

Job Strain and the Risk of Stroke An Individual-Participant Data Meta-Analysis

Eleonor I. Fransson, PhD; Solja T. Nyberg, MSc; Katriina Heikkilä, PhD; Lars Alfredsson, PhD; Jakob B. Bjorner, MD, PhD; Marianne Borritz, MD, PhD; Hermann Burr, PhD; Nico Dragano, PhD; Goedele A. Geuskens, PhD; Marcel Goldberg, MD, PhD; Mark Hamer, PhD; Wendela E. Hoofman, PhD; Irene L. Houtman, PhD; Matti Joensuu, MSc; Markus Jokela, PhD; Anders Knutsson, PhD; Markku Koskenvuo, MD, PhD; Aki Koskinen, MSc; Meena Kumari, PhD; Constanze Leineweber, PhD; Thorsten Lunau, MSc; Ida E.H. Madsen, PhD; Linda L. Magnusson Hanson, PhD; Martin L. Nielsen, MD, PhD; Maria Nordin, PhD; Tuula Oksanen, MD, PhD; Jaana Pentti, BSc; Jan H. Pejtersen, PhD; Reiner Rugulies, PhD; Paula Salo, PhD; Martin J. Shipley, MSc; Andrew Steptoe, DPh; Sakari B. Suominen, MD, PhD; Töres Theorell, MD, PhD; Salla Toppinen-Tanner, PhD; Jussi Vahtera, MD, PhD; Marianna Virtanen, PhD; Ari Väänänen, PhD; Peter J.M. Westerholm, MD, PhD; Hugo Westerlund, PhD; Marie Zins, MD, PhD; Annie Britton, PhD; Eric J. Brunner, PhD; Archana Singh-Manoux, PhD; G. David Batty, PhD; Mika Kivimäki, PhD

Background and Purpose—Psychosocial stress at work has been proposed to be a risk factor for cardiovascular disease. However, its role as a risk factor for stroke is uncertain.

Methods—We conducted an individual-participant-data meta-analysis of 196 380 males and females from 14 European cohort studies to investigate the association between job strain, a measure of work-related stress, and incident stroke.

Results—In 1.8 million person-years at risk (mean follow-up 9.2 years), 2023 first-time stroke events were recorded. The age- and sex-adjusted hazard ratio for job strain relative to no job strain was 1.24 (95% confidence interval, 1.05;1.47) for ischemic stroke, 1.01 (95% confidence interval, 0.75;1.36) for hemorrhagic stroke, and 1.09 (95% confidence interval, 0.94;1.26) for overall stroke. The association with ischemic stroke was robust to further adjustment for socioeconomic status.

Conclusion—Job strain may be associated with an increased risk of ischemic stroke, but further research is needed to determine whether interventions targeting job strain would reduce stroke risk beyond existing preventive strategies. (*Stroke*. 2015;46:557-559. DOI: 10.1161/STROKEAHA.114.008019.)

Key Words: psychological ■ stress ■ stroke ■ work

Stroke is a major cause of morbidity, mortality, and disability worldwide.^{1,2} Psychosocial stress may increase the

risk of developing stroke,³ although prospective evidence to confirm this is scarce. Job strain, for example, is one of the

Received November 4, 2014; final revision received November 4, 2014; accepted November 7, 2014.

From the Department of Natural Science and Biomedicine, School of Health Sciences, Jönköping University, Jönköping, Sweden (E.I.F.); Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (E.I.F., L.A.); Stress Research Institute, Stockholm University, Stockholm, Sweden (E.I.F., C.L., L.L.M.H., T.T., H.W.); Finnish Institute of Occupational Health, Tampere, Finland (S.T.N., K.H.); Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden (L.A.); National Research Centre for the Working Environment, Copenhagen, Denmark (J.B.B., I.E.H.M., R.R.); Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Copenhagen, Denmark (M.B., M.L.N.); Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany (H.B.); Institute for Medical Sociology, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany (N.D., T.L.); Netherlands Organisation for Applied Scientific Research (TNO), Hoofddorp, Netherlands (G.A.G., W.E.H., I.L.H.); Versailles-Saint Quentin University, Versailles, France (M.G., M.Z.); Inserm, Population-based Epidemiologic Cohorts Unit, UMS 011, Villejuif, France (M.G., M.Z.); Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France (A.S.-M.); Department of Epidemiology and Public Health, University College London, London, UK (M.H., M. Kumari, M.J.S., A.S., A.B., E.J.B., A.S.-M., G.D.B., M. Kivimäki); Finnish Institute of Occupational Health, Helsinki, Finland (M. Joensuu, A. Koskinen, S.T.-T., M.V., A.V., M. Kivimäki); Institute of Behavioural Sciences (M. Jokela, M. Kivimäki) and Department of Public Health (M. Koskenvuo), University of Helsinki, Helsinki, Finland; Department of Health Sciences, Mid Sweden University, Sundsvall, Sweden (A. Knutsson); Department of Psychology, Umeå University, Umeå, Sweden (M.N.); Finnish Institute of Occupational Health, Turku, Finland (T.O., J.P., P.S., J.V.); Danish National Centre for Social Research, Copenhagen, Denmark (J.H.P.); Department of Public Health and Department of Psychology, University of Copenhagen, Copenhagen, Denmark (R.R.); Department of Psychology, University of Turku, Turku, Finland (P.S.); Folkhälsan Research Centre, Helsinki, Finland (S.B.S.); Department of Public Health, University of Turku, Turku, Finland (S.B.S., J.V.); Nordic School of Public Health, Gothenburg, Sweden (S.B.S.); Turku University Hospital, Turku, Finland (J.V.); Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden (P.J.M.W.); Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, Edinburgh, UK (G.D.B.); and Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK (G.D.B.).

