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

Running head: Age-related macular degeneration on osteoporosis-related fractures

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Abbreviations and Acronyms:

AMD: age-related macular degeneration, OS: osteoporosis, NHIRD: national health insurance research database, NHI: national health insurance, CIs: confidence intervals, DM: diabetes mellitus, CCI: Charlson comorbidity index, HR: hazard ratio

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Abstract

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

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

Setting: A multicenter study conducted in Taiwan.

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

Intervention: Osteoporotic patients were extracted from Taiwan's NHIRD from 1996 to 2011. Each osteoporotic patient with AMD (ICD-9 codes: 362.50-362.52) was matched with age, sex, and comorbidities to four non-AMD OS patients which served as the control group. A Cox proportional hazard model was used to examine whether AMD were related to incidence of vertebral fractures, hip fractures and humero-radio-ulnar fractures in the multivariate model.

Primary outcome measures: The transitions for OS to spine fracture, OS to hip fracture, OS to humero-radio-ulnar fracture, and OS to death.

Results: A total of 1, 206,247 were diagnosed as OS. The risks of vertebral, hip, and humero-radio-ulnar fractures were all significantly higher in the AMD group (hazard ratio=1.82, 95% confidence interval (CI)=1.76-1.87; hazard

ratio=1.54; 95% CI=1.48-1.60; and hazard ratio=1.76, 95% CI=1.66-1.86, respectively) compared with non-AMD group among OS patients.

Conclusion: Osteoporotic patients with a code for AMD had a greater risk of incident fractures than did patients without a code for AMD. Future study to evaluate the effects of treatment for AMD on reducing fracture incidence is mandatory.

Keywords: age-related macular degeneration; fracture; osteoporosis; population-based, database

Strengths and limitations of this study:

- The current study enrolled a huge numbers of participants with 13,548 patients and 54,336 patients were analyzed in AMD and non-AMD group.
- Each participant can be followed up for up 16 years in the current study even visited different hospital.
- The causal relationship between AMD and subsequent bone fracture in patients with OS has been established in the current study.
- The disease severity of OS is not accessible in the NHIRD due to the application of ICD-9 diagnostic codes.
- Whether severe ocular diseases would lead to more severe facture or higher rate of mortality cannot be decided.

Introduction

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

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

elucidated.

Concerning the ocular disease and fracture, visual impairment is always an important risk factor of hip fracture in elderly population[20-22]. In a previous research, macular degeneration and suspicion of glaucoma would lead to a higher risk of hip fracture[22]. Therefore, it is important to understand the ocular risk factors and prevent future fractures in osteoporotic patients. However, only a limited number of studies have examined the association between fractures in OS patients and specific ocular disorders[22-24]. Specifically, regarding AMD, previous study only focused on patients with AMD and hip fractures, ignoring spine and humero-radio-ulnar fractures.[22-24] In addition, the numbers of participants in previous researches were relative small,[22-24] while a population-based study should be conduct to investigate the relationship between AMD and fracture with OS since both disorders affect a majority of population.[1, 14]

Therefore, we used the Taiwan's National Health Insurance Research Database (NHIRD) in this nationwide study with a retrospective cohort and case-control design to investigate the association between AMD and subsequent fractures in osteoporotic population.

Methods

Ethics declaration

All managements performed in our study involving human participants adhered to the 1964 Declaration of Helsinki and its later amendments. Specifically, the current study was approved by both the National Health Insurance Administration and the Institutional Review Board of Keelung Chang Gung Memorial Hospital, Keelung, Taiwan.

Patient and Public Involvement statement

The current study used the database collected and produced by the National Health Insurance Administration of Taiwan. Because this is a claimed data-based study, no patient recruitment, obtain of informed consent (waived by the National Health Insurance Administration), informed of research question, dissemination of study result to participants or other patient and public involvement is applicable in the current study.

Data source

This population-based cohort study used the NHIRD of Taiwan (approximately 26 million insured individuals) for the time period January 1996 through December 2011. By the end of 2007, NHIRD had enrolled more than 99% of Taiwan's population into this insurance program, which had contracts with 97% of the country's clinics and hospitals. The data available through the NHIRD included all medical services provided to each enrollee from 1996 to

2011, as well as the patients' characteristics and the features of the hospitals and physicians.

