Psychosocial factors at work and health - what have we learned from mega-studies?

Mika Kivimäki

Department of Epidemiology & Public Health University College London, UK
Clinicum, Faculty of Medicine, University of Helsinki and Finnish Institute of Occupational Health, Finland
Outline

- Do we need mega studies?
- What are the benefits?
- What are the drawbacks?
- Long-term goals
Researchers:

- Mika Kivimäki, PhD/Prof, University College London, UK; Finnish Institute of Occupational Health, Finland (Principal Investigator)
- Solja T Nyberg, MSc, Finnish Institute of Occupational Health, Helsinki, Finland
- Töres Theorell, Prof, MD PhD, Stress Research Institute, Stockholm University, Stockholm, Sweden
- Reiner Rugulies, PhD/Prof, MSc, MPH, National Research Centre for the Working Environment, Denmark
- Nico Dragan, PhD/Prof, Institute for Medical Informatics, Biometry, and Epidemiology, University Duisburg-Essen, Germany
- Dirk De Bacquer, PhD/Prof, Department of Public Health, Ghent University, Gent, Belgium
- Els Clays, PhD, Department of Public Health, Ghent University, Belgium
- France Kittel, PhD/Prof, School of Public Health Université libre de Bruxells, Belgium
- Annalisa Casini, PHD, School of Public Health Université libre de Bruxells, Belgium
- Jakob B Bjorner, MD, PhD, National Research Centre for the Working Environment, Copenhagen, Denmark
- Ida E H Madsen, MSc, National Research Centre for the Working Environment, Denmark
- Jaana Pentti, BSc, Finnish Institute of Occupational Health, Turku, Finland
- Marianna Virtanen, PhD/Prof, Finnish Institute of Occupational Health, Helsinki, Finland
- Marcel Goldberg, MD, PhD/Prof, Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France
- Marie Zins, MD, MSc, Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France
- Sébastien Bonenfant, MSc, Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France
- Archana Singh-Manoux, PhD, Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France
- Markku Koskenvuo, MD/Prof, Department of Public Health, University of Helsinki, Finland
- Sakari B. Suominen, MD, PhD, University of Turku, Department of Public Health, Finland
- Jussi Vahtera, Prof, Dep Public Health, University of Turku and Turku University Hospital, Turku, Finland
- Thorsten Lunau, MSc, Institute for Medical Informatics, Biometry, and Epidemiology, University Duisburg-Essen, Germany
- Karl-Heinz Jöckel, Prof., Institute for Medical Informatics, Biometry, and Epidemiology, University Duisburg-Essen, Germany
- Raimund Erbel, Prof. MD, Department of Cardiology, West-German Heart Center Essen, University Duisburg-Essen, Germany
- Martin Lindhardt Nielsen, MD, PhD, Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Denmark
- Katriina Heikkilä, PhD, Finnish Institute of Occupational Health, Helsinki, Finland
- Johannes Siegrist, PhD/Prof, Department of Medical Sociology, University of Duesseldorf, Germany
- Mark Hamer, PhD, Epidemiology and Public Health, UCL, London, UK
- Markus Jokela, PhD, Behavioural Sciences, University of Helsinki, Finland
- .../.
Researchers (...continued)

- **Wendela E, Hooftman**, PhD, TNO, the Netherlands
- **Goedele A. Geuskens**, PhD, TNO, the Netherlands
- **Irene I.L.D. Houtman**, PhD, TNO, the Netherlands
- **Hugo Westerlund**, Prof, PhD, Stress Research Institute, Stockholm University, Stockholm, Sweden
- **Constanze Leineweber**, PhD, Stress Research Institute, Stockholm University, Stockholm, Sweden
- **Aki Koskinen**, MSc, Finnish Institute of Occupational Health, Helsinki, Finland
- **Ari Väänänen**, PhD, Finnish Institute of Occupational Health, Helsinki, Finland
- **Anders Knutsson**, Prof, MD, PhD, Department of Health Sciences, Mid Sweden University, Sundsvall, Sweden
- **Maria Nordin**, PhD, Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, Umeå University, Umeå, Sweden
- **Peter JM Westerholm**, Prof, MD, Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden
- **Lars Alfredsson**, Prof, PhD, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
- **Eleonor I Fransson**, PhD, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
- **G. David Batty**, PhD, UCL Epidemiology & Public Health, UK
- **Hermann Burr**, PhD, Centre for Maritime Health and Safety, Esbjerg, Denmark
- **Linda L Magnusson Hanson**, PhD, Stress Research Institute, Stockholm University, Stockholm, Sweden
- **Paula Salo**, PhD, Finnish Institute of Occupational Health, Turku, Finland
- **Marianne Borritz**, MD, PhD, Head Department of Occupational Medicine, Bispebjerg University Hospital
- **Tuula Oksanen**, MD, PhD, Finnish Institute of Occupational Health, Turku, Finland
- **Anne Kouvonen**, PhD, School of Sociology, Social Policy & Social Work, Queen's University Belfast, Belfast, UK.
- **Karl-Heinz Ladwig**, Prof. Dr., German Research Center for Environmental Health (GmbH), Germany
- **Matti Joensuu**, MSc, Finnish Institute of Occupational Health, Helsinki, Finland
- **Jane E. Ferrie**, PhD, Department of Epidemiology and Public Health, University College London, London, UK
- **Michael G. Marmot**, MD, PhD/Prof, Department of Epidemiology and Public Health, University College London, London, UK
- **Andrew Steptoe**, PhD, DSc/Prof, Department of Epidemiology and Public Health, University College London, London, UK
- **Jürgen Schupp**, Prof, Dr, German Institute for Economic Research, Berlin, Germany
- **Gert G Wagner**, Prof, Dr, German Institute for Economic Research, Berlin, Germany
- **Jan H. Pejtersen**, PhD, The Danish National Centre for Social Research, Herluf Trolles Gade 11, DK-1052 Copenhagen, Denmark
Barry Marshall, quoting historian Daniel Boorstin:

