Job strain as a risk factor for type 2 diabetes: a pooled analysis of 124,808 men and women.

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Job Strain as a Risk Factor for Type 2 Diabetes: A Pooled Analysis of 124 808 Men and Women

Running title: Job Strain and Incident Type 2 Diabetes

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ABSTRACT

OBJECTIVE—The status of psychosocial stress at work as a risk factor for type 2 diabetes is unclear because existing evidence is based on small studies and are subject to confounding by lifestyle factors, such as obesity and physical inactivity. This collaborative study examined whether stress at work, defined as ‘job strain’, is associated with incident type 2 diabetes independent of lifestyle factors.

RESEARCH DESIGN AND METHODS—We extracted individual-level-data for 124,808 diabetes-free adults from 13 European cohort studies participating in the IPD-Work Consortium. We measured job strain with baseline questionnaires. Incident type 2 diabetes at follow-up was ascertained using national health registers, clinical screening, and self-reports. We analyzed data for each study using Cox regression and pooled the study-specific estimates in fixed-effect meta-analyses.

RESULTS—There were 3703 cases of incident diabetes during a mean follow-up of 10.3 years. After adjustment for age, sex and socioeconomic status, the hazard ratio for job strain compared to no job strain was 1.15 (95% CI 1.06–1.25) with no difference between men and women (1.19, 95% CI 1.06-1.34 and 1.13, 95% CI 1.00-1.28, respectively). In stratified analyses, job strain was associated with an increased risk of diabetes both among those with healthy and unhealthy lifestyle habits. In a multivariable model adjusted for age, sex, socioeconomic status and lifestyle habits, the hazard ratio was 1.11 (1.00–1.23).

CONCLUSIONS—Findings from a large pan-European dataset suggest that job strain is a risk factor for type 2 diabetes in men and women independent of lifestyle factors.
Diabetes, a group of diseases of which type 2 diabetes is the most common, is a rapidly growing health problem worldwide (1,2). Type 2 diabetes is a progressive disease in which the advanced stages are characterized by micro- and macrovascular complications (e.g., retinopathy, nephropathy, and neuropathy) and atherosclerosis (3,4). It affects quality of life, and ranks ninth as a cause of global mortality (1).

Physical inactivity and obesity are the most important modifiable risk factors for type 2 diabetes (5,6). Some studies suggest that exposure to job strain, the most widely studied form of work stress (7), is also associated with an increased risk of type 2 diabetes (8-10). An association between job strain and diabetes is biologically plausible (11), because stress response increases secretion of the fight-or-flight hormone cortisol, which stimulates glucose production in the liver and antagonises the action of insulin in peripheral tissues (12-14). However, evidence of a job strain-diabetes association remains scarce and inconsistent. While some studies have shown an association (8-10), other studies have found no evidence for job strain as a risk factor for diabetes (15-17).

A further complication is that lifestyle risk factors for type 2 diabetes tend to cluster in those who also report job strain (18-22). Dissecting out the effects of job strain from those of an unhealthy lifestyle is challenging as few studies are large enough to determine the association between job strain and type 2 diabetes in analysis stratified by lifestyle factors.

To address these limitations, we pooled results from 13 cohort studies and conducted an analysis of individual-participant data on almost 125 000 men and women initially free from diabetes. The size of the data and the number of incident type 2 cases at follow-up exceed those of previous reports.
RESEARCH DESIGN AND METHODS

Studies and participants

Data are drawn from 13 independent cohort studies from Finland, France, Denmark, Sweden, and the UK. All the studies are part of the Individual-Participant-Data meta-analysis in Working populations (IPD-Work) Consortium (23). Details of the study design and participants have been published previously (eText1).

We included a total of 131 955 participants who were employed at the baseline assessment, which took place between 1986 and 2008 depending on the study. We excluded from the analyses 4080 (3%) participants with missing values for sex, age, job strain or diabetes and 3067 (2%) with a diagnosis of diabetes before or at study baseline. Thus, 124 808 participants were included in the analyses.

Each constituent study in the consortium was approved by the relevant local or national ethics committees and all participants gave informed consent (eText1).

Measurement of job strain

Job strain was measured with questions from the validated job-content questionnaire and demand control questionnaire, which were included in the baseline self-report questionnaire of all studies (24,25). We have previously published a detailed description of the job-strain measure, including its validation and harmonization, as part of the Consortium (24). Briefly, participants were asked to answer questions about psychosocial aspects of their job. For each participant, mean response scores were calculated for job-demand items (i.e., enquiries about whether the participant had to work very hard, had excessive amounts of work, conflicting demands, or insufficient time) and job-control items (i.e., enquiries about decision freedom and learning new things at work). The agreement between the harmonized scales used in this
study and the complete versions was mostly good or very good (Kappa statistic > 0.68) with a few exceptions for which agreement was moderate (Kappa between 0.54 and 0.60) (24).

