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Individual and Combined Effects of Job Strain Components on Subsequent Morbidity and Mortality

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*Members of the IPD-Work consortium are listed in Supplement.

In analyses of longitudinal data from 7 to 14 cohort studies, the Individual Participant Data Meta-analysis in Working Populations (IPD-Work) consortium has demonstrated associations of job strain with increased risk of coronary heart disease (CHD),[1] ischaemic stroke,[2] type 2 diabetes[3] and depression.[4] Moreover, among men who already had cardio-metabolic disease, job strain carried a 1.6-fold increased risk of death.[5] In contrast, no association was evident with other health outcomes, such as cancer, chronic obstructive pulmonary disease, asthma, Crohn's disease or irritable bowel syndrome (**Supplement,** p. 2).

In all those analyses, job strain was defined by the combination of high occupational demands with low control,[6] and was selected for investigation because, based on psychological theory,[7,8] it was expected *a priori* to trigger harmful stress responses that might cause or promote chronic disease. Some commentators, however, have challenged this predefined approach and questioned the extent to which the observed associations with cardio-metabolic outcomes and depression reflect effects specific to job strain, or whether they might be driven by independent effects of high occupational demands or low job control.[9]

Here we address that concern by presenting further analyses of the IPD-Work datasets. We report separate risk estimates for each combination of occupational demands and control, taking the combination of 'neither high demands nor low control' as the reference. A description of the study populations and assessment of outcomes (i.e. CHD,[1] ischemic stroke,[2] type 2 diabetes,[3] depression[4] and, among men with cardio-metabolic disease, total mortality)[5] has been published previously, and is summarised in the **Supplement** (p. 1-5).

Table 1 shows the results of previous IPD-Work studies on job strain as a binary exposure (part A) and those of the present analysis on job strain components (parts B and C). For each outcome, the summary risk estimates for job strain in the current component-specific analysis (part B) were similar in direction and magnitude to those previously published for the binary job strain variable (part A). In addition, age-, sex- and socioeconomic status-adjusted hazard ratios for 'high demands with low control' (i.e. job strain) were substantially higher than those for 'high demands in the absence of low control' and 'low control in the absence of high demands' (part B).

Study-specific analyses for incident CHD, ischemic stroke, type 2 diabetes and clinical depression showed that 38 (83%) of the 46 hazard ratios for job strain vs. neither high demands nor low control favoured risk factor status (part C). According to I^2-statistics, heterogeneity in the study-specific hazard ratios was 0% for all outcomes (**Supplement**, p. 5-10). Consistency of study-specific findings was poorer for 'high demands in the absence of low control' (24/46 (52%), max I^2=19%) and 'low control in the absence of high demands' (30/46 (65%), max I^2=53%). Small sample size precluded study-level comparisons for mortality in men with cardio-metabolic disease.

In conclusion, findings from cohort studies from the UK, France, Belgium, Denmark, Sweden and Finland indicate that for each of CHD, ischemic stroke, type 2 diabetes, depression and (among men with cardio-metabolic disease) mortality, risks are highest in individuals with job strain, whereas any effects of high occupational demands in the absence of low control, and of low job control in the absence of high demands, were weaker. Job strain defined as the combination of high job demands and low control is consistent with more general definitions of psychological stress which suggest that stress occurs when demands from external situations are perceived to be beyond coping capacities.[7] As such, our results support the psychological stress theory underpinning our *a priori* decision to examine job strain as a binary risk factor for morbidity and mortality.

[597 words]

References

1. Kivimaki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012; **380**(9852): 1491-7.
2. Fransson EI, Nyberg ST, Heikkila K, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke* 2015; **46**(2): 557-9.
3. Nyberg ST, Fransson EI, Heikkilä K, et al. Job strain as a risk factor for type 2 diabetes: A pooled analysis of 124 808 men and women. *Diabetes Care* 2014; **37**(8): 2268-75.
4. Madsen IEH, Nyberg ST, Magnusson Hanson LL, et al. Job strain as a risk factor for clinical depression: systematic review and meta-analysis with additional individual participant data. *Psychol Med* 2017; **47**(8): 1342-56.
5. Kivimaki M, Pentti J, Ferrie JE, et al. Work stress and risk of death in men and women with and without cardiometabolic disease: a multicohort study. *Lancet Diab Endocrinol* 2018; **6**(9): 705-13.
6. Karasek R. Job demands, job decision latitude, and mental strain: Implications for job redesign. *Adm Sci Q* 1979; **24**(2): 287-308.
7. Lazarus RS. Psychological stress and the coping process. New York: McGraw-Hill; 1966.
8. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**(4): 385-96.
9. Mikkelsen S, Andersen JH, Ingre M. Re: Effort-reward imbalance at work and incident coronary heart disease. *Epidemiol* 2018; **29**(4): e35.

