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# BMJ Open

## Association of age-related macular degeneration on fracture risks among osteoporosis population: A nationwide population-based cohort study

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1 **Association of age-related macular degeneration on fracture risks**  
2 **among osteoporosis population: A nationwide population-based cohort**  
3 **study**

4  
5 **Running head: Age-related macular degeneration on osteoporosis-**  
6 **related fractures**

7  
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24  
25 **Word count: 2542**

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3 26  
45 27 **Abbreviations and Acronyms:**  
67  
8 28 AMD: age-related macular degeneration, OS: osteoporosis, NHIRD: national  
910 29 health insurance research database, NHI: national health insurance, CIs:  
1112 30 confidence intervals, DM: diabetes mellitus, CCI: Charlson comorbidity index,  
1314  
15 31 HR: hazard ratio  
1617 32  
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3 40 **Abstract**  
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8 42 **Objectives:** Visual impairment is an important risk factor of fracture in elderly  
9  
10 43 population. Age-related macular degeneration (AMD) is the leading cause of  
11  
12 44 irreversible visual impairment in elderly people. This study was conducted to  
13  
14 45 explore the relationship between AMD and incident fractures in osteoporosis  
15  
16 46 (OS) patients.

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19 47 **Design:** Retrospective analysis of Taiwan's National Health Insurance  
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21 48 Research Database (NHIRD).

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24 49 **Setting:** A multicenter study conducted in Taiwan.

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26 50 **Participants and Controls:** The current study used the NHIRD in Taiwan  
27  
28 51 between 1996 and 2011. A total numbers of 13,584 and 54,336 patients were  
29  
30 52 enrolled in the AMD group and the non-AMD group respectively.

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33 53 **Intervention:** Osteoporotic patients were extracted from Taiwan's NHIRD  
34  
35 54 from 1996 to 2011. Each osteoporotic patient with AMD (ICD-9 codes:  
36  
37 55 362.50-362.52) was matched with age, sex, and comorbidities to four non-  
38  
39 56 AMD OS patients which served as the control group. A Cox proportional  
40  
41 57 hazard model was used to examine whether AMD were related to incidence of  
42  
43 58 vertebral fractures, hip fractures and humero-radio-ulnar fractures in the  
44  
45 59 multivariate model.

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49 60 **Primary outcome measures:** The transitions for OS to spine fracture, OS to  
50  
51 61 hip fracture, OS to humero-radio-ulnar fracture, and OS to death.

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54 62 **Results:** A total of 1, 206,247 were diagnosed as OS. The risks of vertebral,  
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56 63 hip, and humero-radio-ulnar fractures were all significantly higher in the AMD  
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58 64 group (hazard ratio=1.82, 95% confidence interval (CI)=1.76-1.87; hazard  
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3 65 ratio=1.54; 95% CI=1.48-1.60; and hazard ratio=1.76, 95% CI=1.66-1.86,  
4  
5 66 respectively) compared with non-AMD group among OS patients.  
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7

8 67 **Conclusion:** Osteoporotic patients with a code for AMD had a greater risk of  
9  
10 68 incident fractures than did patients without a code for AMD. Future study to  
11  
12 69 evaluate the effects of treatment for AMD on reducing fracture incidence is  
13  
14 70 mandatory.  
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17 71  
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19 72 **Keywords:** age-related macular degeneration; fracture; osteoporosis;  
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21 73 population-based, database  
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26 75 **Strengths and limitations of this study:**  
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- 28 76 ● The current study enrolled a huge numbers of participants with 13,548  
29  
30 77 patients and 54,336 patients were analyzed in AMD and non-AMD group.  
31  
32  
33 78 ● Each participant can be followed up for up 16 years in the current study  
34  
35 79 even visited different hospital.  
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38 80 ● The causal relationship between AMD and subsequent bone fracture in  
39  
40 81 patients with OS has been established in the current study.  
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43 82 ● The disease severity of OS is not accessible in the NHIRD due to the  
44  
45 83 application of ICD-9 diagnostic codes.  
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48 84 ● Whether severe ocular diseases would lead to more severe fracture or  
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50 85 higher rate of mortality cannot be decided.  
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## 88 Introduction

89 Poor vision is common in the elderly population. Ocular diseases such as  
90 cataract, glaucoma, and age-related macular degeneration (AMD) are  
91 strongly age-related[1-4], and there is accumulating evidence that many  
92 elderly people would benefit from changing eyeglasses[2, 5]. AMD is the  
93 leading cause of irreversible visual impairment in elderly people in developed  
94 countries[6-8]. The estimated incidence of AMD in Taiwan is about 10.8%[9].  
95 While it does not result in complete blindness, however, loss of central vision  
96 can make it difficult to perform other daily activities such as recognizing faces,  
97 driving and reading[10]. According to a previous report, patients with AMD are  
98 in greater fear of falling down which may restrict their social activity[11].  
99 Moreover, the individuals with AMD own a higher probability to fall with a  
100 more unsteady gait pattern[12, 13].

101 Osteoporosis (OS) is a chronic metabolic bone disease in which bones  
102 become relatively weak and more likely to break[14]. The prevalence of OS is  
103 estimated at 11.35% among women over 50 years of age[15]. With regard to  
104 the effect of OS on general health condition, it has been noted that patients  
105 suffered from with OS tend to develop fracture in hip, vertebrae, distal forearm  
106 and humerus[16], while fractures among elderly patients represent an  
107 important public health issue[17]. Taiwan has the world's fastest aging  
108 population,[15] making OS and related fractures pose ever-increasing threat  
109 to elderly population in Taiwan since prevalence climbs rapidly with  
110 age.[14]Because the fracture in elderly would contribute to a higher probability  
111 of mortality despite promptly surgical intervention[18, 19], potential risk factors  
112 for individuals vulnerable to fracture, such as those with OS, should be



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3 113 elucidated.  
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5 114 Concerning the ocular disease and fracture, visual impairment is always  
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8 115 an important risk factor of hip fracture in elderly population[20-22]. In a  
9  
10 116 previous research, macular degeneration and suspicion of glaucoma would  
11  
12 117 lead to a higher risk of hip fracture[22]. Therefore, it is important to understand  
13  
14 118 the ocular risk factors and prevent future fractures in osteoporotic patients.  
15  
16 119 However, only a limited number of studies have examined the association  
17  
18 120 between fractures in OS patients and specific ocular disorders[22-24].  
19  
20 121 Specifically, regarding AMD, previous study only focused on patients with  
21  
22 122 AMD and hip fractures, ignoring spine and humero-radio-ulnar fractures.[22-  
23  
24 123 24] In addition, the numbers of participants in previous researches were  
25  
26 124 relative small,[22-24] while a population-based study should be conduct to  
27  
28 125 investigate the relationship between AMD and fracture with OS since both  
29  
30 126 disorders affect a majority of population.[1, 14]  
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35 127 Therefore, we used the Taiwan's National Health Insurance Research  
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37 128 Database (NHIRD) in this nationwide study with a retrospective cohort and  
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39 129 case-control design to investigate the association between AMD and  
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42 130 subsequent fractures in osteoporotic population.  
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3 132 **Methods**  
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8 134 **Ethics declaration**  
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10 135 All managements performed in our study involving human participants

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12 136 adhered to the 1964 Declaration of Helsinki and its later amendments.

13  
14 137 Specifically, the current study was approved by both the National Health

15  
16 138 Insurance Administration and the Institutional Review Board of Keelung

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18 139 Chang Gung Memorial Hospital, Keelung, Taiwan.  
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24 141 **Patient and Public Involvement statement**  
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26 142 The current study used the database collected and produced by the National

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28 143 Health Insurance Administration of Taiwan. Because this is a claimed data-

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30 144 based study, no patient recruitment, obtain of informed consent (waived by the

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32 145 National Health Insurance Administration), informed of research question,

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34 146 dissemination of study result to participants or other patient and public

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36 147 involvement is applicable in the current study.  
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42 149 **Data source**  
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44 150 This population-based cohort study used the NHIRD of Taiwan

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46 151 (approximately 26 million insured individuals) for the time period January 1996

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48 152 through December 2011. By the end of 2007, NHIRD had enrolled more than

49  
50 153 99% of Taiwan's population into this insurance program, which had contracts

51  
52 154 with 97% of the country's clinics and hospitals. The data available through the

53  
54 155 NHIRD included all medical services provided to each enrollee from 1996 to  
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3 156 2011, as well as the patients' characteristics and the features of the hospitals  
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5 157 and physicians.  
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### 159 **Study Population Enrollment and Exclusion Criteria**

160 From January 1, 1996 to December 31, 2011, we identified patients with  
161 diagnosis of OS, using *International Classification of Diseases, 9th Revision,*  
162 *Clinical Modification* (ICD-9-CM) codes 733.00, 733.01, 733.02, 733.03, and  
163 733.09. The osteoporotic population of the NHIRD was identified by the  
164 presence of either the aforementioned diagnostic codes in their outpatient  
165 records or the discharge codes from hospitalization records. Eligible patients  
166 were those 50 years of age or older with diagnosis of OS. Exclusion criteria  
167 were (1) ever osteoporotic medical treatments for more than 30 days before the  
168 index date, (2) previously documented any fracture (ICD-9 codes 800.x–829.x),  
169 (3) human immunodeficiency virus (ICD-9 codes 042), and (4) metastatic solid  
170 tumors (ICD-9 codes 196.x–198.x). Further, we divided patients into those with  
171 AMD (primary diagnosis codes of ICD-9 362.50-362.52) and those without AMD  
172 which discussed in the following section. After propensity score matching,  
173 13,548 patients and 54,336 patients were analyzed in AMD and non-AMD  
174 group.