“The greatest obstacle to discovery is not ignorance—it is the illusion of knowledge.”

Marshall is the co-discoverer of Helicobacter pylori, the bacterium that causes stomach ulcers, for which he won the 2005 Nobel Prize in Medicine.

Martin Evans:

“Do not necessarily believe anything”

Prospective cohort studies on job strain:

Reed 1989: **No increased risk**, RR=0.9 (0.7-1.4)

Johnson 1989: **Doubling CHD risk**, RR=1.9, 1.2-3.2)

Alterman 1994: **50% excess risk**, RR=1.5 (1.0-2.2)

Kivimäki 2002: **Doubling the CHD risk**, RR=2.2 (1.2-4.2)

Lee 2002: **No increased risk (a non-significant protective effect)**, RR=0.8 (0.5-1.3)

Eaker 2004: **No increased risk**, RR=1.3 (0.7-2.3) in men or 0.8 (02-2.8) in women

Uchiyama 2005: **No increased risk in men**, RR=1.8 (0.5-6.3), a **9-fold increased risk in women** RR=9.1 (1.1-70)

Netterström 2006: **Doubling CHD risk**, RR=2.4 (1.0-5.8)

Bonde 2009: **No increased risk**, RR=1.6 (0.7-3.7)

Netterström 2010: **No increased risk**, RR=1.3 (0.8-2.1)

etc
DON’T LET THE TRUTH GET IN THE WAY OF A GOOD STORY: AN ILLUSTRATION OF CITATION BIAS IN EPIDEMIOLOGIC RESEARCH

Table 1. Number of Citations, Effect Size, Journal Impact Factor, and Scientific Quality for Cohort Studies on Job Strain and Coronary Heart Disease Published From 1989 to 2004

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>No. of Citationsa</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scopus</td>
<td>Web-of-Science</td>
<td></td>
</tr>
<tr>
<td>Kivimäki, 2002 (11)</td>
<td>384</td>
<td>328</td>
<td>2.20</td>
</tr>
<tr>
<td>Johnson, 1989 (8)</td>
<td>255</td>
<td>252</td>
<td>1.94</td>
</tr>
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<td>219</td>
<td>203</td>
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<td>0.94</td>
</tr>
<tr>
<td>Alterman, 1994 (9)</td>
<td>120</td>
<td>116</td>
<td>1.48</td>
</tr>
<tr>
<td>Lee, 2002 (10)</td>
<td>79</td>
<td>70</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a Citations as of January 25, 2014.
b Web of Science journal impact factor for 2013.
c Quality score (range, 0–12) was obtained from a previous review (14). The quality score for Kuper et al. (12) is missing because it was not included in that review.
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<td>255</td>
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<td>1.94</td>
<td>1.15, 3.21</td>
</tr>
<tr>
<td>Kuper, 2003 (12)</td>
<td>219</td>
<td>203</td>
<td>1.57</td>
<td>1.26, 1.96</td>
</tr>
<tr>
<td>Eaker, 1992 (13)</td>
<td>200</td>
<td>189</td>
<td>0.94</td>
<td>0.45, 1.44</td>
</tr>
<tr>
<td>Reed, 1989 (7)</td>
<td>125</td>
<td>147</td>
<td>0.94</td>
<td>0.65, 1.36</td>
</tr>
<tr>
<td>Alterman, 1994 (9)</td>
<td>120</td>
<td>116</td>
<td>1.48</td>
<td>0.98, 2.24</td>
</tr>
<tr>
<td>Lee, 2002 (10)</td>
<td>79</td>
<td>70</td>
<td>0.80</td>
<td>0.48, 1.33</td>
</tr>
</tbody>
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Research Letter

