RESEARCH

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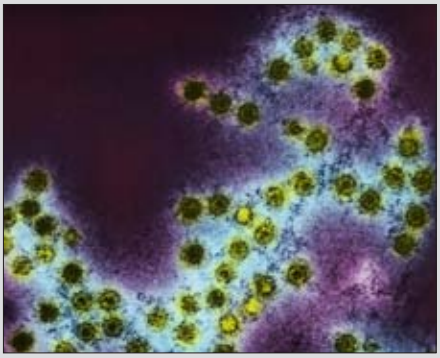
THIS WEEK'S RESEARCH QUESTIONS



CDC/SPL

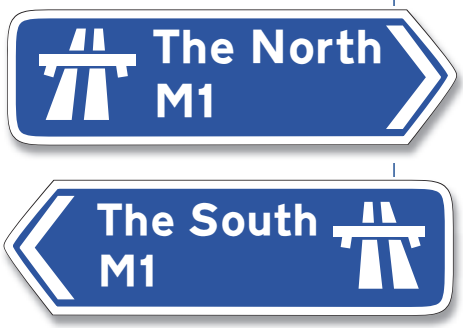
Type 1 diabetes: an infectious link?

This week's Practice and Clinical Review sections focus on the diagnosis and treatment of type 1 diabetes, but what causes the condition in the first place? While genetics is probably involved, infection—specifically, with enteroviruses— is also strongly suspected to play a part. But studies aiming to pin down such a link have had mixed results.

Wing-Chi G Yeung and colleagues reviewed the evidence for a link between enterovirus infection and type 1 diabetes and related autoimmunity through a meta-analysis (p 421). Unlike a previous review (which found no association) they looked at studies that used molecular methods of viral detection, which is now the standard for diagnosis of current infection. The included studies were observational and varied in nature, but the results suggest that a clinically significant association does exist.

The analysis couldn't establish, however, whether enteroviruses actually cause diabetes. Editorialists Didier Hober and Famara Sane say that prospective studies suggest an association between enterovirus infections and subsequent production of autoantibodies against pancreatic β cells, but there's also evidence that viruses may have a protective effect (p 391). The complexities of the viral link remain to be teased out.

It's grim up north

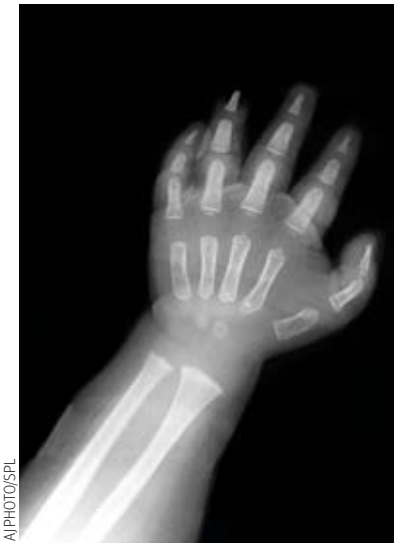


The concept of a "north-south divide" in health and wealth in England—with southerners healthier and better off than their northern counterparts—has existed since as far back as 1066. Plenty has changed healthwise since the Normans conquered the country, yet this divide still persists today. But have medical advances and improvements in quality of life lessened the disparity in recent years?

John Hacking and colleagues have looked at more than 40 years of all cause mortality data to see whether this well established trend has changed since the 1960s (p 424). Having divided England into two parts with a boundary between the Wash and the Severn Estuary, they examined specific mortality rates for each year from 1965 to 2008 by age, sex, and region (north *v* south).

Over the past four decades (and five governments), the percentage excess deaths in the north compared with the south, the so called "northern excess mortality," averaged 13.8% and was significantly larger for males than for females (14.9% *v* 12.7%). Worse, although the inequality decreased from the early 1980s to the late 1990s for both sexes, it increased significantly from 2000 to 2008. The increase was most marked among people aged 20-34, changing from no significant northern excess for 1965 to 1995 to 22.2% for 1996 to 2008. In addition, people in the north were a fifth more likely to die before the age of 75 than were people in the south.

Writing in a linked editorial (p 392), Margaret Whitehead and Tim Doran suggest that the coming government spending cuts and the switch from primary care trusts to general practice consortiums will only serve to widen the divide. "Future prospects," they say, "look grim."