175

### 176 **Outcome Definition**

177 We identified hospitalized patients who were admitted with a primary  
178 diagnosis of hip fracture (ICD-9 codes 820.x), spine fracture (ICD-9 codes  
179 806.x), and humero-radio-ulnar fractures (ICD-9 codes 812.x and 813.x) for the  
180 first time after 2002 (ensuring no previous hip, spine and humero-radio-ulnar

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3 181 fractures between 1996 and 2001) and who received surgery for fractures to  
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5 182 ensuring the diagnostic accuracy (surgery code of NHIRD: 64245C, 64042C,  
6  
7 183 64160B, 64271B, 64271C, 64032B). The date of death was defined as the date  
8  
9 184 of death in the catastrophic illness registry data files, the discharge date from a  
10  
11 185 patient's insurance coverage within one month after critical against medical  
12  
13 186 advice discharge, or the discharge date from a patient's insurance coverage  
14  
15 187 within one month after emergency department discharge with intravenous  
16  
17 188 epinephrine use. We defined it as such because National Health Insurance  
18  
19 189 (NHI) is mandatory in Taiwan; therefore, patients, especially sick ones, can  
20  
21 190 rarely stop their own insurance coverage. If insurance coverage ended, death  
22  
23 191 was most likely the reason. Furthermore, NHI premiums are paid on a monthly  
24  
25 192 basis, so coverage could easily be stopped immediately following a death. The  
26  
27 193 time-to-event outcome was determined as the time from the OS diagnosis date  
28  
29 194 to the date of hip fracture, spine fracture, and humero-radio-ulnar fractures, or  
30  
31 195 all-cause death, respectively.  
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#### 40 197 **Co-variates**

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42 198 The comorbidities were defined as an outpatient diagnosis listed on 2 or more  
43  
44 199 visits or a 1-time inpatient diagnosis before the index date. Study comorbidities  
45  
46 200 included diabetes mellitus, moderate to severe liver disease, chronic renal  
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48 201 disease, hyperthyroidism, rheumatic disease, malignancy, and other eye  
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50 202 diseases. The Charlson Comorbidity Index score was also recorded.  
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#### 55 204 **Statistical Analysis**

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58 205 To compare the AMD and each transition, we performed propensity  
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3 206 score matching. The propensity score was the predicted probability of being  
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5 207 the AMD group given the values of co-variables. These co-variables including  
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7 208 age, sex, rheumatologic diseases, DM without complications, DM with  
8  
9 209 complications, malignancy, moderate to severe liver diseases,  
10  
11 210 hyperthyroidism, chronic renal diseases, cataract, corneal disease, glaucoma,  
12  
13 211 and Charlson Comorbidity Index score. Each patient in the AMD group was  
14  
15 212 matched with 4 counterparts in the non-AMD group to achieve minimal bias.  
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17 213 An absolute standardized mean difference of less than 0.1 between the two  
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19 214 groups after propensity score matching was considered well balanced. The  
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21 215 cumulative incidence of follow-up outcomes was generated; a comparison  
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23 216 between the two groups was made using Cox proportional hazards model in  
24  
25 217 which death was considered a competing risk. We check the proportional  
26  
27 218 hazards assumption using modified Schoenfeld residuals test and residual  
28  
29 219 plots in each Cox model. For the violation of proportional hazards assumption,  
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31 220 we modeled the interaction between the variable and time using step  
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33 221 functions or functions guided from residual plots. To investigate the  
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35 222 cumulative incidence of each of fractures and all-cause of death, we  
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37 223 employed the competing risk model to simultaneously model the transitions  
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39 224 including "OS to spine fracture", "OS to hip fracture", "OS to humero-radio-  
40  
41 225 ulnar fracture", and "OS to death". Finally, in order to facilitate the  
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43 226 interpretation of time-varying coefficients, we conducted post-estimation  
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45 227 simulation techniques and graphs with visual weight to demonstrate the  
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47 228 results. All reported confidence intervals (CIs) and tests were 2-sided with a  
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49 229 5% significance level. All analyses were performed with R version 3.3.0 (R  
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51 230 Foundation for Statistical Computing, Vienna, Austria) with contributed  
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3 231 packages “tableone”, “ReporteRs”, “mstate”, “survival”, “ggplot2”, and  
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## 234 **Results**

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### 236 ***Patient Characteristics***

237 From January 1, 1996 to December 31, 2011, a total of 1,850,205  
238 patients received diagnosis of OS. After applying the exclusion criteria, we  
239 selected a total of 1, 206,247 patients, of whom 15,128 were in AMD group,  
240 and 18,191,119 were in the non-AMD group. After propensity score matching,  
241 13,548 patients and 54,336 patients were analyzed in AMD and non-AMD  
242 group, respectively (**Figure 1**). The selected key characteristics—including  
243 age, sex, rheumatologic diseases, DM without complications, DM with  
244 complications, malignancy, moderate to severe liver diseases,  
245 hyperthyroidism, chronic renal diseases, cataract, corneal disease,  
246 glaucoma, , and CharlsonComorbidity index score—were balanced between  
247 the AMD and non-AMD groups after propensity score matching (**Table 1**).

### 248 ***Estimates of cumulative hazards and probabilities of transition.***

249 During the follow-up period in the study population, 8930 (13.1%) OS  
250 patients converted to spine fracture, 2461 (3.6%) converted to hip fracture,  
251 3470 (5.1%) converted to humero-radio-ulnar fracture, and 8123 (13.0%)  
252 converted to death. The entire study population had higher risks for spine  
253 fracture and death when compared to humero-radio-ulnar fracture and hip  
254 fracture (**Figure 2**).

### 255 ***The effect of AMD on transition of fracture***

256 A multivariable, transition-specific, Cox proportional hazards model was  
257 used to examine the effects of AMD on the four transitions (**Table 2**). AMD was  
258 significantly associated with a higher risk of spine fracture after adjusting for

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3 259 covariates (HR=1.09; 95% CI=1.04-1.15; P<0.001). Similarly, AMD was  
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5 260 significantly associated with a higher risk of hip fracture (HR=1.18; 95%  
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7 261 CI=1.08-1.30; P<0.001). On the contrary, AMD was not associated with risks  
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9 262 for the humero-radio-ulnar fracture. Additionally, multivariable analysis  
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11 263 revealed that all medical comorbidities except hyperthyroidism were  
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13 264 significantly associated with higher risks for death. The effects of ocular  
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15 265 comorbidities on the risk of fractures are diverse. It is interesting to note that  
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17 266 glaucoma was not associated with a higher risk of fractures  
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## 269 **Discussions**

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271 In the current retrospective cohort study, our results showed that patients  
272 with AMD had a 1.09-fold and 1.18-fold greater risk of a subsequent spine  
273 fractures and hip fractures respectively in OS patients older than 50 years old  
274 after adjusting for baseline, ocular, and systemic comorbidities. However,  
275 AMD did not increase the risk of humero-radial-ulnar fracture.

276 Falls become more frequently with advanced age, and accumulating  
277 evidence has shown that about a third of elderly population living in the  
278 community suffered from one or more falls each year.[25]Falls that would not  
279 hurt a person with healthy bones but can probably damage one that has  
280 OS[26]. Therefore, if an elder person superimposed by OS, the falls may  
281 result in severe injury, physical deterioration, institutionalization, and  
282 instances death[26]. Most falls are resulted from the interaction of multiple risk  
283 factors,including age, muscle weakness, poor vision, difficulties with gait and  
284 balance, previous falls, fear of falling and chronic illnesses such as arthritis,  
285 diabetes, stroke, Parkinson's disease, incontinence and dementia[25, 27, 28].  
286 It is well recognized that fall-related risk factors-especially visual impairment-  
287 are also a major contributor to fractures in the elderly,[22] which supported by  
288 the current study.

