RESEARCH

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Model to predict delirium in intensive care patients

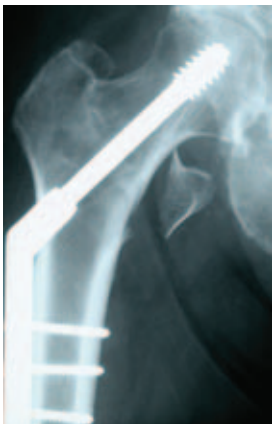
Doug Altman and colleagues' 2009 Research Methods and Reporting series on prognostic research included an article on validating prognostic models. The authors concluded that to be considered useful, a risk score should be "clinically credible, accurate (well calibrated with good discriminative ability), have generality (be externally validated), and, ideally, be shown to be clinically effective—that is, provide useful additional information to clinicians that improves therapeutic decision making and thus patient outcome."

BODENHAM, LTH NHS TRUST/SPL

M van den Boogaard and colleagues developed the PREdiction of DELIRium for Intensive Care patients (PRE-DELIRIC) model in a multicentre observational study in the Netherlands, then temporally validated it in a second prospective cohort in the same hospital, and finally validated it externally in four other Dutch hospitals (p 17). The PRE-DELIRIC score comprised 10 risk factors readily assessable within 24 hours after intensive care admission (age, APACHE-II score, admission group, coma, infection, metabolic acidosis, use of sedatives, use of morphine, urea concentration, and urgent admission) and predicted the onset of delirium much better than doctors' and nurses' clinical assessments.

Editorialist Valerie Page focuses on clinical credibility, arguing that the score is fine but it's now time to move on to identifying treatments to prevent or modify delirium and improve outcomes (p 8).

Proton pump inhibitors and risk of postmenopausal hip fracture



DR P MARAZZI/SPL

In May 2010 the US Food and Drug Administration warned that there might be an association between use of proton pump inhibitors and risk of hip fracture, and called for more research on the question. So Hamed Khalili and colleagues analysed data from the US Nurses' Health study, looking at 893 incident hip fractures during 565 786 person years of follow-up (p 15). The absolute risk of hip fracture among regular users of PPIs was 2.02 events per 1000 person years compared with 1.51 events per 1000 person years among non-users. Women who smoked were at particular risk.

The authors allowed for a broad range of confounding factors, with their fully adjusted model adjusting for age, body mass index, alcohol intake, total energy adjusted calcium intake, history of osteoporosis, level of physical activity, smoking status, vitamin D intake, bisphosphonate use, thiazide use, corticosteroid use, and use of postmenopausal hormone replacement therapy. They acknowledge that there may still be some residual confounding, and rapid responders Alexander Ford and Noor Mohammed think that explains the association (http://bit.ly/xiulSi). Frank de Vries blames recall bias, suggesting that nurses who have a hip fracture may remember their drug exposure differently from those without a hip fracture (http://bit.ly/Ac3oAy).

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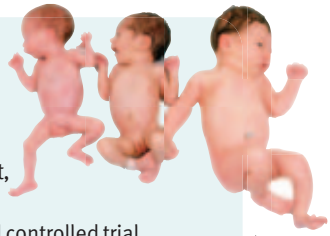

RON SUTHERLAND/SPL

Influence of definition based versus pragmatic birth registration on international comparisons of perinatal and infant mortality
Differences in reported rates of very low birth weight and very early gestation births in industrialised countries probably reflect arbitrary differences in birth registration, which could compromise the validity of international rankings based on perinatal, infant, or child mortality, according to a population based retrospective study by K S Joseph and colleagues (doi:10.1136/bmj.e746).

