-II, DWECS, IPAW and PUMA.

**Conflict of interest:** Töres Theorell receives royalties for books written on various topics, including psychosocial factors; music and health; and Sweden's working life in the 1990s. Hugo Westerlund's institution has received a research grant from Saint-Gobain Ecophon AB, a manufacturer of sound absorbing materials, to study the effect of such materials on stress, job satisfaction and productivity in open-plan offices. Other authors declare no conflicts of interest.

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Table 1. Study characteristics

Study, country	Baseline year	Eligible participants <sup>1</sup>	N with complete data <sup>2</sup>		N (%) job strain at baseline		N severe asthma exacerbations (N hospitalisations/ N deaths)	
			Asthma as primary diagnostic code	Asthma as any diagnostic code	Asthma as primary diagnostic code	Asthma as any diagnostic code	Asthma as primary diagnostic code	Asthma as any diagnostic code
Copenhagen Psychosocial Questionnaire I (COPSOQ-I), Denmark	1997	1 853	1 716	1 707	348 (20.3)	348 (20.5)	22 (22/0)	22 (22/0)
Copenhagen Psychosocial Questionnaire II (COPSOQ-II), Denmark	2004-2005	3 818	3 293	3 280	463 (14.1)	461 (14.1)	15 (15/0)	12 (12/0)
Danish Work Environment Cohort Study (DWECS), Denmark	2000	5 606	5 428	5 375	1 196 (22.0)	1 194 (22.2)	38 (38/0)	36 (36/0)
Finnish Public Sector (FPS), Finland	2000	48 592	44 007	43 652	7 052 (16.0)	6 993 (16.0)	132 (132/0)	371 (369/2)
Health and Social Support (HeSSup), Finland	1998	17 102	15 004	15 004	2 644 (17.6)	2 644 (17.6)	46 (46/0)	47 (46/1)
Intervention Project on Absence and Well-being (IPAW), Denmark	1996-1997	2 068	1 912	1 905	330 (17.3)	330 (17.3)	38 (38/0)	37 (37/0)
Burnout, Motivation and Job Satisfaction study (Danish acronym PUMA), Denmark	1999-2000	1 914	1 723	1 716	257 (14.9)	256 (14.9)	22 (22/0)	20 (20/0)
Still Working, Finland	1986	9 282	8 916	8 911	1 390 (15.6)	1 387 (15.6)	58 (58/0)	117 (117/0)
Whitehall II, United Kingdom	1985-1988	10 308	10 175	10 175	1 421 (14.0)	1 421 (14.0)	42 (35/4)	382 (378/4)
Work Lipids and Fibrinogen (WOLF) Norrland, Sweden	1996-1998	4 718	4 561	4 556	581 (12.7)	579 (12.7)	8 (8/0)	21 (20/1)
Work Lipids and Fibrinogen (WOLF) Stockholm, Sweden	1992-1995	5 698	5 472	5 464	873 (16.0)	871 (15.9)	9 (9/0)	44 (44/0)
<b>All</b>	<b>1985 - 2005</b>	<b>110 959</b>	<b>102 207</b>	<b>101 745</b>	<b>16 555 (16.2)</b>	<b>16 484 (15.7)</b>	<b>430 (430/0)</b>	<b>1 109 (1 101/8)</b>

<sup>1</sup> Eligible participants were men and women who responded to the baseline questionnaire and were employed at study baseline.

<sup>2</sup> Participants with complete data on job strain, asthma and covariates.



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## **Captions**

Table 1. Participant characteristics

Figure 1. Age and sex-adjusted association between job strain and severe asthma exacerbations

Figure 2. Multivariable-adjusted association between job strain and severe asthma exacerbations

Figure 3. Associations between job strain model quadrants and severe asthma exacerbations

Figure 1. Age and sex-adjusted association between job strain and severe asthma exacerbations