289 Many older people living in the community suffer from poor vision or eye  
290 disease[1, 29]. The prevalence of sight threatening conditions such as  
291 cataract, glaucoma and macular degeneration all increase with age[1, 29].  
292 Previous study also demonstrated that AMD is associated with an increased  
293 risk of hip fractures by analyzing medicare database[23, 24, 30]. They found

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3 294 that the risk of hip fractures was significantly higher in cases that were coded  
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5 295 with atrophic (dry) AMD (odds ratio=1.11, 95% CI=1.06-1.16)[30]. However,  
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7 296 the risk was similar in cases that were coded with exudative AMD (odds  
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9 ratio=1.03, 95% CI=0.95-1.12) compared with cases with no AMD[30]. The  
10 297  
11 present study revealed that patients with a code for both types of AMD had an  
12 298  
13 18 % greater risk of hip fractures than did patients without a code for AMD in  
14 299  
15 osteoporotic population. The higher risk in this study reflected the fact that OS  
16 300  
17 patients are a potentially vulnerable population to developing fractures  
18 301  
19 secondary to accidental falls. However, whether AMD subtypes have variable  
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21 risks on hip fracture deserve further evaluation.  
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26 304 Fractures caused by OS most frequently occur in the spine[14]. These  
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28 305 spinal fractures, also called vertebral compression fractures, occur in nearly  
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30 700,000 patients each year in the United States[31]. They are almost twice as  
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32 common as other fractures typically linked to OS, such as hip and wrist  
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34 fractures[31]. Despite that not all vertebral compression fractures are related  
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36 to OS. But when the disease happened, a fracture is often the first sign of a  
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38 weakened skeleton in osteoporotic patient. However, there are very few  
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40 reports on the associated between AMD and spine fractures in patients with  
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42 OS. Spine compression fractures are often resulted from falls[32], but patients  
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44 with OS could suffer a fracture even when doing routine works, such as  
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46 twisting, coughing, and sneezing[33]. In the present study, patients with AMD  
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48 are especially run a greater risk for spine fractures (odds ratio=1.09; 95%  
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50 CI=1.04-1.15). Therefore, it is important to screen ocular co-morbidity like  
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52 AMD in elderly patients with OS to prevent both hip and spine fractures.  
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58 318 On the contrary, AMD was not associated with a greater risk of humero-

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3 319 radial-ulnar fractures. One of the possible explanations is that humerus  
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5 320 fractures usually occur in a relatively young population after physical trauma,  
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7 321 falls, excess physical stress such as baseball games[34]; therefore, the  
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9 322 presence of AMD did not cause significant visual impairment at this stage.  
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12 323 However, proximal humerus fractures most often occur among elderly  
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14 324 patients with OS who fall on an outstretched arm[35]. Age at 70 years or older  
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16 325 was associated with an increased risk of humero-radial-ulnar fractures in this  
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18 326 study (**Table 2**).

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21 327 Ocular co-morbidities such as cataract, glaucoma and corneal diseases  
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23 328 were also increased as advanced age[36]. Other studies have found that  
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25 329 contrast sensitivity, poor visual acuity, and visual field impairment were  
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27 330 significantly associated with falls[37-39]. However, these studies did not show  
28  
29 331 any correlation between glaucoma and the three aforementioned fractures[37-  
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31 332 39]. One possible explanation is that the initial presentation of glaucoma is  
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33 333 mild peripheral visual field defect without visual acuity deterioration.  
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35 334 Therefore, osteoporotic patients still have good central visual acuity and as  
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37 335 such decrease the risk of falls and subsequent fractures.

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40 336 A major limitation in this study is that the disease severity is not  
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42 337 accessible in the NHRI database and the effects of different severity of ocular  
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44 338 co-morbidities on different fractures can't be obtained. However, it seems  
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46 339 unlikely that selection bias was a factor given that the basis of subject  
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48 340 selection was not associated with magnitude of fracture response to severity  
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50 341 of ocular co-morbidities. In addition, a non-differential misclassification of  
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52 342 severity of ocular co-morbidities would cause. It was unlikely that the  
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54 343 observed effects were overestimated. Further investigation with hospital  
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3 344 database such as Chang Gung Research database is mandatory to delineate  
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5 345 the effects of laboratory parameters on fractures and final outcomes.  
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8 346 In conclusion, the current study provides large-scale, population-based  
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10 347 evidence in support of an independent relationship between overall AMD and  
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12 348 spine, hip and humero-radial-ulnar fractures for patients with OS in Taiwan.  
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14 349 We found that osteoporotic patients with AMD were at significantly greater risk  
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16 350 of subsequent development of spine and hip fractures, but not humero-radial-  
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18 351 ulnar fractures than the matched controls. Glaucoma, to our surprise, is not  
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20 352 associated with an increased risk of three fractures in this study. Although  
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22 353 interesting, this association does not prove causation. Further investigations  
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24 354 are warranted to clarify if treatment of AMD such as vitrectomy and intravitreal  
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26 355 anti-vascular endothelial growth factor would prevent second fractures in  
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28 356 osteoporotic patients.  
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35 358 **Acknowledgement:** not applicable  
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40 360 **Contributorship statement:**

41  
42 361 TSH, FPC and CCS contribute to the concept and design of the study, CCS  
43  
44 362 and BYC contributed to analyses of data. CCS, TSF and BYC contributed to  
45  
46 363 interpretation of the data, CYL, FPC and CCS contribute to manuscript  
47  
48 364 writing.  
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50  
51 365 FPC had full access to all the data in the study and takes responsibility for the  
52  
53 366 integrity of the data and the accuracy of the data analysis. All authors included  
54  
55 367 CCS, TSH, TSF, CYL, BYC and FPC contribute to the critical revision of the  
56  
57 368 study and the approval of submission.  
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14 374 **Conflict of interesting:** The authors have no proprietary or commercial  
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17 375 interest in any materials discussed in this article.  
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21 377 **Patient consent form for publication:** not required.  
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26 379 **Data availability statement:** All relevant data of the current study are  
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28 380 involved in the manuscript, no additional data is available.  
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3 488 **Figures and legends:**  
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7 490 **Figure 1.** Flowchart of the patient selection in age-related macular

8 491 degeneration and non-age-related macular degeneration cohort with a one-to-

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10 492 fourmatch  
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13 493 AMD: age-related macular degeneration  
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17 495 **Figure 2.** Estimates of cumulative hazards of transition among osteoporosis

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21 497 OS: osteoporosis  
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499 Table 1. **Baseline characteristics between age-related macular**  
 500 **degeneration and non-age-related macular degeneration population with**  
 501 **1:4 match**

	<b>AMD</b> <b>(N=13,584)</b>	<b>Non-AMD</b> <b>(n=54,336)</b>	<b>P</b> <b>value</b>
Age, median (IQR)	73.8 (67.2, 79.3)	73.8 (67.2, 79.3)	1.00
Age group, No. (%)			
50≤age<60	1277 (9.4)	5075 (9.3)	0.98
60≤age<70	3372 (24.8)	13424 (24.7)	
70≤age<80	5881 (43.3)	23603 (43.4)	
80≤age	3054 (22.5)	12234 (22.5)	
Sex, No. (%)			
Female	8081 (59.5)	32324 (59.5)	1.00
Rheumatologic diseases, No. (%)	846 (6.2)	3384 (6.2)	1.00
DM without complications, No. (%)	4101 (30.2)	16404 (30.2)	1.00
DM with complications, No. (%)	1629 (12.0)	6516 (12.0)	1.00
Malignancy, No. (%)	1470 (10.8)	5880 (10.8)	1.00
Moderate to severe liver diseases, No. (%)	19 (0.1)	76 (0.1)	1.00
Hyperthyroidism, No. (%)	204 (1.5)	816 (1.5)	1.00
Chronic renal diseases, No. (%)	598 (4.4)	2392 (4.4)	1.00
Cataract, No. (%)	10276 (75.6)	41104 (75.6)	1.00
Corneal disease, No. (%)	2665 (19.6)	10660 (19.6)	1.00
Glaucoma, No. (%)	2037 (15.0)	8148 (15.0)	1.00
Charlson Comorbidity index score, median (IQR)	5.00 (3.00, 7.00)	5.00 (3.00, 7.00)	0.22