We defined high job demands as having a job-demand score that was greater than the study-specific median score; similarly, we defined low job control as having a job control score that was lower than the study-specific median score. These are the original and most commonly used categorizations (26). We defined the exposure as a binary variable: job strain (high demands and low control) versus no job strain (all other combinations) according to the job-strain model (25). As an alternative conceptualization, we defined job strain quadrants: high strain job (high demands and low control), active job (high demands, high control), passive job (low demands and low control) and low strain job (low demands and high control). To minimize investigator bias, we validated the job-strain measure before extracting data on incident type 2 diabetes, with investigators masked to outcome information (24).

**Ascertainment of incident type 2 diabetes**

The outcome was the first record of type 2 diabetes, diagnosed corresponding to ICD-10 (International Classification of Diseases) code E11. We collected records from hospital admissions and discharge registers and mortality registers with a mention of diagnosis of type 2 diabetes in any of the diagnosis codes. Additionally, in the Finnish datasets (FPS, HeSSup, Still Working), participants were also defined as an incident type 2 diabetes case the first time they appeared in the nationwide drug reimbursement register as eligible for type 2 diabetes medication (27). In the Whitehall II study, type 2 diabetes was ascertained by 2-hour oral glucose tolerance test administered every five years (11) using WHO criteria, and complemented by self-reports of diabetes diagnosis and medication (28). In the Gazel study, we only had ICD-codes for mortality data so new non-fatal cases were based on self-report
from annual questionnaires. The date of incident diabetes was defined as the date of the first record during the follow-up in any of the previously mentioned sources (eTable 1).

Prevalent (existing) type 2 diabetes cases were defined using information from any of the following: hospital records (all studies except for Gazel and Whitehall II), baseline medical assessment (Whitehall II), self-report from the baseline questionnaire (COPSOQ-II, FPS, Gazel, HeSSup, IPAW, SLOSH, Whitehall II, WOLF N, WOLF S) or drug reimbursement register in Finland (FPS, HeSSup, Still Working). We excluded participants with a diagnosis of either type 1 or type 2 diabetes either before or at the study baseline (ICD-10 codes E10-E11 or ICD-9 and ICD-8 code 250) (eTable 2).

Covariates

In addition to age and sex, we used data on socio-economic status (SES), working hours, body mass index (BMI), leisure time physical activity, smoking, and alcohol consumption as covariates (that is, confounders or mediators). SES was defined based on occupational title, which was register-based (in COPSOQ-I, COPSOQ-II, DWECS, FPS, Gazel, IPAW, PUMA, and Still Working) or self-reported (in Whitehall II, SLOSH, WOLF Norrland and WOLF Stockholm). In HeSSup, SES was based on self-reported highest educational qualification. SES was categorised into low, intermediate, high and other, with participants who were self-employed or whose job title was missing included in the last category.

Working hours were divided into categories of <35, 35-40, 41-48, 49-54, 55+ hours per week with the category 35-40 as the reference. Information on working hours was not available for Still Working, Gazel and those SLOSH participants who responded to the questionnaire in 2006.

All lifestyle covariates were defined and harmonized across cohorts before linkage to outcome data. We calculated BMI using height and weight (weight in kilograms divided by
height in meters squared), which were measured (in Whitehall II, WOLF N, and WOLF S) or self-reported (in COPSOQ-II, DWECs, Gazel, FPS, HeSSup, IPAW, PUMA, and SLOSH) (21). BMI data were not available in COPSOQ-I and Still Working studies. It was categorized according to the World Health Organization recommendations into <18.5 kg/m$^2$ (underweight), 18.5-24.9 kg/m$^2$ (normal weight), 25-29.9 kg/m$^2$ (overweight), 30-34.9 kg/m$^2$ (obese, class I), 35-39.9 kg/m$^2$ (obese, class II), and ≥40 kg/m$^2$ (obese, class III) (29). Participants with BMI values <15 or >50 were excluded from the analysis including BMI.

We grouped participants into three categories according to their level of leisure-time physical activity: sedentary (physically inactive), highly active (at least 2.5 hours of moderate, or at least 1 hour 15 minutes of vigorous, physical activity per week), or moderately active (all levels in between). Information on physical activity was not available for participants in COPSOQ-I (18). Tobacco smoking was self-reported and categorized into never, ex-, and current smoking (19). We used responses to questions about the total number of alcoholic drinks consumed per week to classify participants as nondrinkers, moderate drinkers (one to 14 drinks per week for women, one to 21 drinks per week for men), high to intermediate drinkers (15-20 drinks per week for women, 22-27 drinks per week for men), and heavy drinkers (≥21 drinks per week for women, ≥28 drinks per week for men) (20). Harmonized data on alcohol consumption were not available for participants in COPSOQ-I or SLOSH.

