Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116 000 European men and women

IPD-Work Consortium

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- Research: Personality, lifestyle, and risk of cardiovascular disease and cancer (*BMJ* 2006;332:1359)
- Research: Trends in cause specific mortality across occupations in Japanese men of working age during period of economic stagnation, 1980-2005 (*BMJ* 2012;344:e1191)

STUDY QUESTION

Does work related stress increase the risk of common cancers?

SUMMARY ANSWER

Work related stress, measured and defined as job strain, is not associated with incident colorectal, lung, prostate, or breast cancers.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Work related stress is associated with many adverse health outcomes, such as coronary heart disease and depression. It has been suggested that work stress could also increase the risk of cancer. Thus far, however, the evidence of this association has been inconclusive.

Selection criteria for studies

We used data from 12 independent studies conducted between 1985 and 2008 in Finland, France, the Netherlands, Sweden, Denmark, and the United Kingdom. All studies were part of the IPD-Work (individual-participant-data meta-analysis in working populations) Consortium. The total included population comprised 116 056 men and women aged 17-70, who were free from cancer at study baseline. All participants had complete data on job strain, age, sex, socioeconomic position, body mass index (BMI), smoking, alcohol intake, and incident cancer outcomes. Median follow-up was 12 years.

Primary outcome

The consortium used a predefined two stage data acquisition protocol: in the first stage, baseline data on work stress and sociodemographic and lifestyle factors were acquired and harmonised; in the second stage, these data were linked to register data on disease outcomes, including cancer from national cancer or death registries and registries of admissions to hospital.

Main results and the role of chance

No association was observed between job strain and the risk of colorectal (multivariable adjusted hazard ratio 1.16, 95% confidence interval 0.90 to 1.48), lung (1.17, 0.88 to 1.54), breast (0.97, 0.82 to 1.14), or prostate (0.86, 0.68 to 1.09) cancers. The study specific estimates for the association between job strain and these incident cancers varied in direction and magnitude and their 95% confidence intervals crossed the null value.

Bias, confounding, and other reasons for caution

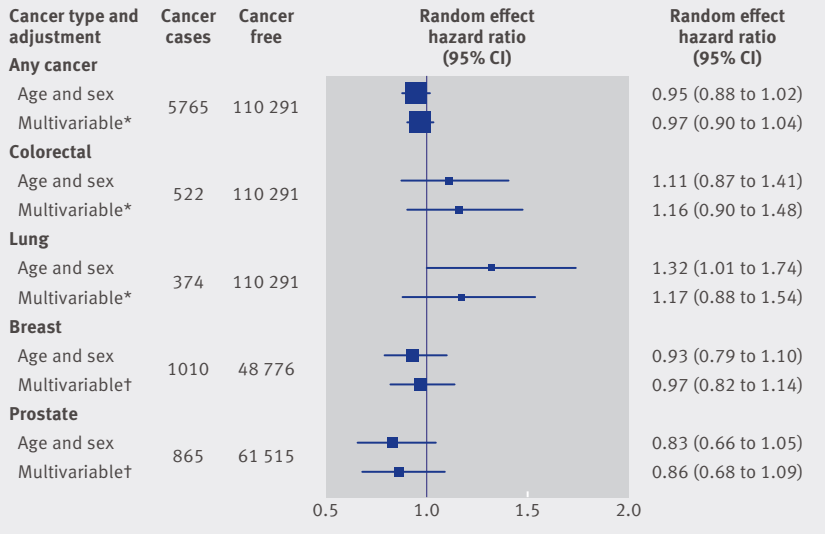
Exposure to work related stress was determined on the basis of only one baseline assessment of job strain. Estimates were adjusted for common cancer risk factors, such as smoking. It remains unknown whether long term exposure to job strain or other indicators of work related stress, such as effort-reward imbalance at work or job insecurity, contribute to cancer risk. We cannot exclude residual confounding—for example, from shift or night time work or exposure to pesticides, fumes, or solvents—from influencing our estimates, though it is unlikely that residual confounding would have masked a strong association.

Based on data from the Nordic countries, continental Europe, and the UK, our findings suggest that job strain is unlikely to be an important risk factor for colorectal, lung, prostate, or breast cancer. We do not know whether these findings are generalisable to working age individuals from other regions, such as Africa, Asia, or the United States.