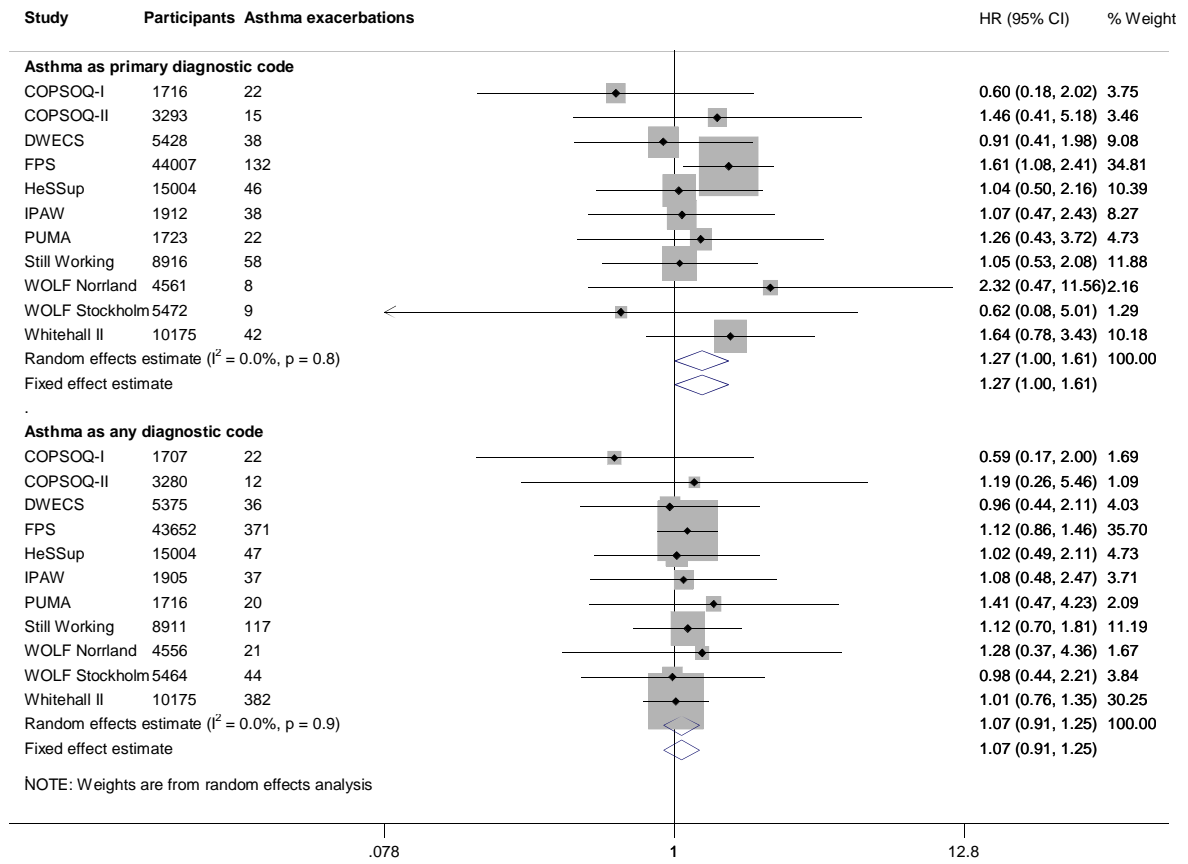
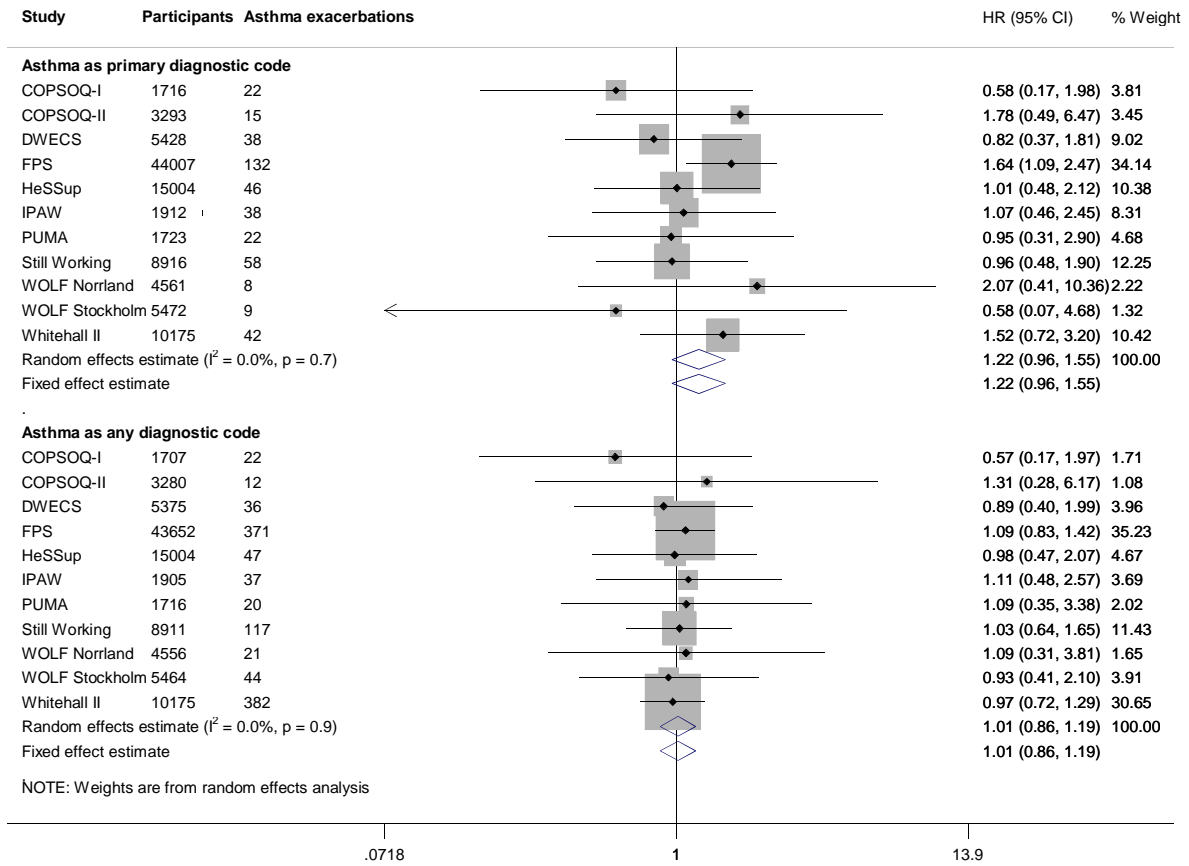