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.008019/-DC1>.

Correspondence to Eleonor Fransson, PhD, School of Health Sciences, Jönköping University, Box 1026, SE-551 11 Jönköping, Sweden. E-mail eleonor.fransson@hhj.hj.se

© 2015 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.114.008019

Table. Characteristics of Participants in 14 Cohort Studies, IPD-Work Consortium

Study*, Country	Baseline Years	Number of Participants	Number (%) With Job Strain	Total Number of Stroke Events per 10000 Person-Years
Whitehall II, UK	1985–1988	10 261	1438 (14)	193 (9.9)
Still Working, Finland	1986	9137	1420 (16)	471 (24.2)
WOLF-S, Sweden	1992–1995	5648	915 (16)	104 (12.8)
IPAW, Denmark	1996–1997	2027	356 (18)	55 (21.4)
WOLF-N, Sweden	1996–1998	4683	599 (13)	95 (17.6)
COPSOQ-I, Denmark	1997	1769	361 (20)	33 (16.0)
Gazel, France	1997	11 260	1630 (14)	312 (20.5)
POLS, Netherlands	1997–2002	24 521	3911 (16)	110 (4.6)
HeSSup, Finland	1998	16 404	2875 (18)	75 (6.6)
PUMA, Denmark	1999–2000	1839	278 (15)	30 (16.4)
DWECS, Denmark	2000	5547	1231 (22)	77 (15.8)
FPS, Finland	2000	47 302	7710 (16)	351 (7.7)
NWCS, Netherlands	2005–2006	45 052	5610 (13)	62 (3.8)
SLOSH, Sweden	2006–2008	10 930	2147 (20)	55 (11.0)
Total	1985–2008	196 380	30 481 (16)	2023 (11.1)

*For study abbreviations and further details, see online-only Data Supplement.

most widely studied measures of psychosocial stress⁴ and has been linked to an increased risk of coronary heart disease.^{5,6} However, an association between job strain, or its components (ie, high job demands and low job control), and stroke has been observed only in part of the studies.^{6–12} To increase understanding about stress and stroke, we conducted an individual-participant-data meta-analysis examining the association between job strain, stroke, and its subtypes in >190 000 employed males and females from 6 European countries.

Material and Methods

We used data provided by investigators from 14 prospective cohort studies (baseline examination between 1985 and 2008) of the Individual-Participant-Data meta-analysis in Working populations Consortium (Table I in the online-only Data Supplement).⁵ Job strain at baseline was defined according to demand-control (job strain) questionnaires.⁴ Individuals exposed to job strain (ie, reporting high

job demands in combination with low control over the work situation) were compared with all others.¹³ Socioeconomic status served as a proxy marker of stroke risk factors. Data on standard stroke risk factors, such as diabetes mellitus, hypertension (based on measured blood pressure), smoking, and heavy alcohol consumption, were available from 3 studies (online-only Data Supplement).

We defined incident stroke using national hospital admission and death registries (ICD-10 codes I60, I61, I63, I64, or the corresponding ICD-9 or ICD-8 codes; for alternative definitions in 2 studies, see online-only Data Supplement). We excluded participants with a history of stroke at baseline (transient ischemic attacks were not considered). Data on stroke subtypes, ischemic (ICD-10 I63) and hemorrhagic (I60, I61), were available from 13 studies (online-only Data Supplement).

The participants were followed up from their assessment of job strain at baseline to the first stroke event, death, or end of follow-up—whichever came first. Using Cox proportional hazard regression, we estimated hazard ratios and 95% confidence intervals (CI) to quantify the associations of job strain with overall, ischemic, and hemorrhagic stroke in each study. All analyses were adjusted for age and sex, with a further adjustment for socioeconomic status and, in sensitivity analyses based on 3 cohorts, standard stroke risk factors. We pooled the study-specific effect estimates in random-effects meta-analyses.

Results

A total of 196 380 participants (mean age 42.4 years, 53% female) had not experienced a stroke event before the study baseline and had complete data on age, sex, socioeconomic status, job strain, and incident stroke events, the analytic sample. The proportion exposed to job strain ranged from 13% to 22%, depending on the study (Table).

During 1 815 848 person-years at risk (mean follow-up 9.2 years), 2023 stroke events were recorded. The age- and sex-adjusted pooled hazard ratio of overall stroke for the job strain group compared with those not exposed to job strain was not statistically significant (1.09; 95% CI, 0.94–1.26), with little heterogeneity in estimates between the studies ($I^2=21.6%$, $P=0.22$; Figure).

In analysis of stroke subtypes (Figure; Figures I–III in the online-only Data Supplement), job strain was associated with an increased risk of incident ischemic stroke (hazard ratio, 1.24; 95% CI, 1.05–1.47) but not hemorrhagic stroke (1.01; 95% CI, 0.75–1.36). Further adjustment for socioeconomic status yielded a hazard ratio of 1.18 (95% CI, 1.00–1.39) for ischemic stroke and 0.95 (95% CI, 0.72–1.27) for hemorrhagic stroke (sensitivity analyses in online-only Data Supplement).

Discussion

In this individual-participant-data meta-analysis of 190 000 working males and females in Europe, job strain was associated with an ≈20% increased risk of acute ischemic stroke. No association with the risk of overall stroke or hemorrhagic stroke was observed.