***Table 1*. Adjusted Hazard Ratios for the Association of Binary Job Strain Variable with Morbidity and Mortality in Previous IPD-Work Studies (A) and Age-, Sex-, and Socioeconomic Status-adjusted Hazard Ratios for the Associations of Job Strain Components with These Outcomes (B, C).**

	Hazard ratio (95% confidence interval)				
	Coronary heart disease	**Ischemic stroke**	**Type 2 diabetes**	**Depression**	**Death (in men with pre-existing cardiometabolic disease)**
A. Published estimates for job strain as a binary exposure[1-5a]					
No job strain (reference)	1.00	1.00	1.00	1.00	1.00
Job strain	1.17 (1.05 – 1.31)	1.18 (1.00 – 1.39)	1.15 (1.06 – 1.25)	1.22 (1.02 – 1.47)	1.66 (1.23 – 2.25)
Published IPD-Work paper	*1*	*2*	*3*	*4*	*5*
B. Summary estimates for combined effects of job strain components					
Neither high demands nor low control (reference)	1.00	1.00	1.00	1.00	1.00
High demands in the absence of low control	1.09 (0.97 – 1.23)	1.03 (0.86 – 1.24)	0.98 (0.90 – 1.08)	1.04 (0.86 – 1.25)	0.98 (0.72 – 1.34)
Low control in the absence of high demands	1.07 (0.90 – 1.27)	1.09 (0.89 – 1.33)	0.97 (0.81 – 1.15)	1.18 (0.99 – 1.41)	1.20 (0.88 – 1.64)
High demands and low control (i.e. job strain)	1.21 (1.05 – 1.39)	1.16 (0.94 – 1.42)	1.13 (1.02 – 1.25)	1.29 (1.06 – 1.56)	1.69 (1.19 – 2.42)
N (cases)	*1965*	*909*	*3703*	*982*	*307*
N (total)	*126,078*	*111,681*	*124,808*	*120,221*	*1975*
C. Study-specific estimates[b]	**Number of studies**				
High demands in the absence of low control					
Studies favouring increased risk	*7*	*5*	*7*	*5*	-
Studies favouring reduced risk	*3*	*4*	*6*	*9*	-
Low control in the absence of high demands					
Studies favouring increased risk	*7*	*6*	*7*	*10*	-
Studies favouring reduced risk	*3*	*3*	*6*	*4*	-
High demands and low control (i.e. job strain)					
Studies favouring increased risk	*9*	*6*	*12*	*11*	-
Studies favouring reduced risk	*1*	*3*	*1*	*3*	-

[a]Published estimates are as shown in IPD-Work papers.[1-5] The estimates are adjusted for age, sex, and socioeconomic status with the exception of depression (additionally adjusted for cohabitation) and death in men (adjusted for age and study). 'No job strain' category includes combinations of 'neither high demands nor low control', 'low control in the absence of high demands' and 'high demands in the absence of low control'.

[b]Hazard ratios >1 favour increased risk and hazard ratios <1 favour reduced risk. Study-level hazard ratios were not available for mortality as the analyses were on pooled data due to small numbers.[5]

eAPPENDIX

IPD-Work consortium

Investigators of the IPD-Work consortium studies on job strain, cardiometabolic disease and depression include Ahola K, Alfredsson L, Batty GD, Bjorner JB, Borritz M, Britton A, Brunner EJ, Burr H, Casini A, Chastang JF, Clays E, De Bacquer D, de Graaf R, Deanfield J, Dragano N, Ferrie JE, Fransson EI, Geuskens GA, Goldberg M, Hamer M, Heikkilä K, Hooftman WE, Houtman IL, Joensuu M, Jokela M, Kawachi I, Kittel F, Kivimäki M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Leineweber C, Lunau T, Luukkonen R, Madsen IE, Magnusson Hanson LL, Marmot MG, Niedhammer I, Nielsen ML, Nordin M, Nyberg ST, Oksanen T, Pejtersen JH, Pentti J, Plaisier I, Rugulies R, Salo P, Shipley MJ, Siegrist J, Singh-Manoux A, Steptoe A, Strandberg T, Suominen S, Ten Have M, Theorell T, Toppinen-Tanner S, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M.

The infrastructure of the consortium was supported by the EU New OSH ERA research programme, NordForsk, the Academy of Finland, and the Finnish Work Environment Fund.

IPD-Work uses predefined exposure definitions (including that for job strain), allowing comparisons across different health outcomes.[w1,w2] In IPD-Work studies, job strain was associated with incident coronary heart disease,[w3] ischemic stroke,[w4] type 2 diabetes,[w5] clinical depression[w6] and, among men with cardiometabolic disease, mortality.[w7] Job strain was not associated with haemorrhagic stroke, cancer (overall and at specific sites), chronic obstructive pulmonary disease, asthma, Crohn's disease or irritable bowel syndrome (*eFigure 1*).[w8-w11]

Contributors

MK wrote the manuscript and all the other authors commented and edited it. DC, with STN and JP, developed the statistical approach of the study with input from other authors. STN, JP, IEHM, LLM-H and Elenor I. Fransson analysed the data. All authors approved the final version of the manuscript.

Data sharing

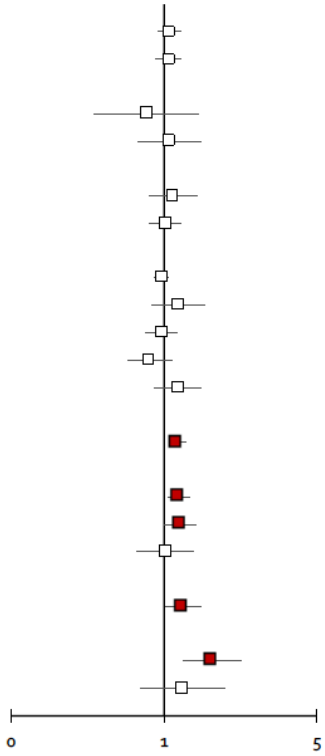
Syntax for data analysis and cohort-specific results of meta-analyses are provided in this Supplement. Our data protection agreements with the participating cohort studies do not allow IPD-Work consortium to share individual-level data from these studies to third parties.