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<tr>
<td>Kivimäki, 2002 (11)</td>
<td>384</td>
<td>328</td>
<td>2.20</td>
<td>1.16, 4.17</td>
<td>17.215</td>
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<tr>
<td>Johnson, 1989 (8)</td>
<td>255</td>
<td>252</td>
<td>1.94</td>
<td>1.15, 3.21</td>
<td>3.775</td>
</tr>
<tr>
<td>Kuper, 2003 (12)</td>
<td>219</td>
<td>203</td>
<td>1.57</td>
<td>1.26, 1.96</td>
<td>3.393</td>
</tr>
<tr>
<td>Eaker, 1992 (13)</td>
<td>200</td>
<td>189</td>
<td>0.94</td>
<td>0.45, 1.44</td>
<td>4.780</td>
</tr>
<tr>
<td>Reed, 1989 (7)</td>
<td>125</td>
<td>147</td>
<td>0.94</td>
<td>0.65, 1.36</td>
<td>4.780</td>
</tr>
<tr>
<td>Alterman, 1994 (9)</td>
<td>120</td>
<td>116</td>
<td>1.48</td>
<td>0.98, 2.24</td>
<td>4.780</td>
</tr>
<tr>
<td>Lee, 2002 (10)</td>
<td>79</td>
<td>70</td>
<td>0.80</td>
<td>0.48, 1.33</td>
<td>6.982</td>
</tr>
</tbody>
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Kivimäki et al. *Am J Epidemiol* 2014
“After controlling for citation-time, we found that each 10% increase in reported excess risk was associated with 16.5 (95% CI: 7.9, 25.0) additional citations in Scopus (P = 0.001, adjusted $R^2 = 0.69$) and 12.4 (95% CI: 1.1, 23.7) additional citations in Web-of-Science (P = 0.03, adjusted $R^2 = 0.31$).”

P. 447
Hard work won't kill you? Well it might actually.

It is often said that "hard work won't kill you."

Long hours at work may boost heart-attack risk
By Amanda Gardner, Health.com
April 4, 2011 -- Updated 2143 GMT (0543 HKT)

UK NEWS
Heart risk of long hours

“A research finding is less likely to be true

- when more teams are involved in a scientific field in chase of statistical significance
- when the studies conducted in a field are smaller
- when effect sizes are smaller
- when there is a greater number and lesser pre-selection of tested relationships
- where there is greater flexibility in designs, definitions, outcomes, and analytical modes
- when there is greater financial and other interest and prejudice.”
EDITORIAL

Post hoc decision-making in observational epidemiology—is there need for better research standards?

Mika Kivimäki,¹* Archana Singh-Manoux,¹,² Jane E Ferrie¹,³ and G David Batty¹,⁴
Alternative measures of job strain

The availability of alternative ways of defining exposures can encourage multiple testing and further contribute to selective reporting and publication bias.

Fransson et al. 2012: **11 different sets of questions** that had been utilised to measures high demands and low job control.

Landsbergis et al. 1994: multiple alternative ways of defining job strain when using identical item content: **the quotient, the quadrant term, the quadrant term using national means, and linear term formulations.**
In a narrative review by Rose-Everson and colleagues, it was concluded that job control might be more important than job demands.

In another narrative review, Eller et al. came to the opposite conclusion: The association of job strain with CHD is likely to be driven by high demands.

Some authors have suggested that the association between job strain and CHD is more pronounced in men,

Others see women as more vulnerable.

A further suggestion is that job strain increases CHD risk in younger employees but that the excess risk attenuates at older ages.

Some critics have suggested that the observed associations are spurious, with job strain being only a marker of other causal risk factors, such as socioeconomic stratification.
Subgroup analysis as a source of spurious findings: An illustration using new data on alcohol intake and CHD

Figure 1 Hazard ratios (95% confidence intervals) for experiencing a major coronary heart disease (CHD) event during 24 years of follow-up in abstainers compared to moderate drinkers by Zodiac sign in the Whitehall II study (n=8517; adjusted for age, gender, socio-economic position and smoking status).

Bell, Kivimäki, Batty. Addiction 2014
The IPD-Consortium

Pooling individual-level data from published and unpublished cohort studies:

- Allows comparison of published and unpublished data.
- With large data sets it is possible to show (and publish) absence of associations convincingly. Also possible to detect small effects.