502 AMD: age-related macular degeneration

503 IQR: interquartile range

504 DM: diabetes mellitus

505

506 Table 2. The effect of age-related macular degeneration on transition of fracture and death.

507

		Osteoporosis to spine fracture		Osteoporosis to hip fracture		Osteoporosis to humero-radial-ulnar fracture	
		Hazard Ratio (95% CIs)	P value	Hazard Ratio (95% CIs)	P value	Hazard Ratio (95% CIs)	P value
AMD	No	Reference		Reference		Reference	
	Yes	1.09 (1.04-1.15)	<0.001	1.18 (1.08-1.30)	0.001	0.98 (0.90-1.06)	0.599
Age	50-59	Reference		Reference		Reference	
	60-69	2.37 (2.11-2.66)	<0.001	3.03 (2.21-4.16)	<0.001	1.08 (0.96-1.22)	0.203
	70-79	3.71 (3.31-4.15)	<0.001	7.92 (5.85-10.73)	<0.001	1.25 (1.12-1.41)	<0.001
	>80	4.70 (4.19-5.29)	<0.001	16.33 (12.04-22.16)	<0.001	1.20 (1.05-1.37)	0.007
Sex	Female	Reference		Reference		Reference	
	Male	0.58 (0.55-0.61)	<0.001	0.66 (0.61-0.72)	<0.001	0.42 (0.39-0.46)	<0.001
Rheumatologic diseases	No	Reference		Reference		Reference	
	Yes	1.20 (1.12-1.29)	<0.001	1.10 (0.96-1.26)	0.156	1.11 (1.00-1.24)	0.059
DM without complications	No	Reference		Reference		Reference	
	Yes	1.00 (0.95-1.05)	0.957	1.04 (0.94-1.15)	0.399	1.12 (1.04-1.22)	0.005
DM with complications	No	Reference		Reference		Reference	
	Yes	0.99 (0.92-1.05)	0.717	1.50 (1.33-1.69)	<0.001	1.05 (0.94-1.17)	0.370

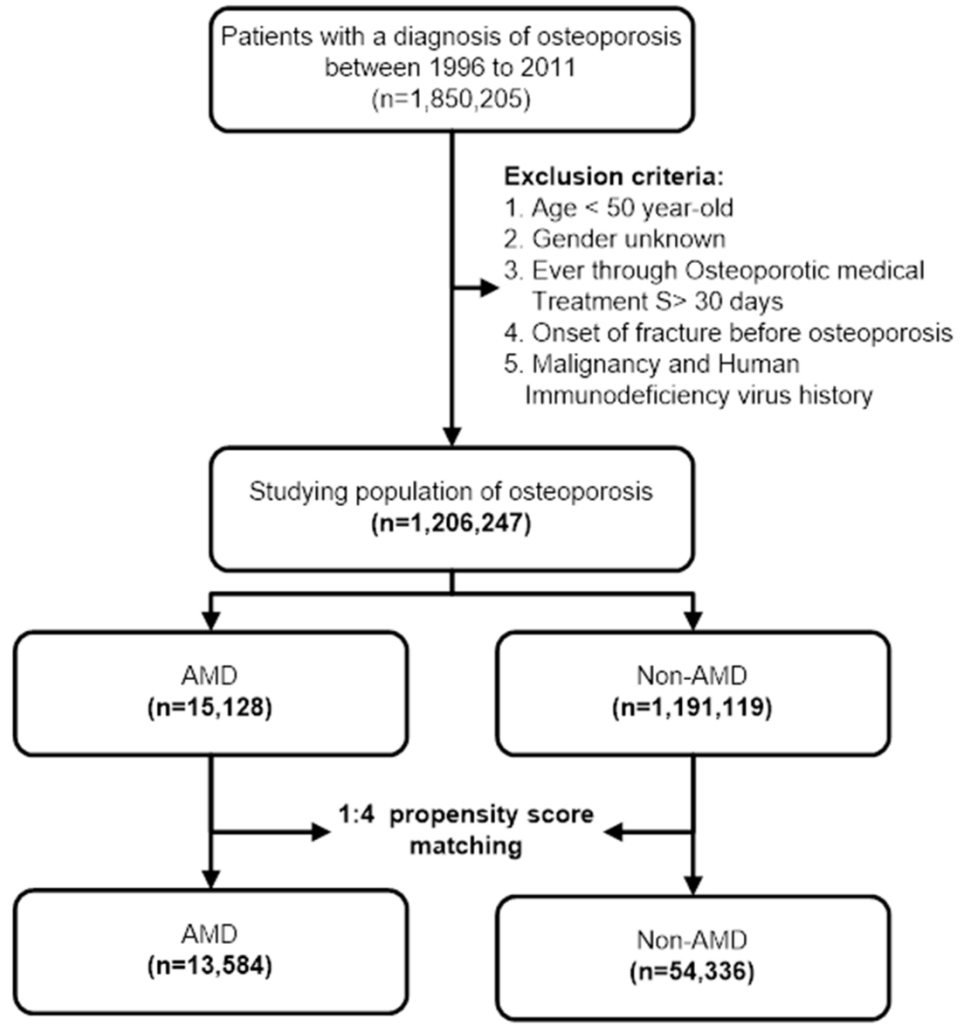
			1.06)			1.69)		
	Malignancy	No	Reference			Reference		Reference
		Yes	1.09 (1.03-1.16)	0.004		1.02 (0.92-1.15)	0.666	1.03 (0.93-1.14) 0.581
	Moderate to severe liver diseases	No	Reference			Reference		Reference
		Yes	1.29 (0.99-1.69)	0.060		1.06 (0.63-1.80)	0.817	0.69 (0.40-1.19) 0.178
	Hyperthyroidism	No	Reference			Reference		Reference
		Yes	1.07 (0.93-1.23)	0.338		1.19 (0.91-1.56)	0.203	1.15 (0.95-1.39) 0.151
	Chronic renal diseases	No	Reference			Reference		Reference
		Yes	1.01 (0.93-1.10)	0.786		1.57 (1.38-1.77)	<0.001	0.99 (0.86-1.14) 0.876
	Cataract	No	Reference			Reference		Reference
		Yes	1.23 (1.17-1.31)	<0.001		1.05 (0.94-1.16)	0.390	1.16 (1.06-1.26) <0.001
	Corneal diseases	No	Reference			Reference		Reference
		Yes	1.18 (1.12-1.23)	<0.001		1.05 (0.96-1.15)	0.322	1.08 (1.00-1.17) 0.041
	Glaucoma	No	Reference			Reference		Reference
		Yes	1.00 (0.95-1.06)	0.871		1.02 (0.92-1.12)	0.773	1.04 (0.96-1.13) 0.355

508 AMD: age-related macular degeneration

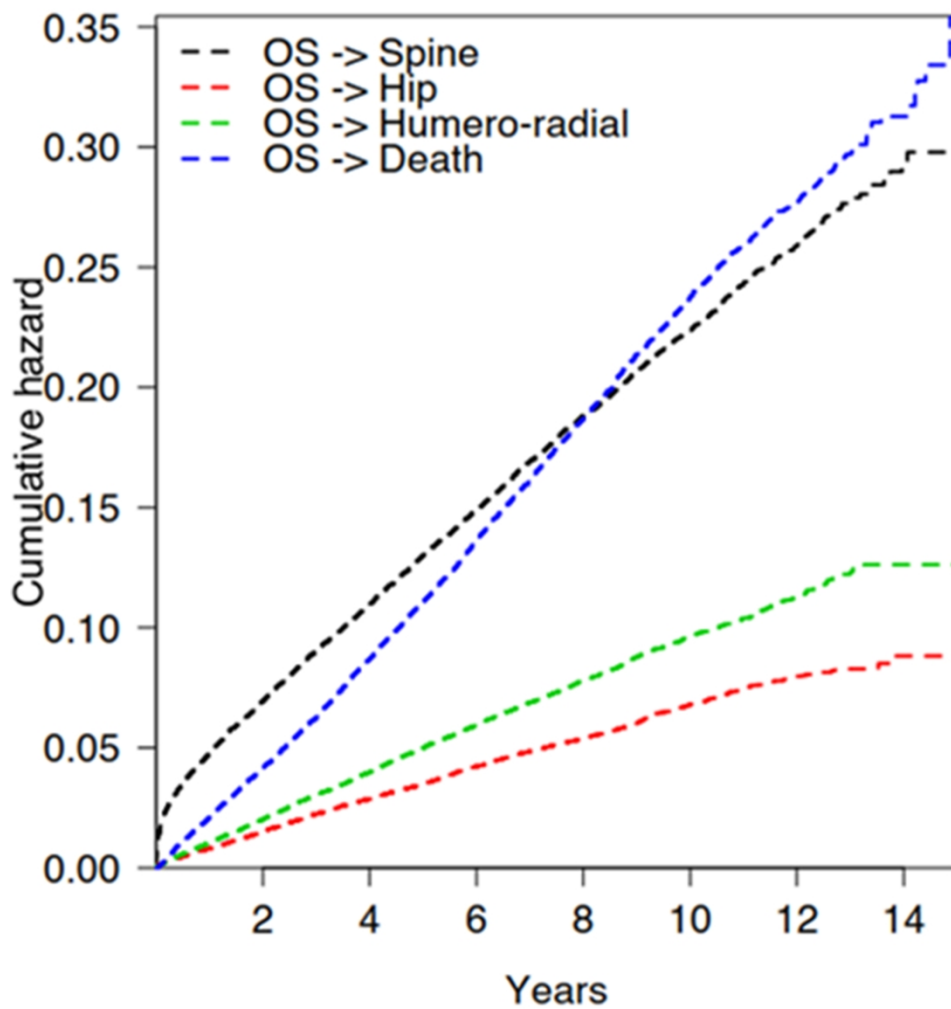
509 CI: confidential intervals

510 DM: diabetes mellitus

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-11
		(b) Describe any methods used to examine subgroups and interactions	9-11
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	10-11
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14-17
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Association of age-related macular degeneration on fracture risks among osteoporosis population: A nationwide population-based cohort study