Study population

The cohort studies available for the present analysis are listed in *eTable 1*. We included the same cohort studies as in the published paper on each outcome[w3-w7] with the exception of two cohort studies which are not anymore part of the IPD-Work collaboration (the Netherlands Working Conditions Survey with 117 CHD cases and 67 all-cause stroke and Permanent Onderzoek Leefsituatie [POLS] with 241 CHD cases and 110 all-cause strokes) and studies in which case numbers were insufficient for a 4-category variable of job strain components: Intervention Project on Absence and Well-being (IPAW) for analyses of coronary heart disease and ischemic stroke and Burnout, Motivation and Job Satisfaction study (Danish acronym: PUMA) for analysis of ischemic stroke. The participating studies comply with the Declaration of Helsinki and were approved by local ethics review boards in accordance with national laws. Informed consent was obtained from all participants.

***eFigure 1*. Association of job strain with chronic disease and death in IPD-Work studies** [w1-w4,1-5]

Disease group (population)	Disease endpoint	Hazard ratio (95% confidence interval)	N (total)
All-cause mortality (disease-free population)	Death, men	1.06 (0.94 — 1.20)	44 508
	Death, women	1.05 (0.91 — 1.20)	102 663
Diseases of the digestive system (disease-free population)	Crohn disease	0.83 (0.48 — 1.43)	95 379
	Ulcerative colitis	1.06 (0.76 — 1.48)	95 379
Diseases of the respiratory system (disease-free population)	Chronic obstructive pulmonary disease	1.10 (0.86 — 1.41)	92 428
	Asthma	1.01 (0.86 — 1.19)	102 175
Neoplasms (disease-free population)	Any cancer	0.97 (0.90 — 1.04)	116 056
	Lung cancer	1.17 (0.88 — 1.54)	116 056
	Breast cancer	0.97 (0.82 — 1.14)	57 205
	Prostate cancer	0.86 (0.68 — 1.09)	58 851
	Colorectal cancer	1.16 (0.90 — 1.48)	116 056
Endocrine, nutritional and metabolic diseases (disease-free population)	Type 2 diabetes	1.15 (1.06 — 1.25)	124 808
Diseases of the circulatory system (disease-free population)	Coronary heart disease	1.17 (1.05 — 1.31)	197 473
	Stroke, ischaemic	1.18 (1.00 — 1.39)	196 380
	Stroke, haemorrhaghic	1.01 (0.75 — 1.17)	196 380
Mental, behavioural and neurodevelopmental disorders (disease-free population)	Depressive disorder	1.22 (1.02 — 1.47)	27 461
All-cause mortality (population with cardiometabolic disease)	Death, men	1.66 (1.23 — 2.25)	1775
	Death, women	1.21 (0.78 — 1.90)	1466



***eTable* 1. Cohort studies participating in IPD-Work by health outcome.**

Cohort study	Coronary heart disease	Ischemic stroke	Type 2 diabetes	Clinical depression	Mortality (men with cardiometabolic disease)
Belstress	√				
Copenhagen Psychosocial Questionnaire version I (COPSOQ-I)	√	√	√	√	
Copenhagen Psychosocial Questionnaire version II (COPSOQ-II)			√	√	
Danish Work Environment Cohort Study 2000 (DWECS)	√	√	√	√	
Danish Work Environment Cohort Study 2005(DWECS)				√	
Finnish Public Sector study (FPS)	√	√	√	√	√
Gazel	√		√		√
Health and Social Support (HeSSup)	√	√	√	√	√
Intervention Project on Absence and Well-being (IPAW)	√	√	√	√	
Burnout, Motivation and Job Satisfaction study (Danish acronym: PUMA)		√	√	√	
Swedish Longitudinal Occupational Survey of Health (SLOSH) 2006		√	√	√	
Swedish Longitudinal Occupational Survey of Health (SLOSH) 2008		√	√	√	
Still Working	√	√	√	√	√
Whitehall II	√	√	√	√	√
WOLF-S (Work, Lipids, and Fibrinogen) Stockholm	√	√	√	√	√
WOLF-N (Work, Lipids, and Fibrinogen) Norrland	√	√	√	√	√

Measurements

The rationale and key principles of IPD-Work studies have been published.[w1] Our dichotomous measure of job strain ('job strain' vs 'no job strain') has been described and validated by Fransson *et al*.[w2] Here, scales of demands and control were dichotomised at the median in each cohort study to construct four categories: 'neither high demands not low control', 'low control in the absence of high demands', 'high demands in the absence of low control' and 'high demands and low control – ie job strain'. As in previous IPD-Work analyses,[w3-w7] socioeconomic status (high, intermediate, or low) was defined on the basis of an occupational title or, in the HeSSup study, a participant's highest educational qualification.