Effect of specific exercise strategy on need for surgery in patients with subacromial impingement syndrome A randomised controlled trial by Theresa Holmgren and colleagues found that a specific exercise strategy (focusing on strengthening eccentric exercises for the rotator cuff and concentric/eccentric exercises for the scapula stabilisers) improved shoulder function and pain in patients with persistent subacromial impingement syndrome in whom earlier conservative treatment has failed. By extension, say the authors, this could reduce the need for surgery within three months. The standardised exercise protocol provides guidance about content, dose, and progression, to enable implementation into everyday practice (doi:10.1136/bmj.e787).

Impact of single centre status on estimates of intervention effects in trials with continuous outcomes
Aïda Bafeta and colleagues report that, on average, single centre clinical trials show slightly larger intervention effects than multicentre trials. Their meta-epidemiological study looked at 26 meta-analyses comprising a total of 292 randomised controlled trials (177 single centre, 115 multicentre) with continuous outcomes published between 2007 and 2010 in the Cochrane database of systematic reviews (doi:10.1136/bmj.e813).

Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial

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STUDY QUESTION Does dietary n-3 long chain polyunsaturated fatty acid (LCPUFA) supplementation of pregnant women with a fetus at high risk of allergic disease reduce immunoglobulin E associated eczema or food allergy at 1 year of age?

SUMMARY ANSWER n-3 LCPUFA supplementation in pregnancy did not reduce the overall incidence of immunoglobulin E associated allergies in the first year of life, although immunoglobulin E associated eczema was lower.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Several mechanistic studies have suggested that higher intakes of n-3 LCPUFA during pregnancy modulate the neonatal immune response towards a less allergenic phenotype. n-3 LCPUFA supplementation in pregnancy did not reduce the incidence of immunoglobulin E associated food allergies in the first year of life, but the incidence of atopic eczema was lower.

Design
Pregnant women were approached to enter the allergy follow-up after randomisation into the Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO) trial. Women were asked to consume either n-3 LCPUFA capsules providing 800 mg of docosahexaenoic acid and 100 mg of eicosapentaenoic acid or vegetable oil capsules without n-3 LCPUFA, daily from 21 weeks' gestation until delivery. Neither the women nor the research staff were aware of the treatment allocated. Infants had a medical review for allergic disease, including skin prick testing, at 12 months of age.

Participants and setting
We enrolled 706 women, whose infants had a first degree relative with medically diagnosed allergic disease (asthma, allergic rhinitis, eczema), from the Women's and Children's Hospital or Flinders Medical Centre, Adelaide.

Primary outcomes(s)
The primary outcome was immunoglobulin E associated allergic disease (eczema or food allergy with sensitisation) at 1 year of age.

Main results and the role of chance
We found no differences between the n-3 LCPUFA and control groups in the overall percentage of infants diagnosed as having immunoglobulin E associated allergic disease at 1 year of age (32/368 (9%) *v* 43/338 (13%); unadjusted relative risk 0.68, 95% confidence interval 0.43 to 1.05, P=0.08; adjusted relative risk 0.70, 0.45 to 1.09, P=0.12). However, the percentage of infants with atopic eczema at 1 year of age was lower in the n-3 LCPUFA group relative to control, whereas the percentage of infants with food allergy did not differ between the groups.

Harms
No anaphylactic reactions were reported.

Bias, confounding, and other reasons for caution
More infants in the n-3 LCPUFA group than in the control group were initially breast fed, whereas more infants in the control group were given cows' milk protein formula in the first six months of life. The groups did not differ for other possible confounding variables that may influence allergic disease.

Generalisability to other populations
Women included in our trial had demographic characteristics comparable to those of Australian women who gave birth in 2006-7, suggesting generalisability of the results to the wider population.

Study funding/potential competing interests
The study was supported by grants from the Australian National Health and Medical Research Council and Australian Egg Corporation Limited. Treatment and placebo capsules were donated by Efamol, UK. MSG, RH, SLP, RAG, and MM have received grants or honorariums from various companies, including the Nestlé Nutrition Institute, Fonterra, Commonwealth Serum Laboratories, Vaxine, GlaxoSmithKline, Healthed, and Nutricia.

