**Little improvement in bone mineral density associated with substantial decrease in hip fractures – Statistical analysis plan**

**Background:**

Hip osteoporotic fracture poses a major public health problem worldwide as it is prevalent and associated with an increased risk of premature mortality, immobility, and reduced quality of life. As many as 20% of women and 37% of men with a hip fracture die within one year after the fracture1.

In observational studies, each standard deviation (about 0.12 g/cm2) lower in bone mineral density (BMD) measured at the femoral neck is associated with about a 2.0 to 2.5-fold increase in hip fracture risk2 3. However, in randomized controlled trials, a 6% (or half standard deviation) increase in femoral neck BMD is associated with 40% reduction in hip fracture risk4. Thus, there seems to be a paradox between observational and interventional data concerning the relationship between BMD and hip fracture risk.

We consider that this paradox can be explained by Rose's axiom5. In a seminal paper about 4 decades ago, by using the relationship between serum cholesterol and cardiovascular disease, Geoffrey Rose postulated that small changes in a key risk factor at the individual level would lead to large changes in disease outcome at the population level5. This public health axiom predicts that shifting the distribution of a risk factor in the entire population will have larger impact on the disease than intervening those individuals at high-risk for the disease.

This study sought to test the Rose's axiom that a small improvement in BMD at the individual level is associated with a large decrease in hip fracture in the general population. The results are expected to be able to provide evidence for a population-based approach that seeks to control the “causes” of hip fracture, which is possible more effective than the currently implemented preventive strategy that identifies and treats osteoporotic individuals.

**Materials and Methods:**

***Study design:***

We use the Dubbo Osteoporosis Epidemiology Study (DOES) data6 that involve two prospective cohorts of elderly people aged 60 years or older in Dubbo city (New South Wales, Australia). The first cohort included 1,311 women and 842 men aged 60 years and older as at 1989. The second cohort included 974 women and 544 men also aged 60 years and older as at 2000. The study has been approved by the St Vincent’s Hospital Human Research Ethics Committee.

Bone mineral density at the femoral neck was measured by dual-energy X-ray absorptiometry (DXA) using a GE-Lunar Prodigy densitometer (GE Corp, Madison, WI, USA). At our center, the coefficient of variation for BMD in normal individuals was 1-3% for femoral neck 3. Data on anthropometric and demographic factors, lifestyle factors, dietary calcium intakes, physical activity, history of falls or prior fractures were collected by a structured questionnaire at baseline and every two years afterwards.

The participants have been followed up biannually for up to 30 years. The incident hip fracture was continuously ascertained by review of X-ray reports from all three radiological services for the entire Dubbo area. We will exclude traumatic fractures or pathological fractures. Mortality was identified using systematic searches of the funeral director lists, local newspapers and Dubbo medial reports and was verified by death certificates from the New South Wales Registry of births, Deaths and Marriages.

***Statistical analysis:***

We conduct two analyses to determine the contribution of the recruitment time periods to (i) the absolute changes in femoral neck BMD and (ii) the change in the incidence of hip fracture.

We first estimate the absolute change in femoral neck BMD between the two cohorts (2000-2010 and 1989-1999) and determine the contribution of the recruitment time periods to the absolute changes in BMD using a multivariable-adjusted linear regression with adjustment for the predefined covariates that included age, BMI, and lifestyle risk score. The 'lifestyle risk score' (LRS) for each participant is calculated as a a linear summation of effects of cumulative exposure to smoking, dietary calcium intake and physical activity7. A multinomial regression will be conducted to determine the association of recruitment time to the likelihood of being osteopenia or osteoporotic, accounting for potential confounding effects.

A multivariable-adjusted Cox’s proportional hazards model is then conducted to quantify the contribution of recruitment time on the change in the incidence of hip fracture. In this model, time to hip fracture was calculated from the date of the first visit (i.e. the recruitment date) to the date of fracture, death or 31 December 2019, whichever came first. The primary predictor was the recruitment time period, and predefined covariates included age, BMI, lifestyle risk score, fall, and prior fractures. Missing data on covariates will be imputed using the multivariate imputation by chained equations (MICE) method8. The proportional hazards odds assumption will be graphically checked using a Schoenfeld’s residuals.

Predefined subgroup analysis was conducted to examine the contribution of the recruitment time in three groups of individuals with normal, osteopenic and osteoporotic BMD by adding an interaction term between recruitment time and bone health conditions into the regression models. The subgroup-specific coefficients were then estimated for each subgroup. Additionally, number of hip fractures potentially prevented over time, attributable to the difference in the time periods of recruitment will be estimated to quantify the potential impact of individual-level improvement.

Three sensitivity analyses will be considered. In the first analysis, we compute the E-value9 to assess the probability that unmeasured confounding factor would modify the observed association between the recruitment period of times and changes in incident hip fracture. The second analysis excludes individuals who had been on bisphosphonate treatment to examine the potential confounding effects of anti-osteoporosis treatment on the association between recruitment time and hip fracture incidence. The third analysis will account for competing risk of death using both the cause-specific and Fine-Gray subdistribution competing risk regressions.

All analyses are conducted using Stata (College Station, TX: StataCorp LLC). and R statistical environment.