Participants with prevalent disease were excluded from analyses of the incidence of that disease.[w3-w6] Incident coronary heart disease was defined as the first non-fatal myocardial infarction or coronary death as ascertained from national hospitalisation and death registries.[w3] Two exceptions were Belstress in which cases of coronary heart disease were registered by the human resources department and occupational health service, and Gazel in which hospitalisation registry data were not available and nonfatal events were based on self-report in annually-distributed questionnaires.[w3]

We defined incident stroke using national hospital admission and death registries.[w4] Incident type 2 diabetes was ascertainment from hospital admissions and discharge registers and mortality registers.[w5] In FPS, HeSSup and Still Working, records in the national drug reimbursement registers as eligible for type 2 diabetes medication were additionally used.[w5] In Whitehall II, data were also collected from a 2-h oral glucose tolerance test administered every 5 years.[w5] In Gazel, diabetes was defined based on self-reports to annually-distributed questionnaires.[w5] Depression was ascertained from hospital registers for in- and out-patient treatment[4] and total mortality was ascertained from national mortality registers in all studies.[w3-w7]

Statistical analysis

We used Cox regression to examine associations of job strain and its components (high demands, low control) with disease endpoints. As in the original studies,[w3-w6] analyses of incident coronary heart disease, ischemic stroke, type 2 diabetes, and depression were computed separately in each cohort study and then cohort-specific estimates were pooled using random-effects meta-analysis (2-step approach). As in the original study on men with cardiometabolic disease,[5] analyses were done in one step using pooled individual-level data from all cohort studies and adding study as a covariate (1-step approach).

In separate models for each endpoint, we computed age, sex and socioeconomic status adjusted hazard ratios for a four-category variable ('low control in the absence of high demands', 'high demands in the absence of low control', 'high demands and low control – i.e. job strain' with 'neither high demands not low control' as the reference) and for a binary job strain variable ('job strain' versus 'no job strain'). When the outcome was depression, the models were additionally adjusted for cohabiting.

In the 2-step analysis, we used SAS for Cox models and Stata for meta-analysis with the following syntax:

Step 1: Study-specific estimates based on Cox regression:

```
proc phreg data=stroke;
class strain4(ref=first) sex ses;
model futime_stroke*isch(0)= strain4 sex age ses/rl;
run;
```

Step 2: Pooling of study-specific estimates using meta-analysis:

```
metan estimate stderr, random by(classval0) label(namevar=study) eform diamopt(lcolor(black))
boxopt(mcolor(black)) nooverall
```

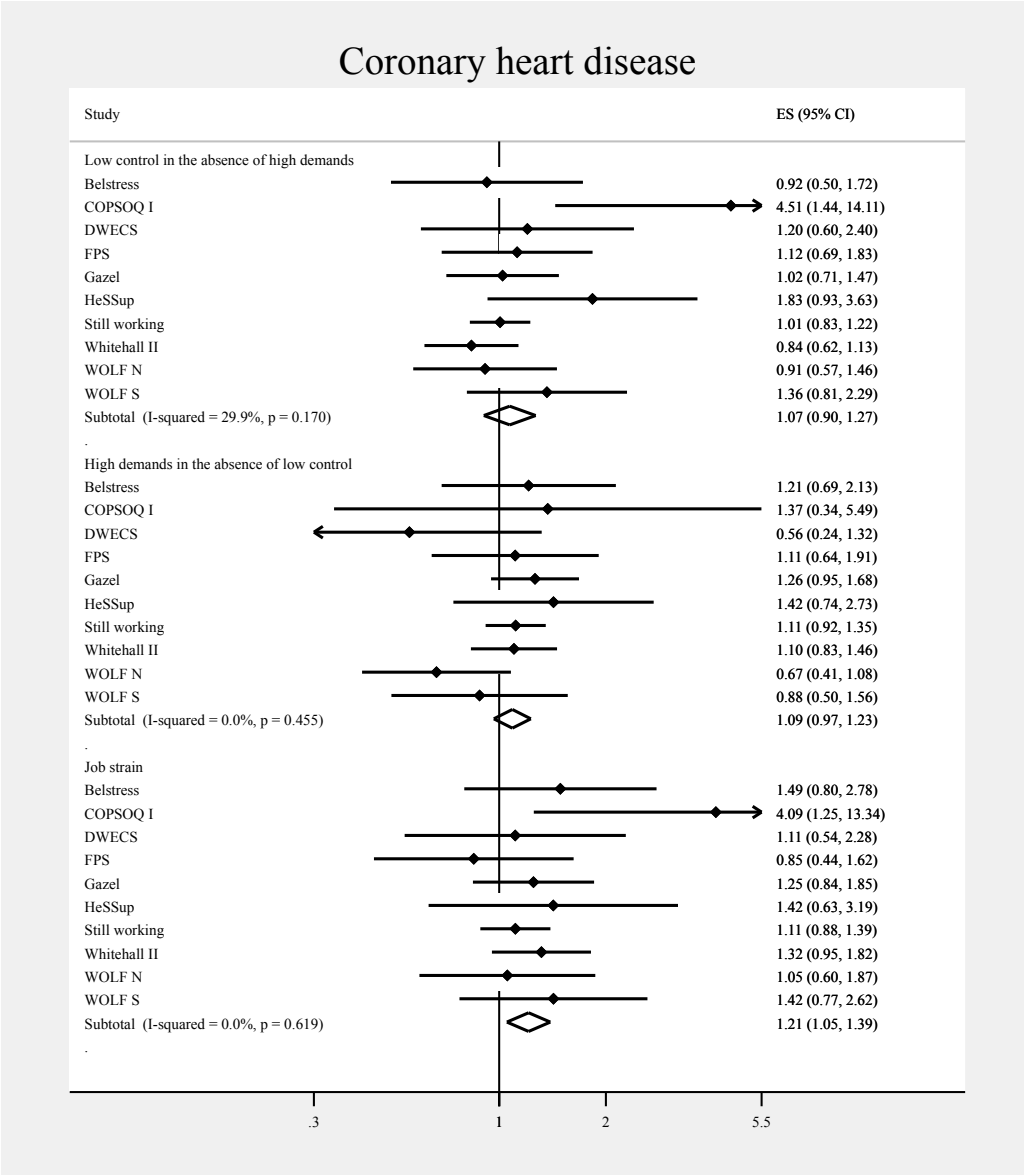
SAS-syntax for the one-step mortality analysis was as follows:

```
proc phreg data=mort;
where sex=1 and disease=1;
class strain4(ref=first) ses study;
model futime_mort*status_mort(0)= strain4 age ses study /rl;
run;
```