For additional adjustment for biological risk markers (representing potential mediators), we included self-reported hypertension or use of antihypertensive medication (FPS, HeSSup, SLOSH, IPAW, COPSOQ-II), self-reported elevated lipids (HeSSup), or measured systolic blood pressure, triglycerides, and high density lipoprotein cholesterol (Whitehall II, WOLF N, WOLF S). Because shift work has been suggested to elevate the risk of type 2 diabetes (30-32), we also identified respondents who worked in shifts or during the
night. Participants who reported day time work only were classified as non-shift workers, while those reporting night time work (between 6 pm and 6 am) or any form of shift work were classified as shift workers. Participants with unclear or missing responses were excluded from this analysis. In addition, data for shift or night time working were not available for COPSOQ-I, COPSOQ-II, DWECs, Gazel, IPAW and PUMA.

**Data analyses**

Follow-up time was calculated from baseline assessment until the first record of type 2 diabetes, death or end of follow-up, whichever came first. Job strain was modeled as a binary exposure (job strain vs. no job strain – the reference) and in sensitivity analysis as a categorical variable (high strain, active, passive, low strain – the reference). All analyses were adjusted for sex, age and SES, and then further adjusted for lifestyle variables (BMI category, physical activity, smoking, and alcohol consumption). The models adjusted for age, sex, SES, and lifestyle factors were also additionally adjusted for biological risk markers. To address reverse causation, we excluded the first three years of follow-up. To minimize the possibility that shift work affected any associations, we repeated the analyses separately in participants who reported working shifts or nights and among those who did not. Participants with missing data were excluded from this analysis.

As in previous studies from the IPD-Work consortium, we also examined risk of diabetes in the four groups created by combining data on job strain and each lifestyle risk factor (33). Dichotomized lifestyle risk factors used in these analyses were current smoking (yes vs. no), heavy alcohol use (\( \geq 21 \) drinks per week for women, \( \geq 28 \) drinks per week for men vs. other), obesity (BMI\( \geq 30 \) vs. <30 kg/m\(^2\)) and physical inactivity (yes vs. no).

Within each study, the association between job strain and incident type 2 diabetes was analyzed using Cox proportional hazards regression models. The study-specific effect
estimates and their standard errors were pooled in fixed- and random effect meta-analyses, and heterogeneity in effect sizes was assessed with the $I^2$ statistic (34,35). Due to low heterogeneity the fixed and random effect estimates were virtually identical and fixed effect estimates are reported here. We additionally pooled data from the studies to construct age-, sex and SES-adjusted survival curves for incident type 2 diabetes by job strain status (individual-level data for pooling were not available from COPSOQ-I, COPSOQ-II, DWECS, IPAW, PUMA, and SLOSH).

SAS 9.2 was used for all analyses, except for the meta-analyses, which were conducted with Stata MP (version 11).

RESULTS—Of the 124 808 participants, 70 802 were women and 54 006 were men (Table 1). Mean age was 44.1 years. The study-specific prevalence of job strain varied from between 13% and 22% and was 16% in the whole population.

During the mean follow-up of 10.3 years a total of 3703 incident type 2 diabetes cases were ascertained. Job strain was associated with increased risk of type 2 diabetes onset across the entire follow-up (eFigure 1). After adjustment for age, sex and SES, the hazard ratio for job strain compared to no job strain was 1.15 (95% CI 1.06-1.25). Figure 1 shows the study-specific estimates. There was no evidence of heterogeneity between these estimates, $I^2 =$0%, $p=0.99$.

As shown in Table 2, the association between job strain and diabetes was robust. The exclusion of cases during the first three years had no discernible impact on the magnitude of the job strain-diabetes relation (age, sex and SES adjusted hazard ratio 1.15, 95% CI 1.05-1.27), suggesting that the association was not biased by reverse causality; a situation where
undiagnosed diabetes at baseline affects job strain. Similarly, the job strain-diabetes association was not dependent on the method of diabetes ascertainment which included oral glucose tolerance test (hazard ratio 1.09, 95% CI 0.86-1.37, Whitehall II), hospitalization and mortality registries (1.35, 95% CI 1.05-1.74, COPSOQ-I, COPSOQ-II, IPAW, DWECS, PUMA, SLOSH, WOLF-N, WOLF-S), drug reimbursement records in addition to hospitalization and mortality registries (1.15, 95% CI 1.03-1.29, FPS, HeSSup, Still Working), self-report and mortality registry (1.08, 95% CI 0.88-1.33, Gazel). There was no evidence of heterogeneity between these estimates, $I^2 = 0\%$, $p=0.5$.