Study Population Enrollment and Exclusion Criteria

From January 1, 1996 to December 31, 2011, we identified patients with diagnosis of OS, using *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes733.00, 733.01, 733.02, 733.03, and 733.09. The osteoporotic population of the NHIRD was identified by the presence of either the aforementioned diagnostic codes in their outpatient records or the discharge codes from hospitalization records. Eligible patients were those 50 years of age or older with diagnosis of OS. Exclusion criteria were (1) ever osteoporotic medical treatments for more than 30 days before the index date, (2) previously documented any fracture (ICD-9 codes 800.x–829.x), (3) human immunodeficiency virus (ICD-9 codes 042), and (4) metastatic solid tumors (ICD-9 codes 196.x–198.x). Further, we divided patients into those with AMD (primary diagnosis codes of ICD-9 362.50-362.52) and those without AMD which discussed in the following section. After propensity score matching, 13,548 patients and 54,336 patients were analyzed in AMD and non-AMD group.

Outcome Definition

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

fractures between 1996 and 2001) and who received surgery for fractures to ensuring the diagnostic accuracy (surgery code of NHIRD: 64245C, 64042C, 64160B, 64271B, 64271C, 64032B). The date of death was defined as the date of death in the catastrophic illness registry data files, the discharge date from a patient's insurance coverage within one month after critical against medical advice discharge, or the discharge date from a patient's insurance coverage within one month after emergency department discharge with intravenous epinephrine use. We defined it as such because National Health Insurance (NHI) is mandatory in Taiwan; therefore, patients, especially sick ones, can rarely stop their own insurance coverage. If insurance coverage ended, death was most likely the reason. Furthermore, NHI premiums are paid on a monthly basis, so coverage could easily be stopped immediately following a death. The time-to-event outcome was determined as the time from the OS diagnosis date to the date of hip fracture, spine fracture, and humero-radio-ulnar fractures, or all-cause death, respectively.

Co-variates

The comorbidities were defined as an outpatient diagnosis listed on 2 or more visits or a 1-time inpatient diagnosis before the index date. Study comorbidities included diabetes mellitus, moderate to severe liver disease, chronic renal disease, hyperthyroidism, rheumatic disease, malignancy, and other eye diseases. The Charlson Comorbidity Index score was also recorded.

Statistical Analysis

To compare the AMD and each transition, we performed propensity

score matching. The propensity score was the predicted probability of being the AMD group given the values of co-variates. These co-variates including age, sex, rheumatologic diseases, DM without complications, DM with complications, malignancy, moderate to severe liver diseases, hyperthyroidism, chronic renal diseases, cataract, corneal disease, glaucoma, and Charlson Comorbidity Index score. Each patient in the AMD group was matched with 4 counterparts in the non-AMD group to achieve minimal bias. An absolutes standardized mean difference of less than 0.1 between the two groups after propensity score matching was considered well balanced. The cumulative incidence of follow-up outcomes was generated; a comparison between the two groups was made using Cox proportional hazards model in which death was considered a competing risk. We check the proportional hazards assumption using modified Schoenfeld residuals test and residual plots in each Cox model. For the violation of proportional hazards assumption, we modeled the interaction between the variable and time using step functions or functions guided from residual plots. To investigate the cumulative incidence of each of fractures and all-cause of death, we employed the competing risk model to simultaneously model the transitions including “OS to spine fracture”, “OS to hip fracture”, “OS to humero-radio-ulnar fracture”, and “OS to death”. Finally, in order to facilitate the interpretation of time-varying coefficients, we conducted post-estimation simulation techniques and graphs with visual weight to demonstrate the results. All reported confidence intervals (CIs) and tests were 2-sided with a 5% significance level. All analyses were performed with R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with contributed

packages “tableone”, “ReporteRs”, “mstate”, “survival”, “ggplot2”, and “simPH”.

Results

Patient Characteristics

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

Estimates of cumulative hazards and probabilities of transition.