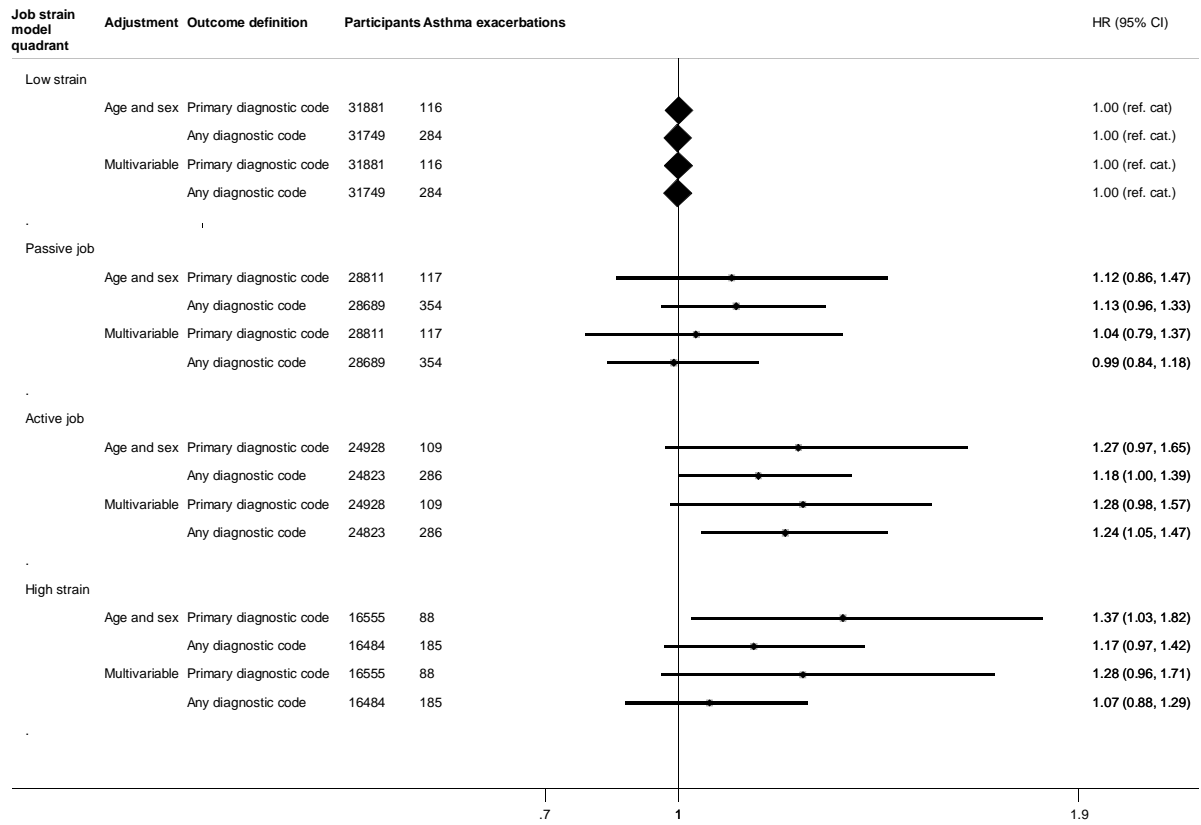