Trial registration number
Australian New Zealand Clinical Trials Registry ACTRN12610000735055.

Clinical allergy assessment outcomes at 12 months of age.

Outcome	n-3 LCPUFA (n=368)	Control (n=338)	Unadjusted relative risk (95% CI)	Adjusted* relative risk (95% CI)
Allergic disease with sensitisation:	32 (9)	43 (13)	0.68 (0.43 to 1.05)	0.70 (0.45 to 1.09)
Eczema with sensitisation	26 (7)	39 (12)	0.61 (0.38 to 0.98)†	0.64 (0.40 to 1.03)
Food allergy with sensitisation	11 (3)	11 (3)	0.94 (0.40 to 2.22)	0.96 (0.41 to 2.25)

LCPUFA=long chain polyunsaturated fatty acid.
*Adjusted for centre, parity, maternal history, and sex.
†P=0.04.

Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study

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STUDY QUESTION Do proton pump inhibitors (PPIs) increase the risk of hip fracture in postmenopausal women even after accounting for other lifestyle and dietary risk factors?

SUMMARY ANSWER Regular use of PPIs was associated with an increased risk of hip fracture in postmenopausal women, particularly among those with a history of smoking.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previous studies of the association between PPI use and hip fracture have had limited information on important lifestyle and dietary factors associated with fracture. This study shows an increased risk of hip fracture even after controlling for these other factors, and risk seems limited to women with history of smoking.

Participants and setting

Postmenopausal women enrolled in the US Nurses' Health Study, who provided biennially updated data on the use of proton pump inhibitors (PPIs) and other risk factors.

Design, size, and duration

We prospectively examined 79 899 postmenopausal women who provided data on the use of PPIs and other risk factors biennially since 2000 and were followed through to 1 June 2008.

Main results and the role of chance

During 565 786 person years of follow-up, we documented 893 incident hip fractures. The absolute risk of hip fracture among regular users of PPIs was 2.02 events per 1000 person years compared with 1.51 events per 1000 person years among non-users. Compared with non-users, the risk of hip fracture among women who regularly used PPIs for at least two years was 35% higher (table), with longer use associated with increasing risk (P_{trend}<0.01).

The risk of hip fracture seemed to differ according to history of cigarette smoking ($P_{interaction}$=0.03). Among women who either previously or currently smoked, the fully adjusted hazard ratio of fracture was 1.51 (95% CI 1.20 to 1.91). In contrast, there was no significant association between PPI use and risk of fracture among women who never smoked (fully adjusted hazard ratio 1.06 (0.77 to 1.46)).

Bias, confounding, and other reasons for caution

Although we had prospectively collected, detailed data on a broad range of potential risk factors for fracture, our study is observational and we cannot exclude the possibility of residual confounding.

Generalisability to other populations

Our data should be generalisable to postmenopausal women. It is unclear if these findings apply to other racial or ethnic groups, premenopausal women, or men.

Study funding/potential competing interests

All researchers are independent of the study funders, the National Institute of Health and the IBD Working Group.

Risk of hip fracture according to use of proton pump inhibitors (PPIs) in postmenopausal women

	Non-users of PPIs	Regular PPI user
No of cases/No of person years	744/492 154	149/73 632
Hazard ratio (95% CI):		
Adjusted for age	1.00	1.35 (1.13 to 1.62)
Adjusted for age + body mass index*	1.00	1.45 (1.21 to 1.73)
Adjusted for age + calcium intake†	1.00	1.35 (1.12 to 1.62)
Multivariable adjusted‡	1.00	1.37 (1.14 to 1.64)
Fully adjusted§	1.00	1.36 (1.13 to 1.63)

