# Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores

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## ABSTRACT

**Objective** To develop and validate two new fracture risk algorithms (QFractureScores) for estimating the individual risk of osteoporotic fracture or hip fracture over 10 years.

**Design** Prospective open cohort study with routinely collected data from 357 general practices to develop the scores and from 178 practices to validate the scores.

**Setting** General practices in England and Wales.

**Participants** 1 183 663 women and 1 174 232 men aged 30-85 in the derivation cohort, who contributed 7 898 208 and 8 049 306 person years of observation, respectively. There were 24 350 incident diagnoses of osteoporotic fracture in women and 7934 in men, and 9302 incident diagnoses of hip fracture in women and 5424 in men.

**Main outcome measures** First (incident) diagnosis of osteoporotic fracture (vertebral, distal radius, or hip) and incident hip fracture recorded in general practice records.

**Results** Use of hormone replacement therapy (HRT), age, body mass index (BMI), smoking status, recorded alcohol use, parental history of osteoporosis, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants, corticosteroids, history of falls, menopausal symptoms, chronic liver disease, gastrointestinal malabsorption, and other endocrine disorders were significantly and independently associated with risk of osteoporotic fracture in women. Some variables were significantly associated with risk of osteoporotic fracture but not with risk of hip fracture. The predictors for men for osteoporotic and hip fracture were age, BMI, smoking status, recorded alcohol use, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants, corticosteroids, history of falls, and liver disease. The hip fracture algorithm had the best performance among men and women. It explained 63.94% of the variation in women and 63.19% of the variation in men. The D statistic values for discrimination were highest for hip fracture in women (2.73) and men (2.68) and were over twice the magnitude of the corresponding values for osteoporotic fracture. The ROC statistics for hip fracture were also high: 0.89 in women and 0.86 for men versus 0.79 and 0.69, respectively, for the osteoporotic fracture outcome. The algorithms were well calibrated with predicted risks closely matching observed risks. The QFractureScore for hip fracture also had good performance for discrimination and calibration compared with the FRAX (fracture risk assessment) algorithm.

**Conclusions** These new algorithms can predict risk of fracture in primary care populations in the UK without laboratory measurements and are therefore suitable for use in both clinical settings and for self assessment (at www. qfracture.org). QFractureScores could be used to identify patients at high risk of fracture who might benefit from interventions to reduce their risk.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Osteoporotic fracture is a major cause of morbidity, and interventions exist that can help reduce risk of fracture

Several international guidelines suggest a targeted approach for identifying high risk patients likely to benefit from interventions based on a 10 year absolute fracture risk

Risk prediction algorithms tend to perform best when they are developed in the clinical setting in which they will be applied

## WHAT THIS STUDY ADDS

These new risk prediction algorithms (QFractureScores) for osteoporotic fracture and hip fracture do not require laboratory measurement and so can be used in primary care or for individual self assessment

The new algorithms include additional variables and were developed in and could be used in large representative primary care populations

The validation statistics, especially for the hip fracture algorithm, suggest that the QFractureScores are likely to be effective at identifying patients at high risk of fracture within primary care in the UK and showed improved performance compared with FRAX

## INTRODUCTION

There is no universally accepted policy for screening for patients at risk of osteoporotic fracture. Some guidelines,[1-4] but not all,[5] recommend a targeted approach based on the 10 year absolute risk of major osteoporotic fracture.

We developed and validated two new fracture clinical risk scores (QFractureScores) derived from a validated clinical research database (www.qresearch.org). We incorporated traditional variables already included in the FRAX (fracture risk assessment) algorithm,[6] added additional variables, extended the age range, and included a more detailed categorisation of alcohol and smoking status. Our new algorithm is based on

variables that are readily available without the need for laboratory tests or clinical measurements.

## METHODS

### Study design and data source

We conducted a prospective cohort study of primary care patients from our database. This contains the health records of over 11 million patients registered from 574 general practices that use the Egton Medical Information System (EMIS) computer system. Practices and patients contained on the database are nationally representative for England and Wales.

*Practice selection*—We included all QResearch practices in England and Wales that had been using their current EMIS system for at least a year. We randomly allocated two thirds of practices to the derivation dataset and the remaining third to the validation dataset.