Table 2 also shows results from analyses adjusted for lifestyle and biological factors. Job strain was independently associated with new onset of type 2 diabetes. In a model adjusted for age, sex, SES, BMI category, physical activity, smoking, and alcohol consumption, the hazard ratio for job strain compared to no job strain was 1.11 (1.00-1.23). After adjustment for age, sex, SES, lifestyle factors, and self-reported or clinically measured biological risk markers, such as hypertension or blood lipid values, the hazard ratio was 1.12 (0.99-1.26) based on data from COPSOQ-II, IPAW, FPS, HeSSup, SLOSH, Whitehall II, WOLF-N, and WOLF-S (n=88 174; 1889 incident diabetes cases). The adjusted hazard ratio based on biological data from clinical examinations in the Whitehall II, WOLF-N, and WOLF-S studies was 1.08, 95% CI 0.87-1.35 (n=16 168; 638 cases). No individual lifestyle factor explained the association between job strain and diabetes, inclusion of these factors in the model did not change estimates.

Our sensitivity analyses showed that the association between job strain and type 2 diabetes was not explained by working hours. After additional adjustment for working hours the hazard ratio was 1.15 (95% CI 1.03-1.29). Similarly, the association was not altered with using job strain as a categorical (job strain quadrants) rather than binary variable: the age, sex and SES-adjusted hazard ratio for high job strain compared with low strain was 1.13 (95% CI
1.02-1.25) while the corresponding hazard ratios for passive and active jobs were 0.96 (0.88-1.05) and 0.98 (0.90-1.08), respectively.

**Stratified analyses**

As expected, all lifestyle risk factors: obesity, physical inactivity, smoking, and heavy alcohol consumption were associated with an increased diabetes risk. The strongest associations were seen for obesity. **Figure 2** shows the risk of diabetes in categories defined by combining measures of job strain with these individual lifestyle risk factors. Job strain was associated with a similar excess risk of type 2 diabetes in both participants exposed and unexposed to lifestyle risk factors.

No difference in the association between job strain and incident type 2 diabetes was observed for men and women (age, sex, and SES adjusted hazard ratios 1.19, 95% CI 1.06-1.34 and 1.13, 95% CI 1.00-1.28, respectively). The association was also similar among employees younger than 50 (1.13, 95% CI 0.99-1.28, incident cases 1685, N=80 798, 13 studies) and those 50 years or older (1.16, 95% CI 1.04-1.31, incident cases 2018, N=44 010, 13 studies). There was very little heterogeneity in the study specific estimates ($I^2=0\%$, all p-values >0.5).

Further subgroup analyses showed that the association between job strain and type 2 diabetes was similar among shift workers (age, sex and SES adjusted hazard ratio 1.28, 95% CI 1.09-1.51; incident cases=779, N=27 955, 6 studies), those not working shifts or nights (hazard ratio 1.07, 95% CI 0.94-1.22; incident cases=1937, N=67 758, 7 studies), and in the low SES group (hazard ratio 1.33, 95% CI 1.18-1.51; incident cases=1376, N=35 038, 13 studies). No significant association was observed in the intermediate SES group (hazard ratio 1.03, 95% CI 0.90-1.18; incident cases=1515, N=55 051, 11 studies) and the association was heterogeneous in high SES groups ($I^2=60\%$, p=0.01, hazard ratio 1.37, 95% CI 0.76-2.47 in
the random-effects model and 1.09, 95% CI 0.80-1.49 in the fixed-effect model; incident cases=725, N=25 220, 8 studies).

CONCLUSIONS—In this pooled analysis of almost 125 000 European adults, job strain was associated with a 1.15-fold increased risk of incident type 2 diabetes, with no evidence of differences in the association by sex. Importantly, the excess risk of type 2 diabetes associated with job strain was similar in magnitude among participants with and without unhealthy lifestyle factors: obesity, physical inactivity, smoking, and heavy alcohol use.

Few studies have examined the association between work-related stress and type 2 diabetes (36). This is the largest prospective study of work-related stress and type 2 diabetes to date that has used job strain as a measure of work stress. Previous reports from the IPD-Work consortium have shown a robust cross-sectional association between job strain and diabetes which was independent of other cardiometabolic risk factors (37).