Pre-defined exposure via 2-stage data extraction:

- A description of our exposure definitions published before any linkage with outcome data (cf trial registration)
- This ensures that associations with outcomes do not affect the way exposures are operationalised (cf double-blinding in trials)
Systolic blood pressure in relation to CVD mortality rates:
the Prospective Studies Collaboration
Systolic blood pressure in relation to CVD mortality rates: the Prospective Studies Collaboration
Systolic blood pressure in relation to CVD mortality rates: the Prospective Studies Collaboration
<table>
<thead>
<tr>
<th>Country</th>
<th>Baseline</th>
<th>Number of 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 CHD events (incidence per 10 000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehall II</td>
<td>1985-88</td>
<td>10250</td>
<td>3398 (33%)</td>
<td>1437 (14%)</td>
<td>44-4 (6-1)</td>
<td>154 980</td>
<td>382 (24-6)</td>
</tr>
<tr>
<td>Still working</td>
<td>Finland</td>
<td>1986</td>
<td>9129</td>
<td>2082 (23%)</td>
<td>40-9 (9-1)</td>
<td>193 809</td>
<td>729 (37-6)</td>
</tr>
<tr>
<td>WOLF-S</td>
<td>Sweden</td>
<td>1992-95</td>
<td>5653</td>
<td>2447 (43%)</td>
<td>41-5 (11-0)</td>
<td>81 516</td>
<td>106 (13-0)</td>
</tr>
<tr>
<td>Belstress</td>
<td>Belgium</td>
<td>1994-98</td>
<td>14 226</td>
<td>2190 (15%)</td>
<td>45-8 (6-0)</td>
<td>44 812</td>
<td>85 (19-0)</td>
</tr>
<tr>
<td>IPAW</td>
<td>Denmark</td>
<td>1996-97</td>
<td>2022</td>
<td>1356 (67%)</td>
<td>41-2 (10-5)</td>
<td>25 801</td>
<td>35 (13-6)</td>
</tr>
<tr>
<td>WOLF-N</td>
<td>Sweden</td>
<td>1996-98</td>
<td>4678</td>
<td>780 (17%)</td>
<td>44-0 (10-3)</td>
<td>53 891</td>
<td>122 (22-6)</td>
</tr>
<tr>
<td>COPSOQ-I</td>
<td>Denmark</td>
<td>1997</td>
<td>1724</td>
<td>824 (48%)</td>
<td>40-8 (10-5)</td>
<td>20 171</td>
<td>33 (16-4)</td>
</tr>
<tr>
<td>GAZEL</td>
<td>France</td>
<td>1997</td>
<td>11 237</td>
<td>3132 (28%)</td>
<td>50-3 (3-0)</td>
<td>125 180</td>
<td>277 (22-1)</td>
</tr>
<tr>
<td>POLS</td>
<td>Netherlands</td>
<td>1997-2002</td>
<td>24 473</td>
<td>10 093 (41%)</td>
<td>38-1 (11-1)</td>
<td>240 570</td>
<td>241 (10-0)</td>
</tr>
<tr>
<td>HeSSup</td>
<td>Finland</td>
<td>1998</td>
<td>16 345</td>
<td>9102 (56%)</td>
<td>39-5 (10-2)</td>
<td>113 761</td>
<td>67 (5-9)</td>
</tr>
<tr>
<td>DWECs</td>
<td>Denmark</td>
<td>2000</td>
<td>5463</td>
<td>2556 (47%)</td>
<td>41-8 (11-0)</td>
<td>48 074</td>
<td>55 (11-4)</td>
</tr>
<tr>
<td>FPS</td>
<td>Finland</td>
<td>2000</td>
<td>47 373</td>
<td>38 317 (81%)</td>
<td>44-6 (9-4)</td>
<td>224 074</td>
<td>109 (4-9)</td>
</tr>
<tr>
<td>NWCS</td>
<td>Netherlands</td>
<td>2005-06</td>
<td>44 900</td>
<td>23 085 (51%)</td>
<td>39-9 (11-8)</td>
<td>162 089</td>
<td>117 (7-2)</td>
</tr>
<tr>
<td>Total</td>
<td>..</td>
<td>1985-2006</td>
<td>197 473</td>
<td>97 172 (49%)</td>
<td>42-3 (9-8)</td>
<td>1488 728</td>
<td>2358 (15-8)</td>
</tr>
</tbody>
</table>