*Body mass index categorised as <20, 20–24.9, 25–29.9, >30.
†Energy adjusted calcium intake calculated from diet and dietary supplements, categorised as <600, 600–899, 900–1200, >1200 mg/day.
‡Adjusted for age (months), body mass index, alcohol intake (<5, 5–15, >15 g/day), total energy adjusted calcium intake, level of physical activity (<1.7, 1.7–4.5, 4.6–10.6, 10.7–22.1, >22.1 metabolic equivalents-hours/week), smoking status (never, past ≥10 years, past <10 years, current <15 cigarettes/day, current >15 cigarettes/day), vitamin D intake (<400, 400–600, >600 IU/day), and history of osteoporosis (yes, no).
§Adjusted for age (years), body mass index, alcohol intake, total energy adjusted calcium intake, history of osteoporosis, level of physical activity, smoking status, vitamin D intake, bisphosphonate use (yes, no), thiazide use (yes, no), corticosteroid use (yes, no), and use of postmenopausal hormone replacement therapy (never, past, current).

Understanding recent trends in incidence of invasive breast cancer in Norway: age-period-cohort analysis based on registry data on mammography screening and hormone treatment use

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STUDY QUESTION To what extent have menopausal hormone treatment and mammography screening contributed to the observed changes in incidence of invasive breast cancer in Norway since the mid-1990s?

SUMMARY ANSWER The changes in incidence trends of invasive breast cancer in Norway over the past 20 years may be fully attributed to mammography screening activity and use of hormone treatment, with about similar contributions of each factor.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Both mammography screening and hormone treatment are known to increase the risk of invasive breast cancer and have been suggested as explanatory factors for the recent changes in incidence trends of invasive breast cancer in many developed countries. By modelling both factors simultaneously, their individual and combined contributions to the observed changes in incidence can be quantified.

Participants and setting

In the analyses we used Norwegian population data, including data from high quality mandatory breast cancer registration, complete sales statistics on menopausal hormone treatment, and details of the public mammography screening programme. The study included 50 102 newly diagnosed cases of invasive breast cancer.

Design, size, and duration

Utilising county level differences, we analysed the trends in incidence of invasive breast cancer for Norwegian women aged 30-90 between 1987 and 2008, using an extended age-period-cohort model with separate mammography screening and hormone treatment variables.

Main results and the role of chance

In 2002, when the incidence among women aged 50-69 was highest, we estimated that 23% of the cases in that age group could be attributed to mammography screening and 27% to the use of hormone treatment. After adding mammography screening and hormone treatment variables to the age-period-cohort model, only minor, statistically non-significant, non-linear period effects remained. Therefore, changes in the incidence of invasive breast cancer in Norway during the past two decades may be explained by mammography screening activity and hormone treatment use. With these large population data, there was only moderate statistical uncertainty in the estimates.

Bias, confounding, and other reasons for caution

Without individual data, the given estimates of screening and hormone treatment effects have to be interpreted with caution. We cannot exclude the possibility that opportunistic screening may to some degree have biased the analysis. Overall, after adding the mammography screening and hormone treatment variables the model fit was good, with no statistically significant over-dispersion or unaccounted for variation.

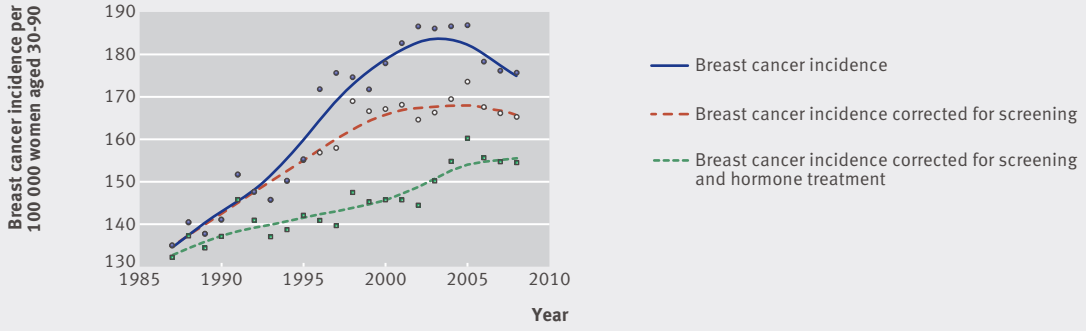
Generalisability to other populations

With similar trends in incidence of invasive breast cancer in many developed countries, our findings suggest that a combination of mammography screening activity and hormone treatment use may explain a considerable proportion of the variation in incidence that has been observed in Norway and some other countries.