In the most recent previous meta-analysis, based on four studies with a combined sample size of 92 485 (36), the point estimate (hazard ratio 1.08, 95% CI 0.84-1.32) was lower than in the present analysis. This summary estimate is within the confidence intervals of our study (age, sex, and SES adjusted hazard ratio for job strain vs. no job strain 1.15, 95% CI 1.06-1.25). Some previous studies have reported an association between job strain and diabetes, but only among women (8-10), while other studies have found no association (15-17). Our results, based on a substantially larger sample (N=125,000), suggests a modest association between job strain and diabetes in both among men and women.

We did not assess any of the potential biological mechanisms underlying the job strain-diabetes association, such as increased cortisol secretion in response to stress (12-14).
Cortisol stimulates glucose production in the liver and antagonises the action of insulin in peripheral tissues; both processes have the potential to contribute to risk of hyperglycaemia. In addition, job strain could increase the risk of diabetes indirectly through effects on lifestyle. For example, job strain is associated with an elevated risk of physical inactivity and longitudinal analyses suggest that higher job strain is associated with a higher risk of obesity (18-22). These indirect effects via lifestyle are likely to explain only part of the job strain-diabetes association as the association was not removed after adjustment for lifestyle risk factors, and was observed among those with and without a healthy lifestyle.

The present pooled analysis has a number of strengths including size (high statistical power even after risk factor stratification), prospective design (reducing the risk of reverse causation bias), and inclusion of well characterized cohort studies (facilitating an assessment of the independent effects of stress). Our analysis is, of course, not without limitations. First, ascertainment of type 2 diabetes varied between the studies. Only the Whitehall II study administered an oral glucose tolerance test, the gold standard, to all participants who had not already been diagnosed with diabetes over the follow-up period. This study was thus able to report on both diagnosed and undiagnosed diabetes, while the other studies, based on health records or self-reports, missed undiagnosed type 2 diabetes cases. In Whitehall II, the age-, sex and SES-adjusted hazard ratio for job strain and diabetes was 1.09, which is in agreement with that in the entire consortium (1.15). Furthermore, I² statistics suggested that the method of outcome ascertainment was not a source of heterogeneity between the studies.

Second, we focused on job strain, which is the most widely studied form of work-related stress. However, there are other conceptualizations of work-related stress, such effort-reward imbalance (38), and other work-related stressors such as job insecurity (39) as well as various sources of stress outside work (7). Thus, our findings on a single work-related stressor are likely to provide an underestimate of the overall impact of life stress on diabetes.
risk. Furthermore, as job strain and lifestyle were measured only at baseline, changes in these factors might have contributed to an under- or over-estimation of the associations. Third, reverse causation remains a potential source of bias in studies of type 2 diabetes, which has a long subclinical phase. To reduce this bias we excluded the first three years of follow-up in subsidiary analyses. This procedure did not attenuate the association, suggesting that reverse causation is likely to explain little, if any, of the observed association. Lastly, our analyses are based on data from observational studies and, as such, preclude direct causal inference. We cannot exclude the possibility that the results were affected by residual confounding caused by imprecisely measured covariates or some other, unmeasured exposures.

In conclusion, we show a modest but robust association between job strain and the development of type 2 diabetes irrespective of lifestyle risk factors such as obesity and physical inactivity. Cluster-randomised controlled trials focused on job strain reduction and with work units or workplaces as the entity for randomization are needed to determine whether stress management could be an effective means to reduce type 2 diabetes risk in working populations. Given the likely sample size requirement of such a trial (as well as the fact that randomised trials frequently produce smaller effect sizes than observational studies),(40) the most cost-effective way to proceed might be to conduct an intervention with surrogate biomarkers of diabetes risk, such as fasting or post-load glucose.
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Nyberg and Kivimaki had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis with the exception of access to data from COPSOQ-I, COPSOQ-II, DW ECS, IPAW, PUMA and SLOSH. Madsen had full access to COPSOQ-I, COPSOQ-II, DW ECS, IPAW and PUMA data and Fransson had access to SLOSH data. All authors contributed to the study:

**Study concept and design:** Nyberg, Kivimaki.

**Acquisition of data:** Nyberg, Fransson, Heikkilä, Ahola, Alfredsson, Bjorner, Borritz, Burr, Dragano, Ferrie, Goldberg, Hamer, Jokela, Knutsson, Koskenvuo, Koskinen, Kouvonen, Leineweber, Madsen, Magnusson Hanson, Marmot, Nielsen, Nordin, Oksanen, Pejtersen,

**Analysis and interpretation of data:** Nyberg, Kivimaki

**Drafting of the manuscript:** Nyberg, Kivimaki.

**Critical revision of the manuscript for important intellectual content:** Nyberg, Fransson, Heikkilä, Ahola, Alfredsson, Björner, Borritz, Burr, Dragano, Ferrie, Goldberg, Hamer, Jokela, Knutsson, Koskenvuo, Koskinen, Kouvonon, Leineweber, Madsen, Magnusson Hanson, Marmot, Nielsen, Nordin, Oksanen, Pejtersen, Pentti, Rugulies, Salo, Siegrist, Steptoe, Suominen, Theorell, Väänänen, Vahtera, Virtanen, Westerholm, Westerlund, Zins, Batty, Brunner, Singh-Manoux, Kivimäki.

