RESEARCH

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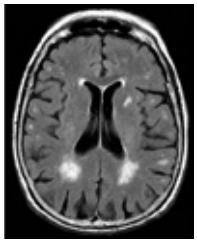


THIS WEEK'S RESEARCH QUESTIONS

Calcium supplements and myocardial infarction

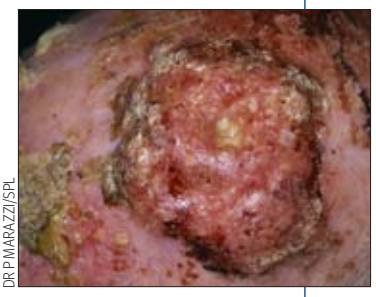
Two years ago Mark J Bolland and colleagues investigated, in a secondary analysis of their own randomised controlled trial in postmenopausal women, the association between calcium supplementation and cardiovascular outcomes (www.bmj.com/cgi/content/full/336/7638/262). They found that the number of women needed to treat (NNT) for five years to prevent one symptomatic fracture was 50 but the corresponding number to cause one myocardial infarction was 44, to cause one stroke was 56, and to cause one cardiovascular event was 29. This proved highly controversial, as the many Rapid Responses attest (www.bmj.com/cgi/eletters/336/7638/262#190701).

Now the same authors' meta-analysis of trials including around 12 000 men and women reports a modestly increased risk of myocardial infarction that was consistent across trials and was independent of age, sex, and type of supplement (p 289). They acknowledge the limitations that the trials were not of combined calcium and vitamin D and none had cardiovascular events as primary end points, but they call for a closer look at the effectiveness and risks of calcium supplementation.

Editorialist John Cleland wonders why calcium might damage vasculature when you'd expect it to improve blood pressure and lipid profiles, and suggests that calcium supplements might simply be causing gastrointestinal symptoms that could be misdiagnosed as cardiac chest pain (p 260). Nonetheless, he concludes that patients with osteoporosis should generally not take calcium supplements, either alone or combined with vitamin D, unless they are also taking an effective treatment for osteoporosis for a recognised indication.

SPL

β human papillomaviruses and squamous cell carcinoma



DR P MARAZZI/SPL

Margaret R Karagas and colleagues helpfully remind us in the full version of their paper that "papillomaviruses are epitheliotropic, non-enveloped, double stranded DNA viruses, of which more than 100 different types have been identified" (*BMJ* 2010;341:c2986). Many cause cancer, but although type 16 genus β human papillomavirus (HPV) is associated with skin cancer in high risk patients, the evidence for this in the general population was shaky. Now their large population based case control study in New Hampshire finds a significant association between this type of HPV and squamous cell carcinoma in adults (p 290). This finding was regardless of age, level of education, smoking status, skin sensitivity to the sun, or number of painful sunburn episodes.

Mind the mortality gap

In his speech as incoming president of the BMA this summer Michael Marmot cited stark evidence from his team's recent report *Fair Society Healthy Lives* (www.marmotreview.org), saying "if everyone over 30 had the mortality rate as low as those with university education we could prevent 202 000 premature deaths, EACH YEAR" and "When I last looked we had found $9 trillion to bail out the banks. For one ninetieth of the money we found to bail out the banks every urban dweller could have clean running water" (*BMJ* 2010;341:c3617).

Bethan Thomas and colleagues add further gloomy evidence, finding in their study of individual mortality data between 1921 and 2007 that the gap in life expectancy between rich and poor in Britain continues to widen (p 291). They dedicate their paper to epidemiologist and social campaigner Jerry Morris, who died last year and who was famous for—among many other things—identifying the relation between deprivation and infant mortality, the minimum income for older people to stay healthy, and the evidence that (in bus conductors and postmen) exercise prevents heart attacks

RESEARCH ONLINE: For this and other new research articles see http://www.bmj.com/channels/research.dtl

Don't dismiss diet in diabetes

Recently we published online a paper reporting the success of an intensive dietary intervention at improving glycaemic control and anthropometric measures in patients with type 2 diabetes (doi:10.1136/bmj.c3337). The research has attracted comments from several advocates of lifestyle interventions for diabetes. Dario Giugliano and Katherine Esposito from Naples, Italy, criticise the "drug intensive style of medicine fuelled by the current medical literature," whereas Rachel Taylor, a patient with type 2 diabetes from New Zealand, describes how lifestyle changes helped lower her glycated haemoglobin concentration from 8.4% to 6% in six months. If you think the *BMJ* is the right journal for your research, please ensure that you've followed our full advice (http://bit.ly/cuGXyb) and then submit your article at: http://submit.bmj.com.