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1 **Association of age-related macular degeneration on fracture**  
2 **risks among osteoporosis population: A nationwide**  
3 **population-based cohort study**

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5 **Running head:** Age-related macular degeneration on osteoporosis-related  
6 fractures

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## 36 Abstract

37

38 **Objectives:** Visual impairment is an important risk factor for fracture in the  
39 elderly population. Age-related macular degeneration (AMD) is the leading  
40 cause of irreversible visual impairment in elderly people. This study was  
41 conducted to explore the relationship between AMD and incident fractures in  
42 osteoporosis (OS) patients.

43 **Design:** Retrospective analysis of Taiwan's National Health Insurance  
44 Research Database (NHIRD).

45 **Setting:** A multicenter study conducted in Taiwan.

46 **Participants and Controls:** The current study used the NHIRD in Taiwan  
47 between 1996 and 2011. A total of 13,584 and 54,336 OS patients were  
48 enrolled in the AMD group and the non-AMD group, respectively.

49 **Intervention:** Patients with OS were included from the Taiwan's NHIRD after  
50 exclusion, and each patient with AMD was matched for age, sex, and  
51 comorbidities to four non-AMD OS patients, who served as the control group.  
52 A Cox proportional hazard model was used for the multivariable analysis.

53 **Primary outcome measures:** Transitions for OS to spine fracture, OS to hip  
54 fracture, OS to humero-radio-ulnar fracture, and OS to death.

55 **Results:** The risks of spine and hip fractures were significantly higher in the  
56 AMD group (hazard ratio [HR] = 1.09, 95% confidence interval [CI] = 1.04–  
57 1.15,  $P < 0.001$ ; HR = 1.18; 95% CI = 1.08–1.30,  $P = 0.001$ , respectively) than  
58 in the non-AMD group. The incidence of humero-radio-ulnar fracture between  
59 AMD and non-AMD individuals was similar (HR = 0.98; 95% CI = 0.90–1.06;  
60  $P = 0.599$ ). However, the risk of death was higher in OS patients with older

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3 61 age, male sex, and all types of co-morbidity ( $P < 0.05$ ) except for  
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5 62 hyperthyroidism ( $P = 0.200$ ).  
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8 63 **Conclusion:** Osteoporotic patients with AMD had a greater risk of spine and  
9  
10 64 hip fractures than did patients without AMD.  
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13 65

14 66 **Keywords:** Age-related macular degeneration; fracture; osteoporosis;  
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17 67 population-based, database  
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20 68

21 69 **Strengths and limitations of this study:**  
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- 23  
24 70 • The current study enrolled a large number of participants 13,548 (AMD  
25  
26 71 group) patients and 54,336 (a non-AMD group) patients.  
27  
28 72 • Each participant can be followed up to 16 years even when visited to  
29  
30 73 different hospitals.  
31  
32 74 • The causal relationship between AMD and subsequent bone fracture in  
33  
34 75 patients with OS has not yet been established in the current study.  
35  
36 76 • The disease severity of OS is inaccessible in the NHIRD because of  
37  
38 77 simply using the ICD-9 diagnostic codes.  
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40 78 • The severity of ocular disease leading to fractures or higher mortality rate  
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42 79 has not yet been determined.  
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## 82 Introduction

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84 Poor vision is common in the elderly population. Ocular diseases such as  
85 cataract, glaucoma, and age-related macular degeneration (AMD) are  
86 strongly age-related,[1–4] and there is accumulating evidence demonstrating  
87 that many elderly people would benefit from changing eyeglasses.[2, 5] AMD  
88 is one of the leading causes of irreversible visual impairment in elderly people  
89 in developed countries.[6–8] The estimated incidence of AMD in Taiwan is  
90 approximately 10.8%.[9] Although, it does not result in complete blindness;  
91 however, the loss of central vision can make it difficult to perform daily  
92 activities such as recognizing faces, driving and reading.[10] According to a  
93 previous report, patients with AMD are in greater fear of falling down, which  
94 can restrict their social activities.[11] Moreover, individuals with AMD have a  
95 higher probability to fall with more unsteady gait patterns.[12, 13]

96 Osteoporosis (OS) is a chronic metabolic bone disease in which bones  
97 become relatively weak and have a probability to break.[14] The prevalence of  
98 OS is estimated to be 11.35% among women over 50 years old.[15] It has  
99 been observed that patients with OS tend to develop fractures of the hip,  
100 vertebrae, distal forearm, and humerus,[16] and fractures among elderly  
101 patients represent an important public health issue.[17] Taiwan's population is  
102 aging at an alarming rate;[15] OS and related fractures pose an  
103 unprecedented threat to the elderly population in Taiwan since the prevalence  
104 of OS increases rapidly with age.[14] As fractures in the elderly would  
105 contribute to a higher probability of mortality despite promptly surgical  
106 intervention,[18, 19] potential risk factors for individuals vulnerable to

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3 107 fractures, such as those with OS, should be further investigated and identified.  
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5 108 Visual impairment is an important risk factor for hip fracture in the elderly  
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8 109 population.[20–22] Studies have revealed that macular degeneration and  
9  
10 110 glaucoma suspect would lead to a higher risk of hip fractures.[22] Therefore, it  
11  
12 111 is important to understand the ocular risk factors and take measures to  
13  
14 112 prevent future fractures in osteoporosis patients. However, only a limited  
15  
16 113 number of studies have examined the association between fractures in OS  
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18 114 patients and specific ocular disorders.[22–24] Taking AMD as an example,  
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20 115 studies focused only on patients with AMD and hip fractures, ignoring spine  
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22 116 and humero-radio-ulnar fractures.[22–24] Moreover, the number of  
23  
24 117 participants in previous studies were relatively small ,[22–24] while a  
25  
26 118 population-based study should be conducted to investigate the relationship  
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28 119 between AMD and fractures in patients with OS since both disorders affect  
29  
30 120 most population.[1, 14]  
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35 121 Therefore, we used the Taiwan's National Health Insurance Research  
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37 122 Database (NHIRD) in this nationwide study with a retrospective cohort and a  
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39 123 case-control design to investigate the association between AMD and  
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41 124 subsequent fractures in osteoporosis patients.  
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## 126 **Methods**

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### 128 **Ethics declaration and patient involvement statement**

129 Participants in this study were adhered to the 1964 Declaration of  
130 Helsinki and its later amendments. The current study was approved by both  
131 the National Health Insurance Administration and the Institutional Review  
132 Board of Chang Gung Memorial Hospital, Taiwan.

133

### 134 **Patient and Public Involvement statement**

135 As this is a claimed data-based study, data was collected and produced  
136 by the National Health Insurance Administration of Taiwan without patient  
137 recruitment; the requirement for informed consent was waived by both the  
138 National Health Insurance Administration and the Institutional Review Board of  
139 Chang Gung Memorial Hospital.

140

### 141 **Data source**

142 This population-based cohort study used the NHIRD of Taiwan  
143 (approximately 26 million insured individuals) for the period January 1996 to  
144 December 2011. By the end of 2007, NHIRD had enrolled more than 99% of  
145 Taiwan's population into this insurance program, which had contracts with 97%  
146 of the country's clinics and hospitals. The data available through the NHIRD  
147 included all medical services provided to each enrollee from January 1<sup>st</sup>, 1996  
148 to December 31<sup>st</sup>, 2011, as well as the patients' characteristics and the features  
149 of the hospitals and physicians.