Figure 2. Multivariable-adjusted\* association between job strain and severe asthma exacerbations



\*Adjusted for age, sex, socioeconomic position, body mass index, smoking and alcohol intake

Figure 3. Associations between job strain model quadrants and severe asthma exacerbations



<sup>1</sup> Adjusted for age, socioeconomic position, body mass index, smoking and alcohol intake.

## **Appendix 1. Studies and participants**

### **Individual-participant Data Meta-analysis of Working populations (IPD-Work) Consortium**

IPD-Work Consortium is a collaborative meta-analysis project that was established at the Four Centers Initiative Meeting (a meeting of stress researchers from University College London, the Institut National de la Santé et de la Recherche in Paris, the University of Dusseldorf in Germany, and Karolinska Institutet in Stockholm) in London in 2008. IPD-Work Consortium consists of 19 prospective European cohort studies. The overarching aim of the consortium is to investigate the effect of work-related stress on chronic diseases using individual-participant data from prospective studies with a measure of work-related stress at baseline and register-based information on incident chronic diseases during follow-up.

Of the 19 studies, 11 studies were included in our meta-analyses and are described below. Six studies were excluded from the current analyses because no register data on severe asthma exacerbations were available (Belstress, GAZEL, Heinz-Nixdorf Recall study, Cooperative Health Research in the Region Augsburg (KORA) study, German Socioeconomic Panel Study (German acronym SOEP) and Netherlands Working Conditions Survey (NWCS)). Further two studies were excluded because the numbers of severe asthma exacerbations were too small to analyse (Swedish Longitudinal Occupational Survey of Health (SLOSH) and Permanent Onderzoek Leefsituatie (POLS)). It is unlikely that these reasons for exclusion would be associated with the study results or introduce bias to our meta-analyses. All studies provided individual-level data or conducted study-specific analyses according to our instructions and provided us with aggregate results. No study team refused to provide data or aggregate results.

IPD-Work Consortium used a pre-defined two-stage data acquisition protocol: in the first stage, baseline data on job strain and other indicators of work-related stress, socio-demographic factors

and lifestyle-related factors were acquired, validated and harmonised (1-7). In the second stage, these data were linked to data on disease outcomes from national hospitalisation and mortality registers (8-10). Record linkage was done using personal identification numbers in the Danish, Finnish and Swedish studies (Copenhagen Psychosocial Questionnaire I and II, Danish Work Environment Cohort Study, Finnish Public Sector study, Health and Social Support , Intervention Project on Absence and Well-being , Burnout, Motivation and Job Satisfaction study, Still Working and Work Lipids and Fibrinogen Norrland and Stockholm studies). In Whitehall II, based in the United Kingdom, the linkage was done using the participants' personal National Health Service numbers. All participants provided informed consent to record linkage.

### **Studies included in the present analyses**

#### *Copenhagen Psychosocial Questionnaire version I (COPSOQ-I)*

COPSOQ-I is a prospective cohort study of a random sample of Danish residents selected from the Danish population register. The participants were aged 20-60 years of age and were in paid employment at the study baseline in 1997. A baseline questionnaire, information about the study and its aims and an invitation to take part was posted to 4 000 people and 2 454 individuals agreed to participate, of whom 1 853 were gainfully employed (11). In Denmark, questionnaire- and register-based studies do not require approval from the Danish National Committee on Biomedical Research Ethics (Den Centrale Videnskabetiske komité). COPSOQ-I was approved by and registered with the Danish Data protection agency (registration number: 2008 - 54 - 0553). Responding to the baseline questionnaire was taken to imply informed consent to take part.