**Statistical analysis:** Nyberg.

**Obtained funding:** Kivimaki, Theorell, Rugulies, Dragano.

**Administrative, technical, or material support:** Nyberg, Heikkilä, Fransson, Madsen.

**Study supervision:** Kivimaki.

**Potential Conflicts 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 soundabsorbing materials, to study the effect of such materials on stress, job satisfaction and productivity in open-plan offices.


<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Baseline</th>
<th>Number of eligible participants</th>
<th>Number (%) of women</th>
<th>Number (%) of participants with job strain</th>
<th>Mean (SD) age at baseline (years)</th>
<th>Person-years</th>
<th>Number of new type 2 diabetes cases (incidence per 10 000 person-years)</th>
<th>Method for diabetes diagnosis *</th>
</tr>
</thead>
<tbody>
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<td>COPSOQ-I</td>
<td>Denmark</td>
<td>1997</td>
<td>1758</td>
<td>855 (49%)</td>
<td>358 (20%)</td>
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<tr>
<td>COPSOQ-II</td>
<td>Denmark</td>
<td>2004-05</td>
<td>3341</td>
<td>1756 (53%)</td>
<td>475 (14%)</td>
<td>42.6 (10.2)</td>
<td>16 575</td>
<td>18 (10.9)</td>
<td>2</td>
</tr>
<tr>
<td>DWECs</td>
<td>Denmark</td>
<td>2000</td>
<td>5522</td>
<td>2581 (47%)</td>
<td>1232 (22%)</td>
<td>41.8 (11.0)</td>
<td>48 659</td>
<td>63 (12.9)</td>
<td>2</td>
</tr>
<tr>
<td>FPS</td>
<td>Finland</td>
<td>2000</td>
<td>46 356</td>
<td>37 561 (81%)</td>
<td>7529 (16%)</td>
<td>44.5 (9.4)</td>
<td>444 925</td>
<td>1175 (26.4)</td>
<td>3</td>
</tr>
<tr>
<td>Gazel</td>
<td>France</td>
<td>1997</td>
<td>10 882</td>
<td>3049 (28%)</td>
<td>1572 (14%)</td>
<td>50.2 (3.0)</td>
<td>139 092</td>
<td>732 (52.6)</td>
<td>4</td>
</tr>
<tr>
<td>HeSSup</td>
<td>Finland</td>
<td>1998</td>
<td>16 127</td>
<td>8989 (56%)</td>
<td>2824 (18%)</td>
<td>39.5 (10.2)</td>
<td>112 026</td>
<td>129 (11.5)</td>
<td>3</td>
</tr>
<tr>
<td>IPAW</td>
<td>Denmark</td>
<td>1996-97</td>
<td>1988</td>
<td>1330 (66%)</td>
<td>346 (17%)</td>
<td>41.1 (10.4)</td>
<td>25 269</td>
<td>56 (22.2)</td>
<td>2</td>
</tr>
<tr>
<td>PUMA</td>
<td>Denmark</td>
<td>1999-2000</td>
<td>1831</td>
<td>1514 (83%)</td>
<td>276 (15%)</td>
<td>42.6 (10.3)</td>
<td>18 246</td>
<td>24 (13.2)</td>
<td>2</td>
</tr>
<tr>
<td>SLOSH</td>
<td>Sweden</td>
<td>2006, 2008</td>
<td>10 644</td>
<td>5771 (54%)</td>
<td>2089 (20%)</td>
<td>47.5 (10.8)</td>
<td>48 625</td>
<td>43 (8.8)</td>
<td>2</td>
</tr>
<tr>
<td>Still Working</td>
<td>Finland</td>
<td>1986</td>
<td>9079</td>
<td>2067 (23%)</td>
<td>1419 (16%)</td>
<td>40.9 (9.1)</td>
<td>191 416</td>
<td>730 (38.1)</td>
<td>3</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>UK</td>
<td>1991-93</td>
<td>7082</td>
<td>2140 (30%)</td>
<td>946 (13%)</td>
<td>48.8 (5.7)</td>
<td>89 430</td>
<td>558 (62.4)</td>
<td>1</td>
</tr>
<tr>
<td>WOLF-N</td>
<td>Sweden</td>
<td>1996-98</td>
<td>4605</td>
<td>767 (17%)</td>
<td>587 (13%)</td>
<td>43.9 (10.3)</td>
<td>53 311</td>
<td>48 (9.0)</td>
<td>2</td>
</tr>
<tr>
<td>WOLF-S</td>
<td>Sweden</td>
<td>1992-95</td>
<td>5593</td>
<td>2422 (43%)</td>
<td>907 (16%)</td>
<td>41.4 (11.0)</td>
<td>80 781</td>
<td>83 (10.3)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1986-2008</td>
<td>124 808</td>
