ABSTRACT

Title

Hearing loss and risk of major osteoporotic fracture: a population-based cohort study in the United Kingdom

Keywords

Hearing Loss, Hearing Impairment, Fracture, Feature Selection, Osteoporosis, Prediction, Survival Analysis,

Study Background and Rationale

The conditions of hearing loss and osteoporosis (OP) are both more common with age. There is some evidence to suggest an association between hearing loss and OP, with an up to 20% increased risk of hearing loss in individuals with low bone mineral density. An increased risk of fracture in individuals with hearing loss has also been found at 2, 5, and 10 years after hearing loss diagnosis. Undergoing an osteoporotic fracture can have a significant impact on a patient's quality of life. Further it can lead to an increased risk of morbidity and mortality. Existing fracture risk prediction tools are designed for the general population and may not include specific information defining hearing loss population. Risk prediction tools tailored to those with hearing loss and using data that are readily available in clinical practice can aid clinical decision-making in treatment pathways and ultimately improve patient outcomes. In this study we added to existing knowledge on the characterization of fractures in hearing loss, and built on existing fracture risk prediction tools by developing a tool specifically for individuals with hearing loss.

Study Feasibility and Futility Considerations

In the protocol we had interrogated CPRD GOLD for the most recent build (May 2021). There were data for 305,463 patients aged 60 or older with at least 1 year of registration before the record of hearing loss within the study period. Of those, 144,672 patients were eligible for linkage to hospital and mortality data.

Research Question and Objectives

Objectives 2 and 3 were analyzed to determine if an association existed between hearing loss/impairment and major osteoporotic fracture risk, as outlined in Objective 1.

Table 1. Primary and secondary objectives

Objectives	**Endpoints**
Primary	
• To assess the association between hearing loss/impairment and major osteoporotic fracture risk (Objective 1)	• Major osteoporotic fracture: clinical spine, wrist/forearm,shoulder/ proximal humerus, and hip fracture o These were identified using previously established lists of READ codes.
Secondary	
• To identify risk factors associated with 1- and 10-year major osteoporotic fracture risk amongst patients with hearing loss/impairment (Objective 2) o To combine key predictors of fracture risk to derive major osteoporotic prediction tools (1- and 10-years) (Objective 3)	• Performance (calibration and discrimination) of major osteoporotic fracture (clinical spine, wrist/forearm, shoulder/proximal humerus or hip fracture) prediction tools for 1- and 10- years
Exploratory	
• NA	• NA

Hypothesis(es)/Estimation

We aimed to test if there was an association between hearing loss and major osteoporotic fracture risk.

Study Design/Type

This is a cohort study using secondary routinely collected health data obtained from UK Clinical Practice Research Datalink (CPRD) GOLD linked to Hospital Episode Statistics (HES) Admitted Patient Care (APC), Indices of multiple deprivation (IMD) and Office for National Statistics [1].

Socio-demographics, medical history, and treatments were provided by CPRD, to be adjusted for in the analysis of objective 1-3.

Hospital Episode Statistics (HES) Admitted Patient Care (HES inpatient) data linkage allowed us to determine hospitalizations which informed risk factors for objective 2 and 3.

Death registration data from the Office for National Statistics (ONS death) was used to inform outcome status (death) in the analysis of objective 3 to account for primary outcome (fracture risk) with a competing risk of death.

Study Population or Data Resource

The study population includes all patients who are registered in CPRD for at least one year before becoming eligible (identified index date). The study period was from January 1, 2001 to December 31, 2020.

Summary of Patient Eligibility Criteria

All the patients with the following criteria were considered for inclusion:

- Registered in CPRD for at least one year before the index date
  The index date definition varies according to the subcohorts:
  - Subcohort 1 – Hearing loss cohort: first diagnosis/record of hearing loss or impairment.
  - Subcohort 2 – Non-hearing-impaired cohort: individuals with no record of hearing loss/impairment matched to each participant in the hearing loss cohort by year of birth, sex, general practice, and year at index date (date of the first diagnosis/record of hearing loss/ impairment for their matched case)
- ≥ 60-years of age at index date
- No prior history of vestibular dysfunction, osteomalacia and/or other secondary osteoporotic causes e.g., Endocrine disorders, Cushing syndrome, Hyperparathyroidism, Type 1 diabetes mellitus, Chronic active hepatitis, Pancreatic insufficiency, ankylosing spondylitis, Multiple sclerosis, Osteogenesis imperfecta or Aromatase Inhibitors use.

Follow-up

Follow-up went from the specified index date until either 1) study event (i.e., major osteoporotic fracture); or 2) censoring at the earliest of death, migration/transfer out, practice last collection date, end of study period (based on data availability at extraction date), end of specific sub-study follow-up period (1 or 10 year after index date).

