RESEARCH

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WHAT OUR READERS ARE SAYING **Association between psychological distress and mortality**

This study was published on bmj.com on 31 July and has prompted several rapid responses. Here's what some of the respondents say:

"Those as puzzled as I am by the mystery factor now said to be responsible for a considerable part of the increased mortality associated with clinical depression and anxiety might like to search for 'family stigma, sexual selection, and the evolutionary origins of severe depression's physiological consequences.' This paper initially struck me as rather implausible but now I am not so sure."

"A lot of scary headlines and misinformation in the media could have been avoided with more modest claims and better epidemiology in this article concerning the mortality

associated with low distress, as well as in its accompanying editorial and press release…It represents yet another instance of the persistent influence of suspect data on our understanding of the association between psychological variables and cancer. Let's keep these data out of the literature, but let's also stick to more modest claims and make a better effort to explain ambiguous results to lay audiences."

"Early exposure to adverse experiences in childhood have been shown to have an adverse effect on health in multiple areas. Life is a marathon, not a sprint, so it is not surprising that being programmed for maladaptive stress responses in childhood has adverse effects on cardiovascular health."

"This article on links is important for two reasons. Firstly, the linkages between immune function and depression and its consequences to morbidity and mortality are becoming increasingly recognised. Secondly, figure 2 illustrates a cycle in mortality over time, with a notable minimum in 2002. This minimum is shared with international trends relating to medical and mental health hospital admissions and bed occupancy, attendance at accident and emergency wards and GP referrals, the incidence of particular cancers, and deaths."

"We encourage greater investigation of the mechanisms linking psychological distress to adverse health outcomes and mortality, and suggest that focused attention be placed on sleep as a potential contributing, yet modifiable, factor."

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NLM

The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema
According to this indirect comparison in a systematic review, no difference exists in effectiveness between bevacizumab and ranibizumab in treating diabetic macular oedema. However, the wide credible intervals cannot exclude the possibility that either drug might be superior, say the authors. Sufficiently powered, direct head to head trials are needed.

Predicting early death in patients with traumatic bleeding
Failure to start appropriate early management in patients with traumatic bleeding is a leading cause of preventable death from trauma. Using data from the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial and the Trauma Audit and Research Network (TARN), Pablo Perel and colleagues developed and validated a prognostic model to predict mortality in such patients. The model is available as a web based calculator and as a chart to be used at the bedside. It can assist in triage and can shorten the time to diagnostic and lifesaving procedures, say the authors.

Suicides associated with the 2008-10 economic recession in England
According to this time trend analysis, the financial crisis that started in 2008 has been associated with about 1000 excess suicides in England. Regions with the largest rises in unemployment have had the largest increases in suicides, particularly among men, say the authors.

Risk of preterm birth after treatment for cervical intraepithelial neoplasia among women attending colposcopy in England
In this retrospective-prospective cohort study, the risk of preterm delivery in women treated by colposcopy in England was substantially less than that in many other studies. The authors conclude that the increased risk seen in studies may be a consequence of confounding and not caused by treatment.

Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies

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EDITORIAL by Lewis

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bmj.com/podcasts
Listen to a podcast interview with Tom C Russ at bmj.com/multimedia

STUDY QUESTION Is psychological distress across the full range of severity associated with mortality?

SUMMARY ANSWER Psychological distress across the full range of scores was associated with increased mortality from all causes, cardiovascular disease, and external causes, even in people who would not usually come to the attention of mental health services; higher levels of distress were similarly associated with cancer deaths.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Previous studies of the association between symptoms of depression and anxiety (commonly referred to as psychological distress) and death from various major mortality outcomes have been unable to reliably ascertain thresholds of risk. We found an elevated risk of mortality across the full range of distress scores, even at lower levels.

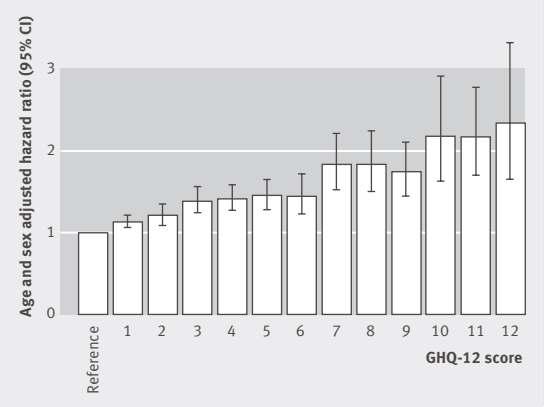
Participants and setting

We included 68 222 adults from general population samples aged 35 years and over, free of cardiovascular disease and cancer, and living in private households in England at study baseline.