<td>70 802 (57%)</td>
<td>20 560 (16%)</td>
<td>44.1 (9.3)</td>
<td>1 288 822</td>
<td>3703 (28.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1 = Repeated oral glucose tolerance tests complemented by self-report
2 = Mortality and hospitalization registers
3 = Special reimbursement register, mortality and hospitalization registers
4 = Self-report based on annual surveys and mortality register
Table 2—The association of job strain with incident type 2 diabetes in relation to study follow-up periods, outcome ascertainment and adjustments.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of diabetes cases</th>
<th>Number of participants</th>
<th>Number of studies</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up period:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full follow-up</td>
<td>3703</td>
<td>124 808</td>
<td>13</td>
<td>1.15 (1.06-1.25)</td>
</tr>
<tr>
<td>Cases with diabetes diagnosed during first 3 years excluded</td>
<td>3241</td>
<td>124 346</td>
<td>13</td>
<td>1.15 (1.05-1.27)</td>
</tr>
<tr>
<td><strong>Method of diabetes ascertainment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td>558</td>
<td>7082</td>
<td>1</td>
<td>1.09 (0.86-1.37)</td>
</tr>
<tr>
<td>Hospitalization and mortality registries</td>
<td>379</td>
<td>35 282</td>
<td>8</td>
<td>1.35 (1.05-1.74)</td>
</tr>
<tr>
<td>Hospitalization, mortality and drug reimbursement registries</td>
<td>2034</td>
<td>71 562</td>
<td>3</td>
<td>1.15 (1.03-1.29)</td>
</tr>
<tr>
<td>Self-report and mortality register</td>
<td>732</td>
<td>10 882</td>
<td>1</td>
<td>1.08 (0.88-1.33)</td>
</tr>
<tr>
<td><strong>Adjustments:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, sex</td>
<td>3703</td>
<td>124 808</td>
<td>13</td>
<td>1.26 (1.16-1.37)</td>
</tr>
<tr>
<td>Age, sex, SES</td>
<td>3703</td>
<td>124 808</td>
<td>13</td>
<td>1.15 (1.06-1.25)</td>
</tr>
<tr>
<td>Age, sex, SES, BMI category</td>
<td>2833</td>
<td>111 984</td>
<td>11</td>
<td>1.12 (1.02-1.24)</td>
</tr>
<tr>
<td>Age, sex, SES, physical activity</td>
<td>3523</td>
<td>120 364</td>
<td>12</td>
<td>1.13 (1.03-1.23)</td>
</tr>
<tr>
<td>Age, sex, SES, smoking</td>
<td>3591</td>
<td>120 495</td>
<td>13</td>
<td>1.14 (1.04-1.24)</td>
</tr>
<tr>
<td>Age, sex, SES, alcohol consumption</td>
<td>3539</td>
<td>110 447</td>
<td>11</td>
<td>1.14 (1.04-1.25)</td>
</tr>
<tr>
<td>Age, sex, SES, lifestyle variables*</td>
<td>2599</td>
<td>95 921</td>
<td>10</td>
<td>1.11 (1.00-1.23)</td>
</tr>
<tr>
<td>Age, sex, SES, lifestyle variables*, biomarkers†</td>
<td>1889</td>
<td>88 174</td>
<td>8</td>
<td>1.12 (0.99-1.26)</td>
</tr>
<tr>
<td>Age, sex, SES, lifestyle variables*, biomarkers‡</td>
<td>638</td>
<td>16 168</td>
<td>3</td>
<td>1.08 (0.87-1.35)</td>
</tr>
</tbody>
</table>

* Lifestyle variables: BMI (6 categories), physical activity (3 categories), smoking (3 categories), alcohol consumption (4 categories).
† Self-reported hypertension or use of antihypertensive medication (FPS, HeSSup, SLOSH, IPAW, COPSOQ-II), self-reported elevated lipids (HeSSup), or measured systolic blood pressure, triglycerides and high density lipoprotein cholesterol (Whitehall II, WOLF N, WOLF S)
‡ Systolic blood pressure, triglycerides and high density lipoprotein cholesterol (Whitehall II, WOLF N, WOLF S)
Figure Legends

