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RESEARCH

NHS

THIS WEEK'S RESEARCH QUESTIONS

1120 How does antibiotic prescribing in primary care affect patients' risk of bacterial resistance?

1121 Is the pH of umbilical cord blood at birth associated with health outcomes in infancy?

1122 Is accelerated functional rehabilitation better for recovery after ankle sprain than current standard treatment?

1123 Do infants of vaccinated women have the same maternal protection against measles as infants of naturally infected women?

1124 Is maternal exposure to ultraviolet radiation in pregnancy linked to risk of multiple sclerosis in offspring?

Immediate rehabilitation for ankle sprains

What should you do if you sprain your ankle? The usual drill for mild to moderate sprains is protection, rest, ice, compression, and elevation, but is this "PRICE" right? The good or bad news, depending on your desire to take it easy, is that your ankle will recover more quickly if you do some rehabilitation exercises. In a randomised controlled trial Chris M Bleakley and colleagues show that exercises in the first week—focusing on muscle strengthening, neuromuscular training, and sports specific function—significantly improved participants' scores on the validated lower extremity functional scale over the next fortnight (p 1122). Eagle eyed readers might spot that Domhnall MacAuley, the *BMJ*'s primary care editor and former editor of the *British Journal of Sports Medicine*, coauthored this paper. In line with our policy we asked an independent editorial adviser to handle the paper's peer review and, in this case, we're very grateful to Sue Morgan for her help (http://resources.bmj.com/bmj/authors/peer-review-process).

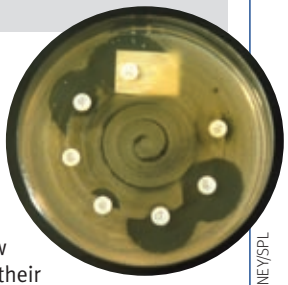

JANE SHEMILT/SPL

Continuing Medical Education at the *BMJ*

CME

We're delighted to say that the *BMJ* and the Center for Continuing Education at the Cleveland Clinic, Ohio have joined forces to offer certified continuing medical education credits to readers (see editorial, p 1091). We're launching this collaboration with research papers, but we plan to extend our CME programme to clinical reviews, practice articles, editorials, and other *BMJ* content over time. Do try the CME modules linked to three of this week's papers (pp 1121, 1122, 1123) and let us know how you get on. We are inviting authors of selected research papers to draft up to five multiple choice CME questions and answers, but only at the provisional acceptance stage (http://resources.bmj.com/bmj/authors/cme), so there is no need to submit papers with modules already prepared.

Antibiotic resistance in primary care

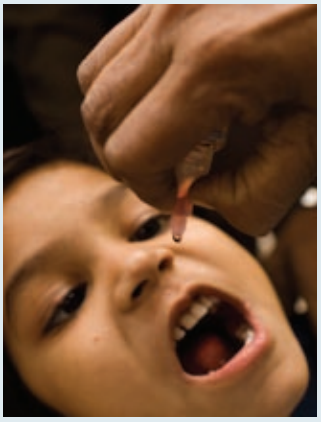

JIM VARNEY/SPL

We've all got the message about resistant bacteria in hospitals and know that actions by individual staff, patients, and even visitors can make a difference. There's plenty of evidence, too, about the general rise in bacterial resistance in the community, some of it due to antibiotics used by farmers. But how much do we know about resistance in primary care, where most people get their antibiotics? Costelloe and colleagues' meta-analysis of observational and experimental studies found strong evidence that resistance of respiratory and urinary tract bacteria develops quickly in primary care and can last up to a year (p 1120). Furthermore, the likelihood of resistance is associated directly with the number of antibiotic courses a patient has over 12 months.

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

Improving immunisation coverage in rural India

Médecins Sans Frontières and Oxfam International recently warned that the global campaign to vaccinate children in poor countries is facing an acute crisis because of high costs (*BMJ* 2010;340:c2576). Abhijit Vinayak Banerjee and colleagues did a cluster randomised controlled trial looking at how to improve immunisation coverage in rural India. They randomised 134 villages to one of three groups: in one intervention, regular, well publicised immunisation clinics ("camps") were held; in the second, similar camps were held and parents were also offered small non-monetary incentives—food or metal plates—to encourage them to immunise their children. A third set of villages formed the control group. The study showed that improving reliability of services through the camps modestly improved immunisation rates. The small incentives, however, greatly improved the uptake of immunisation services in these resource poor areas. This approach, say the authors, is more cost effective than purely improving supply (doi:10.1136/bmj.c2220). Jishnu Das discusses the practicalities of this strategy in an editorial (doi:10.1136/bmj.c2553).