#### *Copenhagen Psychosocial Questionnaire version II (COPSOQ-II)*

COPSOQ-II was carried out in 2004-2005. It included a follow up of respondents from COPSOQ I and also a representative sample of Danish residents aged 20-60 at study baseline. The



questionnaire, with information about the study, was sent to 8 000 individuals from the random sample. The questionnaire could be completed using the posted questionnaire or via the internet (12). Of the 4 732 individuals who responded to the baseline questionnaire, 3 817 were gainfully employed and of these, 3 427 had data on job strain and were eligible for our meta-analyses. In Denmark, questionnaire- and register-based studies do not require ethics committee approval. COPSOQ-II was approved by and registered with the Danish Data protection agency (registration number: 2004-54-1493). Responding to the baseline questionnaire was taken to imply informed consent to take part.

#### *Danish Work Environment Cohort Study (DWECS)*

DWECS is a split panel survey of working age Danish people. The cohort was established in 1990, when a simple random sample of men and women, aged 18-59, was drawn from the Danish population register. The participants have been followed up at five year intervals and data from the year 2000 was used for the IPD-Work. That year 11 437 individuals were invited to participate and 8 583 agreed to do so (13, 14). Of these, 5 606 individuals were gainfully employed. In Denmark, questionnaire- and register-based studies do not require ethics committee approval. DWECS was approved by and registered with the Danish Data protection agency (registration number: 2007-54-0059). Participants were provided information about the study with the baseline questionnaire and responding was taken to imply informed consent to take part.

#### *Finnish Public Sector study (FPS)*

The Finnish Public Sector study is a prospective cohort study comprising the entire public sector personnel of 10 towns (municipalities) and 21 hospitals in the same geographical areas. Participants, recruited from employers' records in 2000-2002, were individuals who were employed in the study organisations at the time of the questionnaire survey (15). 48 592

individuals (9 337 men and 39 255 women, aged 17 to 65) responded to the questionnaire. Ethical approval was obtained from the ethics committees of the Finnish Institute of Occupational Health and Helsinki and Uusimaa Hospital District. According to the Finnish law, written consent is not required for survey and register-based research, as long as that participation is voluntary, and the participants have been informed about the aims of the study and possible register linkages (16). Thus, responding to the questionnaire voluntarily (having had access to information on the study aims and possible register linkages) was taken to imply written consent.

### *Health and Social Support (HeSSup)*

The Health and Social Support (HeSSup) study is a prospective cohort study of a stratified random sample of the Finnish population in the following four age groups: 20–24, 30–34, 40–44, and 50–54. The participants were identified from the Finnish population register and posted an invitation to participate, along with a baseline questionnaire, in 1998 (17). Of the 25 898 respondents 17 102 were gainfully employed. Turku University Central Hospital Ethics Committee approved the study. All participants gave written informed consent to take part.

### *Intervention Project on Absence and Well-being (IPAW)*

IPAW is a 5-year psychosocial work environment intervention study including 22 intervention and 30 control work places in three organisations (a large pharmaceutical company, municipal technical services and municipal nursing homes) in Copenhagen, Denmark (18, 19). The baseline questionnaire was posted to all the employees at the selected work-sites between 1996 and 1997. Of the 2 721 employees who worked at the 52 IPAW sites, 2 068 men and women completed the baseline questionnaire. IPAW was approved by and registered with the Danish Data Protection Agency (registration number: 2000-54-0066). Participants were provided information about the

study and with the baseline questionnaire and responding was taken to imply informed consent to take part.

#### *Burnout, Motivation and Job Satisfaction study (Danish acronym: PUMA)*

Burnout, Motivation and Job Satisfaction study (Danish acronym: PUMA) is an intervention study of burn-out among employees in the human service sector (20). Selection criteria for the participating organisations was that they had between 200 and 500 employees, that occupational groups within each organisation were willing to participate and that the organisations would commit to the entire five-year study period. At study baseline in 1999-2000, 1 914 employees agreed to take part. Participants gave consent to having their national identity numbers collected and used in later record linkages to Danish hospitalisation and cause of death registries (Hospitalsindlæggelsesregisteret, Dødsårsagsregisteret. PUMA was approved by the Scientific Ethical Committees (Videnskabsetisk Komiteer) in the counties in which the study was conducted and approved by and registered with the Danish Data Protection Agency (registration number: 2000-54-0048).