Table: Characteristics of eligible participants

Kivimäki et al. *Lancet* 2012
<table>
<thead>
<tr>
<th>Job demand</th>
<th>Belstres (JCQ), GAZEL (JCQ), HeSSup (JCQ), SLOSH (DCQ), WOLF N (DCQ), WOLF S (DCQ)</th>
<th>COPSOQ (DCQ)</th>
<th>DWECs (Other)</th>
<th>FPS (JCQ)</th>
<th>HNR (JCQ)</th>
<th>IPAW (DCQ)</th>
<th>KORA (JCQ)</th>
<th>NWCS (Other)</th>
<th>POLS (Other)</th>
<th>PUMA (Other)</th>
<th>Still Working (Other)</th>
<th>WH II (DCQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Working very fast</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2. Working very hard/intensively</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3. No excessive amount of work/too much effort</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4. Enough time</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5. Conflicting demands</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Job control</th>
<th>Belstres (JCQ), GAZEL (JCQ), HeSSup (JCQ), SLOSH (DCQ), WOLF N (DCQ), WOLF S (DCQ)</th>
<th>COPSOQ (DCQ)</th>
<th>DWECs (Other)</th>
<th>FPS (JCQ)</th>
<th>HNR (JCQ)</th>
<th>IPAW (DCQ)</th>
<th>KORA (JCQ)</th>
<th>NWCS (Other)</th>
<th>POLS (Other)</th>
<th>PUMA (Other)</th>
<th>Still Working (Other)</th>
<th>WH II (DCQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Learn new things</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>2. High level of skill</td>
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<td></td>
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<td>X</td>
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<tr>
<td>3. Creativity/initiative</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>4. Repetitive work</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>5. A lot of say/what to do</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>6. Little freedom/how to do</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Highlights of IPD-Work results on disease endpoints

- Coronary heart disease
- Stroke
- Diabetes
- Cancer
- Respiratory disease
- Hospital-tREATED depression
Highlights of IPD-Work results on disease endpoints

- Coronary heart disease
  - Stroke
  - Diabetes
  - Cancer
  - Respiratory disease
  - Hospital-treated depression
Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data


Lancet 2012; 380: 1491-97

Figure 2: Association of job strain with incident coronary heart disease in relation to study follow-up periods, adjustments, publication status for data, and geographical region.
Studies on job strain and CHD after the IPD-Work paper in 2012
Building a more comprehensive data base

A

3705 studies identified through database search
1898 PubMed
1807 Embase

3700 excluded
877 duplicates
2823 missing data

5 published cohort studies
20 cohort studies with unpublished data

25 studies included in meta-analysis of coronary heart disease*

B

1958 studies identified through database search
789 PubMed
1169 Embase

1957 excluded
639 duplicates
1318 missing data

1 published cohort study
16 cohort studies with unpublished data

17 studies included in meta-analysis of stroke

http://dx.doi.org/10.1016/S0140-6736(15)60295-1
Cumulative meta-analysis of published and unpublished data of the association between long working hours and incident coronary heart disease (from Kivimäki et al. Lancet 2015).

<table>
<thead>
<tr>
<th>Published studies</th>
<th>Total (N)</th>
<th>Events (N)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
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<tr>
<td>Holtermann (2010)</td>
<td>4943</td>
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<td>Virtanen (2010)</td>
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<td>750</td>
<td>1.50 (1.03-2.19)</td>
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<tr>
<td>Netterstrom (2010)</td>
<td>12103</td>
<td>854</td>
<td>1.40 (0.96-2.05)</td>
<td>0.0821</td>
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<tr>
<td>Toker (2012)</td>
<td>20941</td>
<td>947</td>
<td>1.30 (1.03-1.66)</td>
<td>0.0301</td>
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<tr>
<td>O’Reilly (2013)</td>
<td>435890</td>
<td>1904</td>
<td>1.25 (1.06-1.47)</td>
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</table>