Cohort-specific results from meta-analyses

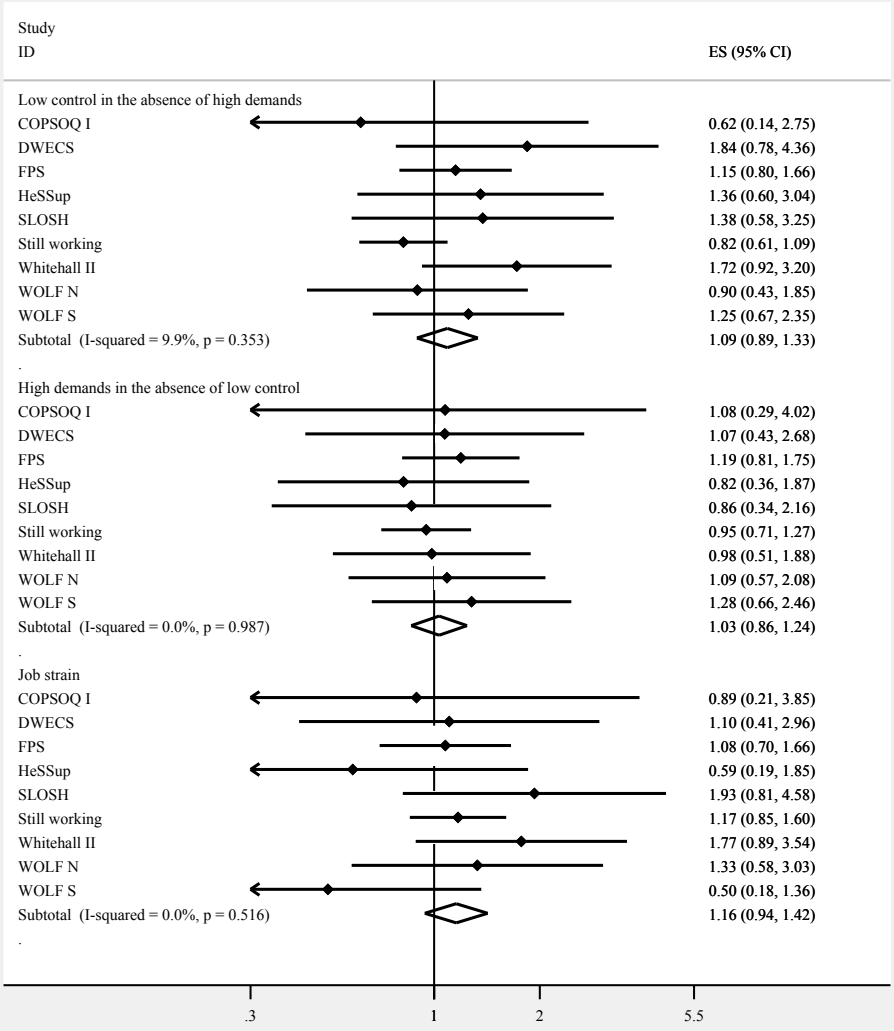
eFigures 2 to 5 show forest plots including cohort-specific results and summary estimates incident coronary heart disease, ischemic stroke, type 2 diabetes and depression. I^2 statistics suggest little heterogeneity in study-specific estimates except for 'low control in the absence of high demands' for which heterogeneity in study-specific estimates was moderate in relation to incident diabetes (I^2 = 53.4%, p = 0.012, *eFigure 4*).

***eFigure 2*. Random effect meta-analyses for age-, sex- and socioeconomic status-adjusted hazard ratios for the associations of job strain and its components with incident coronary heart disease**