*Cohort selection*—We identified an open cohort of patients aged 30-85 at the study entry date, drawn from patients registered with eligible practices during the 15 years between 1 January 1993 and 30 June 2008. See bmj.com.

### Primary outcomes

Our two primary outcomes were the first (incident) diagnosis of an osteoporotic fracture (hip, vertebral, or distal radius) as recorded on the general practice computer records and incident diagnosis of hip fracture.

### Fracture risk factors

We examined 18 explanatory variables in our analysis, all of which are known or thought to affect fracture risk and are also likely to be recorded within the patients' electronic records as part of routine clinical practice. See bmj.com.

### Model derivation and development

We calculated crude incidence rates of osteoporotic fracture (hip, vertebral, or distal radius fracture) and hip fracture by age and sex in the derivation and validation cohorts. We used Cox's proportional hazards models in the derivation dataset to estimate the coefficients and hazard ratios associated with each potential risk factor for the first ever recorded diagnosis of osteoporotic fracture and hip fracture for men and women separately. We compared models using the Akaike information criterion (AIC) and the Bayes information criterion (BIC). We used fractional polynomials to model non-linear risk relations with continuous variables where appropriate. We tested for interactions between different variables and included significant interactions when they improved the model fit.

After conducting a complete case analysis, we used multiple imputation to replace missing values for alcohol, smoking status, and BMI, and used these values in our main analyses. We took the regression coefficients for each variable from the final model and used these as weights for the QFractureScores and derived risk equations for 10 years' follow-up. In women we determined the hazard ratios for fracture overall and for hip fracture by HRT use at baseline categorised by (unopposed, cyclical, or continuous) oestrogen dose (high or low) and type of oestrogen (equine *v* non-equine). These results were incorporated in the QFractureScores for women. We also used a time varying Cox regression analysis to examine the effects of duration of use of HRT and time since stopping HRT on risk of fracture in women. See bmj.com.

### Validation of the QFractureScore

We tested the performances of the final models in the validation dataset. We calculated the 10 year estimated risk of sustaining a fracture or hip fracture for each patient in the validation dataset using multiple imputation to replace missing values as in the derivation dataset. We calculated the mean predicted fracture risk and the observed fracture risk at 10 years and compared these by 10th of predicted risk. We calculated the D statistic, an $R^2$ statistic, and calculated the area under the receiver operating characteristics (ROC) curve at 10 years.

### Validation against FRAX (fracture risk assessment)

We compared the performance of the QFractureScore in predicting risk of hip fracture with the performance of the FRAX algorithm using the above validation statistics. FRAX predicts 10 year absolute risk of hip fracture and osteoporotic fracture.[6] It is not currently in widespread use in primary care in the United Kingdom. We used the UK version of the score from the FRAX website (www.shef.ac.uk/FRAX/index.htm) and the version that does not incorporate bone mineral density to calculate the 10 year predicted risk of hip fracture for all patients aged 40-85 in the validation dataset.

## RESULTS

### Description of the derivation and validation dataset

Overall, 535 practices in England and Wales met our inclusion criteria, of which 357 were randomly assigned to the derivation dataset and 178 to the validation dataset. In the derivation cohort there were 1 204 222 women (1 187 354 men) aged 30-85 at baseline, of whom 20 559 (13 122) had a recorded fracture before the start of the study and were therefore excluded, leaving 1 183 663 (1 174 232) free of fracture at baseline for analysis. In the validation cohort there were 653 789 women (640 943 men) aged 30-85 at baseline, of whom 11 636 (7179) had a fracture before the start of the study and were therefore excluded, leaving 642 153 (633 764) free of fracture at baseline for analysis.

The baseline characteristics in the validation cohort were similar to those for the derivation cohort across all measures in both men and women. See bmj.com. During the 7 898 208 person years of follow-up for women in the derivation cohort 24 350 fractures were recorded (hip, vertebral, or distal radius), giving an overall incidence rate of 3.08 per 1000 person years (95% confidence interval 3.04 to 3.12). For men, there were 7934 incident fractures arising from 8 049 306 person years, giving an incidence rate of 0.99 per 1000 person years (0.96 to 1.01). In women, 38.2% of the fractures were hip fractures, in men the corresponding figure was