Study funding/potential competing interests

The IPD-Work Consortium is supported by the EU New OSH ERA research programme (funded by the Finnish Work Environment Fund, Finland, the Swedish Research Council for Working Life and Social Research, Sweden, the Danish National Research Centre for the Working Environment, Denmark), the Academy of Finland, the BUPA Foundation, and the Economic and Social Research Council (ESRC), UK. One of the included studies (POLS) is funded by the Ministry of Social Affairs and Employment, the Netherlands. Various authors have received funding from the Medical Research Council, ESRC, the British Heart Foundation, and the Wellcome Trust (see the full paper on bmj.com for further details).

Association between job strain and cancer



*Adjusted for age (as timescale in model), sex, socioeconomic position, BMI, smoking, and alcohol intake
†Adjusted for age (as timescale in model), socioeconomic position, BMI, smoking, and alcohol intake

Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials

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- Editorial: Dual renin-angiotensin system blockade (*BMJ* 2012;344:e656)
- Research: The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury (*BMJ* 2012;344:e42)

STUDY QUESTION

What is the efficacy and safety of dual blockade of the renin-angiotensin system compared with monotherapy?

SUMMARY ANSWER

Dual blockade of the renin-angiotensin system improved admissions to hospital for heart failure without any improvement in all cause mortality and cardiovascular mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure when compared with monotherapy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Combining various blockers of the renin-angiotensin system for treatment of heart failure, hypertension, and diabetic nephropathy remains common practice among doctors despite strong evidence against benefits from several large trials. In our meta-analysis dual therapy was associated with a significant increase in the risk of adverse events, without any beneficial effect on mortality.

Selection criteria for studies

We searched PubMed, Embase, and CENTRAL from January 1990 to August 2012 for randomised control trials enrolling at least 50 patients and comparing dual blockade of the renin-angiotensin system (any two of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or direct renin inhibitor) with monotherapy.

Primary outcomes

We studied long term efficacy (duration ≥1 year for all cause mortality, cardiovascular mortality, and admissions to hospital for heart failure) and safety events (duration ≥4 weeks for hyperkalaemia, hypotension, renal failure, and withdrawal owing to drug related adverse events) reported in these studies.

Main results and role of chance

33 randomised controlled trials with 68 405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks were included. Dual therapy was not associated with any significant benefit for all cause mortality (relative risk 0.97, 95% confidence interval 0.89 to 1.06) or for cardiovascular mortality (0.96, 0.88 to 1.05) compared with monotherapy. Dual therapy was associated with an 18% reduction in admissions to hospital for heart failure compared with monotherapy (0.82, 0.74 to 0.92). When compared with monotherapy, however, dual therapy was associated with a 55% increase in the risk of hyperkalaemia (P<0.001), 66% increase in the risk of hypotension (P<0.001), 41% increase in the risk of renal failure (P=0.01), and 27% increase in the risk of withdrawal owing to adverse events (P<0.001). Efficacy and safety results were consistent in cohorts with and without heart failure when comparing dual therapy with monotherapy except for all cause mortality, which was higher in the cohort without heart failure than with (P=0.04 and P=0.15) and renal failure, which was significantly higher in the cohort with heart failure than without (P<0.001 and P=0.79).

Bias, confounding, and other reasons for caution

The results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration, different doses of drugs, different definitions for safety outcomes, and different patient groups. Owing to lack of data in each trial, we did not adjust our analysis for adherence to therapy. Analysis of safety events is also prone to biases since the data in each study varied for quality, incidence, severity, and adjudication.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not for profit sectors. SB is on the advisory boards of Boehringer Ingelheim and Daiichi Sankyo. FHM is the ad hoc consultant and speaker for Novartis, Daiichi Sankyo, Pfizer, Takeda, Abbott, Medtronic, Servier, and Bayer.

Risk of long term and safety outcomes with dual blockade of the renin-angiotensin system compared with monotherapy

Outcomes	No of studies	No of patients	Dual therapy *v* monotherapy: relative risk (95% CI)	P value
Long term outcomes:				
All cause mortality	7	56 824	0.97 (0.89 to 1.06)	0.50
Cardiovascular mortality	6	51 814	0.96 (0.88 to 1.05)	0.38
Hospital admissions for heart failure	5	42 071	0.82 (0.74 to 0.92)	0.0003
Safety outcomes:				
Hyperkalaemia	23	60 638	1.55 (1.32 to 1.82)	<0.001
Hypotension	18	61 252	1.66 (1.38 to 1.98)	<0.001
Renal failure	20	64 320	1.41 (1.09 to 1.84)	0.01
Withdrawal owing to drug related adverse events	26	62 020	1.28 (1.17 to 1.39)	<0.001

Influenza A/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: multicentre study

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- Research: Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death (*BMJ* 2012;344:e2794)
- Research: Effectiveness of vaccine against pandemic influenza A/H1N1 among people with underlying chronic diseases (*BMJ* 2012;344:d7901)

STUDY QUESTION

Is vaccination with MF59 adjuvanted influenza A/H1N1 vaccine associated with adverse perinatal events compared with unvaccinated pregnant women?