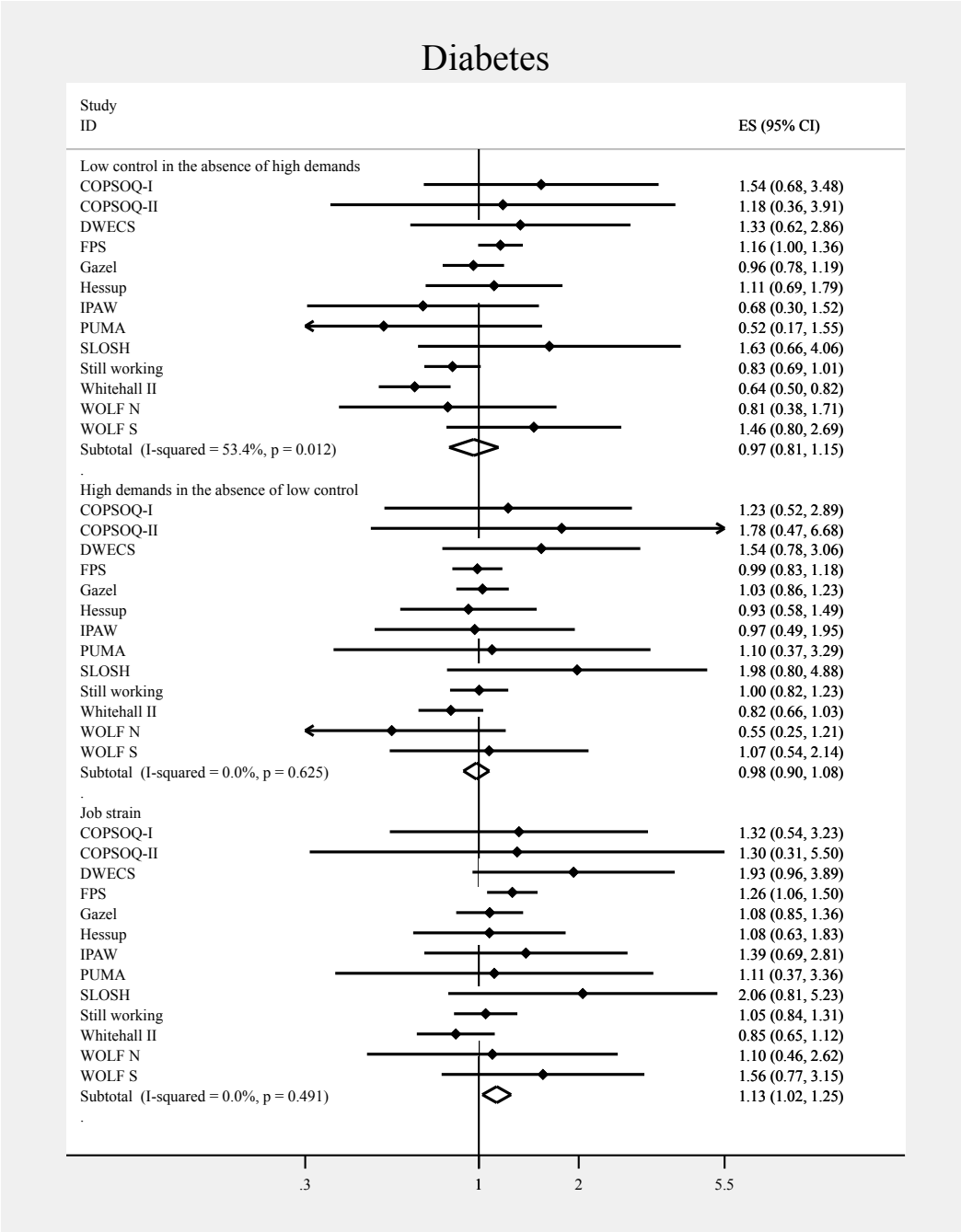


***eFigure 3*. Random effect meta-analyses for age-, sex- and socioeconomic status-adjusted hazard ratios for the associations of job strain and its components with incident ischemic stroke**