Clinical examples for patients who would be reclassified with QRISK2 instead of NICE modified Framingham equation

| Age (years) | Ethnic group | Family history | Systolic blood pressure | BMI | Cholesterol/HDL ratio | Smoker | Treated hypertension | Type 2 diabetes* | Chronic kidney disease | Townsend score† | Framingham score 10 year risk (%) | QRISK2 10 year risk (%) (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | | | | | | | | | | | | |
| 65 | Indian | Yes | 100 | 24.7 | 3.3 | No | No | No | No | 5 | 17 | 31.3 (30.9 to 31.7) |
| 54 | Bangladeshi | No | 142 | 27.0 | 4.2 | No | Yes | No | No | 10 | 17 | 23.5 (22.8 to 24.1) |
| 54 | Black African | No | 150 | 21.0 | 7.3 | No | No | No | No | 4 | 23 | 9.0 (7.7 to 10.3) |
| 55 | Indian | No | 156 | 27.0 | 4.7 | No | No | No | No | −4 | 24 | 12.7 (12.2 to 13.2) |
| 65 | Caribbean | No | 146 | 29.1 | 5.4 | No | No | No | No | 4 | 26 | 14.8 (14.2 to 15.5) |
| 42 | White | Yes | 132 | 36.0 | 5.3 | Yes | Yes | No | No | 11 | 17 | 35.2 (34.9 to 35.5) |
| Women | | | | | | | | | | | | |
| 64 | Indian | No | 130 | 23.1 | 5.3 | No | Yes | No | No | 5 | 12 | 24.7 (24.4 to 25.0) |
| 60 | Bangladeshi | No | 132 | 36.0 | 4.3 | No | Yes | No | No | 11 | 9 | 21.1 (20.6 to 21.6) |
| 48 | Pakistani | Yes | 140 | 33.2 | 4.5 | No | Yes | No | No | 8 | 9 | 26.1 (25.7 to 26.4) |
| 58 | White | No | 154 | 34.0 | 3.4 | Yes | Yes | No | No | 10 | 16 | 21.4 (21.3 to 21.5) |

BMI=body mass index; HDL=high density lipoprotein cholesterol.

*NICE lipid modification guideline does not include diabetes so this is for illustrative purposes only.

†Interval score ranges between −6 (most affluent) and 11 (most deprived).

38.9%. Similar incidence rates were found in the validation cohort. Incidence rates were higher in women than in men and rose steeply with age. See bmj.com.

### Model development

The results of the multivariate final Cox regression analysis for osteoporotic fracture and hip fracture in men and women based on a complete case analysis and using multiply imputed data are shown on bmj.com.

*Risk factors for fracture in men*—After adjustment for all other variables in the model, we found significant associations with overall risk of fracture and risk of hip fracture in men for age, BMI, smoking status, alcohol use, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, use of tricyclic antidepressants, history of falls, liver disease, and use of corticosteriods. These variables were included in both final algorithms for men.

*Risk factors for fracture in women*—After adjustment for all other variables in the model, we found significant associations with overall fracture risk in women for use of HRT, smoking status, use of alcohol, parental history of osteoporosis, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants, use of corticosteroids, history of falls, menopausal symptoms, chronic liver disease, gastrointestinal malabsorption, and other endocrine disorders. There were also significant associations with age and BMI with fractional polynomial terms. The final algorithms for osteoporotic fracture and hip fracture in women included all of these variables.

### Effect of hormone replacement therapy on fracture risk

Overall, 168 536 women (14.24% of 1 183 663) were prescribed HRT at baseline. We found significant associations between risk of fracture and some types of HRT. See bmj.com and also some significant associations in the time varying analyses for duration of use of HRT and time since stopping HRT.

### Validation of the QFractureScores

The table shows the discrimination statistics for the QFractureScores. There was close correspondence between predicted and observed 10 year risks within each 10th of predicted risk in the validation cohort. For example, in the top 10th of risk for osteoporotic fracture in women, the mean predicted 10 year risk of fracture was 12.9% and the observed risk was 13.0%. See bmj.com.

### Validation of the fracture clinical risk score against FRAX

We calculated a hip fracture score using the FRAX algorithm for 454 499 women aged 40-85 and 424 336 men aged 40-85 in the validation cohort. The D statistic for hip fracture for the FRAX algorithm was 2.26 (2.21 to 2.30) for women and 2.22 (2.14 to 2.30) for men. The FRAX algorithm explained 54.83% (54.43% to 55.12%) of the variation in women and 54.07% (52.10% to 53.65%) in men. The ROC value for the FRAX algorithm was 0.845 for women and 0.817 for men.