SUMMARY ANSWER

MF59 adjuvanted A/H1N1 influenza vaccine did not result in an increased risk of adverse perinatal events, and the risk seemed to be lower in vaccinated women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Influenza vaccination is considered an essential element of prenatal care, but data on the safety of MF59 adjuvanted vaccines during pregnancy are scarce.
This study provides new information for healthcare providers and policy makers to make informed decisions about vaccination policies and increase the uptake of vaccination against influenza A/H1N1 among pregnant women.

Participants and setting

A consecutive sample of women who delivered their children from September 2010 to May 2011 in 49 public hospitals in major cities in Argentina participated in this study.

Design

This was a multicentre, cross sectional study. We interviewed women delivering a live or stillborn baby at 22 weeks or more of gestational age or a baby weighing at least 500 g at or immediately after birth and reviewed their medical records.

Primary outcome(s)

The main endpoint was a composite outcome combining the occurrence of low birth weight, preterm delivery, or fetal or early neonatal death up to seven days postpartum.

Main results and the role of chance

We included 30 448 mothers (7293 vaccinated) and their 30 769 newborns. Vaccinated women had a lower risk of the primary composite outcome (7.0% *v* 9.3%; adjusted odds ratio 0.80, 95% confidence interval 0.72 to 0.89) and secondary outcomes of low birth weight (0.74, 0.65 to 0.83), preterm delivery (0.79, 0.69 to 0.90), and perinatal mortality (0.68, 0.42 to 1.06). These findings were consistent in further subgroup analysis. We found no significant differences in maternal outcomes. We used multiple logistic regression and a propensity score approach to adjust for confounders.

Bias, confounding, and other reasons for caution

Selection bias could be a potential explanation for our results. Participating women signed an informed consent form, and therefore might have a lower probability of severe morbidity. In addition, we did not have adequate data on women admitted to intensive care or on those who died. We did several pre-specified sensitivity analyses considering the different definitions of exposure and risk categories defined in the protocol, to explore different scenarios and possible interactions of the effect of MF59 adjuvanted vaccine on adverse perinatal outcomes in different risk subgroups. Although this analytical approach cannot control for all residual confounding or eliminate potential biases, we believe that these consistent findings strengthen our conclusion.

Generalisability to other populations

Our results are in agreement with several other studies in different countries, and we believe that the consistent results across different risk subgroups allow us to generalise these findings to pregnant women vaccinated in other settings in developing and developed countries.

Study funding/potential competing interests

This study was funded by an independent grant from Novartis Argentina SA.

Crude and adjusted main perinatal outcomes in vaccinated and non-vaccinated women

	No (%)		Odds ratio (95% CI)	
Outcome	Vaccinated H1N1 (n=7293)	Non-vaccinated H1N1 (n=23 195)	Crude	Multiple logistic regression adjusted*
Preterm + low birth weight + perinatal mortality	513 (7.0)	2160 (9.3)	0.74 (0.67 to 0.81)	0.80 (0.72 to 0.89)
Preterm (<37 weeks)	354 (4.8)	1505 (6.5)	0.73 (0.65 to 0.83)	0.79 (0.69 to 0.90)
Low birth weight	357 (4.8)	1606 (6.9)	0.69 (0.61 to 0.78)	0.74 (0.65 to 0.83)
Perinatal mortality	54 (0.7)	257 (1.1)	0.63 (0.46 to 0.86)	0.68 (0.42 to 1.06)

*Adjusted for number of antenatal visits, level of education, maternal age, income, parity, smoking, and history of pregnancy induced hypertension.
†Propensity score was entered in model as five level dummy variable, both in fifths of probability of vaccination and range of probability, from 0-10% to >40%.

Medical school gift restriction policies and physician prescribing of newly marketed psychotropic medications: difference-in-differences analysis

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EDITORIAL by Kesselheim

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STUDY QUESTION

Does attending a medical school with an active policy that restricts gifts from the pharmaceutical industry influence subsequent prescribing behavior?