Previous smaller-scale studies on job strain and the risk of stroke^{6–8,10–12} were underpowered to detect a 20% elevated risk. The strength of the association between job strain and ischemic

Stroke subtypes, adjusted for sex and age

All strokes	N=196 380, 2023 events
Ischemic	N=185 120, 1049 events
Hemorrhagic	N=179 573, 476 events

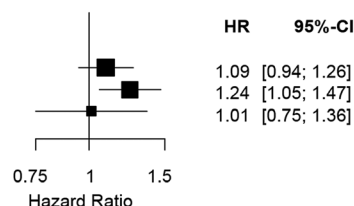


Figure. Age- and sex-adjusted association between job strain and subtypes of stroke.

stroke found in the present study corresponds to the association observed in our previous meta-analysis on job strain and coronary heart disease.⁵ The pathogenesis of coronary heart disease and ischemic stroke is partially overlapping, with atherosclerosis as the major common factor. Job strain might have an effect on the cardiovascular system through activation of the neuro-endocrine stress response, dysregulation of the hypothalamic–pituitary–adrenal axis, the metabolic syndrome, or indirectly via unhealthy behaviors, such as physical inactivity and poor diet.¹⁴

We did not have complete data on standard stroke risk factors, leaving residual confounding as a potential alternative explanation for the results. Although our sample size was large, the number of ischemic and hemorrhagic stroke events was relatively low and the diagnoses were not always confirmed by brain imaging; thus, further research is needed to confirm the findings. Additional research should also examine the mechanisms underlying the association between job strain and ischemic stroke and determine the extent to which interventions targeting job strain might reduce stroke risk beyond existing preventive strategies.

Sources of Funding

The IPD-Work Consortium was supported by the European Union-based New and Emerging Risks in Occupational Safety and Health research programme (funded by the Finnish Work Environment Fund, Finland, the Swedish Research Council for Health, Working Life and Welfare, Sweden, the German Social Accident Insurance, Germany, and the Danish National Research Centre for the Working Environment, Denmark); the Academy of Finland, Finland; the Ministry of Social Affairs and Employment, the Netherlands. Dr Kivimäki is supported by the Medical Research Council, UK (K013351), the US NIH (R01HL036310; R01AG034454), the Finnish Work Environment Fund, Finland, the Economic and Social Research Council, UK, and the British Heart Foundation, UK.

Disclosures

None.

References

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden

- of Disease Study 2010. *Lancet*. 2012;380:2197–2223. doi: 10.1016/S0140-6736(12)61689-4.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0.
3. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3.
4. Karasek R, Theorell T. *Healthy Work: Stress, Productivity and the Reconstruction of Working Life*. New York, NY: Basic Books, Inc; 1990.
5. Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, et al; IPD-Work Consortium. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet*. 2012;380:1491–1497. doi: 10.1016/S0140-6736(12)60994-5.
6. Slopen N, Glynn RJ, Buring JE, Lewis TT, Williams DR, Albert MA. Job strain, job insecurity, and incident cardiovascular disease in the Women's Health Study: results from a 10-year prospective study. *PLoS One*. 2012;7:e40512. doi: 10.1371/journal.pone.0040512.
7. Kivimäki M, Gimeno D, Ferrie JE, Batty GD, Oksanen T, Jokela M, et al. Socioeconomic position, psychosocial work environment and cerebrovascular disease among women: the Finnish public sector study. *Int J Epidemiol*. 2009;38:1265–1271. doi: 10.1093/ije/dyn373.
8. Tsutsumi A, Kayaba K, Kario K, Ishikawa S. Prospective study on occupational stress and risk of stroke. *Arch Intern Med*. 2009;169:56–61. doi: 10.1001/archinternmed.2008.503.
9. Toivanen S. Job control and the risk of incident stroke in the working population in Sweden. *Scand J Work Environ Health*. 2008;34:40–47.
10. Kuper H, Adami HO, Theorell T, Weiderpass E. The socioeconomic gradient in the incidence of stroke: a prospective study in middle-aged women in Sweden. *Stroke*. 2007;38:27–33. doi: 10.1161/01.STR.0000251805.47370.91.
11. Torén K, Schiöler L, Giang WK, Novak M, Söderberg M, Rosengren A. A longitudinal general population-based study of job strain and risk for coronary heart disease and stroke in Swedish men. *BMJ Open*. 2014;4:e004355. doi: 10.1136/bmjopen-2013-004355.
12. André-Petersson L, Engström G, Hedblad B, Janzon L, Rosvall M. Social support at work and the risk of myocardial infarction and stroke in women and men. *Soc Sci Med*. 2007;64:830–841. doi: 10.1016/j.socscimed.2006.10.020.
13. Fransson EI, Nyberg ST, Heikkilä K, Alfredsson L, Bacquer de D, Batty GD, 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. doi: 10.1186/1471-2458-12-62.
14. Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. Work stress and coronary heart disease: what are the mechanisms? *Eur Heart J*. 2008;29:640–648. doi: 10.1093/eurheartj/ehm584.