GATES FOUNDATION

Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

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EDITORIAL by So et al
ANALYSIS p 1115

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Listen to an interview with coauthor Alastair Hay at http://podcasts.bmj.com/bmj/

STUDY QUESTION What is the effect of antibiotic use on the emergence of resistance for individual patients in primary care?

SUMMARY ANSWER Individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop bacterial resistance that is greatest in the month immediately after treatment but may persist for up to 12 months.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The relation between prescription and resistance in individuals has not been well defined. We found that prescription of antibiotics to an individual in primary care was consistently associated with urinary and respiratory bacterial resistance to those antibiotics in that individual. The greater the number of antibiotic courses prescribed in the previous 12 months, the higher the likelihood that resistant bacteria would be isolated from that patient. This effect increases population carriage of organisms resistant to first line antibiotics and creates the conditions for increased use of second line antibiotics in the community.

Selection criteria for studies

We systematically reviewed the literature for studies that investigated subsequent antibiotic resistance in individuals prescribed antibiotics in primary care. Observational and experimental studies were identified through Medline, Embase, and Cochrane searches. Electronic searches using MeSH terms and text words identified 4373 papers. Two independent reviewers assessed the quality of eligible studies and extracted data. Meta-analyses were done for studies that presented similar outcomes.

ASSOCIATION BETWEEN RESISTANCE AND ANTIBIOTIC EXPOSURE

Exposure to antibiotic	Pooled odds ratio (95% CI)
Urinary bacteria	
Exposure in previous 2 months	2.5 (2.1 to 2.9)
Exposure in previous 12 months	1.3 (1.2 to 1.5)
Respiratory bacteria	
Exposure in previous 2 months	2.4 (1.4 to 3.9)
Exposure in previous 12 months	2.4 (1.2 to 4.5)

Primary outcome(s)

Pooled odds ratios for resistance among bacteria isolated from different sites (for example, urinary, respiratory) from patients who were exposed and unexposed to antibiotics during varying time periods.

Main results and the role of chance

Twenty four studies were included, of which 22 involved patients with symptomatic infection and two involved healthy volunteers. The table shows the association between resistance and exposure to antibiotics. The 95% confidence intervals suggest that these associations are not chance findings.

Study funding/potential competing interests

This work was undertaken by the University of Bristol in collaboration with the University of Oxford, who both received a proportion of their funding from the Department of Health's NIHR School for Primary Care Research. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health. No competing interests declared.

What types of article does the *BMJ* consider?

We are delighted to receive articles for publication—from doctors and others—on the clinical, scientific, social, political, and economic factors affecting health. We give priority to articles that will help doctors to make better decisions. Please see our advice to authors at http://resources.bmj.com/bmj/authors, and if you would like to submit an article do so via our online editorial office at http://submit.bmj.com.

All original research articles are submitted, although we may invite submission (without promising acceptance) if we come across research being presented at conferences, if we see it in abstract form, or if the authors make an inquiry about the suitability of their work before submission.

We are also pleased to consider submitted articles for sections which carry a mix of commissioned and submitted articles—editorials, analysis, clinical review, practice, fillers, and Career Focus. Please follow the specific advice on each of these article types (see http://resources.bmj.com/bmj/authors/types-of-article) before submitting your article. Some types of article—news, features, observations, head to head, views and reviews—are commissioned by the editors.

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CME

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Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis

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EDITORIAL by Neilsen
See EDITORIAL by Kawczak and Patrick

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STUDY QUESTION Is there an association between the pH of umbilical cord blood at birth and perinatal and long term outcomes?

SUMMARY ANSWER Low arterial cord pH showed strong, consistent, and temporal associations with clinically important outcomes, including neonatal mortality, hypoxic ischaemic encephalopathy, seizures, intraventricular haemorrhage, and cerebral palsy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Neonatal and childhood mortality and morbidity, including cerebral palsy, are attributed to fetal acidosis, as defined by low cord pH at birth. Existing reports of the link between cord pH and adverse outcomes are conflicting. Our review found that low cord pH is substantially associated with neonatal mortality and morbidity, and cerebral palsy.