<table>
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<th>Unpublished studies</th>
<th>Total (N)</th>
<th>Events (N)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
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<tr>
<td>WOLF-S</td>
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<td>2016</td>
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<tr>
<td>Belstress</td>
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<td>2089</td>
<td>1.21 (0.99-1.49)</td>
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<tr>
<td>WOLF-N</td>
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<td>2222</td>
<td>1.21 (1.00-1.47)</td>
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<td>COPSOQ-I</td>
<td>459580</td>
<td>2259</td>
<td>1.20 (1.01-1.44)</td>
<td>0.0417</td>
</tr>
<tr>
<td>HeSSup</td>
<td>475730</td>
<td>2327</td>
<td>1.22 (1.04-1.44)</td>
<td>0.0154</td>
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<tr>
<td>FPS</td>
<td>520295</td>
<td>2548</td>
<td>1.19 (1.00-1.42)</td>
<td>0.0500</td>
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<td>HNR</td>
<td>522069</td>
<td>2586</td>
<td>1.19 (1.02-1.39)</td>
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<tr>
<td>DWECs</td>
<td>527604</td>
<td>2652</td>
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<tr>
<td>COPSOQ-II</td>
<td>530993</td>
<td>2664</td>
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<td>0.0231</td>
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<tr>
<td>NWCS</td>
<td>574503</td>
<td>2780</td>
<td>1.17 (1.02-1.35)</td>
<td>0.0225</td>
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<tr>
<td>Alameda</td>
<td>575946</td>
<td>2905</td>
<td>1.16 (1.01-1.33)</td>
<td>0.0297</td>
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<tr>
<td>NHANES</td>
<td>580868</td>
<td>3185</td>
<td>1.17 (1.03-1.33)</td>
<td>0.0160</td>
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<tr>
<td>WLSS</td>
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<td>4234</td>
<td>1.16 (1.03-1.29)</td>
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<tr>
<td>MIDUS</td>
<td>593591</td>
<td>4566</td>
<td>1.14 (1.03-1.27)</td>
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<tr>
<td>HILDA</td>
<td>598470</td>
<td>4652</td>
<td>1.13 (1.02-1.26)</td>
<td>0.0159</td>
</tr>
</tbody>
</table>

http://dx.doi.org/10.1016/S0140-6736(15)60295-1
Highlights of IPD-Work results on disease endpoints

- Coronary heart disease
- Stroke
- Diabetes
- Cancer
- Respiratory disease
- Hospital-treated depression
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. Björner, MD, PhD; Marianne Borritz, MD, PhD; Hermann Burr, PhD; Nico Dragano, PhD; et al.

*Stroke. 2015;46:557-559*
Cumulative meta-analysis of published and unpublished data of the association between long working hours and incident stroke

Estimates adjusted for age, sex, and socioeconomic status.

<table>
<thead>
<tr>
<th>Published studies</th>
<th>Total (N)</th>
<th>Events (N)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Reilly (2013)</td>
<td>414 949</td>
<td>215</td>
<td>1.38 (0.88–2.17)</td>
<td>0.1616</td>
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<tr>
<td>Unpublished studies</td>
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<td></td>
</tr>
<tr>
<td>WOLF-S</td>
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<td>312</td>
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<td>COPSOQ-I</td>
<td>422 343</td>
<td>349</td>
<td>1.30 (0.87–1.93)</td>
<td>0.2053</td>
</tr>
<tr>
<td>HeSSup</td>
<td>438 549</td>
<td>427</td>
<td>1.46 (1.03–2.07)</td>
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<tr>
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<td>760</td>
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<td>DWEC5</td>
<td>488 629</td>
<td>852</td>
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<td>COPSOQ-II</td>
<td>492 117</td>
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<td>Whitehall II</td>
<td>499 782</td>
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<td>Alameda</td>
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<td>WLSG</td>
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<td>1535</td>
<td>1.33 (1.11–1.61)</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Kivimäki et al. *Lancet* 2015
Association of categories of weekly working hours with incident stroke

Estimates adjusted for age, sex, and socioeconomic status. *For trend from standard to long working hours.

<table>
<thead>
<tr>
<th>Events (N)</th>
<th>Total (N)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
<th>Dose-response p value*</th>
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<td>36–40 h</td>
<td>774</td>
<td>1.00 (reference)</td>
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<tr>
<td>41–48 h</td>
<td>241</td>
<td>1.10 (0.94–1.28)</td>
<td>0.2401</td>
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<tr>
<td>49–54 h</td>
<td>117</td>
<td>1.27 (1.03–1.56)</td>
<td>0.0265</td>
<td>&lt;0.0001</td>
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<tr>
<td>≥55 h</td>
<td>132</td>
<td>1.33 (1.11–1.61)</td>
<td>0.0022</td>
<td></td>
</tr>
</tbody>
</table>

Decreased risk

Increased risk

Kivimäki et al. *Lancet* 2015
Association of long working hours with incident stroke in relation to study follow-up, adjustments, outcome ascertainment, publication status, and region