Job Strain and the Risk of Stroke: An Individual-Participant Data Meta-Analysis

Eleonor I. Fransson, Solja T. Nyberg, Katriina Heikkilä, Lars Alfredsson, Jakob B. Björner, Marianne Borritz, Hermann Burr, Nico Dragano, Goedele A. Geuskens, Marcel Goldberg, Mark Hamer, Wendela E. Hooftman, Irene L. Houtman, Matti Joensuu, Markus Jokela, Anders Knutsson, Markku Koskenvuo, Aki Koskinen, Meena Kumari, Constanze Leineweber, Thorsten Lunau, Ida E.H. Madsen, Linda L. Magnusson Hanson, Martin L. Nielsen, Maria Nordin, Tuula Oksanen, Jaana Pentti, Jan H. Pejtersen, Reiner Rugulies, Paula Salo, Martin J. Shipley, Andrew Steptoe, Sakari B. Suominen, Töres Theorell, Salla Toppinen-Tanner, Jussi Vahtera, Marianna Virtanen, Ari Väänänen, Peter J.M. Westerholm, Hugo Westerlund, Marie Zins, Annie Britton, Eric J. Brunner, Archana Singh-Manoux, G. David Batty and Mika Kivimäki

Stroke. 2015;46:557-559; originally published online January 6, 2015;
doi: 10.1161/STROKEAHA.114.008019

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/46/2/557>

Data Supplement (unedited) at:

<http://stroke.ahajournals.org/content/suppl/2015/01/30/STROKEAHA.114.008019.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

SUPPLEMENTAL MATERIAL

Fransson et al. Job Strain and the Risk of Stroke: An Individual-Participant Data Meta-analysis. *Stroke*.

Description of the IPD-Work studies

Characteristics of the participants in the 14 cohort studies are shown in **Supplemental Table I**. The following section provides a brief description of each study.

Copenhagen Psychosocial Questionnaire version I (COPSOQ-I)

The 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 and an invitation to take part was posted to 4 000 people and 2 454 individuals agreed to participate.¹ Of the 1 858 gainfully employed participants, 1 776 men and women had data on job strain and were eligible for our meta-analyses. 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). The proportion of immigrants in Denmark at study baseline was approximately 7%, but the proportion of immigrants in participants is likely to be lower because the study questionnaires were available only in Danish.

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.^{2, 3} Of the 5 606 individuals who were employed, 5 574 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. DWECS was approved by and registered with the Danish Data protection agency (registration number: 2007-54-0059). 95.3% of the participants were Danish.

Finnish Public Sector study (FPS)

The FPS 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, who were recruited from employers' records in 2000-2002, were individuals who had been employed in the study organisations for at least six months prior to data collection.⁴ 48 592 individuals (9 337 men and 39 255 women aged 17 to 65) responded to the questionnaire. Of these, 48 034 had data on job strain and were eligible for our meta-analyses. Ethical approval was obtained from the ethics committee of the Finnish Institute of Occupational Health. The proportion of immigrants in the cohort is <1%.

Gazel

Gazel is a prospective cohort study of 20 625 employees (15 011 men and 5 614 women) of France's national gas and electricity company, Electricité de France-Gaz de France (EDF-GDF).^{5, 6} Since the study baseline in 1989, when the participants were aged 35–50 years, they have been posted an

annual follow-up questionnaire to collect data on health, lifestyle, individual, familial, social, and occupational factors. Job strain was measured in Gazel in 1997, which we treated as a baseline year for our analyses. The 11 448 individuals who participated at that time and had data on job strain were eligible for our meta-analysis. The GAZEL study received approval from the national commission overseeing ethical data collection in France (Commission Nationale Informatique et Liberté). This cohort does not include immigrants.

Health and Social Support (HeSSup)

The 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 1998.⁷ Job strain was measured in 1998 and of the 25 898 individuals who responded to the questionnaire, 16 447 were in employment and had data on job strain and were thus eligible for our meta-analyses. The Turku University Central Hospital Ethics Committee approved the study. The proportion of immigrants is less than 1%.

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.^{8, 9} 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. Interventions took place at 22 workplaces during 1996-98 at the organisational and interpersonal level. Job strain was measured in 1996-1997 and the 2 031 participants, who had data on job strain, were eligible for our meta-analysis. IPAW was approved by and registered with the Danish Data Protection Agency (registration number: 2000-54-0066). The proportion of immigrants in the cohort is likely to be less than 7%.

The Netherlands Working Conditions Survey (NWCS)

The NWCS is a yearly cross-sectional survey on working conditions in the Netherlands. NWCS is conducted among employees aged 15 to 64 years. Individuals are sampled randomly from the Dutch working population database of Statistics Netherlands. This database contains information on all jobs which fall under employee national insurance schemes and are liable to income tax. Participants filled out the questionnaire with a pencil or via internet. Data from the surveys conducted in 2005 and 2006 are included in the IPD-Work consortium. In total, 47 511 men and women participated in the surveys of 2005 and 2006.^{10, 11} The proportion of immigrants in the cohort is unknown.

Permanent Onderzoek Leefsituatie (POLS)

POLS is a series of annual cross-sectional health and lifestyle surveys of Dutch men and women.¹² The participants are a representative sample of the Dutch population, drawn from the Municipal Population Register (Gemeentelijke Basis Administratie, GBA). Only those living in a private household were included. Most of the data collection is done using computer assisted personal interviewing. At study baseline in 1997- 2002, 59 441 men and women participated in the surveys. Of these, 24 761 were in paid employment, aged 15-85 and had job strain measure available and were eligible for our meta-analyses. POLS was approved by the medical ethics committee of the

Netherlands Organisation for Applied Scientific Research. The proportion of immigrants in the cohort is unknown.