We recalculated the validation statistics for the QFractureScores restricting the population to patients aged 40-85. The D statistic for hip fracture was 2.37 (2.32 to 2.42) for women and 2.39 (2.30 to 2.48) for men. The QFractureScores explained 57.29% (57.18% to 58.09%) of the variation in women and 57.67% (56.78% to 58.57%) in men (figure).

## DISCUSSION

### Summary of main findings

A new risk prediction algorithm (the QFractureScore) for estimating the 10 year absolute risk of hip fracture in men and women shows some evidence of improved discrimination and calibration compared with the FRAX algorithm. Given that FRAX was developed in multiple selected cohorts from across the world, the marginally poorer performance is not unexpected.

Our new algorithms do not require any laboratory testing or clinical measurements. They can be implemented within clinical computer systems in primary care and used to stratify the practice population by risk on a continuing basis without the need for manual data entry. The QFractureScores could therefore act as a basis for a systematic population based programme to identify high risk patients for further assessment and support the implementation of evolving clinical
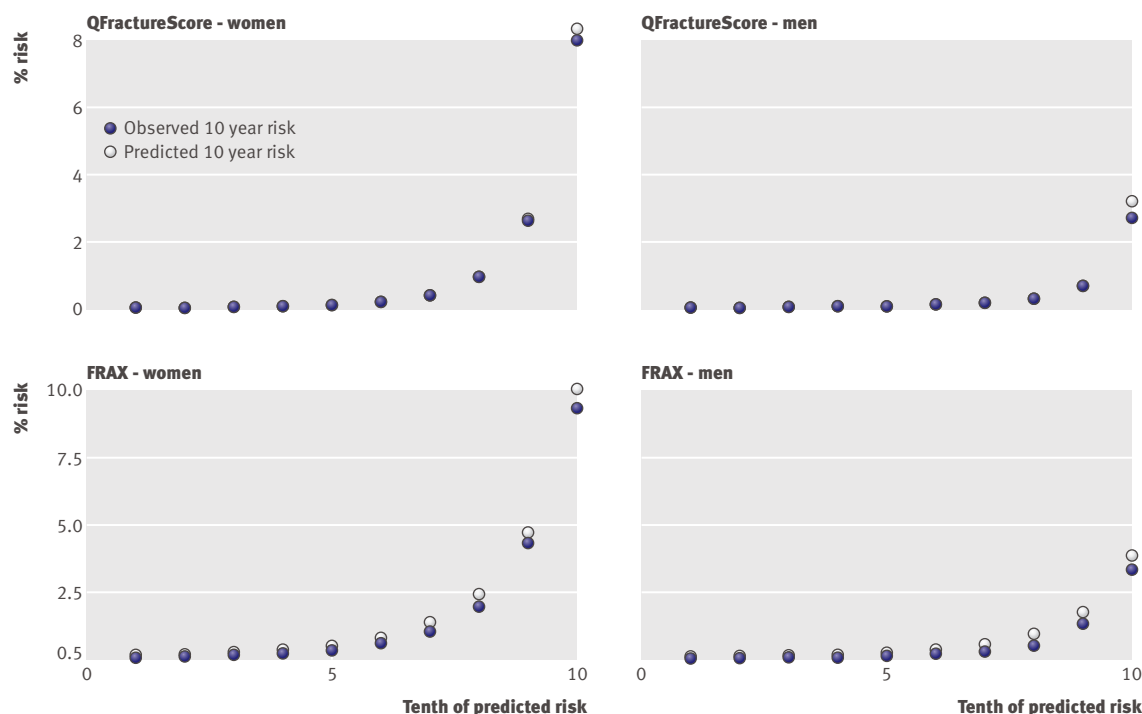
Predicted and observed risk of hip fracture with QFractureScore and FRAX

guidelines in the UK. At the level of the individual patient, the algorithms can be used for self assessment in a web based calculator (www.qfracture.org).