<table>
<thead>
<tr>
<th></th>
<th>Events (N)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
<th>Meta-regression p value</th>
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<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td><strong>Follow-up</strong></td>
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<tr>
<td>Full</td>
<td>1535</td>
<td>1.33 (1.11-1.61)</td>
<td>0.0020</td>
<td>0.73</td>
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<tr>
<td>First 3 years excluded</td>
<td>672</td>
<td>1.42 (0.98-2.05)</td>
<td>0.0638</td>
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<tr>
<td><strong>Adjustment</strong></td>
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<tr>
<td>Minimum</td>
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<td>0.84</td>
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<td>Maximum</td>
<td>1247</td>
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<tr>
<td><strong>Outcome ascertainment</strong></td>
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<td>Health records</td>
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<td>Self-report</td>
<td>509</td>
<td>1.31 (0.94-1.83)</td>
<td>0.1108</td>
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<tr>
<td><strong>Publication status</strong></td>
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<td>Published</td>
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<td>1.38 (0.88-2.17)</td>
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<td>0.88</td>
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<td>Unpublished</td>
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<td>1.33 (1.08-1.62)</td>
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<td><strong>Region</strong></td>
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<tr>
<td>USA</td>
<td>509</td>
<td>1.31 (0.94-1.83)</td>
<td>0.1108</td>
<td>0.98</td>
</tr>
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<td>Europe</td>
<td>1026</td>
<td>1.34 (1.05-1.71)</td>
<td>0.0187</td>
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</tr>
</tbody>
</table>
Is the effect clinically meaningful?

In absolute terms, the 10-year stroke incidence is:
- Approximately **6 events per 1000** in individuals working long hours and
- **4.5 events per 1000** in those working standard hours
- A difference of **1.5 events per 1000 per 10 years**.

The corresponding population attributable risk (PAR), assuming the association is causal, is **6%** in a population of full-time employees.

This PAR is comparable to
- Established stroke risk factors that are relatively high in population prevalence but weak in their association with stroke, such as **dyslipidemia**
- Established risk factors that reveal strong relationships but are less common, such as **asymptomatic carotid stenosis** or **nonvalvular atrial fibrillation** below age 70 years

Kivimäki et al. *Lancet* 2015
Highlights of IPD-Work results on disease endpoints

- Coronary heart disease
- Stroke
- **Diabetes**
- Cancer
- Respiratory disease
- Hospital-treated depression
Independent associations of job strain and lifestyle factor with diabetes risk
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 | DOI: 10.2337/dc13-2936

Solja T. Nyberg,1 Eleonor I. Fransson,2,3,4 Katriina Heikkilä,1 Kirsi Ahola,1 Lars Alfredsson,3,5 Jakob B. Bjorner,6 et al.

Obesity without job strain: HR=5.99

Obesity with job strain: HR=7.22
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 | DOI: 10.2337/dc13-2936

Solja T. Nyberg,1 Eleonor I. Fransson,2,3,4 Katriina Heikkilä,1 Kirsi Ahola,1 Lars Alfredsson,3,5 Jakob B. Bjorner,6 et al.

Physical inactivity without job strain: HR=1.61

Physical inactivity with job strain: HR=1.83
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 | DOI: 10.2337/dc13-2936

Solja T. Nyberg,1 Eleonor I. Fransson,2,3,4 Katriina Heikkilä,1 Kirsi Ahola,1 Lars Alfredsson,3,5 Jakob B. Bjorner,6 et al.

Smoking without job strain: HR=1.45

Smoking with job strain: HR=1.70
Heavy drinking without job strain: HR=1.37

Heavy drinking with job strain: HR=1.76
Highlights of IPD-Work results on disease endpoints

- Coronary heart disease
- Stroke
- Diabetes
- Cancer
- Respiratory disease
- Hospital-treated depression
Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116 000 European men and women

Katriina Heikkilä specialist researcher¹, Solja T Nyberg statistician¹, Töres Theorell professor et al.

BMJ 2013;346:f165

**NO association with common cancers**

Fig 2 Multivariable adjusted associations between job strain and incident cancers
Benefits of big data

Improved precision (narrow confidence intervals)

Convincing evidence to rule out type 1 error (a chance finding), especially in subgroup analyses

Convincing evidence to show an absence of an association

Reduction of research waste (”last word” research on simple associations)

Visibility
Researchers Link Longer Work Hours and Stroke Risk

By CATHERINE SAINT LOUIS

AUGUST 19, 2015 6:28 PM

People who work 55 hours or more per week have a 33 percent greater risk of stroke and a 13 percent greater risk of coronary heart disease than those working standard hours, researchers reported on Wednesday in the Lancet.

The new analysis includes data on more than 600,000 individuals in Europe, the United States and Australia, and is the largest study thus far of the relationship between working hours and cardiovascular health. But the analysis was not designed to draw conclusions about what caused the increased risk and could not account for all relevant confounding factors.

"Earlier studies have pointed to heart attacks as a risk of long working hours, but not stroke," said Dr. Urban Janlert, a professor of public health at Umea University in Sweden, who wrote an accompanying editorial. "That's surprising."