Variables

- Outcome Variable(s)
  Major osteoporotic fracture: clinical spine, wrist/forearm, shoulder/proximal humerus, and hip fracture
- Exposure Variable(s)
  Exposure is hearing loss defined as: first diagnosis/record of hearing loss or impairment.
- Other Covariate(s)
  Risk factors included in the QFracture™ [2] prediction tool (https://qfracture.org/) plus other risk factors described in the literature (socio-economic status, occupation, family history and previous meningitis)

Study Sample Size

Current guidelines suggest that a minimum of 100 patients with the outcome of interest and 100 patients without the event of interest are required to provide reliable estimates of model performance [3]. In this study, the dataset consisted of 4416 patients who had experienced a fracture within one year of the index date and 22394 patients who had experienced a fracture within ten years of the index date, with outcome ratios of 1.86% and 9.44%, respectively. These numbers exceeded the recommended minimums, indicating that our dataset was appropriate for creating a dependable predicting model for fracture risk in patients with hearing loss.

Data Analysis

- Association analysis between hearing loss/impairment and fracture risk:
  absolute (incidence rate) and relative risk (proportional hazard Cox models) estimates of overall major fractures and of each major fracture subtype associated with hearing loss (hearing loss patients compared to matched non-hearing-impaired subjects), clustered by age, sex, general practice, and stratified by high risk of fracture (prior history of fractures, OP diagnosis and/or anti-OP treatment). Risk factors with statistically significant interactions will be evaluated in sub-group analyses.

- Identification of the risk factors associated with 1- and 10-year major osteoporotic fracture risk amongst patients with hearing loss/impairment, and the consequent model development.

Results

A total of 1,066,728 individuals were included in the study, including 237,297 in the hearing loss cohort and 829,431 matched non-hearing-impaired cohort patients.

Objective 1: There were 24,222 in the hearing loss cohort and 60,224 non-hearing-impaired cohort with the outcome during the study period, with incidence rate per 1000 person-years of 20.1 (95% confidence interval 20.0 to 20.3) in hearing loss cohort patients and 16.6 (16.4 to 16.7) in non-hearing-impaired cohort patients. Patients with hearing loss had higher risk of major osteoporotic fracture (adjusted hazard ratio 1.10, 95%CI 1.08 to 1.12).

Among different subtypes of fractures, spine fracture was associated with the highest increased risk (1.17 (1.11 to 1.23) and hip fracture with the lowest increased risk (1.08 (1.05 to 1.11).

Objective 2: Leading risk factors for 1-year risk of fracture in those with hearing loss included previous fracture history and age, each with a 2-3 fold increased risk (e.g. fracture history in the previous 12 months OR (95% CI) 3.1 (1.22 -7.89) and age>89 2.85 (2.51-3.25) for the outcome all fractures and a manifold increased risk for outcome hip fractures (e.g. age>89 13.28 (9.81-17.99), femur fracture history within 6 months 6.68 (2.33 - 19.11). Frailty 1.27 (1.02 -1.57) and Charlson comorbidity score 1.16 (1.04 -1.29) were identified as additional risk factors not currently included in tools such as Qfracture™.

Key risk factors for 10-year risk of fracture were similar to the 1-year risk factors with the addition of blind loop which had a 4-fold increased risk for 10-year OR 4.05 (0.52- 31.62) however this was not statistically significant.

Objective 3: Excellent discrimination and calibration performance (overall and stratified by age and sex) was achieved for 1-year risk prediction models for hip fractures, with a pooled AUC of 0.81(0.77-0.85) and calibration slope of 0.979563; good discrimination and calibration performance was achieved for 1-year all fractures, with a pooled AUC of 0.73 (0.71 -0.76) and calibration slope of 1.02.

For 10-year risk prediction, model performance of the time-to-event models was evaluated using concordance and brier score, with values of 0.736 and 0.133 respectively. Key predictors combined into the final prediction equation included risk factors included in existing tools with the addition of frailty and comorbidity

score for 1 year outcome. Whereas 10-year outcome additionally included blind loop as a key predictor

Discussion

This general population-based study found increased risk of major osteoporotic fracture associated with hearing loss or impairment. Further, the study investigated the association of hearing loss and other risk factors with fracture at 1 year and 10 years. A total of 58 key risk factors (organised as 98 dummy variables) were studied. Odds ratios of all risk factors of hip fracture and all fracture within the hearing loss cohort were derived. Key risk factors were combined into prediction models to estimate the person-level risk of hip and all fractures. Key risk factors included and were not limited to age and previous fracture history, in line with literature on fracture risk factors in the general population and in high-fracture risk populations. Additionally identified risk factors not included in current tools included frailty and comorbidity score. Prediction models were built using 16 different combinations of all available risk factors. Prediction models for hip and all fractures showed comparable or potentially better performance than existing tools such as Qfracture™, while utilizing fewer variables and routinely available measurements. The findings suggest that the presented models have the potential to become part of a useful tool for assessing the risk of fracture in populations with routinely available measurements.

Marketing Authorization Holder(s)

Names and Affiliations of Principal Investigators

Sara Khalid, Oxford University
Daniel Prieto Alhambra, Oxford University
Yana Vinogradova, Nottingham University
Nadeem Qureshi, Nottingham University