### Hormone replacement therapy and fracture risk

We have shown an overall protective effect of HRT with a decreased risk with unopposed oestrogen. The effect is more marked for vertebral, distal radial, and hip fractures combined rather than hip fracture alone, probably because of lower numbers of patients with hip fracture by individual type of HRT. Our findings are consistent with those from other studies.[7-9] The loss of the protective effect of HRT on risk of fracture after stopping treatment is consistent with some[9 10] but not other studies.[11]

### Validation

The QFractureScores have good discrimination and explain over 60% of the variation for hip fracture. The practices used for the validation use the same clinical computer system (EMIS) as those used to derive the algorithm. The EMIS system, however, is currently in use in 60% of UK general practices and so the QFractureScores are at least likely to perform well for over half of the UK's population. Validation using the THIN database is currently under way.

### Comparison with other risk prediction algorithms

Unlike FRAX, the QFractureScores can be used in younger patients and can be used to estimate risk at one, two, five, and 10 years rather than just 10 years. Our new algorithms use more detailed variables and we hypothesise that the QFractureScores will be better at estimating risk for the individual patient by taking account of more information regarding the patient's history.

One potential limitation of the QFractureScores com-

pared with FRAX is that they don't include measurement of bone mineral density, but that does mean the scores can be applied without the need for expensive tests to identify high risk patients. Another potential limitation is that they are more complex than FRAX and some might think it is more difficult to implement. The main use of the QFractureScores, however, is likely to be integrated into general practice clinical computer systems, as well as a web based calculator (at www.qfracture.org), where software can automatically extract the necessary variables, perform the calculations, and present the results to the clinician and individuals as appropriate. Open source software is also available from www.qfracture.org to help ensure reliable implementation of QFracture. In contrast, the FRAX algorithm is not publically available for clinical or research use.

Our algorithms also improve on the recent algorithm based on the Women's Health Initiative cohort[12] as they are estimated over a longer period than five years and include additional variables, such as HRT and have improved validation statistics.

### Methodological considerations

*Generalisability and measurement of outcomes*—One strength of our study is its prospective cohort design based on the analysis of a large representative population from a validated database. The analyses can be updated as population characteristics change and as statistical methods advance. Our study has good validity as our hazard ratios for risk of hip fracture were similar to those found in other studies. In particular, our analysis supports a dose-response relation for current smokers with lower risks among former smokers. We also found no association between hip fracture and deprivation, which confirmed findings reported elsewhere.[13]

*Sources of bias and unmeasured confounding*—Several variables are reported by patients, such as alcohol, smoking, and parental history of hip fracture and might be subject to information or reporting bias. As the QFractureScores are intended for use within general practice clinical computer systems, however, similar conditions will apply and so the variables incorporated in the algorithm have intrinsic face validity. The study population is representative and unlikely to be affected by selection bias, in contrast with purpose designed clinical cohorts or clinical trials.[9] [14] We did not have objective measurements of some factors that might affect fracture risk, such as physical activity, and we had insufficient numbers of events within each ethnic group to allow for analyses by ethnicity. This should, however, improve over time as recording rates for ethnicity improve on GP clinical computer systems.

*Missing data*—We used multiple imputation to substitute missing values for alcohol use, BMI, or smoking status. For other variables we assumed that if there was no recorded value the patient did not have that exposure, which might have led to some misclassification.

1    Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008;19:399-428.
2    Dawson-Hughes B, Tosteson A, Melton L, Baim S, Favus M, Khosla S, et al. Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int* 2008;19:449-58.
3    Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX—assessment and intervention thresholds for the UK. *Osteoporos Int* 2008;19:1395-408.
4    National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal men and women from the age of 50 in the UK. National Osteoporosis Guideline Group, 2008.
5    National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE, 2008.
6    Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19:385-97.
7    Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
8    Howard L, Kirkwood G, Leese M. Risk of hip fracture in patients with a history of schizophrenia. *Br J Psychiatry* 2007;190:129-34.
9    Banks E, Beral V, Reeves G, Balkwill A, Barnes I. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004;291:2212-20.
10   Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SAA, Brzyski R, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-45.
11   Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004;34:728-35.
12   Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. *JAMA* 2007;298:2389-98.
13   West J, Hippisley-Cox J, Coupland C, Price G, Groom L, Kendrick D, et al. The effect of deprivation, rurality and ethnicity on falls and hip fracture in elderly people in Trent 1992-1997: an ecological study. *Public Health* 2004;8:576-81.
14   Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000;342:1878-86.