AJPHOTO/SPL

Radiation in early life

Earlier reports suggest an association between in utero exposure to radiation from diagnostic radiography and an increased risk of childhood cancer, but do these procedures pose a risk when done in early infancy? The results of Preetha Rajaraman and colleagues' case-control study suggest so (p 423)—data from medical records showed that exposure to diagnostic radiography in the first 100 days of life was associated with a small increase in risk of all childhood cancer and leukaemia, and a significant increase in lymphoma. The possible risks were seen with radiation at doses lower than those associated with commonly used procedures such as computed tomography, indicating that such methods should be used cautiously when investigating a very young child or a pregnant woman's abdomen or pelvis. However, no excess risk of childhood cancer was seen with in utero exposure to ultrasound scans.

Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies

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EDITORIAL by Hober and Sane

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STUDY QUESTION

Is there an association between current enterovirus infection diagnosed with molecular testing and development of autoimmunity or type 1 diabetes?

SUMMARY ANSWER

Analysis of results from 33 studies shows a strong association between enterovirus infection and type 1 diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Many observational studies have shown an association between enteroviruses and type 1 diabetes, but a systematic review of serological studies found no relation. The current systematic review and meta-analysis shows an association between current enterovirus infection and type 1 diabetes.

Selection criteria for studies

Studies were identified by searches of PubMed and Embase (until May 2010; no language restrictions), reference lists of identified articles, and contact with authors. Studies were eligible for inclusion if they were controlled cohort or case-control studies measuring enterovirus RNA or viral protein in the blood, stool, or tissue of patients with pre-diabetes and diabetes, with adequate data to calculate an odds ratio and 95% confidence intervals.

Primary outcomes

The primary outcomes were detection of one or more autoantibodies associated with type 1 diabetes and diagnosis of type 1 diabetes.

Main results and role of chance

We identified and included 22 relevant papers and two abstracts (all case-control studies), with a total of 4448 participants. Seven papers contained more than one study, giving a total of 33 studies: nine pre-diabetes and 24 diabetes studies. The overall quality of the studies was good, as assessed by the Newcastle-Ottawa scale. Study design varied greatly, with a high level of heterogeneity. Meta-analysis showed a significant association between enterovirus infection and type 1 diabetes related autoimmunity (odds ratio 3.7, 95% confidence interval 2.1 to 6.8) and clinical type 1 diabetes 9.8 (5.5 to 17.4). The association remained significant after a sensitivity analysis. When we excluded studies with poor methodological quality (score <5) from the clinical diabetes group, the combined odds ratio was 9.0 (4.6 to 17.5).

SUMMARY COMBINED ODDS RATIOS FOR ASSOCIATION BETWEEN ENTEROVIRUS INFECTION (DETECTED WITH MOLECULAR TESTING) AND TYPE 1 DIABETES

Study outcome	No of studies	OR (95% CI)*
Pre-diabetes	9	3.7 (2.1 to 6.8)
Type 1 diabetes	25	9.8 (5.5 to 17.4)
Type 1 diabetes (NOS score >5)	18	9.0 (4.6 to 17.5)
Newly diagnosed type 1 diabetes	12	12.7 (6.4 to 25.2)
Established type 1 diabetes	11	10.8 (3.99 to 29.4)

NOS=Newcastle-Ottawa scale.
*All P<0.001.

Bias, confounding, and other reasons for caution

As a meta-analysis of case-control studies, there are limits to the ability of our study to detect a true association between enterovirus infection and type 1 diabetes because of possible confounding and biases. Important confounding factors are age, genetic risk, geographical location, and sampling time. Only 10 studies matched for three or more of these factors, and we could not adjust for their potential influence in our analysis. Most of the included studies used children without diabetes or who were negative for antibodies as controls, but there could have been unmeasured factors influencing their risk of developing diabetes (such as levels of vitamin D). There was also significant heterogeneity between studies, probably because of methodological differences, particularly in method of polymerase chain reaction, sample collection site, and case definition.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CME

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Improving cardiovascular health at population level: 39 community cluster randomised trial of Cardiovascular Health Awareness Program (CHAP)

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STUDY QUESTION What is the effect on hospital admissions for acute myocardial infarction, stroke, and congestive heart failure of a locally delivered but standardised and centrally supported community-wide cardiovascular health promotion and disease prevention programme targeting older adults?

SUMMARY ANSWER A collaborative, multi-pronged, community based health promotion and prevention programme targeting older adults reduced cardiovascular disease related hospital admissions at the population level.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The importance of small shifts in the distribution of risk factors on the overall cardiovascular health of the population has been underscored repeatedly in the literature, but robust evidence supporting community-wide interventions to precipitate such shifts remains sparse. Reductions in rates of hospital admission for cardiovascular disease with CHAP were significant both statistically and from a population health perspective.