Figure 1. Fixed effect meta-analysis of age-, sex- and SES-adjusted association between job strain and incident type 2 diabetes

Figure 2. Associations of job strain and incident type 2 diabetes in healthy and unhealthy lifestyle subgroups
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases (N)</th>
<th>Participants (N)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPSOQ-I</td>
<td>44</td>
<td>1758</td>
<td>1.05 (0.50, 2.21)</td>
</tr>
<tr>
<td>COPSOQ-II</td>
<td>28</td>
<td>3342</td>
<td>1.08 (0.31, 3.74)</td>
</tr>
<tr>
<td>DWEC5</td>
<td>63</td>
<td>5522</td>
<td>1.53 (0.87, 2.70)</td>
</tr>
<tr>
<td>FPS</td>
<td>1175</td>
<td>46356</td>
<td>1.17 (1.01, 1.36)</td>
</tr>
<tr>
<td>Gazel</td>
<td>732</td>
<td>10882</td>
<td>1.08 (0.88, 1.33)</td>
</tr>
<tr>
<td>HeSSup</td>
<td>129</td>
<td>16127</td>
<td>1.06 (0.67, 1.66)</td>
</tr>
<tr>
<td>IPAW</td>
<td>56</td>
<td>1988</td>
<td>1.55 (0.84, 2.86)</td>
</tr>
<tr>
<td>PUMA</td>
<td>24</td>
<td>1831</td>
<td>1.36 (0.50, 3.68)</td>
</tr>
<tr>
<td>SLOSH</td>
<td>43</td>
<td>10644</td>
<td>1.37 (0.68, 2.77)</td>
</tr>
<tr>
<td>Still Working</td>
<td>730</td>
<td>9079</td>
<td>1.13 (0.93, 1.37)</td>
</tr>
<tr>
<td>WOLF N</td>
<td>48</td>
<td>4005</td>
<td>1.36 (0.61, 3.07)</td>
</tr>
<tr>
<td>WOLF S</td>
<td>83</td>
<td>5593</td>
<td>1.27 (0.72, 2.22)</td>
</tr>
<tr>
<td>Whitthall II</td>
<td>55</td>
<td>7083</td>
<td>1.09 (0.86, 1.37)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.15 (1.06, 1.25)</td>
</tr>
</tbody>
</table>

Decreased risk ← → Increased risk
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases (N)</th>
<th>Participants (N)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity - job strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No - No</td>
<td>1423</td>
<td>84437</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>No - Yes</td>
<td>286</td>
<td>16379</td>
<td>1.13 (0.99 – 1.28)</td>
</tr>
<tr>
<td>Yes - No</td>
<td>904</td>
<td>9135</td>
<td>5.99 (5.49 – 6.53)</td>
</tr>
<tr>
<td>Yes - Yes</td>
<td>220</td>
<td>2033</td>
<td>7.22 (6.22 – 8.37)</td>
</tr>
<tr>
<td><strong>Physical inactivity - job strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No - No</td>
<td>1954</td>
<td>80365</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>No - Yes</td>
<td>395</td>
<td>15104</td>
<td>1.14 (1.02 – 1.27)</td>
</tr>
<tr>
<td>Yes - No</td>
<td>948</td>
<td>20351</td>
<td>1.61 (1.48 – 1.74)</td>
</tr>
<tr>
<td>Yes - Yes</td>
<td>226</td>
<td>4544</td>
<td>1.83 (1.59 – 2.11)</td>
</tr>
<tr>
<td><strong>Smoking - job strain</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No - No</td>
<td>2167</td>
<td>78855</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>No - Yes</td>
<td>445</td>
<td>14811</td>
<td>1.13 (1.02 – 1.25)</td>
</tr>
<tr>
<td>Yes - No</td>
<td>790</td>
<td>21865</td>
<td>1.45 (1.33 – 1.58)</td>
</tr>
<tr>
<td>Yes - Yes</td>
<td>189</td>
<td>4964</td>
<td>1.70 (1.46 – 1.98)</td>
</tr>
<tr>
<td><strong>Heavy drinking - job strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No - No</td>
<td>2631</td>
<td>86891</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>No - Yes</td>
<td>569</td>
<td>16670</td>
<td>1.14 (1.04 – 1.25)</td>
</tr>
<tr>
<td>Yes - No</td>
<td>287</td>
<td>5873</td>
<td>1.37 (1.21 – 1.55)</td>
</tr>
<tr>
<td>Yes - Yes</td>
<td>52</td>
<td>1013</td>
<td>1.76 (1.34 – 2.32)</td>
</tr>
</tbody>
</table>