Predicting the risk of osteoporotic fracture in Men and Women in the UK: prospective derivation and validation of an updated QFracture Score

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1 Introduction

Osteoporotic fractures are a major and increasing cause of morbidity in the population and a considerable burden to health services. Hip fractures, in particular, result in considerable pain, loss of function and hospitalisation making prevention a high priority for patients, physicians and for public health. Therapeutic and lifestyle interventions exist which may reduce risk of osteoporosis and hence an individual's risk of fracture[1]. The challenge now is to improve methods for accurate identification of individuals at high risk who might benefit from a therapeutic or preventative intervention. Guidelines[2-6] now recommend a targeted approach to the prevention of osteoporosis based on the ten year absolute risk of major osteoporotic fracture. Risk prediction utilities are therefore required to accurately estimate individual risk as well as enable a systematic targeted population based screening approach.

In 2009, we published a new risk prediction algorithm called QFracture[7] designed to estimate absolute risk of osteoporotic fracture and hip fracture in primary care. The QFracture algorithm is based on variables which are readily available in patients electronic primary health care records[8] or which the patient themselves would be likely to know without needing laboratory tests or clinical measurements. This approach is designed to enable the algorithms to be readily and cost-effectively implemented in routine clinical practice or used by individual patients. QFracture (2009) included established risk factors already incorporated into the FRAX algorithm (age, sex, body mass index, parental history of hip fracture, smoking, steroid treatment, rheumatoid arthritis, secondary osteoporosis and use of alcohol)[9]. QFracture also included additional risk factors not included in FRAX but highlighted by NICE guidance[10], National Osteoporosis Guideline[5] or the World Health Organisation[11]. These included history of falls, type 2 diabetes, chronic liver disease, gastro-intestinal malabsorption, cardiovascular disease, asthma, use of HRT and use of tricyclic antidepressants[5 12 13 14] as well as a more detailed categorisation of smoking and alcohol status[7]. The original QFracture algorithm (2009) performed well on a separate set of practices from the QResearch database compared with FRAX[7] with better discrimination and calibration. QFracture (2009) also performed well in an more stringent independent validation team using an separate set of practices contributing to the THIN database[15].

In February 2012, NICE published draft guidance called "Osteoporosis: assessing the risk of fragility fracture"[6]. This included a number of recommendations regarding further developments in order to improve the utility of QFracture including extending the age range to include patients aged over 85 years; inclusion of additional variables such as prior fragility fracture[6], ethnic group[16]; epilepsy and use of anticonvulsants[17]; care home residents[18 19]; additional inflammatory arthropathies; chronic obstructive airways disease[6]; type 1 diabetes[20]; other causes of immobility[6] (such as Parkinson's disease[21] or dementia). We also recognised that our original definition of osteoporotic fracture included hip, wrist and vertebral fractures but not proximal humerus fracture although this does represent an osteoporotic fracture.

We have therefore decided to update the original QFracture algorithms using the most recent version of the QResearch and to test the performance of the updated algorithms in a separate set of practices from those used to develop the updated model. This is a protocol for the update

2 Methods

2.1 Study design and data source

We will conduct a prospective cohort study studying a large primary care population of patients from version 32 of the QResearch database (data last updated October 2011). QResearch is a large validated primary care electronic database containing the health records of over 13 million patients registered from over 620 general practices using the Egton Medical Information System (EMIS) computer system. Practices and patients contained on the database are nationally representative for the UK and similar to those on other large national primary care databases using other clinical software systems[22]. We will include all QResearch practices once they had been using their current EMIS system for at least a year so as to ensure completeness of recording of morbidity and prescribing data. We will randomly allocate two-thirds of practices to the derivation dataset and the remaining one-third to the validation dataset.

2.1.1 Cohort selection

We will identify an open cohort of patients aged 30-100 years at the study entry date, drawn from patients registered with eligible practices during the 15 years between 01 January 1993 and 01 Oct 2011. We will use an open cohort design, rather than a closed cohort design, as this allows patients to enter the population throughout the whole study period rather than require registration on a fixed date; reflecting the realities of routine clinical practice. For each patient, we will determine an entry date to the cohort, which is the latest of the following dates: 30th birthday; date of registration with the practice; date on which the practice computer system is installed plus one year; and the beginning of the study period (i.e. 01 January 1993). We will only include patients in the analysis once they had a minimum of one year's complete data in their medical record[23]. For each patient we will also determine an exit date, which is the earliest date of: date of recorded fracture, date of death, date of deregistration with the practice, date of last upload of computerised data, or the study end date (01 Oct 2011).

2.2 Primary outcomes

We will have two primary outcomes. These are the (a) combined fracture defined as first diagnosis of an osteoporotic fracture ie hip fracture, vertebral fracture, proximal humerus or distal radius fracture) and (b) incident diagnosis of hip fracture either on the GP record or

the linked death record. In contrast with QFracture (2009), the combined fracture definition also included fracture of the proximal humerus.

2.3 Fracture risk factors

We will examine risk factors currently included in QFracture (2009) as well as additional risk factors which have been highlighted by NICE.