Design, size, and duration

We conducted an individual participant meta-analysis of 10 large prospective cohort studies from the Health Survey for England, done between 1994 and 2004. Baseline psychological distress was measured by the 12 item General Health Questionnaire (GHQ-12), and mortality from death certification. We computed study-specific Cox proportional hazards models for the association between baseline psychological distress and later mortality from all causes, cardiovascular disease, cancer, and external causes over a mean follow-up of 8.2 years (standard deviation 3.5); we meta-analysed these using random effects models. In addition to age and sex adjusted models, we incorporated occupational social class, diabetes, body mass index, systolic blood pressure, physical activity, smoking, and alcohol consumption, both individually and in fully adjusted models.

Association between psychological distress and risk of death from all causes



Main results and the role of chance

Psychological distress was associated with total mortality in a dose-response pattern (age and sex adjusted hazard ratio for GHQ-12 scores of 1-3 *v* score 0: 1.20, 95% confidence interval 1.13 to 1.27; scores 4-6: 1.43, 1.31 to 1.56; and scores 7-12: 1.94, 1.66 to 2.26; P<0.001 for trend). This association remained after adjustment for a range of potentially confounding and mediating variables. We saw a similar association for deaths from cardiovascular disease and external causes. Cancer death was only associated with psychological distress at higher levels

Bias, confounding, and other reasons for caution

We incorporated many important behavioural and lifestyle factors into the models, thus exploring several potentially confounding and mediating pathways. Classification of causes of death may not always have been perfectly accurate, but it is likely that use of the broad causes of death in the present study were sufficiently valid. Data were missing for one or more variables in 39.4% (n=26 860) of the sample, but a sensitivity analysis using multiple imputation did not materially alter effect sizes. The diminishing magnitude of the association with increasing duration of follow-up across studies could reflect reverse causality, although excluding deaths occurring within the first five years of follow-up left the association essentially unchanged.

Generalisability to other populations

Results were based on large samples that were representative of the community dwelling adult population (age range 35-102 years) in England, therefore generalisability was high.

Study funding/potential competing interests

The study received no specific funding. Author funding provided by Alzheimer Scotland, Chief Scientist Office (TCR, JMS); Lifelong Health and Wellbeing Initiative, Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and United Kingdom Medical Research Council (TCR, JMS, GDB); National Institute for Health Research (ES); Medical Research Council, Academy of Finland, United States National Institutes of Health (MK); and the Wellcome Trust (GDB). All researchers are independent from the funders.

Shift work and vascular events: systematic review and meta-analysis

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STUDY QUESTION

Is shift work associated with major adverse vascular outcomes?

SUMMARY ANSWER

Shift work is associated with myocardial infarction, ischaemic stroke, and coronary events.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Disruption of circadian rhythm may predispose shift workers to vascular events. Shift work is associated with myocardial infarction, coronary events, and ischaemic stroke; the relative risks are modest, but population attributable risks are important.

Selection criteria for studies

We screened online databases and reference lists for observational studies of shift work and any vascular outcome or all cause mortality. Control groups could include day workers or the general population.

Primary outcome(s)

The primary outcomes were myocardial infarction, ischaemic stroke, and any coronary event.

Main results and role of chance

We identified 34 studies in 2 011 935 people. Shift work was associated with myocardial infarction (risk ratio 1.23, 95% confidence interval 1.15 to 1.31; I^2=0) and ischaemic stroke (1.05, 1.01 to 1.09; I^2=0). Coronary events were also increased (risk ratio 1.24, 1.10 to 1.39), albeit with significant heterogeneity across studies (I^2=85%). Results were consistent in adjusted and unadjusted analyses. Shift work was not associated with increased rates of mortality (whether vascular cause specific or overall). On the basis of the Canadian prevalence of shift work of 32.8%, the population attributable risks were 7.0% for myocardial infarction, 7.3% for all coronary events, and 1.6% for ischaemic stroke.

Bias, confounding, and other reasons for caution

Relatively few studies were available for ischaemic stroke (n=2). Observational studies cannot adjust for all potential sources of confounding, so a causal relation is difficult to establish. Definitions of outcomes differed somewhat across studies.

Study funding/potential competing interests

The study was not funded.