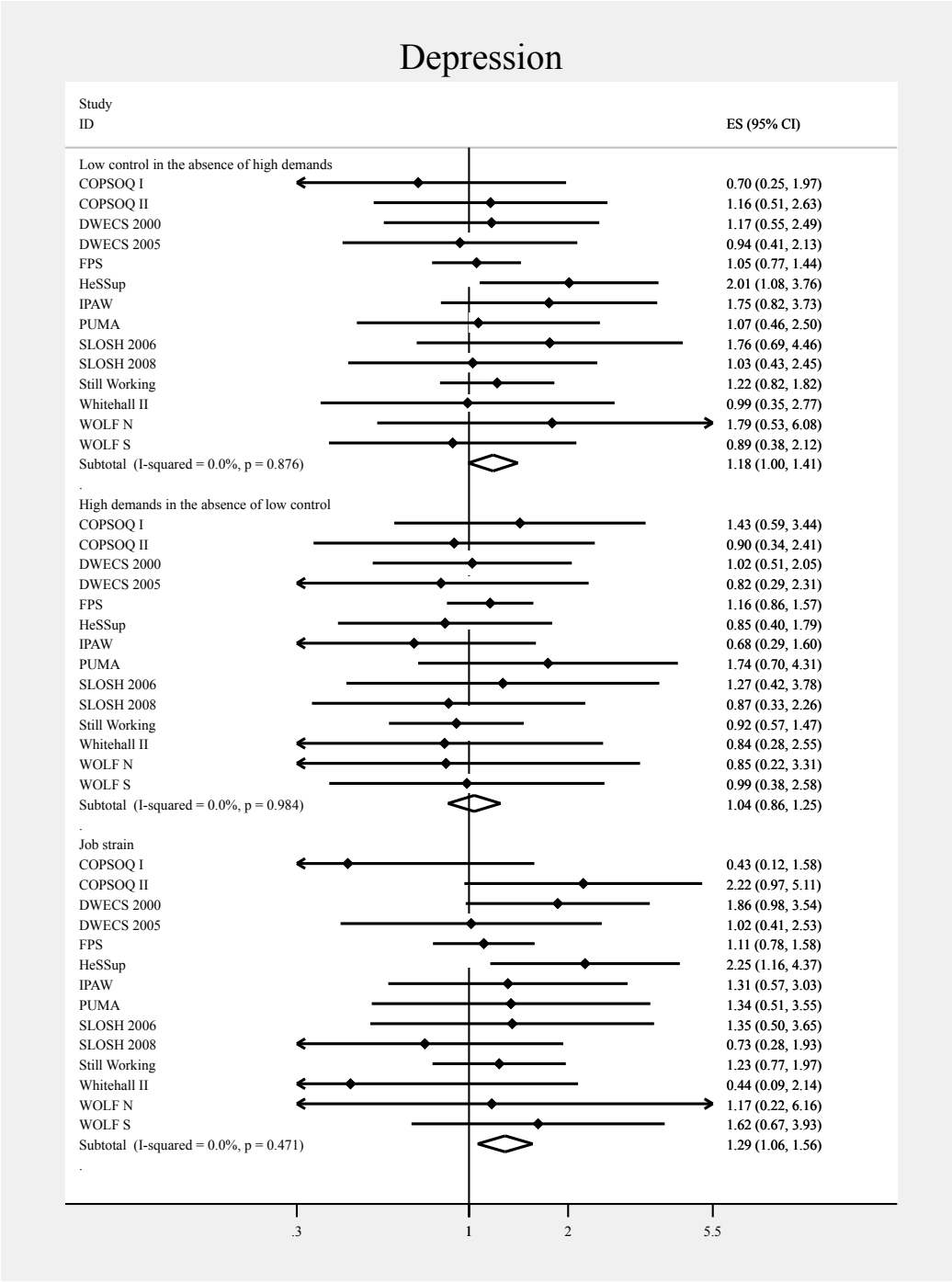
Ischemic stroke



***eFigure 4*. Random effect meta-analyses for age-, sex- and socioeconomic status-adjusted hazard ratios for the associations of job strain and its components with incident type 2 diabetes**



***eFigure 5*. Random effect meta-analyses for age-, sex- and socioeconomic status-adjusted hazard ratios for the associations of job strain and its components with incident clinical depression**



References

w1. Kivimäki M, Singh-Manoux A, Ferrie JE, Batty GD. Post hoc decision-making in observational epidemiology--is there need for better research standards? *Int J Epidemiol* 2013; 42: 367-70.
w2. Fransson EI, Nyberg ST, Heikkila K, et al. Comparison of alternative versions of the job demand-control scales in 17 European cohort studies: the IPD-Work consortium. *BMC Public Health* 2012;12:62.
w3. Kivimäki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012; 380: 1491-7.
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w8. Heikkila K, Nyberg ST, Theorell T, et al. Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116,000 European men and women. *BMJ* 2013; 346: f165.
w9. Heikkila K, Madsen IE, Nyberg ST, et al. Job strain and the risk of inflammatory bowel diseases: individual-participant meta-analysis of 95,000 men and women. *PLoS One* 2014; 9: e88711.
w10. Heikkila K, Madsen IE, Nyberg ST, et al. Job strain and COPD exacerbations: an individual-participant meta-analysis. *Eur Resp J* 2014; 44: 247-51.
w11. Heikkila K, Madsen IE, Nyberg ST, et al. Job strain and the risk of severe asthma exacerbations: a meta-analysis of individual-participant data from 100 000 European men and women. *Allergy* 2014; 69: 775-83.

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Here we ~~To~~ address ~~this~~ that concern by~~, we have~~ ~~carryingied out~~presenting further analyses of the IPD-Work datasets. We report~~to derive~~ separate risk estimates for each combination of occupational demands and control, taking the combination of 'neither high demands nor low control' as the reference. A description of the s~~S~~tudy populations and assessment of outcomes (i.e. CHD~~coronary heart disease~~,[1] ischemic stroke,[2] type 2 diabetes,[3] depression[4] and, among men with cardio-metabolic disease, total mortality)[5] ~~have~~ has been published~~described~~ previously, and is ~~also available~~summarised in~~(for details of methodology in the present study, see~~ the **Supplement**~~,~~ (p. 1-5).

Table 1 ~~summarises~~shows t~~T~~he results of previous IPD-Work studies on job strain as a binary exposure (part A) and those of the present analysis on job strain components (parts B and C)~~ are summarised in **table 1**~~. For each outcome, the summary risk estimates for job strain in the current component-specific analysis (part B) were similar in direction and magnitude to those previously published for the binary job strain ~~analysed as a binary~~ variable (part A). In addition, age-, sex- and socioeconomic status-adjusted hazard ratios for 'high demands with low control' (i.e. job strain) were substantially higher than those for

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'high demands in the absence of low control' and 'low control in the absence of high demands' (~~the effect estimate for job strain was more than multiplicative, **table 1,** ~~part B).

~~S~~Results from ~~s~~study-specific analyses ~~on~~ for incident CHD~~coronary heart disease~~, ischemic stroke, type 2 diabetes and clinical depression ~~also~~ showed that 38 (83%) of the 46 hazard ratios for job strain ~~associations~~ vs. neither high demands nor low control favoured risk factor status (~~**table 1,** ~~part C). According to I^2 ~~-~~statistics, heterogeneity in the study-specific hazard ratios was 0% for all outcomes (**Supplement**, p. 5-10). Consistency~~Reproducibility~~ of study-specific findings ~~across different cohort studies and health outcomes~~ was poorer~~lower~~ for 'high demands in the absence of low control' (24/46 (52%), max I^2=19%) and 'low control in the absence of high demands' (30/46 (65%), max I^2=53%). Small sample size precluded study-level comparisons for mortality in men with cardio-metabolic disease.