# Unwise words: now that wasn't very clever

When doing an oncology outpatient clinic, I wheeled into the clinic room to see a patient for follow-up of his condition; I use a wheelchair after spinal injury many years ago resulted in permanent paralysis from the chest down. After we had made our introductions, The patient asked, "Why are you in a wheelchair?"

Whenever my wheelchair is mentioned, I try to focus the attention back on the patient, rather than explaining my situation. On this occasion, however, I said, "I broke my back almost 20 years ago."

The usual, "Rugby? Car accident?" came back, and I answered, "No, on a skiing holiday."

He then replied with, "Now that wasn't very clever."

Taken aback by this comment, I didn't really know how to respond. Did it even deserve an answer? I had to bite my lip, remembering that patient needs come first in terms of the outcome of a consultation. I indicated that the accident hadn't been planned—after all, it wouldn't otherwise have been an accident—and quickly moved on to addressing how the patient was.

This experience did, however, remind me that living with disability is not only physically tiring, time consuming, and financially costly, but that it is also mentally demanding. You can get unwanted comments, most often when people respond with a clichéd phrase blurted out in a reflex manner to fill a verbal void. Unwise words are rarely maliciously intended, and it is usually best to respond gracefully. Disability, by testing your physical and mental resilience, teaches you to focus on the important things in life—the value of independence and surrounding yourself with positive and considerate people. Another lesson, of course, is the importance of either choosing your words carefully or saying nothing at all.

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## *p i c o*

# Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies

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**STUDY QUESTION** Is there a causal relation between levels of salt intake and the incidence of stroke and total cardiovascular outcomes?

**SUMMARY ANSWER** High salt intake is associated with significantly greater risk of both stroke and total cardiovascular disease.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** The potential benefits of less dietary salt in the prevention of cardiovascular disease have been extrapolated from the observed reduction in blood pressure with lower salt intake. This meta-analysis shows a significant direct association between higher habitual salt intake and risk of stroke and cardiovascular disease.

### Selection criteria for studies

Search of Medline (1966-2008), Embase (from 1988), AMED (from 1985), CINAHL (from 1982) Psychinfo (from 1985), and the Cochrane Library with no language restrictions. Manual search of references from recent reviews and relevant published original studies, and examination of reference lists. Studies had to be original articles published between January 1966 and December 2008, population based prospective studies, assess salt intake as baseline exposure, have either stroke or total cardiovascular disease as outcome, follow-up participants for at least three years, study adults, and indication of the number of participants exposed and the rate or number of events in different categories of salt intake. We recorded publication reference, total number of participants, country, sex, age, recruitment time, follow-up, outcome, assessment methods for exposure and outcome, number (rate) of events, and salt intake in different categories. The pooled relative risk of stroke or cardiovascular disease for higher versus lower salt intake referred to a weighted average difference in habitual salt intake of 85 mmol or 5 g of salt per day.

### Primary outcomes

The primary outcomes were fatal and non-fatal strokes and fatal and non-fatal total cardiovascular disease events.

### Main results and role of chance

Thirteen studies reported on 19 independent cohorts, which included 177 025 participants from six countries. Eleven studies recruited both men and women, while two studies recruited only men. Follow-up ranged from 3.5 to 19 years. Four studies reported only strokes, three only cardiovascular disease, and six both. Salt intake was assessed by 24 hour dietary recall (n=4), food frequency questionnaire (n=4), 24 hour urine excretion (n=5), and questionnaire (n=1). There were 5346 strokes and 5161 cardiovascular events. In pooled analyses, an 85 mmol (or 5 g/day) higher salt intake was associated with greater risk of stroke (relative risk 1.23, 95% confidence interval 1.06 to 1.43; P=0.007). There was also an association between higher salt intake and risk of cardiovascular disease (1.17, 1.02 to 1.34; P=0.02). The effect seemed to be dose dependent for stroke and increased with the duration of follow-up.

### Bias, confounding, and other reasons for caution

There was no evidence of publication bias. Heterogeneity, detected for both stroke and cardiovascular disease, was explored with meta-regression, sensitivity, and subgroup analyses.