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.¹³ 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. 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. At study baseline in 1999-2000, 1 914 participants agreed to take part. Of these, 1 847 individuals had data on job strain and were eligible for our meta-analyses. 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). The proportion of immigrants in the cohort is likely to be less than 7%.

Swedish Longitudinal Occupational Survey of Health (SLOSH)

SLOSH is an on-going prospective cohort study following up individuals who participated in the Swedish Work Environment Survey (SWES) in 2003 or 2005. SWES, conducted biennially by Statistics Sweden, is based on a sample of gainfully employed people aged 16-64 years drawn from the Labour Force Survey (LFS). These individuals were first sampled into LFS through stratification by county, sex, citizenship and inferred employment status. Data from the 2006 and 2008 data collection waves of SLOSH were used in the analyses. In both years, data were collected using postal self-completion questionnaires. In 2006, 5,985 individuals responded to the questionnaire. Of these, 5,141 people worked at least 30% of full time working hours.¹⁴ In 2008, a further 6,751 individuals responded to the questionnaire.¹⁵ Of these, 5,895 men and women worked at least 30% of full time working hours. SLOSH has been approved by the Regional Research Ethics Board in Stockholm. The proportion of immigrants in the cohort is approximately 7%.

Still Working

Still Working is an ongoing prospective cohort study. 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.^{16, 17} At baseline, 9 282 individuals responded, and of these 9 165 had data on job strain and were eligible for our meta-analyses. The study was approved by the ethics committee of the Finnish Institute of Occupational Health. The proportion of immigrants in the cohort is less than 1%.

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.¹⁸ Data on job strain, measured at study baseline were available for 10 285 men of the men and women who were eligible for our meta-analyses. 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. Information about

immigrant status is not available for participants but the proportion of immigrants in British civil service was presumably very low in 1985-1988.

Work, Lipids, and Fibrinogen Stockholm (WOLF-S) and Norrland (WOLF-N) studies

The 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.¹⁹ WOLF Norrland is a prospective cohort of 4 718 participants aged 19-65 working in companies in Jämtland and Västernorrland counties.²⁰ 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 1996-1998. The Regional Research Ethics Board in Stockholm, and the ethics committee at Karolinska Institutet, Stockholm, Sweden approved the study. The proportion of immigrants in WOLF Stockholm is 13% and in WOLF Norrland 3%.

Measurements at baseline

Job strain at baseline was defined according to demand-control (job strain) questionnaires harmonized across the participating cohort studies before obtaining disease outcome data.²¹ The Pearson correlation coefficient between the harmonized scales and the complete versions was >0.9, except for Still Working study in which it was 0.8.²¹ As in previous IPD-Work analyses, individuals exposed to job strain (i.e. reporting high job demands in combination with low control over the work situation) were compared to all others.²²⁻²⁵ Socioeconomic status (SES; low, intermediate, high, other), defined on the basis of occupational title or education, served as a proxy marker of stroke risk factors. Data on standard stroke risk factors, such as diabetes, hypertension (systolic/diastolic blood pressure >140/90mmHg), smoking, and heavy alcohol consumption (>28 units of alcohol per week for men and >21 units for women), were available in 3 studies, Whitehall II, WOLF-Norrland and WOLF-Stockholm (due to small numbers, less than 20 per study, atrial fibrillation was not possible to include in as a risk factor in the analysis). The age-and sex-adjusted odds ratio for low compared to high SES was 2.26 (95%CI: 1.45-3.54) for diabetes, 1.47 (1.24-1.57) for hypertension, 3.30 (2.93-3.73) for smoking, and 0.76 (0.63-0.93) for heavy alcohol use.

Ascertainment of incident stroke

We defined incident stroke using national hospital admission and death registries (ICD-10 codes I60, I61, I63, I64, or the corresponding ICD-9 or ICD-8 codes). In Whitehall II, self-reports in follow-up questionnaires and event tracing were additionally used.²⁶ In GAZEL, only self-reports from annual follow-up surveys and mortality records were used. We excluded participants with a history of stroke at baseline (TIAs were not considered). Data on stroke subtypes, ischemic (ICD-10 I63) and hemorrhagic (I60, I61), were available from 13 studies; according to validation analyses relating to 9 studies the diagnosis was confirmed by brain scan (magnetic resonance imaging and/or computed tomography) or autopsy in 68.8% to 100% of cases depending on the study. Information about the validity of stroke diagnosis in each cohort study is shown in **Supplemental Table II**.

Supplemental Table I. Characteristics of participants in 14 cohort studies, IPD-Work Consortium