150

## 151 **Study Population Enrollment and Exclusion Criteria**

152 We identified patients with diagnosis of OS using the *International*  
153 *Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9) codes  
154 733.00, 733.01, 733.02, 733.03, and 733.09. The osteoporotic population of the  
155 NHIRD was identified by the presence of either the abovementioned diagnostic  
156 codes in their outpatient records or the discharge codes from hospitalization  
157 records. Eligible patients were those 50 years of age or older with diagnosis of  
158 OS. Exclusion criteria were (1) received osteoporotic medical treatments for  
159 more than 30 days before the index date; (2) any fractures documented before  
160 the index date (ICD-9 codes 800.x–829.x); (3) having a diagnosis of human  
161 immunodeficiency virus (ICD-9 codes 042); and (4) being diagnosed with  
162 metastatic solid tumors (ICD-9 codes 196.x–198.x). Furthermore, we divided  
163 patients into those with AMD (AMD group with primary diagnosis codes of ICD-  
164 9 362.50–362.52) and those without AMD (non-AMD group). After propensity  
165 score matching, 13,548 patients and 54,336 patients were analyzed in the AMD  
166 and non-AMD group, respectively.

167

## 168 **Outcome Definition**

169 We identified hospitalized patients who were admitted with a primary  
170 diagnosis of hip fracture (ICD-9 codes 820.x), spine fracture (ICD-9 codes  
171 806.x), and humero-radio-ulnar fractures (ICD-9 codes 812.x and 813.x) for the  
172 first time after 2002 (ensuring no previous hip, spine and humero-radio-ulnar  
173 fractures between 1996 and 2001) and who received surgery for fractures to  
174 make sure the diagnostic accuracy (surgery code of NHIRD: 64245 C, 64042  
175 C, 64160 B, 64271 B, 64271 C, 64032 B). The date of death was defined as

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3 176 the expired date recorded in the catastrophic illness registry data files, the  
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5 177 discharge date from a patient's insurance coverage within one month after  
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8 178 being critical against medical advice discharge or the discharge date from a  
9  
10 179 patient's insurance coverage within one month after emergency department  
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12 180 discharge with intravenous epinephrine use. We defined it as such because the  
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14 181 National Health Insurance (NHI) is mandatory in Taiwan; therefore, patients,  
15  
16 182 especially sick ones, can rarely stop their own insurance coverage. If the  
17  
18 183 insurance coverage ended, death was the reason. Furthermore, NHI premiums  
19  
20 184 are paid monthly, so coverage can be stopped immediately following a death.  
21  
22 185 The time-to-event outcome was determined as the time from the OS diagnosis  
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24 186 date to the date of hip fracture, spine fracture, and humero-radio-ulnar fractures,  
25  
26 187 or all-cause death, respectively.  
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### 33 189 **Covariates**

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35 190 The comorbidities were defined as an outpatient diagnosis listed on two or  
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37 191 more visits or a one-time inpatient diagnosis before the index date. Study  
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39 192 comorbidities included diabetes mellitus (DM), moderate to severe liver disease,  
40  
41 193 chronic renal disease, hyperthyroidism, rheumatic disease, malignancy,  
42  
43 194 hyperparathyroidism and ocular diseases including cataract, corneal diseases  
44  
45 195 and glaucoma. The Charlson Comorbidity Index score (CCIs) that merges the  
46  
47 196 abovementioned diseases into one numerical score was also recorded.  
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### 52 198 **Statistical Analysis**

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55 199 To compare the AMD and each transition, we performed propensity score  
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57 200 matching. The propensity score was the predicted probability of being the  
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3 201 AMD group given the values of covariates including age, sex, rheumatologic  
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5 202 diseases, DM with and without complications, malignancy, moderate to  
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7 203 severe liver diseases, hyperthyroidism, chronic renal diseases, cataract,  
8  
9 204 corneal disease, glaucoma, hyperparathyroidism, and CCI. Each patient in  
10  
11 205 the AMD group was matched with four counterparts in the non-AMD group to  
12  
13 206 achieve minimal bias. The cumulative incidence of follow-up outcomes was  
14  
15 207 generated and the comparisons between the two groups for the risk of spine,  
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17 208 hip and humero-radio-ulnar fractures were made using the Cox proportional  
18  
19 209 hazards model in which death was considered a competing risk. We checked  
20  
21 210 the proportional hazards assumption using modified Schoenfeld residuals test  
22  
23 211 and residual plots in each Cox model. For the violation of proportional hazards  
24  
25 212 assumption, we demonstrated the interaction between the variable and time  
26  
27 213 using step functions or functions guided from residual plots. To investigate the  
28  
29 214 cumulative incidence of each fracture and cause of death, we engaged in the  
30  
31 215 competing risk model with the hazard ratio (HR) adjusted all the above  
32  
33 216 mentioned covariates to analyze the transitions, including “OS to spine  
34  
35 217 fracture,” “OS to hip fracture,” “OS to humero-radio-ulnar fracture” between  
36  
37 218 AMD and non-AMD subjects, and the transition of “OS to death” for the  
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39 219 abovementioned covariates. Finally, to facilitate the interpretation of time-  
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41 220 varying coefficients, we conducted post-estimation simulation techniques and  
42  
43 221 graphs with visual weight to demonstrate the results. All reported confidence  
44  
45 222 intervals (CIs) and tests were two-sided with a 5% significance level. All  
46  
47 223 analyses were performed with R version 3.3.0 (R Foundation for Statistical  
48  
49 224 Computing, Vienna, Austria) with contributed packages “tableone,”  
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51 225 “ReporteRs,” “mstate,” “survival,” “ggplot2,” and “simPH.”  
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## 226 Results

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### 228 Patient Characteristics

229 A total of 1,850,205 OS patients were enrolled in this nationwide study.

230 After applying the exclusion criteria, a total of 1,206,247 patients participated,

231 of which 15,128 were in the AMD group, and 18,191,119 were in the non-

232 AMD group. After propensity score matching, 13,548 patients and 54,336

233 patients were analyzed in the AMD and non-AMD group, respectively (**Figure**

234 **1**). The selected characteristics—including age, sex, related covariates, and

235 CCI—were well balanced between the AMD and non-AMD groups after

236 propensity score matching (**Table 1**).

237

238 Table 1. Baseline characteristics between the AMD and non-AMD groups

	AMD (N = 13,584)	Non-AMD (N = 54,336)	P value
Age, median (IQR)	73.8 (67.2, 79.3)	73.8 (67.2, 79.3)	1.00
Age group, No. (%)			0.98
50 ≤ age < 60	1277 (9.4)	5075 (9.3)	
60 ≤ age < 70	3372 (24.8)	13424 (24.7)	
70 ≤ age < 80	5881 (43.3)	23603 (43.4)	
80 ≤ age	3054 (22.5)	12234 (22.5)	
Sex, No. (%)			1.00
Female	8081 (59.5)	32324 (59.5)	
Rheumatologic diseases, No. (%)	846 (6.2)	3384 (6.2)	1.00
DM without complications, No. (%)	4101 (30.2)	16404 (30.2)	1.00
DM with complications, No. (%)	1629 (12.0)	6516 (12.0)	1.00
Malignancy, No. (%)	1470 (10.8)	5880 (10.8)	1.00
Moderate to severe liver diseases, No. (%)	19 (0.1)	76 (0.1)	1.00
Hyperthyroidism, No. (%)	204 (1.5)	816 (1.5)	1.00
Chronic renal diseases, No. (%)	598 (4.4)	2392 (4.4)	1.00
Cataract, No. (%)	10276 (75.6)	41104 (75.6)	1.00
Corneal disease, No. (%)	2665 (19.6)	10660 (19.6)	1.00
Glaucoma, No. (%)	2037 (15.0)	8148 (15.0)	1.00
CCIs, median (IQR)	5.00 (3.00, 5.00)	5.00 (3.00, 5.00)	0.22

7.00) 7.00)

239 AMD: age-related macular degeneration

240 No.: number of patients

241 IQR: interquartile range

242 DM: diabetes mellitus

243 CCI: Charlson comorbidity index score

244

245

246 **Estimates of cumulative hazards and probabilities of transition**

247 During the follow-up period in the study population, 8930 (13.1%) OS  
 248 patients had spine fractures, 2461 (3.6%) hip fractures, humero-radio-ulnar  
 249 fractures occurred in 3470 (5.1%) OS patients, and 8123 (13.0%) OS patients  
 250 unfortunately died. During the follow-up period, the entire study population had  
 251 higher risks for spine fracture and death compared to humero-radio-ulnar  
 252 fracture and hip fracture (**Figure 2**).