### Study funding/potential competing interests

| POOLED RELATIVE RISK ESTIMATES OF INCIDENT STROKES AND TOTAL CARDIOVASCULAR EVENTS ASSOCIATED WITH DIFFERENCE IN SALT INTAKE OF ABOUT 85 MMOL (5 G OF SALT) A DAY | | | |
|---|---|---|---|
| | Size of effect | Heterogeneity | Publication bias |
| **Incident strokes** | | | |
| 14 cohorts, 154 282 participants, 5346 events | 1.23 (1.06 to 1.43), P=0.007 | $I^2$=61%, P=0.04 | P=0.26 |
| **Incident total cardiovascular events** | | | |
| 14 cohorts, 104 933 participants, 5161 events | 1.14 (0.99 to 1.32), P=0.07 | $I^2$=80%, P<0.01 | P=0.39 |
| 12 cohorts*, 101 996 participants, 5044 events | 1.17 (1.02 to 1.34), P=0.02 | $I^2$=80%, P<0.01 | P=0.16 |

*Without outliers, based on sensitivity analysis

# pico

# Socioeconomic inequalities in survival and provision of neonatal care: population based study of very preterm infants

Lucy K Smith, Elizabeth S Draper, Bradley N Manktelow, David J Field

**STUDY QUESTION** Are there socioeconomic inequalities in the survival and provision of neonatal care among very preterm infants?

**SUMMARY ANSWER** After very preterm birth, survival rates and neonatal care are similar for infants from all areas.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** Areas of high deprivation have high rates of neonatal and infant mortality and very preterm birth. The higher burden of mortality and increased neonatal care costs for very preterm infants in deprived areas is probably because of higher incidence rates and not differences in their individual severity of condition.

### Participants and setting

All infants born between 22+0 and 32+6 weeks' gestation who were alive at the onset of labour and whose mothers lived in the former Trent health region of the United Kingdom.

### Design, size, and duration

This was a prospective cohort study of infants born between 1 January 1998 and 31 December 2007 and followed until discharge from neonatal care. Detailed data on the infants and the provision of neonatal care were combined with mortality data and socioeconomic data based on the UK IMD2004 deprivation score at super output area level.

### Primary outcomes

We calculated survival to discharge from neonatal care per 1000 total births and per 1000 very preterm births. Provision of neonatal care for very preterm infants surviving to discharge was assessed with length of stay, provision of ventilation, and respiratory support.

### Main results and the role of chance

In the 10 year period there were 7402 very preterm singleton births. The incidence was nearly twice as high in the most deprived areas than in the least deprived. Consequently rates of mortality because of very preterm birth per 1000 total births were almost twice as high in the most deprived areas than in the least deprived (incidence rate ratio 1.94, 95% confidence interval 1.62 to 2.32). Mortality rates per 1000 very preterm births showed little variation across all deprivation fifths (1.02 (0.86 to 1.20) for most deprived fifth versus least deprived). For infants surviving to discharge, measures of length of stay and provision of ventilation and respiratory support were similar across all deprivation fifths. Of very preterm infants surviving to discharge, 69% stayed in hospital more than 28 days, 47% needed ventilation at some point during their stay, and 78% needed at least one days' respiratory support.

### Bias, confounding, and other reasons for caution

We had no access to individual level measures of deprivation, which might show inequalities in survival, risk profiles, or provision of neonatal care not seen with area level measures. Obtaining individual data, however, is more time consuming and costly. Our methods using area level measures are relatively straightforward to undertake and allow constant monitoring of services for health service planners. The use of length of stay and ventilation and respiratory support reflect the major components of inpatient provision of neonatal care but clearly do not represent a detailed cost analysis.

### Generalisability to other populations

The results are likely to be generalisable within England as the study area represents about an eleventh of births in England and has a similar deprivation profile to England as a whole, with a slight excess of more deprived areas. These results might also be generalisable to countries with similar provision and access to neonatal care.

### Study funding/potential competing interests

| INCIDENCE OF VERY PRETERM BIRTH AND RELATIVE RISK OF MORTALITY BEFORE DISCHARGE FROM NEONATAL CARE BY DEPRIVATION FIFTH (95% CONFIDENCE INTERVALS) IN INFANTS ALIVE AT ONSET OF LABOUR | | | |
|---|---|---|---|
| | **Least deprived fifth (n=1026)** | **Most deprived fifth (n=1957)** | **All (n=7402)** |
| Incidence of very preterm birth per 1000 births | 9.5 (8.9 to 10.1) | 18.1 (17.3 to 18.9) | 13.7 (13.4 to 14.0) |
| No of deaths before discharge | 180 | 349 | 1289 |
| Relative risk for mortality per 1000 total births | 1 | 1.94 (1.62 to 2.32) | — |
| Relative risk for mortality per 1000 very preterm births | 1 | 1.02 (0.86 to 1.20) | — |

## *p i c o*

# The economy-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment

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**STUDY QUESTION** What is the potential economic impact of pandemic influenza, and associated palliative responses, in the United Kingdom?