The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis

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EDITORIAL by Wallin and Fladby

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STUDY QUESTION

Are white matter hyperintensities on brain magnetic resonance images associated with risk of stroke, cognitive decline, dementia, and death?

SUMMARY ANSWER

White matter hyperintensities are indeed an important indicator of all of these risks.

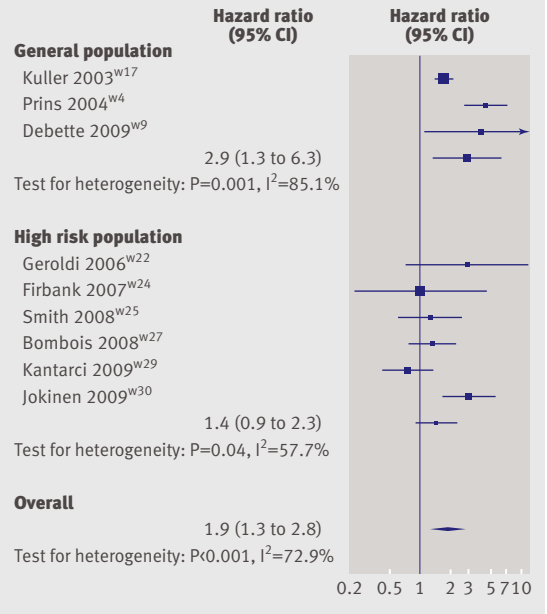
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Brain magnetic resonance imaging often leads to the incidental discovery of white matter lesions, appearing as hyperintensities on T2 weighted images.
Previous studies on associations between these lesions and disease risk have had conflicting results, with heterogeneity in study design, imaging type, and study population. This systematic review and meta-analysis of longitudinal studies provides strong and compelling evidence of increased disease risk.

Selection criteria for studies

We carried out a systematic review of prospective longitudinal studies that assessed the impact of magnetic resonance imaging based measures of white matter hyperintensities volume on risk of incident stroke, cognitive decline, dementia, and death. We searched PubMed from 1966 to 23 November 2009 using predefined search terms and inclusion criteria. Studies that provided risk estimates for a categorical measure of white matter hyperintensities were also included in a meta-analysis assessing the impact of white matter hyperintensities on risk of stroke, dementia, and death.

INVERSE VARIANCE META-ANAYLYSIS OF STUDIES TESTING ASSOCIATION OF WHITE MATTER HYPERINTENSITIES WITH INCIDENT DEMENTIA



Primary outcome(s)

The primary outcome measures were the association of white matter hyperintensities load with incident stroke, cognitive decline, dementia, and death.

Main results and role of chance

We identified 46 longitudinal studies that evaluated the association of white matter hyperintensities with risk of stroke (n=12), cognitive decline (n=19), dementia (n=17), or death (n=10). Twenty two studies could be included in a meta-analysis (nine of stroke, nine of dementia, eight of death). White matter hyperintensities were associated with an increased risk of stroke (hazard ratio 3.3, 95% confidence interval 2.6 to 4.4), dementia (1.9, 1.3 to 2.8), and death (2.0, 1.6 to 2.7). An association of white matter hyperintensities with a faster decline in global cognitive performance, executive function, and processing speed was also suggested.