Design

In this community cluster randomised trial, eligible communities were stratified by population size and geographical location and randomly allocated to receive either the Cardiovascular Health Awareness Program (CHAP; n=20) or no intervention (n=19). Patients in CHAP communities were invited to attend volunteer run cardiovascular risk assessment and education sessions held in community based pharmacies over a 10 week period. Automated blood pressure readings and self reported risk factor data were collected and shared with patients and their family physicians and pharmacists.

Participants and setting

We did the study in 39 mid-sized communities in Ontario, Canada. Participants were community dwelling residents aged 65 years or over, family physicians, pharmacists, volunteers, community nurses, and local lead organisations.

COMPARISON OF MEAN HOSPITAL ADMISSION RATES PER 1000 BY STUDY ARM

	Pre-intervention rate (1 September 2005 to 31 August 2006)		Post-intervention rate (1 September 2007 to 31 August 2008)		
Hospital admissions	CHAP (n=67 874)	Control (n=72 768)	CHAP (n=69 942)	Control (n=75 499)	Rate ratio (95% CI); P value
Composite	30.15	29.36	27.90	30.13	0.91 (0.86 to 0.97); <0.01
Acute myocardial infarction	10.24	10.26	9.54	10.81	0.87 (0.79 to 0.97); <0.01
Congestive heart failure	11.19	11.11	10.51	12.22	0.90 (0.81 to 0.99); 0.03
Stroke	8.71	7.99	7.86	7.10	0.99 (0.88 to 1.12); 0.89

Primary outcome(s)

The primary end point was a composite of hospital admissions for acute myocardial infarction, stroke, and congestive heart failure among all community residents aged 65 years and over in the year before compared with the year after implementation of CHAP. Analysis was by intention to treat at the cluster (community) level.

Main results and the role of chance

All 20 intervention communities successfully implemented CHAP. In all, 15 889 unique participants received 27 358 cardiovascular assessments with the assistance of 577 peer volunteers. After adjustment for hospital admission rates in the year before the intervention, CHAP was associated with a 9% relative reduction in our composite end point (rate ratio 0.91, 95% confidence interval 0.86 to 0.97; P=0.002) or 3.02 fewer annual hospital admissions for cardiovascular disease per 1000 people aged 65 and over. We found statistically significant reductions favouring the intervention communities in hospital admissions for acute myocardial infarction and congestive heart failure but not for stroke.

Bias, confounding, and other reasons for caution

We cannot know which specific components of CHAP were responsible for the observed reductions in hospital admissions for cardiovascular disease. The reduction in admission rates for acute myocardial infarction and congestive heart failure but not for stroke is probably due to the lower incidence of stroke and the fact that these rates declined in both intervention and control communities during the follow-up period.

Generalisability to other populations

CHAP was designed to target older adults, and our approach and findings are probably not generalisable to younger people. Our findings may not hold for larger urban centres or countries where healthcare delivery is organised differently. Recruitment, training, and retention of qualified and committed volunteers may be less feasible in some countries.

Study funding/potential competing interests

The study was funded in part by the Canadian Stroke Network and the Ontario Ministry of Health Promotion and supported by the Institute for Clinical Evaluative Sciences, a non-profit research corporation funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Trial registration number

Current controlled trials ISRCTN50550004.

Trends in mortality from 1965 to 2008 across the English north-south divide: comparative observational study

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EDITORIAL by Whitehead and Doran

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STUDY QUESTION

What are the rates and trends in the mortality of the north of England compared with the south (the north-south divide) over the four decades from 1965?

SUMMARY ANSWER

The north-south divide in all cause mortality has been both severe and persistent over the past four decades. Males were affected more than females, and the variation across age groups was substantial. The rise in this inequality from 2000 to 2008 was notable and occurred despite the public policy emphasis in England over this period on reducing inequalities in health.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A longstanding significant north-south divide in England exists for most health metrics. This paper adds a precise quantification of the size and trends of the divide in all cause mortality by sex and age from 1965 to 2008—showing, on average, a fifth more premature deaths in the north, and a recent worsening despite policies to reduce health inequalities.

Population and setting

All residents in England in each year from 1965 to 2008 divided into north and south (five northernmost versus four southernmost government office regions, with the dividing line approximately from the Wash to the Severn Estuary).

Design

Population wide comparative observational study of mortality.

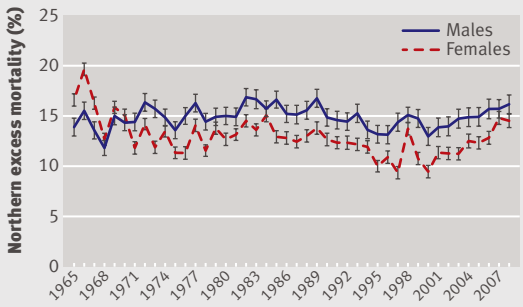
Primary outcomes

Death rate ratios of north over south England by age band and sex. Northern excess mortality (percentage excess deaths in north compared with south, adjusted for age and sex and examined for annual trends using Poisson regression).