SUMMARY ANSWER

Physicians who attended a medical school with an active gift restriction policy were less likely to prescribe a newly marketed psychotropic medication over older alternatives in two of the three classes examined. Among cohorts of students who had a longer exposure to the policy or were exposed to more stringent policies, prescribing rates were further reduced.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Our study provides some preliminary evidence that exposure to a gift restriction policy during medical school may reduce the likelihood that a physician will prescribe newly introduced psychotropic medications over older alternatives within the same drug class.

Participants and setting

Using a dataset that covers 60% of prescriptions written in the United States, we compared prescribing patterns in 2008 and 2009 of physicians attending one of the 14 medical schools with a gift restriction policy in place by 2004 with those of physicians graduating from the same schools before implementation of the policy, as well as a set of contemporary matched controls.

Design

A difference-in-differences estimation was used to examine the effect of medical school gift restriction policies on physicians' subsequent propensity to prescribe a newly introduced drug over older alternatives within the same class. Two additional analyses used the same design to examine the effect of policy strength and duration of policy exposure on subsequent prescribing behavior.

Primary outcomes

The probability that a physician would prescribe a newly marketed medication over existing alternatives. We examined three newly introduced medications in three psychotropic classes: lisdexamfetamine among stimulants, paliperidone among antipsychotics, and desvenlafaxine among antidepressants. All of these medications relied on mechanisms of action that were not novel.

Main results and the role of chance

For two of the three medications examined, attending a medical school with an active gift restriction policy was associated with reduced prescribing of the newly marketed drug. Physicians who attended a medical school with an active conflict of interest policy were less likely to prescribe lisdexamfetamine over older stimulants (adjusted odds ratio 0.44; P=0.02) and paliperidone over older antipsychotics (0.25; P=0.03). A significant effect was not observed for desvenlafaxine (1.54; P=0.20). In analyses examining physicians who had been exposed to a policy for a longer duration or attended a school with a stricter policy, further reductions in prescribing were observed.

Bias, confounding, and other reasons for caution

We were able to examine only schools that adopted a policy before 2004 to allow adequate time for physicians to complete residency and begin independent prescribing. These early policies were typically more limited in scope and less stringent than policies implemented by medical schools in recent years. In addition, we were unable to examine the role that residency plays in moderating the effect of exposure to a gift restriction policy in medical school.

Generalisability to other populations

Our analyses were limited to prescribing of three newly marketed psychotropic medications. We cannot be certain that the same associations would have been observed for prescribing of other medication classes. Given that none of the three medications we examined was a first in class product on the market, we were unable to examine how these policies might affect the adoption of medications that are clear improvements over existing alternatives.

Any US medical school with a policy on restriction of gifts from pharmaceutical industry before 2004

	Stimulant (lisdexamfetamine)		Antipsychotic (paliperidone)		Antidepressant (desvenlafaxine)	
Variables	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Exposed to policy	0.44 (0.22 to 0.88)	0.02	0.25 (0.07 to 0.85)	0.03	1.54 (0.79 to 3.03)	0.20
Period of exposure	1.26 (0.96 to 1.66)	0.10	1.17 (0.48 to 2.89)	0.73	0.81 (0.52 to 1.26)	0.35
Prescribing volume (100s)	1.05 (1.03 to 1.08)	<0.001	1.04 (1.00 to 1.08)	0.03	1.02 (1.00 to 1.03)	0.10
Cash payment	0.67 (0.55 to 0.81)	<0.001	1.92 (1.24 to 2.97)	0.003	0.94 (0.73 to 1.22)	0.66
Medicaid payment	0.82 (0.66 to 1.02)	0.07	1.65 (1.09 to 2.50)	0.02	0.50 (0.28 to 0.90)	0.02
Psychiatry	0.61 (0.46 to 0.80)	0.001	3.83 (1.18 to 12.4)	0.03	1.53 (0.77 to 3.06)	0.22
General medicine	0.46 (0.35 to 0.59)	<0.001	0.93 (0.26 to 3.36)	0.92	1.72 (0.94 to 3.12)	0.08
Male	0.96 (0.77 to 1.18)	0.69	1.07 (0.53 to 2.13)	0.86	1.14 (0.83 to 1.57)	0.41

Authors' calculations based on data from IMS LifeLink Information Assets-LRx Longitudinal Prescripton Database, 2008-09, IMS Health. Third party is the omitted insurance category. Other is the omitted provider specialty. All models include school fixed effects. Standard errors clustered by prescriber.