#### *Still Working*

Still Working is an ongoing prospective cohort study. At study baseline in 1986, the employees (n = 12 173) at all Finnish centres of operation of Enso Gutzeit (a forestry products manufacturer) were invited to participate in a questionnaire survey on demographic, psychosocial and health-related factors and 9 282 individuals participated. The study was approved by the ethics committee of the Finnish Institute of Occupational Health (21, 22). Responding to the questionnaire voluntarily was taken to imply written consent.

#### *Whitehall II*

The Whitehall II study is a prospective cohort study set up to investigate socioeconomic determinants of health. At study baseline in 1985-1988, 10 308 civil service employees (6 895 men and 3 413 women) aged 35-55 and working in 20 civil service departments in London were invited to participate in the study (23, 24). The Whitehall II study protocol was approved by the University College London Medical School committee on the ethics of human research. Written informed consent was obtained at each data collection wave.

*WOLF (Work, Lipids, and Fibrinogen) Norrland and Stockholm studies*

The WOLF (Work, Lipids, and Fibrinogen) Norrland is a prospective cohort of 4 718 participants aged 19-65 working in companies in Jämtland and Västernorrland counties (25). WOLF Stockholm study is a prospective cohort study of 5 698 people (3 239 men and 2 459 women) aged 19-70 and working in companies in Stockholm county (26). At study baseline the participants underwent a clinical examination and completed a set of health questionnaires. For WOLF Stockholm, the baseline assessment was undertaken at 20 occupational health units between November 1992 and June 1995 and for WOLF Norrland at 13 occupational health service units in 1996-98. The Regional Research Ethics Board in Stockholm, and the ethics committee at Karolinska Institutet, Stockholm, Sweden approved the study. The participants received written and verbal information about the study and participation was voluntary. Answering the baseline questionnaire was taken to imply informed consent to participate.

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## **Appendix 2. Potential confounders**

We adjusted our analyses for age, sex, socioeconomic position, body mass index (BMI), tobacco smoking and alcohol intake. Information on sex and age was obtained from population registries or interview (COPSOQ-I, COPSOQ-II, DWECS, FPS, IPAW, PUMA, Still Working, WOLF Norrland and WOLF Stockholm) or from participant-completed questionnaires (in HeSSup and Whitehall II). Socioeconomic position was based on occupation, which was ascertained from the employers' or other registers (in COPSOQ-I, COPSOQ-II, DWECS, FPS, IPAW, PUMA and Still Working) or participant-completed questionnaires (in HeSSup Whitehall II, WOLF Norrland and WOLF Stockholm). In HeSSup, socioeconomic position was based on the highest educational qualification reported by each participant. We harmonised socioeconomic position into low (routine and manual occupations or comprehensive education), intermediate (non-manual intermediate occupations or vocational education), high (higher managerial, administrative and professional occupations or university-level education) and other (for those with missing data on job title) (1).

Smoking and alcohol intake were participant-reported in all studies. Smoking was harmonised into never, ex- and current (2). Alcohol intake was ascertained from questions on the total number of alcoholic drinks (defined as one unit, one glass or 10g of ethanol) the participants consumed in a week. Alcohol intake was harmonised into none, moderate (women: 1-14 drinks/week, men: 1-21 drinks/week), intermediate (women: 15-20 drinks/week, men: 22-27 drinks/week) and heavy (women:  $\geq 21$  drinks/wk, men:  $\geq 28$  drinks/week) (3). In Still Working, we were only able to categorise alcohol intake approximately as none, moderate and heavy. Body mass index (BMI: weight in kilograms divided by height in meters squared) was calculated using data on height and weight, which were self-reported in six studies (COPSOQ-II, DWECS, FPS, HeSSup, IPAW and

PUMA) and measured in three studies (Whitehall II, WOLF Norrland and WOLF Stockholm). We harmonised BMI according to the World Health Organization recommendations into underweight ( $<18.5 \text{ kg/m}^2$ ), normal weight (18.5-24.9), overweight (25-29.9) and obese ( $\geq 30$ )(4). Participants with BMI  $<15$  or  $>50$  were excluded from the analysis. In COPSOQ-I no data were collected on BMI and alcohol intake. Similarly, no BMI data were collected in Still Working. The multivariable-adjusted analyses in these studies were adjusted for all other covariates apart from the ones that were not available.



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