Study, country	Baseline years	Number of participants	Number (%) of women	Number (%) participants with job strain	Mean (SD) age at baseline	Person-years	Total number of stroke events (incidence per 10,000 person-years)
Whitehall II, UK	1985-1988	10 261	3389 (33)	1438 (14)	44.4 (6.1)	195 672	193 (9.9)
Still Working, Finland	1986	9137	2076 (23)	1420 (16)	40.9 (9.1)	194 608	471 (24.2)
WOLF-S, Sweden	1992-1995	5648	2443 (43)	915 (16)	41.5 (11.0)	81 360	104 (12.8)
IPAW, Denmark	1996-1997	2027	1355 (67)	356 (18)	41.2 (10.5)	25 696	55 (21.4)
WOLF-N, Sweden	1996-1998	4683	779 (17)	599 (13)	44.0 (10.3)	54 029	95 (17.6)
COPSOQ-I, Denmark	1997	1769	860 (49)	361 (20)	40.7 (10.6)	20 683	33 (16.0)
Gazel, France	1997	11 260	3114 (28)	1630 (14)	50.3 (3.0)	152 242	312 (20.5)
POLS, Netherlands	1997-2002	24 521	10 098 (41)	3911 (16)	38.2 (11.1)	241 479	110 (4.6)
HeSSup, Finland	1998	16 404	9112 (56)	2875 (18)	39.6 (10.2)	114 102	75 (6.6)
PUMA, Denmark	1999-2000	1839	1518 (83)	278 (15)	42.6 (10.3)	18 315	30 (16.4)
DWECS, Denmark	2000	5547	2594 (47)	1231 (22)	41.8 (11.0)	48 841	77 (15.8)
FPS, Finland	2000	47 302	38 252 (81)	7710 (16)	44.6 (9.4)	456 312	351 (7.7)
NWCS, Netherlands	2005-2006	45 052	23 082 (51)	5610 (13)	40.0 (11.8)	162 618	62 (3.8)
SLOSH, Sweden	2006-2008	10 930	5901 (54)	2147 (20)	47.6 (10.8)	49 891	55 (11.0)
Total	1985-2008	196 380	104 573 (53)	30 481 (16)	42.4	1 815 848	2023 (11.1)

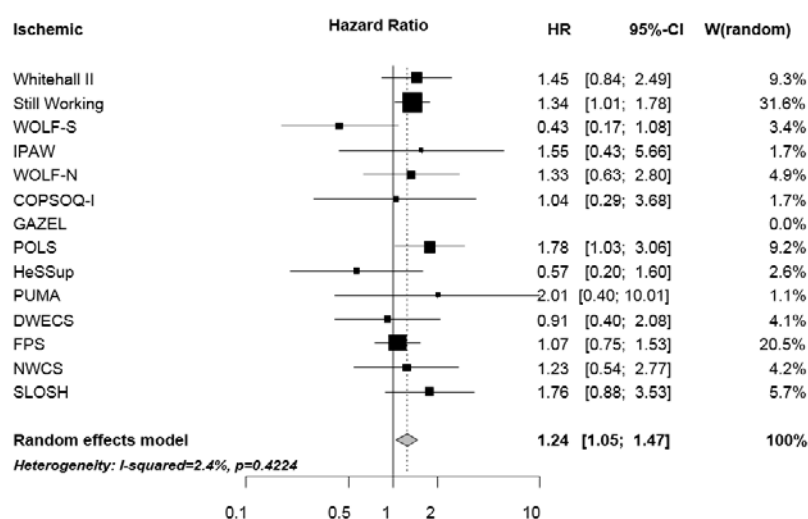
Supplemental Table II. Positive predictive value (PPV)* for diagnosis in validation studies and the proportion of ascertainment of the diagnosis by imaging or autopsy.

Study	PPV* or proportion of stroke diagnoses confirmed by brain imaging or autopsy (reference if a validation study available)
COPSOQ-I	PPV 73.9% (hemorrhagic), PPV 97% (ischemic) ²⁷
DWECS	PPV 73.9% (hemorrhagic), PPV 97% (ischemic) ²⁷
FPS	Imaging/autopsy 99%, ²⁸ PPV 84% (ischemic) ²⁹
Gazel	Self-reported data not used in subtype analyses
HeSSup	Imaging/autopsy 99% ²⁸
IPAW	PPV 73.9% (hemorrhagic), PPV 97% (ischemic) ²⁷
NWCS	Unknown
POLS	Unknown
PUMA	PPV 73.9% (hemorrhagic), PPV 97% (ischemic) ²⁷
Still Working	Imaging/autopsy 83.5% ²⁸
SLOSH	Imaging/autopsy \geq 97.7%, PPV 94% (all strokes) ³⁰
Whitehall II	Imaging/autopsy approx. 69% between 2006-2009 ^{26,31}
Wolf-N	Imaging/autopsy 97.6% in 2001, before unknown ³²
Wolf-S	Imaging/autopsy 97.6% in 2001, before unknown ³²

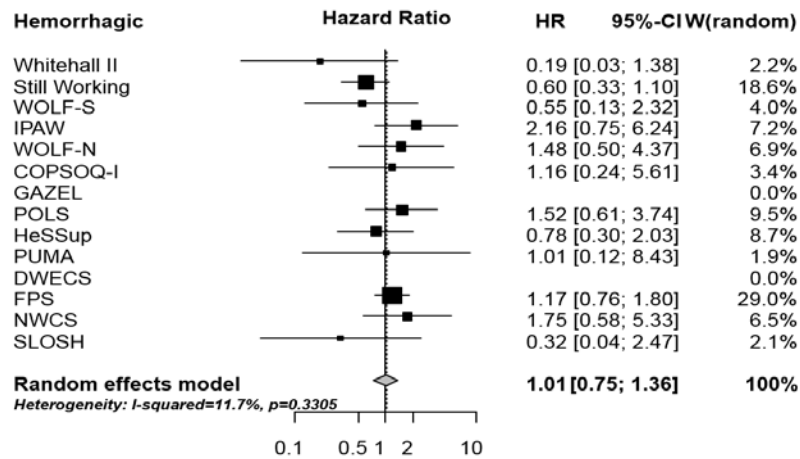
*Positive predictive value is the number of correctly diagnosed stroke cases /the number of all diagnosed stroke cases.

Supplemental Figures I to III present forest plots with study-specific estimates on the associations of job strain with incident ischemic, hemorrhagic and overall strokes.