**Dummy tables**

**Table 1: Baseline characteristics of participants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Women** | | **Men** | |
| **1989 - 1999**  **(n = 1311)** | **2000 - 2010**  **(n = 974)** | **1989 - 1999**  **(n = 842)** | **2000 - 2010**  **(n = 544)** |
| Age (years) |  |  |  |  |
| Weight (kg) |  |  |  |  |
| BMI (kg/m2) |  |  |  |  |
| Calcium intake (mg/day) |  |  |  |  |
| Calcium intake index |  |  |  |  |
| Physical activity |  |  |  |  |
| Physical activity index |  |  |  |  |
| Maximal alcohol intake |  |  |  |  |
| Alcohol intake index |  |  |  |  |
| Smoking\* |  |  |  |  |
| No. of packages/years |  |  |  |  |
| Smoking index |  |  |  |  |
| Prior fracture after 50 years old\* |  |  |  |  |
| History of falls in previous year\* |  |  |  |  |
| Lifestyle risk scores FN |  |  |  |  |
| Lifestyle risk scores LS |  |  |  |  |
| Comorbidities\* |  |  |  |  |
| * CVD |  |  |  |  |
| * DM |  |  |  |  |
| * Hypertension |  |  |  |  |
| * Cancer |  |  |  |  |
| * COPD |  |  |  |  |
| * Neurological disorders |  |  |  |  |
| * Rheumatologic disorders |  |  |  |  |

*Data presented as mean (SD) and the difference is mean difference (95% CI) estimated from Student’s t test, unless otherwise indicated. \*: data presented as number (%) and the difference is assessed by chi-squared test. FN= Femoral neck; :S= Lumbar spine; CVD = cardiovascular disease; DM = type II diabetes; COPD = chronic obstructive pulmonary disease.*

**Table 2: Comparison of bone mineral density, prevalence of osteoporosis, and hip fracture incidence between 1989-1999 and 2000-2010 in women and men**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Cohort 1989-1999** | **Cohort 2000-2010** | **Age-adjusted difference** | | **Multivariable\* adjusted difference** | |
| **Women** |  |  |  | |  | |
| Follow-up time: median (IQR) |  |  |  | |  | |
| FN BMD (g/cm2) |  |  |  | |  | |
| Bone health: |  |  |  | |  | |
| * Normal |  |  |  | |  | |
| * Osteopenia |  |  |  | |  | |
| * Osteoporosis |  |  |  | |  | |
| Incident hip fracture: |  |  |  | |  | |
| *All participants:* |  |  |  | |  | |
| * Number of fractures |  |  |  | |  | |
| * Incidence |  |  |  | |  | |
| *Normal BMD participants:* |  |  |  | |  | |
| * Number of fractures |  |  |  | |  | |
| * Incidence |  |  |  | |  | |
| *Osteopenic BMD participants:* |  |  |  | |  | |
| * Number of fractures |  |  |  | |  | |
| * Incidence |  |  |  | |  | |
| *Osteoporotic BMD participants:* |  |  |  | |  | |
| * Number of fractures |  |  |  | |  | |
| * Incidence |  |  |  | |  | |
| **Men** |  |  | |  | |  | |
| Follow-up time: median (IQR) |  |  | |  | |  | |
| FNBMD (g/cm2) |  |  | |  | |  | |
| Bone health: |  |  | |  | |  | |
| * Normal |  |  | |  | |  | |
| * Osteopenia |  |  | |  | |  | |
| * Osteoporosis |  |  | |  | |  | |
| Incident hip fracture: |  |  | |  | |  | |
| *All participants:* |  |  | |  | |  | |
| * Number of fractures |  |  | |  | |  | |
| * Incidence |  |  | |  | |  | |
| *Normal BMD participants:* |  |  | |  | |  | |
| * Number of fractures |  |  | |  | |  | |
| * Incidence |  |  | |  | |  | |
| *Osteopenic BMD participants:* |  |  | |  | |  | |
| * Number of fractures |  |  | |  | |  | |
| * Incidence |  |  | |  | |  | |
| *Osteoporotic BMD participants:* |  |  | |  | |  | |
| * Number of fractures |  |  | |  | |  | |
| * Incidence |  |  | |  | |  | |

*\*adjusted for age, weight, BMI, prior fracture, history of falls and lifestyle factors (physical activity, smoking, calcium intake, alcohol consumption, lifestyle risk score).*

**Table 3: Association between femoral neck bone mineral density and hip fracture between the period of 1989-1999 and 2000-2010**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Women** | | **Men** | |
| **1989 - 1999**  **(n = 1311)** | **2000 - 2010**  **(n = 974)** | **1989 - 1999**  **(n = 842)** | **2000 - 2010**  **(n = 544)** |
| Age - adjusted |  |  |  |  |
| Multivariable\*- adjusted |  |  |  |  |

*Data are shown in hazard ratio (HR) per 0.10 g/cm2 increase (~ every 1 SD) and 95% confidence interval on the risk of hip fracture.*

*\*adjusted for age, weight, BMI, prior fracture, history of falls and lifestyle factors (physical activity, smoking, calcium intake, alcohol consumption, lifestyle risk score). Bold font indicates statistical significance.*

**References:**

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