Selection criteria for studies

We searched Medline, Embase, the Cochrane Library, and Medion without language restrictions. The reference lists of selected articles were screened and authors contacted for information. We included studies if they contained data on infants with umbilical cord blood obtained at birth and had documented any measure of compromise of neonatal or childhood wellbeing, such as neonatal mortality, neonatal morbidity including hypoxic ischaemic encephalopathy, and long term outcomes such as cerebral palsy. Observational studies that allowed estimation of the relation between test result and outcomes were included. Studies with five or fewer cases were excluded, because of unreliability.

Primary outcome(s)

We carried out meta-analyses to calculate odds ratios and 95 % confidence intervals according to index test—that is, arterial cord pH, venous cord pH, and base excess—and outcome measures, including neonatal mortality, a composite measure of neonatal morbidity, and cerebral palsy. We also assessed the component morbidity outcomes of hypoxic ischaemic encephalopathy, seizures, or intraventricular haemorrhage or periventricular leucomalacia. We calculated the estimated predictive interval for each meta-analysis, which relates to the predicted effect of a new study, allowing calculation of the full uncertainty around inferences.

Main results and role of chance

Of 5690 citations, 51 studies met our criteria and were included in the review. Arterial cord pH was substantially associated with neonatal mortality in both the high risk population (odds ratio 4.2, 95% confidence interval 2.6 to 6.9, estimated predictive interval 1.3-13.7) and unselected population (16.9, 9.7 to 29.5, 5.0-57.3). The association with neonatal morbidity was also significant in the high risk population (3.4, 2.3 to 4.9, 1.4-8.4) and unselected population (10.6, 4.7 to 24.1, 0.8-135.8). Further analyses were carried out to examine the effect of varying pH thresholds and the association of venous cord pH and base excess with neonatal morbidity.

Bias, confounding, and other reasons for caution

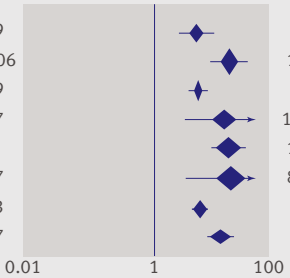
The Harbord test suggested that the meta-analysis of the association between arterial cord pH and neonatal morbidity might be affected by small study bias. The quality of the primary studies varied. The poor reporting of population characteristics limited the subgroup analysis according to risk factors; for example, several papers with an "unselected" population did not fully report characteristics such as birth weight or gestational age, making it difficult to extrapolate our findings to the general obstetric population. The extent to which our results can be used to counsel parents and target interventions for infants born with a low cord pH is limited.

Study funding/potential competing interests

GLM is funded by the Mary Crosse fellowship, Birmingham Women's Foundation Trust. RKM is funded by Medical Research Council/Royal College of Obstetrics and Gynaecology clinical research training fellowship.

META-ANALYSIS OF ASSOCIATION BETWEEN LOW ARTERIAL CORD PH AND OUTCOMES

Meta-analysis according to outcome	No of studies	No of neonates	Odds ratio (95% CI); EPI
Neonatal mortality: high risk population I^2=35.1%	11	3959	4.2 (2.6 to 6.9); 1.3-13.7
Neonatal mortality: unselected population I^2=0.0%	4	466 406	16.9 (9.7 to 29.5); 5.0-57.3
Composite morbidity: high risk population I^2= 26.4%	18	4339	3.4 (2.3 to 4.9); 1.4-8.4
Composite morbidity: unselected I^2=66.4%	12	5977	10.6 (4.7 to 24.1); 0.8-135.8
HIE: any population I^2=0.0%	7	827	13.8 (6.6 to 28.9); 5.2-36.4
Seizures: any population I^2=66.3%	9	5147	8.1 (3.0 to 21.9); 0.4-153.6
IVH/PVL: any population I^2=0.0%	12	2853	2.9 (2.1 to 4.1); 2.0-4.3
Cerebral palsy: any population I^2=0.0%	7	1117	2.3 (1.3 to 4.2); 1.1-5.0



EPI=estimated predictive interval; HIE=hypoxic ischaemic encephalopathy; IVH=intraventricular haemorrhage; PVL=periventricular leucomalacia

CME

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Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial