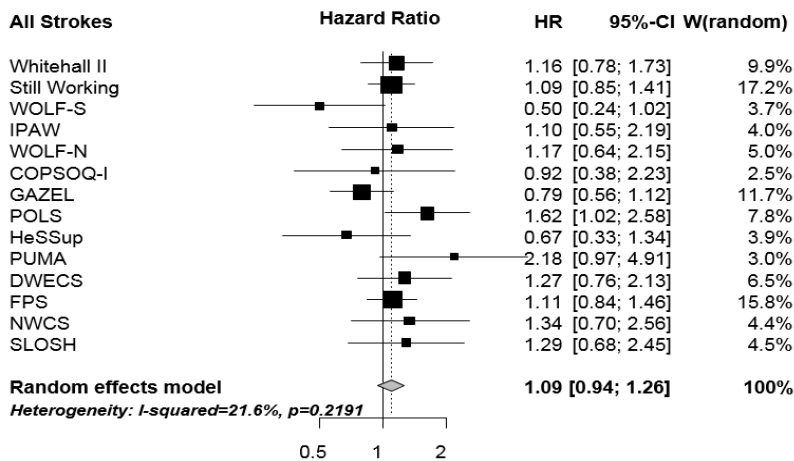
Supplemental Figure I. Study-specific hazard ratios for job strain and ischemic stroke, adjusted for age and sex.



Supplemental Figure II. Study-specific hazard ratios for job strain and hemorrhagic stroke, adjusted for age and sex.



Supplemental Figure III. Study-specific hazard ratios for job strain and overall stroke, adjusted for age and sex.



Sensitivity analysis

In the main analysis, we used socioeconomic status (SES) as a proxy marker for stroke risk factors. Sensitivity analysis was performed in the three studies with data on stroke risk factors (diabetes, hypertension, smoking and heavy alcohol use). Atrial fibrillation at baseline was not possible to include in the analysis due to low numbers (less than 20 cases per study). Low socioeconomic status (SES) was strongly associated with stroke risk factors, except for alcohol use, whereas the associations of job strain with stroke risk factors were weak or non-existent (**Supplemental Table III**). Adjustment for SES attenuated the association between job strain and ischemic stroke approximately the same extent (0-16%) as did the adjustment for standard stroke risk factors (4-24%). More specifically, in Whitehall II, the age- and sex-adjusted hazard ratio for the association between job strain and incidence ischemic stroke was 1.45 (95%CI 0.84-2.49). This hazard ratio was 1.38 (95%CI 0.80-2.38) after further adjustment for SES (attenuation 16%) and 1.43 (95%CI 0.83-2.46) after adjustment for age, sex and stroke risk factors (attenuation 4%). The corresponding figures were 1.33 (95%CI 0.63-2.80), 1.34 (95%CI 0.63-2.85, attenuation 0%) and 1.26 (95%CI 0.57-2.78, attenuation 24%) for WOLF-Norrland. As is shown in **Supplemental Figure I**, the hazard ratio for job strain and ischemic stroke in WOLF-Stockholm was below one preventing us to calculate effect attenuation after adjustments in this cohort.

Supplemental Table III. Age- and sex-adjusted associations of socioeconomic status (SES) and job strain with stroke risk factors at baseline in three studies (Whitehall II, Wolf-N and Wolf-S)

Exposure	Age- and sex-adjusted summary odds ratio for			
	Diabetes	Hypertension	Current smoking	Heavy alcohol use
Low SES vs high SES	2.26 (1.45-3.54)	1.47 (1.24-1.57)	3.30 (2.93-3.73)	0.76 (0.63-0.93)
Job strain vs no job strain	0.96 (0.65-1.40)	0.94 (0.84-1.04)	1.13 (1.03-1.24)	1.10 (0.94-1.28)

References

1. Kristensen TS, Hannerz H, Hogh A, Borg V. The Copenhagen Psychosocial Questionnaire--a tool for the assessment and improvement of the psychosocial work environment. *Scand J Work Environ Health*. 2005;31:438-449
2. Burr H, Bjorner JB, Kristensen TS, Tüchsen F, Bach E. Trends in the Danish work environment in 1990–2000 and their associations with labor-force changes. *Scand J Work Environ Health*. 2003;29:270-279
3. Feveile H, Olsen O, Burr H, Bach E. Danish Work Environment Cohort Study 2005: From idea to sampling design. *Statistics in Transition*. 2007;8:441-458
4. Kivimäki M, Lawlor DA, Smith GD, Kouvonen A, Virtanen M, Elovainio M, et al. Socioeconomic Position, Co-Occurrence of Behavior-Related Risk Factors, and Coronary Heart Disease: the Finnish Public Sector Study. *Am J Public Health*. 2007;97:874-879
5. Goldberg M, Leclerc A, Bonenfant S, Chastang JF, Schmaus A, Kaniewski N, et al. Cohort profile: the GAZEL Cohort Study. *Int J Epidemiol*. 2007;36:32-39.