253

254 **The effect of AMD on transition of fractures**

255 In the multivariate analysis, an OS patient with AMD was significantly  
 256 associated with a high risk of spine fracture after adjusting for covariates (HR  
 257 = 1.09; 95% CI = 1.04–1.15;  $P < 0.001$ ) compared to a non-AMD individual.  
 258 Similarly, AMD was significantly associated with a high risk of hip fracture (HR  
 259 = 1.18; 95% CI = 1.08–1.30;  $P < 0.001$ ) than a patient without AMD. However,  
 260 AMD was not associated with risks for the humero-radio-ulnar fracture (HR =  
 261 0.98; 95% CI = 0.90–1.06;  $P = 0.599$ ). Additionally, multivariate analysis also  
 262 revealed that older age, male sex and all non-ocular medical comorbidities,  
 263 except for hyperthyroidism ( $P = 0.200$ ) were significantly associated with  
 264 higher risks for death ( $P < 0.05$ ) (**Table 2**). The fact that with increasing age



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3 265 and being female are vulnerable to any type of incident fractures is also  
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5 266 shown in our results (**Table 2**). It is also noteworthy that other ocular co-  
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7 267 morbidities, including cataract and corneal diseases are associated with a  
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9 268 high risk of spine fractures (HR = 1.23; 95% CI = 1.17–1.31;  $P < 0.001$  & HR  
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11 269 = 1.18; 95% CI = 1.12–1.23;  $P < 0.001$ ) and humero-radio-ulnar fractures (HR  
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13 270 = 1.16; 95% CI = 1.06–1.26;  $P < 0.001$  & HR = 1.08; 95% CI = 1.00–1.17;  $P =$   
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15 271 0.041). However, an OS patient with glaucoma is not associated with a high  
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17 272 risk of any incident fractures, which is due to the relatively fewer cases and  
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19 273 the heterogeneous disease stages in this study cohort.  
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274 Table 2. The effect of AMD on transition of fractures and death.

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		Osteoporosis to death		Osteoporosis to spine fracture		Osteoporosis to hip fracture		Osteoporosis to humero-radio-ulnar fracture	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AMD	No	N/A		Reference		Reference		Reference	
	Yes	N/A	N/A	1.09 (1.04–1.15)	< 0.001	1.18 (1.08–1.30)	0.001	0.98 (0.90–1.06)	0.599
Age	50–59	Reference		Reference		Reference		Reference	
	60–69	1.46 (1.28–1.66)	< 0.001	2.37 (2.11–2.66)	< 0.001	3.03 (2.21–4.16)	0.001	1.08 (0.96–1.22)	0.203
	70–79	2.67 (2.36–3.02)	< 0.001	3.71 (3.31–4.15)	< 0.001	7.92 (5.85–10.73)	0.001	1.25 (1.12–1.41)	< 0.001
	> 80	4.72 (4.16–5.36)	< 0.001	4.70 (4.19–5.29)	< 0.001	16.33 (12.04–22.16)	0.001	1.20 (1.05–1.37)	0.007
Sex	Female	Reference		Reference		Reference		Reference	
	Male	1.30 (1.24–1.36)	< 0.001	0.58 (0.55–0.61)	< 0.001	0.66 (0.61–0.72)	0.001	0.42 (0.39–0.46)	< 0.001
Rheumatologic	No	Reference		Reference		Reference		Reference	

diseases

	Yes	1.11 (1.03–1.20)	0.005	1.20 (1.12–1.29)	<0.001	1.10 (0.96–1.26)	0.156	1.11 (1.00–1.24)	0.059
DM without complications	No	Reference		Reference		Reference		Reference	
	Yes	1.27 (1.21–1.34)	<0.001	1.00 (0.95–1.05)	0.957	1.04 (0.94–1.15)	0.399	1.12 (1.04–1.22)	0.005
DM with complications	No	Reference		Reference		Reference		Reference	
	Yes	1.41 (1.33–1.50)	<0.001	0.99 (0.92–1.06)	0.717	1.50 (1.33–1.69)	0.001	1.05 (0.94–1.17)	0.370
Malignancy	No	Reference		Reference		Reference		Reference	
	Yes	4.41 (4.19–4.63)	<0.001	1.09 (1.03–1.16)	0.004	1.02 (0.92–1.15)	0.666	1.03 (0.93–1.14)	0.581
Moderate to severe liver diseases	No	Reference		Reference		Reference		Reference	
	Yes	4.69 (4.24–5.18)	<0.001	1.29 (0.99–1.69)	0.060	1.06 (0.63–1.80)	0.817	0.69 (0.40–1.19)	0.178
Hyperthyroidism	No	Reference		Reference		Reference		Reference	
	Yes	0.90 (0.76–1.06)	0.200	1.07 (0.93–1.23)	0.338	1.19 (0.91–1.56)	0.203	1.15 (0.95–1.39)	0.151

Chronic renal diseases	No	Reference		Reference		Reference		Reference	
	Yes	2.22 (2.10–2.35)	< 0.001	1.01 (0.93–1.10)	0.786	1.57 (1.38–1.77)	0.001	0.99 (0.86–1.14)	0.876
Cataract	No	N/A		Reference		Reference		Reference	
	Yes	N/A	N/A	1.23 (1.17–1.31)	< 0.001	1.05 (0.94–1.16)	0.390	1.16 (1.06–1.26)	< 0.001
Corneal diseases	No	N/A		Reference		Reference		Reference	
	Yes	N/A	N/A	1.18 (1.12–1.23)	< 0.001	1.05 (0.96–1.15)	0.322	1.08 (1.00–1.17)	0.041
Glaucoma	No	N/A		Reference		Reference		Reference	
	Yes	N/A	N/A	1.00 (0.95–1.06)	0.871	1.02 (0.92–1.12)	0.773	1.04 (0.96–1.13)	0.355
Hyperparathyroidism	No	Reference		N/A		N/A		N/A	
	Yes	1.89 (1.42–2.52)	< 0.001	N/A	N/A	N/A	N/A	N/A	N/A
CCIs	Every point increase	1.08 (1.07–1.08)	< 0.001	N/A	N/A	N/A	N/A	N/A	N/A

276 AMD: age-related macular degeneration

277 CI: confidential intervals

278 CCIs: Charlson comorbidity index score

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279 HR: hazard ratio  
280 DM: diabetes mellitus  
281 N/A: the analysis did not perform since it is not necessary for the purpose of the current study

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284 **Discussion**

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286 In this study, our results showed that AMD incurred a 1.09-fold and 1.18-fold risk of subsequent spine hip fractures, respectively,  
287 in OS patients older than 50 years after adjusting for demography, ocular, and systemic comorbidities. However, AMD did not  
288 increase the risk of humero-radio-ulnar fracture in this multivariate model.

289 About a third of the elderly population living in the community suffered from one or more falls each year,[25] which can damage  
290 one that has OS easily and lead to severe injury, physical deterioration, institutionalization, and incident deaths.[26] Most falls  
291 resulted from the interactions of multiple risk factors, including age, muscle weakness, poor vision, difficulties with gait and balance,  
292 previous falls, fear of falling and chronic illnesses such as arthritis, DM, stroke, Parkinson’s disease, incontinence and  
293 dementia.[25, 27, 28] It is well recognized that fall-related ocular risk factors are also major contributors to fractures in the  
294 elderly,[22] which was supported by the findings of the current study.

295 Many older people living in the community were affected by poor vision or eye disease such as cataract, glaucoma and  
296 macular degeneration.[1, 29] Studies have also demonstrated that AMD is associated with an increased risk of hip fractures by

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5 297 analyzing the medicare database.[23, 24, 30] Anastasopoulos et al. found that the risk of hip fractures was significantly higher in  
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7 298 cases that were coded with atrophic (dry) AMD.[30] However, the risk was similar in cases that were coded with exudative AMD  
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9 299 and cases with no AMD.[30] This study revealed that patients with a code for both types of AMD had significantly greater risk of hip  
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11 300 fractures than patients without a code for AMD in osteoporotic population. The higher risk in this study reflected the fact that OS  
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13 301 patients are a potentially vulnerable population to developing fractures secondary to an accidental fall.

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16 302 Fractures caused by OS most frequently occur in the spine.[14] These spinal fractures occur in nearly 700,000 patients each  
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18 303 year in the United States, is twice as common as other OS-related fractures such as hip and wrist fractures.[31] Generally, spinal  
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20 304 compression fractures result from falls,[32] but patients with OS can suffer fractures even when doing routine works, such as  
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22 305 twisting, coughing, and sneezing.[33] However, there are very few reports on the association between AMD and spine fractures in  
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24 306 patients with OS. In this study, patients with AMD have a significantly greater risk of spine fractures. Therefore, it is important to  
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26 307 screen ocular co-morbidity such as AMD in elderly patients with OS to prevent both hip and spine fractures.

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30 308 This study demonstrated that AMD was not associated with a greater risk of humero-radio-ulna fractures. Primarily because  
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32 309 humerus fractures occur in a relatively young population after physical trauma, falls, excess physical stress such as baseball  
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34 310 games [34] and even with the presence of AMD, it did not cause significant visual impairment at a relatively younger age. However,  
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36 311 proximal humerus fractures occur among elderly patients with OS who fall on an outstretched arm,[35] which corresponded to our  
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5 312 finding in which 70 years or older were associated with an increased risk of humero-radio-ulnar fractures (**Table 2**).