In conclusion, findings from cohort studies from the UK, France, Belgium, Denmark, Sweden and Finland indicate that for each of CHD~~coronary heart disease~~, ischemic stroke, type 2 diabetes, depression and (among men with cardio-metabolic disease) mortality, risks are highest in individuals with job strain, whereas any effects of high occupational demands in the absence of low control, and of low job control in the absence of high demands, were weaker. Job strain defined as the combination of high job demands and low control is consistent with more general definitions of psychological stress which suggest that stress occurs when demands from external situations are perceived to be beyond coping capacities.[7] As such, our~~These~~ results support the psychological stress theory underpinning our *a priori* decision to examine job strain as a binary risk factor for morbidity and mortality.

[597~~2~~ words]

References

1. Kivimaki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012; **380**(9852): 1491-7.
2. Fransson EI, Nyberg ST, Heikkila K, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke* 2015; **46**(2): 557-9.
3. Nyberg ST, Fransson EI, Heikkilä K, et al. Job strain as a risk factor for type 2 diabetes: A pooled analysis of 124 808 men and women. *Diabetes care* 2014; **37**(8): 2268-75.
4. Madsen IEH, Nyberg ST, Magnusson Hanson LL, et al. Job strain as a risk factor for clinical depression: systematic review and meta-analysis with additional individual participant data. *Psychological medicine* 2017; **47**(8): 1342-56.
5. Kivimaki M, Pentti J, Ferrie JE, et al. Work stress and risk of death in men and women with and without cardiometabolic disease: a multicohort study. *The lancet Diabetes & endocrinology* 2018; **6**(9): 705-13.
6. Karasek R. Job demands, job decision latitude, and mental strain: Implications for job redesign. Adm Sci Q 1979; **24**(2): 287-308.
7. Lazarus RS. Psychological stress and the coping process. New York: McGraw-Hill; 1966.
8. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of health and social behavior* 1983; **24**(4): 385-96.
9. Mikkelsen S, Andersen JH, Ingre M. Re: Effort-reward imbalance at work and incident coronary heart disease. *Epidemiology* 2018; **29**(4): e35.

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***Table 1*. Adjusted Hazard Ratios for the Association of Binary Job Strain Variable with Morbidity and Mortality in Previous IPD-Work Studies (AB) and Age-, Sex-, and Socioeconomic Status-adjusted Hazard Ratios for the Associations of Job Strain Components with These Outcomes (B, C).**

	Hazard ratio (95% confidence interval)				
	Coronary heart disease	**Ischemic stroke**	**Type 2 diabetes**	**Depression**	**Death (in men with pre-existing cardiometabolic disease)**
A. Published estimates for job strain as a binary exposure[1-5a]					
No job strain (reference)	1.00	1.00	1.00	1.00	1.00
Job strain	1.17 (1.05 – 1.31)	1.18 (1.00 – 1.39)	1.15 (1.06 – 1.25)	1.22 (1.02 – 1.47)	1.66 (1.23 – 2.25)
Published IPD-Work paper	*1*	*2*	*3*	*4*	*5*
B. Summary estimates for combined effects of job strain components					
Neither high demands nor low control (reference)	1.00	1.00	1.00	1.00	1.00
High demands in the absence of low control	1.09 (0.97 – 1.23)~~1.02 (0.86 – 1.18)~~	1.03 (0.86 – 1.24)	0.98 (0.90 – 1.08)	1.04 (0.86 – 1.25)	0.98 (0.72 – 1.34)
Low control in the absence of high demands	1.07 (0.90 – 1.27)~~0.98 (0.86 – 1.11)~~	1.09 (0.89 – 1.33)	0.97 (0.81 – 1.15)	1.18 (0.99 – 1.41)	1.20 (0.88 – 1.64)
High demands and low control (i.e. job strain)	1.21 (1.05 – 1.39)~~1.16 (0.99 – 1.33)~~	1.16 (0.94 – 1.42)	1.13 (1.02 – 1.25)	1.29 (1.06 – 1.56)	1.69 (1.19 – 2.42)
N (cases)	*1965*	*909*	*3703*	*982*	*307*
N (total)	*126,078*	*111,681*	*124,808*	*120,221*	*1975*
C. Study~~Cohort~~-specific estimates[+b]	**Number of studies**				
High demands in the absence of low control					
Studies favouring increased risk	*7*	*5*	*7*	*5*	-
Studies favouring reduced risk	*3*	*4*	*6*	*9*	-
Low control in the absence of high demands					
Studies favouring increased risk	*7*	*6*	*7*	*10*	-
Studies favouring reduced risk	*3*	*3*	*6*	*4*	-
High demands and low control (i.e. job strain)					
Studies favouring increased risk	*9*	*6*	*12*	*11*	-
Studies favouring reduced risk	*1*	*3*	*1*	*3*	-

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[a] Published estimates are as shown in IPD-Work papers.[1-5] The estimates are adjusted for age, sex, and socioeconomic status with the exception of depression (additionally adjusted for cohabitation) and death in men (adjusted for age and study). 'No job strain' category includes combinations of 'neither high demands nor low control', 'low control in the absence of high demands' and 'high demands in the absence of low control'.

[b] Hazard ratios >1 favour increased risk and hazard ratios <1 favour reduced risk. Study-level hazard ratios were not available for mortality as the analyses were on pooled data due to small numbers.[5]

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