Primary outcomes

Analysis	Events (studies)	Risk ratio (95% CI)	I^2
Random effects			
Myocardial infarction	6598 (10)	1.23 (1.15 to 1.31)	0%
All coronary events	17 359 (28)	1.24 (1.10 to 1.39)	85%
Ischaemic stroke	1854 (2)	1.05 (1.01 to 1.09)	0%
Sensitivity analyses			
Myocardial infarction, unadjusted	4408 (5)	1.41 (1.17 to 1.70)	70%
Myocardial infarction, adjusted	4408 (5)	1.27 (1.10 to 1.45)	35%
Coronary events, unadjusted	8154 (12)	1.21 (1.06 to 1.39)	76%
Coronary events, adjusted	8154 (12)	1.17 (1.05 to 1.31)	56%
Ischaemic stroke, unadjusted	1854 (2)	1.09 (1.04 to 1.14)	0%
Ischaemic stroke, adjusted	1854 (2)	1.05 (1.01 to 1.09)	0%
Trim and filled estimates			
Myocardial infarction	(12)	1.22 (1.15 to 1.30)	NA
All coronary events	(32)	1.19 (1.06 to 1.34)	NA
Ischaemic stroke	—	—	—

NA=not applicable.

Response on bmj.com

"There is some evidence that night shift work can worsen the severity of sleep apnoea in patients already diagnosed as having obstructive sleep apnoea syndrome (OSAS), can significantly increase the blood pressure compared with non-OSAS patients, and all of this may intensify the importance of OSAS as a cardiovascular risk factor. The number of people working night shifts is increasing and OSAS should be investigated in shift workers."

Salvador Diaz-Lobato and S Mayoralas, Hospital Ramon y Cajal, Madrid, Spain

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Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study

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STUDY QUESTION

Is the increased risk of cardiovascular events observed in people who use systemic glucocorticoids associated with the presence of iatrogenic Cushing's syndrome?

SUMMARY ANSWER

Compared with patients prescribed glucocorticoids and without iatrogenic Cushing's syndrome, those with a cushingoid appearance have nearly a three times greater risk of cardiovascular disease, including coronary heart disease, heart failure, and cerebrovascular disease. This risk increases to over fourfold when compared with people not prescribed systemic glucocorticoids.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Glucocorticoid treatment is associated with an increased risk of cardiovascular events but the risk is higher in people who develop iatrogenic Cushing's syndrome. Patients prescribed glucocorticoids who exhibit a cushingoid appearance should be aggressively targeted for early screening and management of cardiovascular risk factors.

Participants and setting

We identified participants from The Health Improvement Network (THIN) database. Participants were those prescribed glucocorticoids with either a diagnosis of iatrogenic Cushing's syndrome (n=547) or no diagnosis of iatrogenic Cushing's syndrome (n=3231) and those not prescribed glucocorticoids (n=3282).

Design, size, and duration

This was a prospective observational cohort study. We assessed the incidence of cardiovascular events in the three groups within a year after diagnosis of iatrogenic Cushing's syndrome or after a randomly selected date for people without a diagnosis of iatrogenic Cushing's syndrome.

Main results and the role of chance

417 cardiovascular events occurred in 341 patients. Taking into account only the first event by patient, the incidence rates of cardiovascular events per 100 person years at risk were 15.1 (95% confidence interval 11.8 to 18.4) in those prescribed glucocorticoids with iatrogenic Cushing's syndrome, 6.4 (5.5 to 7.3) in those prescribed glucocorticoids without Cushing's syndrome, and 4.1 (3.4 to 4.8) in those not taking glucocorticoids. In multivariate analyses the relation between iatrogenic Cushing's syndrome and cardiovascular events was strong.

Bias, limitations, and generalisability

Iatrogenic Cushing's syndrome is not always recorded by doctors and some milder forms were probably missed. This may have led to an underestimation of the effect of iatrogenic Cushing's syndrome on the risk of cardiovascular disease. On the other hand, it is likely that the most severe forms were recorded. No assessment of fat redistribution using reference methods such as dual x ray absorptiometry was available. The generalisability is probably good as people in this study were from a primary care database, of both sexes, selected across all age groups, and had a wide range of diseases.

Study funding/potential competing interests

No funding.