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7 313 The risk of death was significantly higher in OS patients with older age, male sex and the majority of systemic diseases in the  
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9 314 current study. It is reasonable since the factors are related to a relatively unhealthy status; however, the non-significant relationship  
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11 315 between hyperparathyroidism and death in OS individuals needs further validation. Although the chance of death is increased in  
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13 316 OS patients with systemic co-morbidities, attention should be paid to the fact that these patients with additional AMD diagnosis  
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15 317 have a higher risk of spine and hip fractures and subsequent death caused by fractures.[18, 19] Therefore, we should aggressively  
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17 318 treat AMD to prevent fractures in OS patients should they are not affected by severe systemic diseases.

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19 319 A major limitation of this study is that the disease severity is inaccessible in the NHIRD and the effects of different severities of  
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21 320 ocular co-morbidities on different fractures cannot be obtained. However, it seemed unlikely that selection bias was a factor given  
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23 321 that the basis of subject selection was not associated with the magnitude of fractures and the severity of ocular co-morbidities. A  
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25 322 minor limitation lies in the absence of outcome measures after treatment for both AMD and OS, which cannot provide therapeutic  
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27 323 guidelines.

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29 324 In conclusion, osteoporosis patients with AMD are at a significantly higher risk of subsequent development of spine and hip  
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31 325 fractures, but not humero-radio-ulnar fractures than matched controls. Moreover, older age, male sex and major systemic co-  
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33 326 morbidities in OS patients are related to death. Further investigations are needed to clarify if the treatment of AMD, such as  
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5 327 vitrectomy and intravitreal anti-vascular endothelial growth factor injection, would prevent primary fractures in osteoporosis patients.  
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9 329 **Acknowledgment:** We extend our deepest gratitude to Biostatistics Consultation Center at Chang Gung Memorial Hospital,  
10  
11 330 Keelung, Taiwan, for offering us informative suggestions along the way regarding statistical analysis.  
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15  
16 332 **Contribution statement:**

17  
18 333 TSH, FPC, and CCS contributed to the concept and design of the study, CCS-and BYC contributed to analyses of data. CCS, TSF  
19  
20 334 and BYC contributed to interpretation of the data, CYL, FPC and CCS contributed to manuscript writing.

21  
22 335 FPC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data  
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24 336 analysis. All authors included CCS, TSH, TSF, CYL, BYC and FPC contributed to the critical revision of the study and the approval  
25  
26 337 of submission.  
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33 340 CMRPG2D0372, CMRPG2D0373, CLRPG2G0081, CLRPG2G0082 and CLRPG2G0083).  
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5 342 **Conflicts of interest:** The authors have no proprietary or commercial interest in any materials discussed in this article.

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9 344 **Patient consent form for publication:** not required.

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14 346 **Data availability statement:** All relevant data of the current study are involved in the manuscript; no additional data are available.

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5 415 **Figures and legends:**

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9 417 **Figure 1.** Flowchart of the patient selection in age-related macular degeneration and non-age-related macular degeneration cohort  
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11 with a one-to-four match

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14 419 AMD: age-related macular degeneration

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18 421 **Figure 2.** Estimates of cumulative hazards of transition among osteoporosis patients

19 422 OS: osteoporosis

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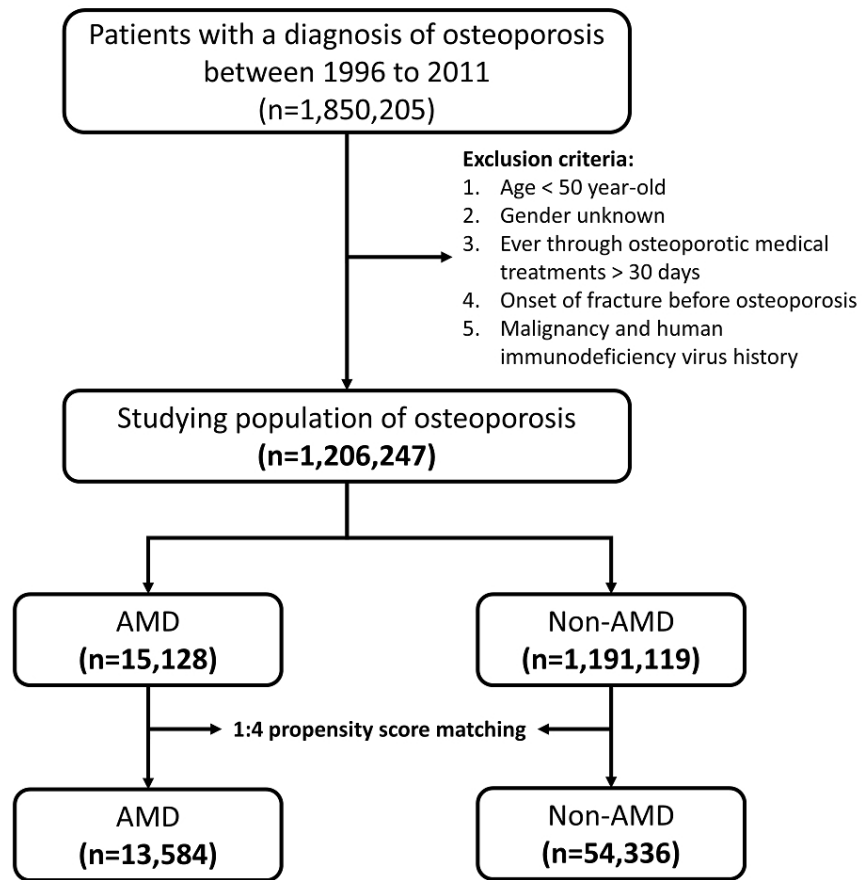


Figure 1

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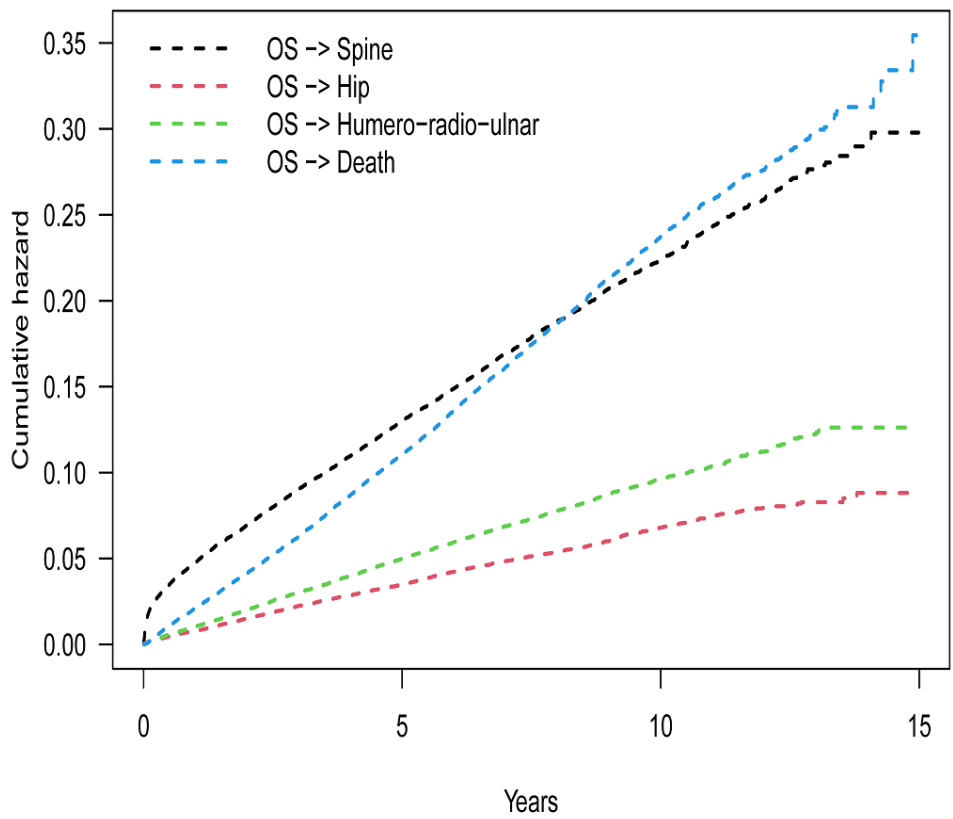


Figure 2

90x90mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-11
		(b) Describe any methods used to examine subgroups and interactions	9-11
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	10-11
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(b) Report category boundaries when continuous variables were categorized	12-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14-17
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).