Main results and the role of chance

Over the past four decades the northern excess mortality has remained substantial, at an average of 13.8% (95% confidence interval 13.7% to 13.9%). This geographical inequality was significantly larger for males than for females (14.9%, 14.7% to 15.0% *v* 12.7%, 12.6% to12.9%, P<0.001). The inequality decreased significantly although temporarily from the early 1980s to the late 90s for both sexes, followed by a significant steep increase from 2000 to 2008. Inequality varied with age, being higher for ages 0-9 and 40-74 years and lower for ages 10-39 and over 75 years. Time trends also varied with age. The strongest trend over time by age group was the increase among people aged 20-34, from no significant northern excess for 1965 to 1995 to 22.2% (18.7% to 26.0%) for 1996 to 2008. Overall, the north experienced a fifth more premature (<75 years) deaths than the south, which was significant: a pattern that changed only by a slight increase between 1965 and 2008.

PERCENTAGE (95% CONFIDENCE INTERVAL) OF NORTHERN EXCESS DEATHS FOR MALES AND FEMALES OF ALL AGES, 1965 TO 2008



The reduction in northern excess mortality in the early 80s and also in the late 80s/early 90s corresponds to periods of economic recession, whereas the increase from 2000 coincides with an economic boom, when wealth in the south grew faster than in the north. The economic and income disparity between north and south (26.2% more disposable income in the south than in the north in 2008, up from 20.9% in 1995) continues.

Bias, confounding, and other reasons for caution

Mortality from all causes is a reliable measure for comparing the health experience of large geographical areas over time because it has been gathered with negligible bias over many years. Inaccuracies in population estimates that might affect studies examining smaller geographies are less likely to affect this study.

Study funding/potential competing interests

The researchers were not specifically funded to do this research. We have no competing interests.

Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer: case-control study

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STUDY QUESTION

Is exposure to diagnostic radiographic examinations or ultrasound scans in utero or in early infancy (age 0-100 days) associated with risk of childhood cancer?

SUMMARY ANSWER

Exposure to x rays in utero and in early infancy was associated with small, non-statistically significant increases in risk of all childhood cancers and leukaemia; exposure in early infancy was additionally associated with a statistically significant increase in childhood lymphoma (based on small numbers).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Earlier studies have reported that in utero exposure to radiation from diagnostic radiography is associated with increased risk of childhood cancer, but the association between postnatal radiographs and risk of childhood cancer has been unclear. The new findings indicate possible risks of cancer from radiation at doses lower than those associated with commonly used procedures such as computed tomography scans.

Participants and setting

Participants were 2690 cases with childhood cancer and 4858 age, sex, and region matched controls from the UK Childhood Cancer Study (UKCCS), born in 1976-96 in England and Wales.

Design, size, and duration

We analysed data for this case-control study by using conditional logistic regression adjusted for age, sex, study region, maternal age, and child's birth weight.

Primary outcome(s), risks, exposures

The primary outcomes were risk of all childhood cancer, leukaemia, lymphoma, and central nervous system tumours, measured by odds ratios and 95% confidence intervals. Information on exposure to ultrasound scans and diagnostic radiographic procedures in utero and in early infancy (0-100 days) came from medical records.

Main results and the role of chance

We found no increased risk of childhood cancer with in utero exposure to ultrasound scans and some indication of a non-statistically significant elevated risk after in utero exposure to x rays for all cancers (odds ratio 1.14, 95% confidence interval 0.90 to 1.45) and leukaemia (1.36, 0.91 to 2.02). Exposure to diagnostic radiography in early infancy was associated with small, non-significant excess risks for all cancers and leukaemia as well as increased risk of lymphoma (odds ratio 5.14, 1.27 to 20.8, on the basis of small numbers).

Bias, confounding, and other reasons for caution

Despite the large number of cases of childhood cancer, our study had low power to detect a small increase in risk because of low prevalence of exposure to diagnostic radiation and probable decreases in doses of radiation over time. We cannot rule out the possibility that the increased risk of lymphoma in young infants exposed to radiography may be due to some factor related to disease rather than exposure to radiation.

Generalisability to other populations

We did this analysis in children diagnosed as having cancer (1992-6) and control children participating in the UKCCS epidemiological study for whom medical records could be abstracted. Whether these results are generalisable to all children is unclear.

Study funding/potential competing interests

This research was supported in part by intramural funds from the US National Institutes of Health. The UKCCS is sponsored and administered by Leukaemia and Lymphoma Research.