Adjusted hazard ratios* (95% confidence intervals) of cardiovascular events in patients with iatrogenic Cushing's syndrome

	Comparator groups with glucocorticoid users with iatrogenic Cushing's syndrome	
Cardiovascular events	Glucocorticoid users without iatrogenic Cushing's syndrome†	No glucocorticoids
Coronary heart disease (n=177)	2.27 (1.48 to 3.47)	2.68 (1.62 to 4.44)
Cerebrovascular event (n=63)	2.23 (0.96 to 5.17)	2.14 (0.97 to 4.73)
Heart failure (n=101)	3.77 (2.41 to 5.90)	13.31 (7.24 to 24.51)

*Adjusted for age, sex, underlying disease, smoking status, and use of aspirin, oral anticoagulants, diabetes drugs, antihypertensive drugs, and cholesterol lowering drugs.
†Additionally adjusted for initial dosage of glucocorticoids and duration of use.

Screening for colorectal cancer and advanced colorectal neoplasia in kidney transplant recipients: cross sectional prevalence and diagnostic accuracy study of faecal immunochemical testing for haemoglobin and colonoscopy

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STUDY QUESTION

What is the prevalence of advanced colorectal neoplasia in asymptomatic kidney transplant recipients over the age of 50 years, and how accurately does a faecal immunochemical test for haemoglobin detect this?

SUMMARY ANSWER

The prevalence of advanced colorectal neoplasia is high (13%) in asymptomatic kidney transplant recipients; faecal haemoglobin testing is not accurate at detecting this, with poor sensitivity but reasonable specificity.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Kidney transplant recipients, compared with the general population, have an increased risk of developing colorectal cancer and have inferior outcomes once cancer develops. Colonoscopy surveillance rather than faecal haemoglobin screening may be a better option to reduce the risks of colorectal cancer in kidney transplant recipients.

Participants and setting

We included prevalent kidney transplant recipients in South Australia who were aged at least 50 years and attending routine outpatient follow-up.

Design, size, and duration

We did a cross sectional study of prevalence and diagnostic accuracy between June 2008 and October 2011, using a faecal immunochemical test for haemoglobin (Enterix Insure) as the index test and colonoscopy with blinded histological analysis of retrieved samples as the reference standard. Outcome measures were the prevalence of advanced colorectal neoplasia—an adenoma at least 10 mm in diameter, villous features, high grade dysplasia, or colorectal cancer—and the diagnostic accuracy of faecal haemoglobin. We identified 360 potential participants; 229 (64%) completed the study. Mean age was 61.5 years, 66% were male, and the median time post-transplant was 6.5 years.

Final diagnosis in study participants, according to most advanced lesion

Diagnosis	No (%) (n=229)
Normal or non-neoplastic disease	157 (69)
Non-advanced adenoma	43 (19)
Advanced adenoma:	24 (10)
Tubular adenoma ≥10 mm	11 (5)
Villous/tubulovillous adenoma (regardless of size)	9 (4)
High grade dysplasia (regardless of size)	4 (2)
Colorectal cancer	5 (2)
Prevalence of advanced colorectal neoplasia	29 (13, 95% CI 9 to 18)

Main results and the role of chance

We found advanced colorectal neoplasia in 29 (13%, 95% confidence interval 9% to 18%) participants. Faecal haemoglobin was positive in 28 (12.2%) participants; sensitivity, specificity, and positive and negative predictive values for advanced colorectal neoplasia were 31.0% (15.3% to 50.8%), 90.5% (85.6% to 94.2%), 32.1% (15.9% to 52.4%), and 90.1% (85.1% to 93.8%). No significant adverse outcomes from colonoscopy occurred. To identify one case of advanced neoplasia, 8 (6 to 12) colonoscopies were needed.

Bias, confounding, and other reasons for caution

Twenty-six participants submitted faecal haemoglobin tests but did not have colonoscopy and were excluded; sensitivity analyses did not indicate significant verification bias. We were unable to blind endoscopists to faecal results (as is the case in usual clinical practice), so positive results might have led to a greater search for lesions during colonoscopy ("expectation" bias) and increased diagnostic accuracy. Seventy-eight (34%) participants had had colonoscopy more than one year before the study, and this might have led to a lower prevalence of neoplasia (conservative bias), than would have been found in a population naive to colonoscopy.

Generalisability to other populations

We included a broad range of patients from metropolitan and regional settings (not just those cared for at a transplanting centre), who had colonoscopies done in a variety of settings by a variety of operators; our results should therefore be generalisable to transplant populations elsewhere where colonoscopies are done in local centres rather than in a "research" environment. The demographic and comorbidity profiles of the participants in this study are similar to those reported in Australian registry data and in international comparison studies. The achieved high participation rate could reflect a cohort of patients that is more compliant and cooperative than might be found in other jurisdictions.

Study funding/potential competing interests

This study was supported by the Queen Elizabeth Hospital Research Foundation, Roche Products Pty Australia, and Enterix Australia.