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

The effect of AMD on transition of fracture

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

covariates (HR=1.09; 95% CI=1.04-1.15; P<0.001). Similarly, AMD was significantly associated with a higher risk of hip fracture (HR=1.18; 95% CI=1.08-1.30; P<0.001). On the contrary, AMD was not associated with risks for the humero-radio-ulnar fracture. Additionally, multivariable analysis revealed that all medical comorbidities except hyperthyroidism were significantly associated with higher risks for death. The effects of ocular comorbidities on the risk of fractures are diverse. It is interesting to note that glaucoma was not associated with a higher risk of fractures

Discussions

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

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

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

that the risk of hip fractures was significantly higher in cases that were coded with atrophic (dry) AMD (odds ratio=1.11, 95% CI=1.06-1.16)[30]. However, the risk was similar in cases that were coded with exudative AMD (odds ratio=1.03, 95% CI=0.95-1.12) compared with cases with no AMD[30]. The present study revealed that patients with a code for both types of AMD had an 18 % greater risk of hip fractures than did patients without a code for AMD in osteoporotic population. The higher risk in this study reflected the fact that OS patients are a potentially vulnerable population to developing fractures secondary to accidental falls. However, whether AMD subtypes have variable risks on hip fracture deserve further evaluation.

Fractures caused by OS most frequently occur in the spine[14]. These spinal fractures, also called vertebral compression fractures, occur in nearly 700,000 patients each year in the United States[31]. They are almost twice as common as other fractures typically linked to OS, such as hip and wrist fractures[31]. Despite that not all vertebral compression fractures are related to OS. But when the disease happened, a fracture is often the first sign of a weakened skeleton in osteoporotic patient. However, there are very few reports on the associated between AMD and spine fractures in patients with OS. Spine compression fractures are often resulted from falls[32], but patients with OS could suffer a fracture even when doing routine works, such as twisting, coughing, and sneezing[33]. In the present study, patients with AMD are especially run a greater risk for spine fractures (odds ratio=1.09; 95% CI=1.04-1.15). Therefore, it is important to screen ocular co-morbidity like AMD in elderly patients with OS to prevent both hip and spine fractures.

On the contrary, AMD was not associated with a greater risk of humero-

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

Ocular co-morbidities such as cataract, glaucoma and corneal diseases were also increased as advanced age[36]. Other studies have found that contrast sensitivity, poor visual acuity, and visual field impairment were significantly associated with falls[37-39]. However, these studies did not show any correlation between glaucoma and the three aforementioned fractures[37-39]. One possible explanation is that the initial presentation of glaucoma is mild peripheral visual filed defect without visual acuity deterioration. Therefore, osteoporotic patients still have good central visual acuity and as such decrease the risk of falls and subsequent fractures.

A major limitation in this study is that the disease severity is not accessible in the NHRI database and the effects of different severity of ocular co-morbidities on different fractures can't be obtained. However, it seems unlikely that selection bias was a factor given that the basis of subject selection was not associated with magnitude of fracture response to severity of ocular co-morbidities. In addition, a non-differential misclassification of severity of ocular co-morbidities would cause. It was unlikely that the observed effects were overestimated. Further investigation with hospital

database such as Chang Gung Research database is mandatory to delineate the effects of laboratory parameters on fractures and final outcomes.

In conclusion, the current study provides large-scale, population-based evidence in support of an independent relationship between overall AMD and spine, hip and humero-radial-ulnar fractures for patients with OS in Taiwan. We found that osteoporotic patients with AMD were at significantly greater risk of subsequent development of spine and hip fractures, but not humero-radial-ulnar fractures than the matched controls. Glaucoma, to our surprise, is not associated with an increased risk of three fractures in this study. Although interesting, this association does not prove causation. Further investigations are warranted to clarify if treatment of AMD such as vitrectomy and intravitreal anti-vascular endothelial growth factor would prevent second fractures in osteoporotic patients.

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Contributorship statement:

TSH, FPC and CCS contribute to the concept and design of the study, CCS and BYC contributed to analyses of data. CCS, TSF and BYC contributed to interpretation of the data, CYL, FPC and CCS contribute to manuscript writing.

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 analysis. All authors included CCS, TSH, TSF, CYL, BYC and FPC contribute to the critical revision of the study and the approval of submission.