Mika Kivimaki, a professor of epidemiology at University College London, and his colleagues combined the results of multiple studies and tried to account for factors that might skew the results. In addition to culling data from published studies, the researchers also compiled unpublished information from public databases and asked authors of previous work for additional data...

Working longer hours increases stroke risk, major study finds

Danger highlighted by research suggesting those working a 55-hour week face 33% increased risk of stroke than those working a 35- to 40-hour week

Sarah Boseley Health editor

Thursday 20 August 2015 00.01 BST Last modified on Monday 24 August 2015 17.20 BST

Shares: 3,496

Comments: 215

The likely toll of long working hours is revealed in a major new study which shows that employees still at their desks into the evening run an increased risk of stroke — and the longer the hours they put in, the higher the risk.

The largest study conducted on the issue, carried out in three continents and led by scientists at University College London, found that those who work more than 55 hours a week have a 33% increased risk of stroke compared with those who work a 35- to 40-hour week. They also have a 13% increased risk of coronary heart disease...

Workaholics may question whether spending so much time in the office is really worth it: those working 55 or more hours a week are 33% more likely to suffer a stroke, research suggests
IPD-Work consortium: Evidence of impact

• Citations (Thompson Reuters ISI Web of Science)
  
  • IPD-Work Lancet 2012 paper has been cited 144 times within the first 3 years and is in the top 1% of the academic field of Clinical Medicine based on a highly cited threshold for the field and publication year (Thompson Reuters ISI Web of Science)

• Altmetrics statistics (social relevance):
  
  • #12 in Altmetric Top 100 in the world in 2015 list.
Drawbacks

Harmonisation is time consuming and often imperfect

Only simple associations (main effects) can be studied – hypothesis testing rather than hypothesis generating

Shifting funding streams

Vulnerable to similar biases as smaller studies (example), but potential damage from misleading results is greater
Antidepressants and diabetes risk: why are there discrepant findings from cohort studies based on electronic patient records and those based on serial phenotyping?

Exposure to antidepressants

Andersohn et al. *Am J Psychiatry* 2009
UK Primary care register

Kivimäki et al. *Biol Psychiatry* 2011
The Whitehall II study
Summary

- **Do we need mega studies?** Yes, we do

- **What are the benefits?** Precision, better protection against publication bias, reduction of research waste, visibility/impact

- **What are the drawbacks?** Simplified, greater damage from misleading findings

- **Long-term goals:** public health surveillance, clinical guidelines, policy, improvement in public health
Figure 1. Assessment of the Quality of Evidence on Long Working Hours as a Risk Factor for Stroke According the GRADE System

Evidence for long working hours as a risk factor for stroke

Observational data (initial quality rating “low”): Yes

Limitations to downgrade quality rating to “very low”
- Risk of bias: Small, marginal risk estimates attenuation after adjustment for confounders in meta-analyses
- Inconsistency: No, little evidence of heterogeneity in study-specific effect estimates. No evidence of differences in effect estimates between subgroups or settings.
- Indirectness: No, evidence not limited to surrogate markers, but includes data on incident stroke in a wide-range of working populations
- Imprecision: No, summary estimate is precise as evidenced by relatively narrow confidence intervals (hazard ratio 1.3, 95% CI 1.1-1.6)
- Publication bias: The effect estimate similar in published and unpublished studies. Funnel plot analysis suggests no publication bias.

Evidence to downgrade quality rating to “very low”: No

Strengths to upgrade quality rating to “moderate”
- Large effect: No, the relative risk for individuals working long hours is less than 2 compared to those working standard hours
- Dose-response: Yes, in full-time workers, the longer working hours, the higher the risk of stroke
- Null effect evidenced by attenuated risk ratios: No, after adjustment for confounding factors, the relationship holds

Evidence to upgrade quality rating to “moderate”: Yes

GRADE rating for quality of evidence: “Moderate”
Options to upgrade quality rating: New RCTs or natural experiments
Open questions

Time spent working is heterogeneous, depending on the type of work and the extent it is associated with stressful versus rewarding aspects of work.

- If the excess stroke risk arises from some specific aspects of work only rather than working long hours per se, one may argue that universal recommendations to shorten long working hours might be premature in relation to stroke prevention.

The mechanistic pathways linking long working hours to stroke remain unclear.

- **Direct effect**: A repetitive triggering of the stress response with adverse effects on neuroendocrine function (such as enhanced activation of the HPA axis and sympathetic nervous system, increased cardiac arrhythmias, elevated inflammatory response, destabilization of atherosclerotic plaques, and hemodynamic perturbations etc).

- **Indirect effect** through health related behaviours.