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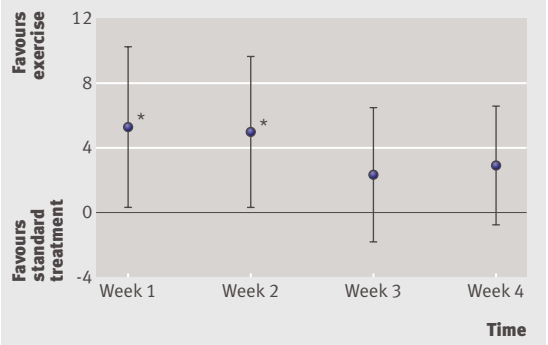
STUDY QUESTION Is accelerated functional rehabilitation better for recovery after ankle sprain than current standard treatment?

SUMMARY ANSWER Using an accelerated exercise protocol after ankle sprain resulted in improved short term ankle function compared with standard care.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Protection, rest, ice, compression, and elevation (PRICE) are commonly recommended in the acute management of ankle sprains, but few randomised controlled trials have studied the effectiveness of this intervention. Incorporating therapeutic exercises during the first week after ankle sprain resulted in significant improvements in short term ankle function.

DIFFERENCE IN TREATMENT AFTER ADJUSTMENT FOR LOWER EXTREMITY FUNCTIONAL SCALE SCORES, WEEKS 1 TO 4



Dots are point estimates for difference and whiskers are 98.75% confidence intervals
*Difference in treatment adjusted for baseline values, P<0.0125

Design

We used a randomised controlled trial design with the outcome assessor blinded to treatment group. Block randomisation was undertaken with computer generated allocation. Intervention during the first week was either an accelerated exercise protocol with early therapeutic exercise (exercise group) or a standard PRICE intervention (standard group). Treatment was standardised in both groups from weeks 1-4 and consisted of ankle rehabilitation exercises.

Participants and setting

Participants were 101 adults aged 16-65 with acute (<7 days) grade 1 or 2 ankle sprain. Participants were recruited from an accident and emergency department or sports injury clinic.

Primary outcome(s)

The primary outcome, subjective ankle function, was assessed using a lower extremity functional scale. Ankle function was recorded at baseline and at one, two, three, and four weeks after injury. The primary outcome was also assessed at 16 weeks along with the rate of reinjury.

Main results and the role of chance

We undertook a constrained linear mixed model analysis based on intention to treat. The exercise group had significantly higher levels of function at week 1 (baseline adjusted difference in treatment 5.28, 98.75% confidence interval 0.31 to 10.26; P=0.008) and week 2 (4.92, 0.27 to 9.57; P=0.0083). Secondary outcomes did not differ significantly. Four reinjuries occurred, two in each group.

Harms

No adverse events were reported in the first four weeks. The rate of reinjury was 4%; all reinjuries were sustained between 12 and 16 weeks after the initial injury, and during sporting activity.

Bias, confounding, and other reasons for caution

Despite showing a significant improvement in subjective ankle function, we did not achieve our target sample size. The power was not sufficient to show a difference in the secondary outcomes and, overall, the dropout rate was higher in the exercise group. One participant from the standard group was excluded after randomisation when follow-up radiography revealed a fracture. Owing to ethical considerations this participant was excluded from the analysis.

Generalisability to other populations

Our population was based on people with minor and moderate ankle sprains, and therefore our findings are not generalisable to people with more severe ankle injuries. Treatment was standardised in both groups from weeks 1-4 and consisted of ankle rehabilitation exercises focusing on muscle strengthening, neuromuscular training, and sports specific functional exercises. This protocol is not standard practice within accident and emergency departments, and may have lowered the reinjury rate at week 16.

Study funding/potential competing interests

This trial was funded by grants from the Physiotherapy Research Foundation and Strategic Priority Fund (Department of Employment and Learning, Northern Ireland). The researchers were independent of the funding agency.

Trial registration number

Current Controlled Trials ISRCTN13903946.