Bias, confounding, and other reasons for caution

Although we corrected for statistical heterogeneity in the meta-analysis, there was substantial variability in the way white matter hyperintensities were measured and analysed. Another limitation is that some studies could not be included in the meta-analysis because white matter hyperintensities were studied as a continuous variable only using different scales. The pooled hazard ratios for dichotomous measures of white matter hyperintensities burden need to be interpreted with caution, given the heterogeneous definitions of these measures across studies and should not be extrapolated to estimate the individual risk of stroke, dementia, or death in an individual with white matter hyperintensities on magnetic resonance imaging. We could not assess the modifying effect of vascular risk factors on the associations we reported, as the nature and definition of vascular risk factors included in the analyses varied substantially across studies.

Study funding/potential competing interests

SD was supported by a grant from the European Neurological Society, a Fulbright grant, and received an award from the Bettencourt-Schueller and the Lilly foundations.

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

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EDITORIAL by Cleland et al

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STUDY QUESTION

Do calcium supplements (without coadm inistered vitamin D) affect the risk of cardiovascular events?

SUMMARY ANSWER

In a meta-analysis of trials totalling 12 000 participants studied over a mean period of four years, calcium supplements increased the risk of myocardial infarction by about 30%.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A randomised placebo controlled trial suggested that calcium supplements might increase the risk of myocardial infarction and cardiovascular events. In this meta-analysis of all trials with data on cardiovascular events, calcium supplements increased the risk of myocardial infarction by about 30%, suggesting that a reassessment of the role of calcium supplements in the prevention and management of osteoporosis is warranted.

Selection criteria for studies

We searched Medline, Embase, Cochrane Central Register of Controlled trials, reference lists of published meta-analyses, and two clinical trial registries for randomised placebo controlled trials of calcium supplements. Studies were included if they were randomised, double blind, placebo controlled trials; elemental calcium was administered at a dose of ≥500 mg/day; the participants' mean age at baseline was more than 40 years; 100 or more participants were randomised; and the trial duration was more than one year. The lead author of each eligible study was asked to provide patient level data on cardiovascular events that occurred during the study. When such data were not available, we requested summary data at trial level.

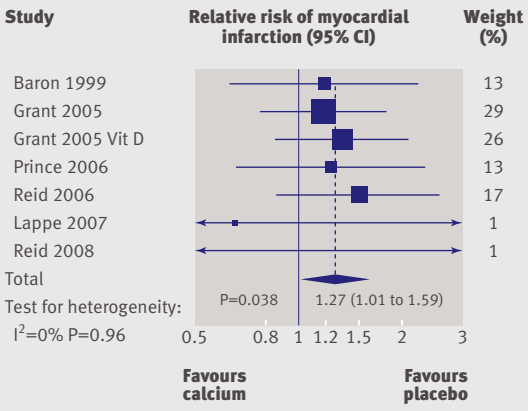
Primary outcome(s)

The prespecified primary end points were time to first myocardial infarction, time to first stroke, and time to first event for the composite end point of myocardial infarction, stroke, or sudden death.

Main results and role of chance

Fifteen trials were eligible for inclusion, with patient level data available for five studies and trial level data for 11. In studies contributing patient level data (8151 participants, median follow-up 3.6 years), 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, P=0.035). Increases were not significant for incidence of stroke (1.20, 0.96 to 1.50, P=0.11), the composite end point (1.18, 1.00 to 1.39, P=0.057), and death (1.09, 0.96 to 1.23, P=0.18). The meta-analysis of trial level data (11 921 participants, mean duration 4.0 years) showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038).

EFFECT OF CALCIUM SUPPLEMENTATION ON RISK OF MYOCARDIAL INFARCTION



Bias, confounding, and other reasons for caution

As we excluded studies that compared coadministered calcium and vitamin D supplements with placebo, the results may not apply to combined calcium and vitamin D. None of the trials had cardiovascular outcomes as the primary end points, and data on cardiovascular events were not gathered in a standardised manner. However, unless differential misclassification or misreporting of cardiovascular events in people treated with calcium occurred, this is unlikely to alter the results.

Study funding/potential competing interests

This review was funded by the Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation. IRR has received research support from and acted as a consultant for Fonterra. JAB, IRR, AA, and GSMacL had study drugs for clinical trials of calcium supplementation supplied by Wyeth (JAB), Mission Pharmacal (IRR), Shire Pharmaceuticals and Nycomed (AA, GSMacL).