**SUMMARY ANSWER** The economic impact of disease alone is small, but school closures could greatly increase this impact and widespread absence from work in an attempt to avoid infection could provoke large costs with few benefits. An effective vaccine could greatly reduce the economic costs of a pandemic.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** Government sanctioned school closure in response to a flu pandemic could have a substantial economic impact which may not be balanced by health benefits. Our model suggests that vaccines play the major role in mitigating the economic impact of a pandemic and also estimates the impact of fear-induced behavioural change.

## Main results

Results are presented for low, medium, and high clinical attack rate and low, high, and extreme case fatality rates, yielding nine disease scenarios. The costs related to illness alone are likely to range between 0.5% and 1.0% of gross domestic product (GDP) (£8.4bn to £16.8bn) for low fatality scenarios, 3.3% and 4.3% (£55.5bn to £72.3bn) for high fatality scenarios, and larger still for an extreme pandemic. School closure increases the economic impact, particularly for mild pandemics. If there is widespread prophylactic absence from work, the economic impacts could be greatly increased with few health benefits. Vaccination (at 60% coverage) with a pre-pandemic vaccine could save 0.13-2.3% of GDP (£2.2bn-£38.6bn), while a single dose of matched vaccine could save 0.3-4.3% (£5.0bn-£72.3bn) and a double dose of matched vaccine could limit the overall economic impact to about 1% of GDP for all disease scenarios.



**IMPACT OF PANDEMIC INFLUENZA ON GROSS DOMESTIC PRODUCT BY VARIOUS DISEASE AND MITIGATION SCENARIOS**

## Design

A computable general equilibrium model of the UK economy was specified for various combinations of mortality and morbidity from pandemic influenza, vaccine efficacy, school closures, and prophylactic absenteeism based on published pandemic data.

## Source(s) of effectiveness

Vaccine efficacy is estimated from published studies of influenza vaccines, and estimation of the efficacy of school closures to mitigate the disease are taken from modelling studies and other published sources.

## Data sources

Parameter assumptions (and their sources) are tabulated in the paper. Disease estimates are taken from pandemic planning documents, assumptions about absenteeism from work in response to school closures are taken from published surveys, and mitigation impacts are estimated from published models. Published studies of social networking theory are used to estimate a transition point for prophylactic absenteeism.

## Results of sensitivity analysis

The unpredictability of influenza pandemics does not permit confidence intervals for sensitivity. Instead, we present scenarios with varying severity of disease to show the sensitivity of our results. Our results are sensitive in particular to changes in fatality rate. Closure of schools for 15 weeks rather than 4 weeks results in an increased impact of about 2.5% of GDP. Our results are not very sensitive to changes in the efficacy of school closures to mitigate the pandemic.
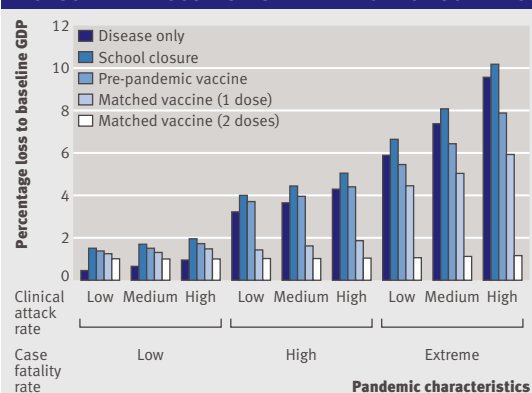
## Limitations

This work does not take into account consumption effects from avoidance of public places and changes in shopping patterns. The strength of our findings depends on the underlying assumptions which, while based on published evidence where possible, are subject to the bias of surveys and the unpredictability of the disease and its resultant impact on policies and behavioural changes. There is also potential for wide variations in our social networking estimates when theory gives way to mid-pandemic practice.

## Study funding/potential competing interests

None declared.