2.3.1 Factors already in QFracture[7]

1. Age at study entry (in single years)
2. Body mass index (continuous)[24]
3. Smoking status (non-smoker, ex-smoker; light smoker: <10 cigarettes/day, moderate smoker: 10-19 cigarettes per day, heavy smoker: 20 or more cigarettes per day) [25-27]
4. Parental history of osteoporosis or hip fracture in a first degree relative (binary variable yes/no)[28]
5. Cardiovascular disease (binary variable yes/no)[12]
6. Alcohol (none, trivial <1 unit/day, light 1-2 units/day, medium 3-6 units/day, heavy 7-9 units/day, very heavy >9 units/day)[29]
7. Rheumatoid arthritis (binary variable yes/no)[30]
8. Type 2 diabetes (binary variable yes/no)[31]
9. Asthma (binary variable yes/no)
10. History of falls prior (binary variable yes/no)
11. Chronic liver disease (binary variable yes/no)
12. Gastrointestinal conditions likely to result in malabsorption (i.e. Crohn's disease, ulcerative colitis, celiac disease, steatorrhoea, blind loop syndrome) at baseline (binary variable yes/no)[9]
13. Other endocrine conditions (thyrotoxicosis, primary or secondary hyperparathyroidism, Cushing's syndrome) at baseline (binary variable yes/no)
14. At least two prescriptions for systemic corticosteroids in the six months preceding baseline (binary variable yes/no)[32].
15. At least two prescriptions for tricyclic antidepressants in the six months preceding baseline (binary variable yes/no)[14]
16. At least two prescriptions for hormone replacement therapy (in women) in the six months preceding baseline[13]
17. Menopausal symptoms

2.3.2 New factors

In addition to the above factors, we will examine the following variables which have all been associated with increased risk of osteoporosis.

1. Self-assigned ethnicity (White/not recorded, Indian, Pakistani, Bangladeshi, Other Asian, Black African, Black Caribbean, Chinese, Other including mixed) [16]

2. Other antidepressants apart from tricyclic antidepressants
3. Chronic obstructive pulmonary disease
4. Epilepsy[17]
5. Prescribed anticonvulsants[17]
6. Dementia
7. Parkinson's disease[21]
8. Cancer
9. Systemic lupus erthythematosis
10. Chronic renal disease[33]
11. Type 1 diabetes[20]
12. Car or nursing home status[18 19]

We will restrict all values of these variables to those which had been recorded in the person's electronic health care record prior to baseline, except for body mass index, alcohol and smoking status where we will use the values recorded closest to study entry date and recorded before the diagnosis of osteoporotic fracture (or prior to censoring for those who did not develop a fracture). We will assume that if there is no recorded value of a diagnosis, prescription or family history then the patient does not have that exposure.

2.4 Model derivation and development

We will use 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 overall fracture and hip fracture for men and women separately. We will compare models using the Akaike Information Criterion (AIC) and the Bayes Information Criterion (BIC)[34]. We will use fractional polynomials to model non-linear risk relationships with continuous variables where appropriate[35]. Continuous variables will be centred for analysis. We will use multiple imputation to replace missing values for alcohol, smoking status and body mass index, and use these values in our main analyses[36-39]. We will use the ICE procedure in Stata[40] to obtain five imputed datasets.

In view of the large number of variables under consideration and the need to ensure that the resulting algorithm can be used in everyday clinical practice, we will explore whether any new variables could be combined with any of the existing variables. We will do this where the new variables represented a condition or medication similar to an existing variable. For example, systemic lupus erthythematosis is an inflammatory arthropathy similar to rheumatoid arthritis; asthma is a respiratory condition similar to chronic obstructive airways disease; SSRIs are antidepressants like tricyclics. We will evaluate this by running a model with separate terms for each factor and if each variables is significant (ie had a hazard ratio of <0.8 or > 1.20 and had a p value 0f < 0.01), we undertake a direct test of the two similar variables. If this is not significant (P <0.01) or if the hazard ratios are within 0.2, then we combined the variables into a new variable (either rheumatoid arthritis or systemic lupus erthythematosis).

Our final model is fitted based on multiply imputed datasets using Rubin's rules to combine effect estimates and estimate standard errors to allow for the uncertainty due to missing

data[41] [42]. We will take the regression coefficient (i.e. the log of the hazard ratio) for each variable from the final model using multiply imputed data and use these as weights for QFracture. As in previous studies[43] [44], we will combine these weights with the baseline survivor function for diagnosis of fracture or hip fracture obtained from the Cox model evaluated at 10 years and centred on the means of continuous risk factors to derive a risk equation for 10 years' follow-up. We will also develop risk equations for each year from 1-15 years so that the user can select the time period over which fracture risk is to be estimated. We will not include interactions with age since this is previously found to significantly increase the complexity of the algorithm without any corresponding improvement in its performance[7].

2.5 Validation of the QFracture

We will test the performances of the final models in the validation dataset. We will calculate the 5 year and 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 for alcohol, smoking status and body mass index, as in the derivation dataset. We will calculate the mean predicted fracture risk and the observed fracture risk at 5 years and 10 years[44] and compared these by tenth of predicted risk. The observed risk at 5 years and 10 years is obtained using Kaplan-Meier estimates. We will calculate the D statistic (a measure of discrimination where higher values indicate better discrimination)[45] and an R-squared statistic (which is a measure of explained variation for survival data, where higher values indicate more variation is explained)[46]. We will calculate the area under the Receiver Operator Curve (ROC) at 5 years and 10 years, where higher values indicate better discrimination. We will compare the performance of the updated score with the original QFracture score. We will not undertake a further comparison with FRAX as the algorithms are not published or available from the authors.

We will use all the available data on the QResearch® database and therefore will not do a pre-study sample size calculation. All analyses are conducted using Stata® (version 11). We will use a significance level of 0.01 (two tailed) since we are considering several variables as potential risk factors in a large dataset, and wanted to reduce the risk of having an overly complex model including variables with limited prognostic value.

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