Genus β human papillomaviruses and incidence of basal cell and squamous cell carcinomas of skin: population based case-control study

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STUDY QUESTION Does an association exist between genus β human papillomaviruses and the incidence of non-melanocytic skin cancer in the general population?

SUMMARY ANSWER The findings support a relation between genus β human papillomavirus infection and the incidence of squamous cell carcinoma of the skin.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS These viruses are associated with non-melanocytic skin cancer among organ transplant recipients and people with epidermodysplasia verruciformis. Antibody positivity to genus β papillomaviruses was related to risk of squamous cell carcinoma, with a clear increasing trend in risk with number of genus β types positive and a stronger association among people with a history of prolonged glucocorticoid use.

Participants and setting

We selected newly diagnosed cases of basal cell and squamous cell carcinoma among people aged 25 to 74 years residing in New Hampshire from a population based surveillance system. Controls came from population lists and were frequency matched on age and sex to represent the combined distribution of the cases.

Design, size, and duration

This population based case-control study included 2366 newly diagnosed skin cancer cases (663 invasive squamous cell carcinomas, 898 basal cell carcinomas) and controls (n=805), who were interviewed about risk factors for skin cancer and use of immunosuppressive drugs. We used multiplex serology to test plasma samples for L1 antibodies to 16 genus β human papillomaviruses.

Primary outcome(s), risks, and exposures

We calculated the odds ratios for squamous cell and basal cell carcinoma associated with seropositivity to β human papillomaviruses (overall and by individual types).

Main results and the role of chance

Cases of squamous cell, but not basal cell, carcinoma had a higher prevalence of each of the β papillomaviruses assayed compared with controls. The odds ratio for squamous cell carcinoma increased with the number of β papillomavirus types positive. With limited statistical power, the association between seropositivity to any β human papillomavirus type and squamous cell carcinoma was stronger among long term users of systemic glucocorticoids (3.21, 1.22 to 8.44) than among non-users (1.23, 0.97 to 1.55).

Bias, confounding, and other reasons for caution

Selection bias and confounding are inherent to observational studies. By design, blood samples were collected after the diagnosis of a case, so the onset of skin cancer might have altered the prevalence of antibodies to human papillomaviruses. We included a large number of genus β papillomaviruses, but further work encompassing other cutaneous human papillomavirus types is warranted. Our study had limited statistical power to detect interactions with immunosuppressive treatment.

Generalisability to other populations

The study is based on a US, almost exclusively white, population. Generalisability to other, especially non-white, populations is uncertain.

Study funding/potential competing interests

This study was funded in part by grants CA118443 and CA57494 of the National Institutes of Health, National Cancer Institute and grant QLK2-CT-2002-01179 of the European Community.

ODDS RATIOS FOR BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA WITH β HUMAN PAPILLOMAVIRUS (HPV) ANTIBODY POSITIVITY

		Basal cell carcinoma (n=898)		Squamous cell carcinoma (n=663)	
HPV serology results	Control—No (%) (n=805)	No (%)	Adjusted odds ratio* (95% CI)	No (%)	Adjusted odds ratio* (95% CI)
β HPV seronegative	436 (54.2)	502 (55.9)	1.00 (referent)	311 (46.9)	1.00 (referent)
β HPV seropositive	369 (45.8)	396 (44.1)	0.97 (0.80 to 1.19)	352 (53.1)	1.30 (1.04 to 1.61)
1 β HPV type positive	155 (19.3)	180 (20.0)	1.03 (0.79 to 1.33)	118 (17.8)	0.99 (0.74 to 1.33)
2-3 β HPV types positive	93 (11.6)	98 (10.9)	0.97 (0.70 to 1.34)	101 (15.2)	1.44 (1.03 to 2.01)
4-8 β HPV types positive	71 (8.8)	71 (7.9)	0.92 (0.63 to 1.33)	73 (11.0)	1.51 (1.03 to 2.20)
>8 β HPV types positive	50 (6.2)	47 (5.2)	0.90 (0.58 to 1.38)	60 (9.1)	1.71 (1.12 to 2.62)
		P for trend (categorical)=0.54; P for trend (continuous)=0.55		P for trend (categorical)<0.001; P for trend (continuous)=0.003	

*Adjusted for age, sex, level of education, cigarette smoking status one year before reference date (for squamous cell carcinoma only), skin sensitivity as measured by skin reaction after one hour of sun exposure first time in summer, and number of lifetime painful sunburns.