CME

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Early waning of maternal measles antibodies in era of measles elimination: longitudinal study

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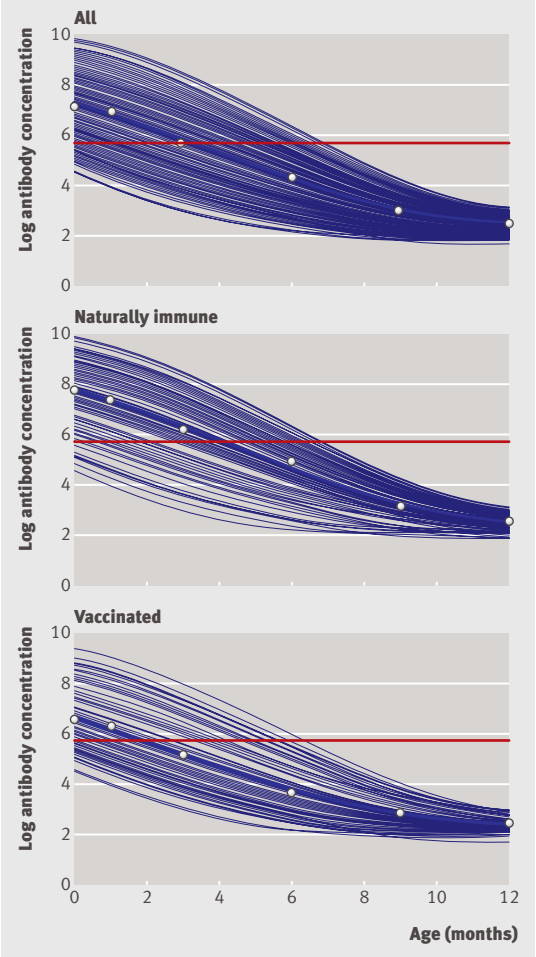
STUDY QUESTION How well protected against measles are infants of women vaccinated against measles and those of naturally immune women?

SUMMARY ANSWER An increasing gap of susceptibility exists in all infants between the loss of maternal antibodies and the administration of a first dose of vaccine.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Infants of vaccinated women have shorter maternal protection against measles compared with infants of naturally infected women. This study underlines the importance of timeliness of administration of a first measles containing vaccine at 12 months of age, in view of recent outbreaks in industrialised countries.

FITTED INDIVIDUAL PROFILES FOR DECAY IN LOG ANTIBODY CONCENTRATION



Horizontal red line indicates threshold of 300 mIU/ml; thick curve is predicted mean curve in each group with observed means at birth and 1, 3, 6, 9, and 12 months as open circles

Participants and setting

We recruited pregnant women in five hospitals in the province of Antwerp, Belgium, and divided them into a vaccinated group (n=87) and a naturally immune group (n=120) on the basis of vaccination documents and history.

Design, size, and duration

This longitudinal study took place between May 2006 and November 2008. Of 221 pregnant women recruited, we included 207 healthy woman-infant pairs. Blood samples were taken at seven different time points (maternal sample, cord blood, and 1, 3, 6, 9, and 12 months of age) and analysed by enzyme linked immunosorbent assay (ELISA). We used linear mixed models to model decay of maternal antibodies in infants over time.

Main results and the role of chance

The concentration of IgG antibody was significantly lower in vaccinated women (geometric mean titre 764 (95% confidence interval 581 to 1045) mIU/ml) compared with naturally infected women (2674 (2126 to 3373) mIU/ml) (P<0.001). Infants of vaccinated women had significantly lower antibody concentrations than did infants of naturally infected women (P<0.001 at all time points). Presence of maternal antibodies endured for a median of 2.61 months—3.78 months for infants of naturally infected women and 0.97 months for infants of vaccinated women. At 6 months of age, more than 99% of infants of vaccinated women and 95% of infants of naturally immune women had lost maternal antibodies according to the model. The figure shows individual infants' profiles for decay of maternal measles antibodies (log antibody concentration).

Bias, confounding, and other reasons for caution

The threshold of the commercial ELISA test used (300 mIU/ml), chosen according to the optical density value, is questionable. However, even if this value is overestimated and lower values are still in the protective range, most antibodies had disappeared early in both groups of infants.

Generalisability to other populations

The results are generalisable to other populations in industrialised countries where universal vaccination programmes against measles are in place.

Study funding/potential competing interests

EL obtained a research grant from the Faculty of Medicine (University of Antwerp). An unrestricted educational grant from GlaxoSmithKline, Belgium, covered part of the nursing activities.

Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis

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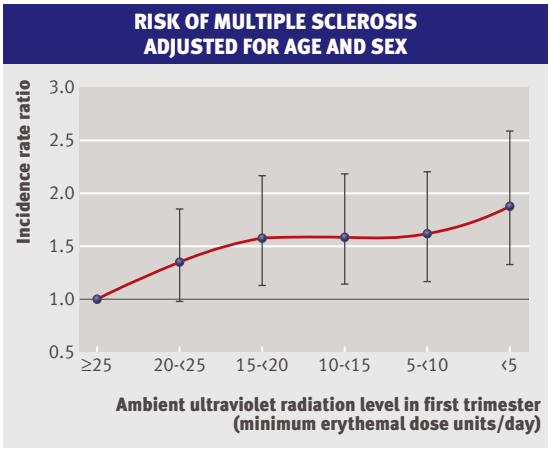
STUDY QUESTION Is there a link between maternal exposure to ultraviolet radiation (UVR) during pregnancy and subsequent risk of multiple sclerosis in offspring?

SUMMARY ANSWER Region of birth and low maternal exposure to UVR during the first trimester are independently associated with risk of multiple sclerosis in Australia.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Vitamin D is generated by UVR. In the northern hemisphere, there is a pattern between month of birth and risk of multiple sclerosis. In Australia, there is a corresponding pattern that reflects maternal UVR exposure in the first trimester. These results are consistent with the hypothesis that low vitamin D in the prenatal and postnatal period increases the risk of multiple sclerosis.



Participants and setting

Data on patients with multiple sclerosis born in Australia, including sex and region of birth for each birth month of every (birth) year, 1920-1950, were obtained from multiple sclerosis prevalence surveys carried out in 1981. Population denominators were derived from the 1981 Australian census and Australian birth registers 1920-50.

Design, size, and duration

In a longitudinal analysis of 2 468 779 births, 1524 patients with multiple sclerosis were identified. Exposure to ambient UVR at birth was measured from monthly averages of the daily total amount of ambient UVR by region. Negative binomial regression models were used to investigate the association between month of birth, exposure to ambient UVR during pregnancy, and the incidence rate of multiple sclerosis.

Main results and the role of chance

Month of birth and risk of multiple sclerosis were associated (adjusted incidence rate ratio 1.32, 95% confidence interval 1.10 to 1.58, P<0.01, for November-December compared with May-June). After adjustment for region of birth and other risk factors, there was an inverse link between ambient UVR in the first trimester and risk (with ≥25 erythemal dose units as reference, the adjusted incidence rate ratios were 1.54 (1.10 to 2.16) for 20-<25 units; 1.58 (1.12 to 2.22) for 15-<20 units; 1.65 (1.17 to 2.33) for 10-<15 units; 1.65 (1.18 to 2.29) for 5-<10 units; and 1.67 (1.18 to 2.37) for <5 units). After adjustment for UVR during early pregnancy, there was no residual association between month of birth and multiple sclerosis (P=0.58).

Bias, confounding, and other reasons for caution

Level of ambient UVR experienced by the mother during her gestation was a proxy for vitamin D status of the fetus. This does not take into account individual personal behaviour, concurrent dietary vitamin D intake, or skin pigmentation. Such omissions would probably block out rather than create the patterns observed. Although recent work indicates that levels of ambient erythemal UVR can be used to indicate vitamin D status during pregnancy, we cannot evaluate whether the effect of prenatal UVR was acting solely through UVR derived vitamin D. We could not control other factors that could be associated with prenatal exposure to UVR in the first trimester and that could also determine multiple sclerosis risk. There was, however, strong a priori evidence indicating that sun exposure or vitamin D, or both, is probably the central exposure and little a priori evidence for any other strong determinants for multiple sclerosis likely to be linked to maternal ambient exposure to UVR in the first trimester.

Generalisability to other populations

In Australia, UVR exposure is the major determinant of vitamin D stores. If the findings are due to UVR derived vitamin D, then in other regions where dietary or supplementary sources of vitamin D are important the association between prenatal UVR exposure and risk of multiple sclerosis might be less evident.

Study funding/potential competing interests

The research was supported by an Australian National University (ANU) Graduate School scholarship and a supplementary scholarship from the National Centre for Epidemiology and Population Health, ANU, awarded to JS.

bmj.com archive

- Research: Timing of birth and risk of multiple sclerosis (*BMJ* 2005;330:120)
- Research: Past exposure to sun, skin phenotype, and risk of multiple sclerosis (*BMJ* 2003;327:316)