ADJUSTED ODDS RATIOS (95% CI) FOR CHILDHOOD CANCER WITH EXPOSURE IN UTERO AND IN EARLY INFANCY TO DIAGNOSTIC RADIOGRAPHIC AND ULTRASOUND SCAN EXAMINATION

Exposure	All childhood cancers	Leukaemia	Lymphoma	Central nervous system
In utero:				
Radiography	1.14 (0.90 to 1.45)	1.36 (0.91 to 2.02)	1.06 (0.55 to 2.06)	1.06 (0.64 to 1.77)
Ultrasound	0.93 (0.79 to 1.09)	0.87 (0.68 to 1.11)	1.25 (0.80 to 1.95)	1.08 (0.77 to 1.52)
Early infancy (0-100 days)*:				
Radiography	1.19 (0.82 to 1.74)	1.35 (0.81 to 2.27)	5.14 (1.27 to 20.8)	0.94 (0.31 to 2.92)
Ultrasound	1.55 (0.89 to 2.70)	0.68 (0.30 to 1.53)	–	–

*Examinations in two year period before diagnosis of cancer excluded from analysis.

Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC)

EDITORIAL by Keavney

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STUDY QUESTION

Is concentration of C reactive protein causally relevant to coronary heart disease?

SUMMARY ANSWER

Large scale genetic data indicate the association between C reactive protein concentration and risk of coronary heart disease is not causal.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Blood concentrations of C reactive protein are strongly and continuously associated with future risk of coronary heart disease, though it is not known whether this association reflects cause and effect.

Mendelian randomisation analysis using variants of the gene encoding C reactive protein, that influence its circulating concentration but are unrelated to other variables, were not associated with risk of coronary heart disease. C reactive protein concentration itself is unlikely to be even a modest causal factor in coronary heart disease.

Participants and setting

The investigation looked at data from 194 418 participants, including 46 557 patients with prevalent or incident coronary heart disease. Data were available on four *CRP* gene tagging single nucleotide polymorphisms (rs3093077, rs1205, rs1130864, rs1800947), concentration of C reactive protein, and levels of established and other emerging risk factors, and coronary heart disease events.

Design, size, and duration

Mendelian randomisation meta-analysis of data from individual participants in 47 epidemiological studies in 15 countries.

Main results and the role of chance

CRP variants were each associated with up to 30% per allele differences in C reactive protein concentration (P<0.001) and were unrelated to other risk factors. Risk ratios for coronary heart disease per additional copy of a C reactive protein raising allele were 0.93 (95% confidence interval 0.87 to 1.00) with rs3093077, 1.00 (0.98 to 1.02) with rs1205, 0.98 (0.96 to 1.00) with rs1130864, and 0.99 (0.94 to 1.03) with rs1800947. In a combined analysis, the risk ratio for coronary heart disease was 1.00 (0.90 to 1.13) per 1 SD higher genetically raised ln (natural log) concentration of C reactive protein. The genetic findings were discordant with the risk ratio observed for coronary heart disease of 1.33 (1.23 to 1.43) per 1 SD higher circulating ln concentration in prospective studies (P=0.001 for difference).

Bias, confounding, and other reasons for caution

There is the possibility of residual confounding by unrecognised effects of genotypes on other risk factors and by adaptation during early life to compensate for genetically raised concentrations of C reactive protein, though there is no evidence of their impact in the current context.

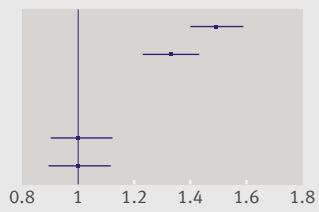
Generalisability to other populations

Our participants were mainly of European descent, which could limit generalisability to other populations.

Study funding/potential competing interests

The coordinating centre is supported by grant SP/08/007 from the British Heart Foundation. Various sources supported recruitment, follow-up, and laboratory measurements in the contributing studies.

CIRCULATING AND GENETICALLY RAISED CONCENTRATIONS OF C REACTIVE PROTEIN (CRP) AND RISK FOR CORONARY HEART DISEASE



	Risk ratio (95% CI) for CHD per 1 SD higher ln CRP (mg/L)
Circulating usual concentrations of CRP	
Adjusted for age, sex, and ethnicity	1.49 (1.40 to 1.59)
Further adjusted for other risk factors	1.33 (1.23 to 1.43)
Genetically raised concentrations of CRP	
Single nucleotide polymorphism analyses	1.00 (0.90 to 1.13)
Haplotype analyses	1.00 (0.89 to 1.12)