Inequalities in premature mortality in Britain: observational study from 1921 to 2007

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Response on bmj.com

"This study of patterns of mortality inequalities, which relies largely on measures that are functions of relative differences in death rates, is undermined by the failure to recognise that, for reasons related to the shapes of the underlying risk distributions, as mortality declines, relative differences in death rates tend to increase whereas relative differences in survival rates tend to decrease"
James Scanlan, attorney, Washington, DC

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STUDY QUESTION

What is the extent of inequality in premature mortality in Britain?

SUMMARY ANSWER

Inequality in premature mortality has persisted and continues to increase, both for mortality under the age of 75 since 1990 and for mortality under the age of 65 since the 1920s, with geographical inequalities in mortality highest in the most recent time period.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Inequalities in mortality between areas are great. These gaps are still increasing.

Participants and setting

We studied the entire population of Great Britain aged under 75 from 1990 to 2007 and the entire population of Great Britain aged under 65 for the longer historical period from 1921 to 2007.

Design, size, and duration

We aggregated individual level mortality data for those aged under 75 using the most up to date information available. For premature mortality in those aged under 65, over the longer historical period we aggregated mortality data to areas amalgamated from the pre-1974 local authorities.

We calculated age and sex standardised mortality ratios for all cause mortality under the age of 75 and sorted by area tenth of poverty for 1990-2007. For the longer historical series, we calculated ratios for those aged under 65 and sorted by population tenth of the ratio. We then calculated the ratio between the worst and best tenths and the relative index of inequality using all available information. The relative index of inequality is the relative rate of mortality for the hypothetically worst-off compared with the hypothetically best-off person in the population, assuming a linear association between socioeconomic position and risk of mortality. The ratio of inequality is the ratio of the standardised mortality ratio of the most deprived tenth to the least deprived tenth.

Main results and role of chance

Geographical inequalities in mortality have increased according to all ways we measured. For those aged under 75, the ratio between the poorest and richest tenths increased from 1.61 (95% confidence interval 1.61 to 1.62) in 1990-1 to 1.88 (1.87 to 1.88) in 2006-7, while the relative index of inequality increased from 1.61 (1.52 to 1.69) to 2.14 (2.02 to 2.27) over this period. The historical series of premature mortality in those aged under 65 saw the ratio of highest mortality tenth to lowest mortality tenth increase from 1.91 to 2.12 and the relative index of inequality increase from 2.50 to 2.79 from 1921-30 to 1999-2007.

Bias, confounding, and other reasons for caution

We did not examine migration, which will have a bearing on the results shown here. We considered only all cause mortality and did not look at changes in the underlying causes of death.

Generalisability to other populations

The results apply only to the population of Great Britain.

Study funding/potential competing interests

The research was unfunded.

MORTALITY RATE COMPARED WITH GENERAL POPULATION BY INEQUALITY IN GREAT BRITAIN

	Early years	Later years
Mortality tenths for ages 0-64		
Dates	1921-30	1999-2007
SMR for highest mortality tenth	138	149
SMR for lowest mortality tenth	72	70
Ratio of worst to best*	1.91	2.12
Relative index of inequality*	2.50	2.79
Income tenths for ages 0-74		
Dates	1990-1	2006-7
SMR for poorest tenth	129	140
SMR for richest tenth	80	75
Ratio of worst to best (95% CI)	1.61 (1.61 to 1.62)	1.88 (1.87 to 1.88)
Relative index of inequality (95% CI)	1.61 (1.52 to 1.69)	2.14 (2.02 to 2.27)

SMR=standardised mortality ratio.
*No confidence intervals are available for historical data series.