Study funding/potential competing interests

This work was supported by the Norwegian Cancer Society through a postdoctoral scholarship to HW-F (PK01-2008-0080). We have no competing interests.

Changes in invasive breast cancer incidence with and without adjustment for screening or combined screening and hormone treatment use



Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study

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STUDY QUESTION Can delirium be predicted in intensive care patients?

SUMMARY ANSWER Within 24 hours of admission, the PREdiction of DELIRium for Intensive Care patients (PRE-DELIRIC) model predicts delirium for the complete length of stay in the intensive care unit.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Delirium is a frequent and serious disorder related to different risk factors in intensive care patients, but no delirium prediction model was available. A delirium prediction model has been developed and validated; it may facilitate early identification of patients at high risk and allow targeted early initiation of preventive measures.

Formula for PRE-DELIRIC model

Risk of delirium = 1/(1+exp–(–6.31
+ 0.04 × age
+ 0.06 × APACHE-II score
+ 0 for non-coma or 0.55 for drug induced coma or 2.70 for miscellaneous coma or 2.84 for combination coma
+ 0 for surgical patients or 0.31 for medical patients or 1.13 for trauma patients or 1.38 for neurology/neurosurgical patients
+ 1.05 for infection
+ 0.29 for metabolic acidosis
+ 0 for no morphine use or 0.41 for 0.01-7.1 mg/24 h morphine use or 0.13 for 7.2-18.6 mg/24 h morphine use or 0.51 for >18.6 mg/24 h morphine use
+ 1.39 for use of sedatives
+ 0.03 × urea concentration (mmol/L)
+ 0.40 for urgent admission))

The scoring system's intercept is expressed as –6.31; the other numbers represent the shrunken regression coefficients (weight) of each risk factor.

Participants and setting

Patients were included if they were not delirious within 24 hours after admission to intensive care and assessment of delirium with the confusion assessment method—intensive care unit (CAM-ICU) was feasible.

Design, size, and duration

This was an observational study in 3056 patients aged at least 18 years and admitted to intensive care. We first developed the PRE-DELIRIC model and then validated it in a second prospective cohort in the same hospital. Our subsequently external validation used data from four other Dutch hospitals.

Main results and the role of chance

All adult patients admitted to intensive care were screened for delirium, and 25 potentially important risk factors were collected within 24 hours after admission. We included 1613 consecutive intensive care patients to develop the model and 549 to temporally validate it. For external validation, we collected data from 894 patients in four other hospitals. The PRE-DELIRIC model contains 10 risk factors—age, acute physiology and chronic health evaluation (APACHE)-II score, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, urea concentration, and urgent admission. The model had a high predictive value in the development phase, which remained during the temporal validation phase and the external validation phase. The overall area under the receiver operating characteristics curve in 3056 patients was 0.85 (95% confidence interval 0.84 to 0.87), whereas prediction by nurses and physicians was significantly lower (both 0.59, 0.49 to 0.70).

Bias, confounding, and other reasons for caution

The model is not suitable for use in patients aged under 18. It does not take into account changes in the health condition of patients during their stay in intensive care.

Generalisability to other populations

The delirium prediction model can be used in all general intensive care units for adult patients and may be applicable in other countries comparable to the Netherlands.

Study funding/potential competing interests

This study was not funded.

Trial registration number

Clinical trials NCT00604773 (development study) and NCT00961389 (validation study).