6. Zins M, Leclerc A, Goldberg M. The French GAZEL Cohort Study: 20 Years of Epidemiological Research. *Advances in Life Course Research*. 2009;14:135-146
7. Korkeila K, Suominen S, Ahvenainen J, Ojanlatva A, Rautava P, Helenius H, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol*. 2001;17:991-999
8. Nielsen M, Kristensen T, Smith-Hansen L. The Intervention Project on Absence and Well-being (IPAW): design and results from the baseline of a 5-year study. *Work and Stress*. 2002;16:191-206
9. Nielsen ML, Rugulies R, Christensen KB, Smith-Hansen L, Bjorner JB, Kristensen T. Impact of the psychosocial work environment on registered absence from work: a two-year longitudinal study using the IPAW cohort. *Work and Stress*. 2004;18:323-335
10. Bossche van den S, Hupkens, CLH., Ree de, SJM., Smulders, PGW. Nationale Enquête Arbeidsomstandigheden 2005: methodologie en globale resultaten. [Netherlands Working Conditions Survey 2005: methodology and overall results]: Hoofddorp: TNO Work & Employment; 2006.
11. Hooff van M, van den Bossche SNJ, Smulders P. The Netherlands Working Conditions Survey. Highlights 2003-2006. Hoofddorp: TNO Work & Employment; 2008.
12. de Groot W, Dekker R. The Dutch System of Official Social Surveys. Mannheim: Mannheim Centre for European Social Research; 2001. Report No.: 30.
13. Borritz M, Rugulies R, Bjorner JB, Villadsen E, Mikkelsen OA, Kristensen TS. Burnout among employees in human service work: design and baseline findings of the PUMA study. *Scand J Public Health*. 2006;34:49-58.
14. Magnusson Hanson LL, Theorell T, Oxenstierna G, Hyde M, Westerlund H. Demand, control and social climate as predictors of emotional exhaustion symptoms in working Swedish men and women. *Scand J Public Health* 2008;36:737-743
15. Hasson D, Theorell T, Westerlund H, et al. Prevalence and characteristics of hearing problems in a working and non-working Swedish population. *J Epidemiol Community Health* 2010;64:453-460
16. Kalimo R, Toppinen S. Organizational well-being: ten years of research and development: in a forest industry corporation. In: Kompier M, Cooper C, eds. Preventing Stress, Improving Productivity: European Case Studies in the Workplace. London: Routledge; 1999:52-85.
17. Väänänen A, Murray M, Koskinen A, Vahtera J, Kouvonen A, Kivimäki M. Engagement in cultural activities and cause-specific mortality: prospective cohort study. *Prev Med*. 2009;49:142-147
18. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet*. 1991;337:1387-1393
19. Peter R, Alfredsson L, Hammar N, Siegrist J, Theorell T, P. W. High effort, low reward, and cardiovascular risk factors in employed Swedish men and women: baseline results from the WOLF Study. *J Epidemiol Community Health*. 1998;52:540-547

20. Alfredsson L, Hammar N, Fransson E, de Faire U, Hallqvist J, Knutsson A, et al. Job strain and major risk factors for coronary heart disease among employed males and females in a Swedish study on work, lipids and fibrinogen. *Scand J Work Environ Health*. 2002;28:238-248
21. Fransson EI, Nyberg ST, Heikkilä K, Alfredsson L, De Bacquer D, Batty GD, 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
22. Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, et al. Job strain as a risk factor for coronary heart disease: A collaborative meta-analysis of individual participant data. *Lancet*. 2012;380:1491-1497
23. Heikkilä K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB, et al. Work stress and cancer risk: A meta-analysis of 5 700 incident cancer events in 116 000 European men and women. *BMJ*. 2013;346:f165
24. Heikkilä K, Madsen IEH, Nyberg ST, Fransson EI, Ahola K, Alfredsson L, et al. Job strain and chronic obstructive pulmonary disease exacerbations: An individual participant meta-analysis of 92 000 individuals. *Eur Resp J*. 2014;44:247-251
25. Nyberg ST, Fransson EI, Heikkilä K, Ahola K, Alfredsson L, Bjorner JB, et al. Job strain as a risk factor for type 2 diabetes: A pooled analysis of 124 808 men and women. *Diabetes Care*. 2014;37:2268-2275
26. Britton A, Milne B, Butler T, Sanchez-Galvez A, Shipley M, Rudd A, et al. Validating self-reported strokes in a longitudinal UK cohort study (Whitehall II): extracting information from hospital medical records versus the Hospital Episode Statistics database. *BMC Med Res Methodol*. 2012;12:83
27. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a national register of patients. *Neuroepidemiology*. 2007;28:150-154.
28. Sivenius J, Torppa J, Tuomilehto J, Immonen-Räihä P, Kaarisalo M, Sarti C, et al. Modelling the burden of stroke in Finland until 2030. *Int J Stroke*. 2009;4:340-345
29. Malmivaara A, Meretoja A, Peltola M, Numerato D, Heijink R, Engelfriet P, et al. Comparing ischaemic stroke in six European countries. [published online ahead of print September 7, 2014]The EuroHOPE register study. *Eur J Neurol*. 2014.
<http://onlinelibrary.wiley.com/doi/10.1111/ene.12560/abstract>. Accessed November 4, 2014.
30. Köster M, Asplund K, Johansson Å, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. *Neuroepidemiology*. 2013;40:240-246
31. Lazzarino AI, Palmer W, Bottle A, Aylin P. Inequalities in stroke patients' management in English public hospitals: A survey on 200,000 patients. *PLoS ONE*. 2011;6:e17219
32. Analyserande rapport från Riks-Stroke för helåren 2001 och 2002 [Analysing report from the Swedish Stroke Register for the years 2001 and 2002] Riks-Stroke, Årsrapporter [Swedish Stroke register, Yearly reports] <http://www.riksstroke.org/wp-content/uploads/2014/05/Rapport01-02.pdf> Accessed November 4, 2014.