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Figures and legends:

Figure 1. Flowchart of the patient selection in age-related macular degeneration and non-age-related macular degeneration cohort with a one-to-fourmatch

AMD: age-related macular degeneration

Figure 2. Estimates of cumulative hazards of transition among osteoporosis patients

OS: osteoporosis

Table 1. **Baseline characteristics between age-related macular degeneration and non-age-related macular degeneration population with 1:4 match**

		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. (%)	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

AMD: age-related macular degeneration

IQR: interquartile range

DM: diabetes mellitus

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

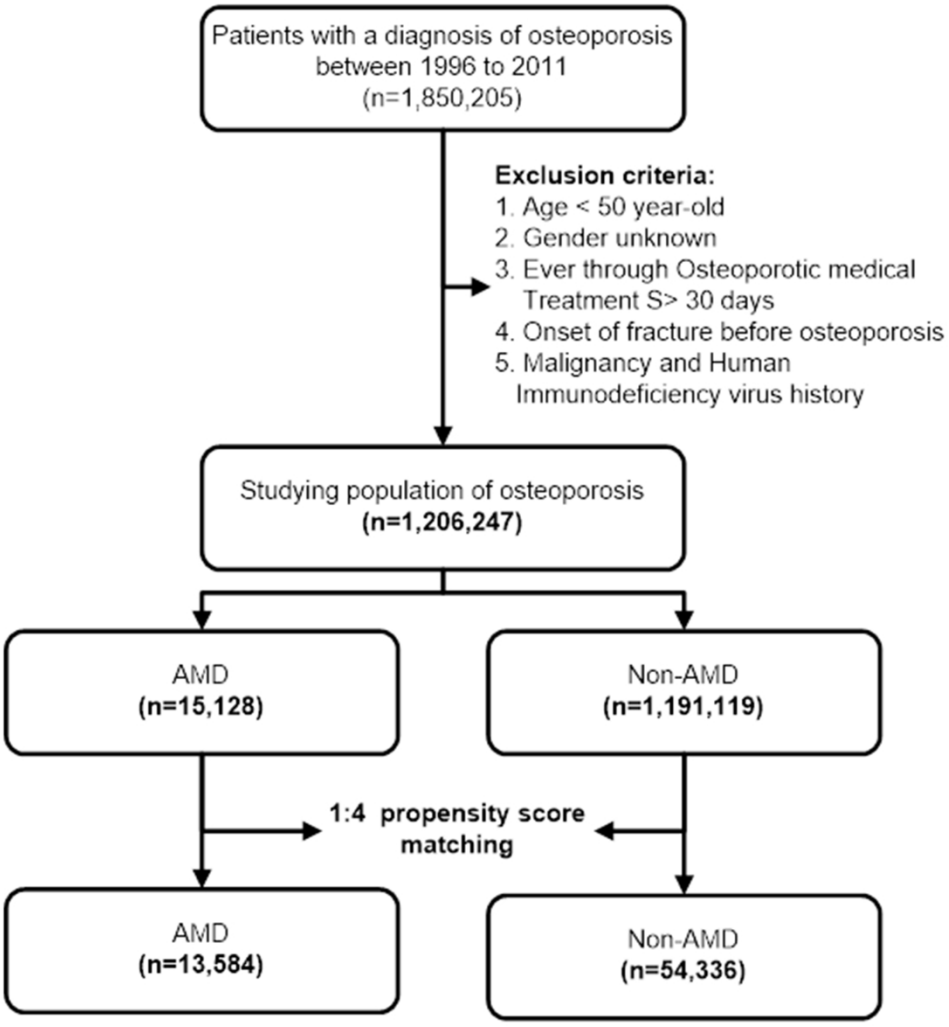
		Osteoporosis to spine fracture		Osteoporosis to hip fracture		Osteoporosis to humero-radial-ulnar fracture	
		Hazard Ratio (95% CIs)	P value	Hazard Ratio (95% CIs)	P value	Hazard Ratio (95% CIs)	P value
AMD	No	Reference		Reference		Reference	
	Yes	1.09 (1.04-1.15)	<0.001	1.18 (1.08-1.30)	0.001	0.98 (0.90-1.06)	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-	0.717	1.50 (1.33-	<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

AMD: age-related macular degeneration

CI: confidential intervals

DM: diabetes mellitus



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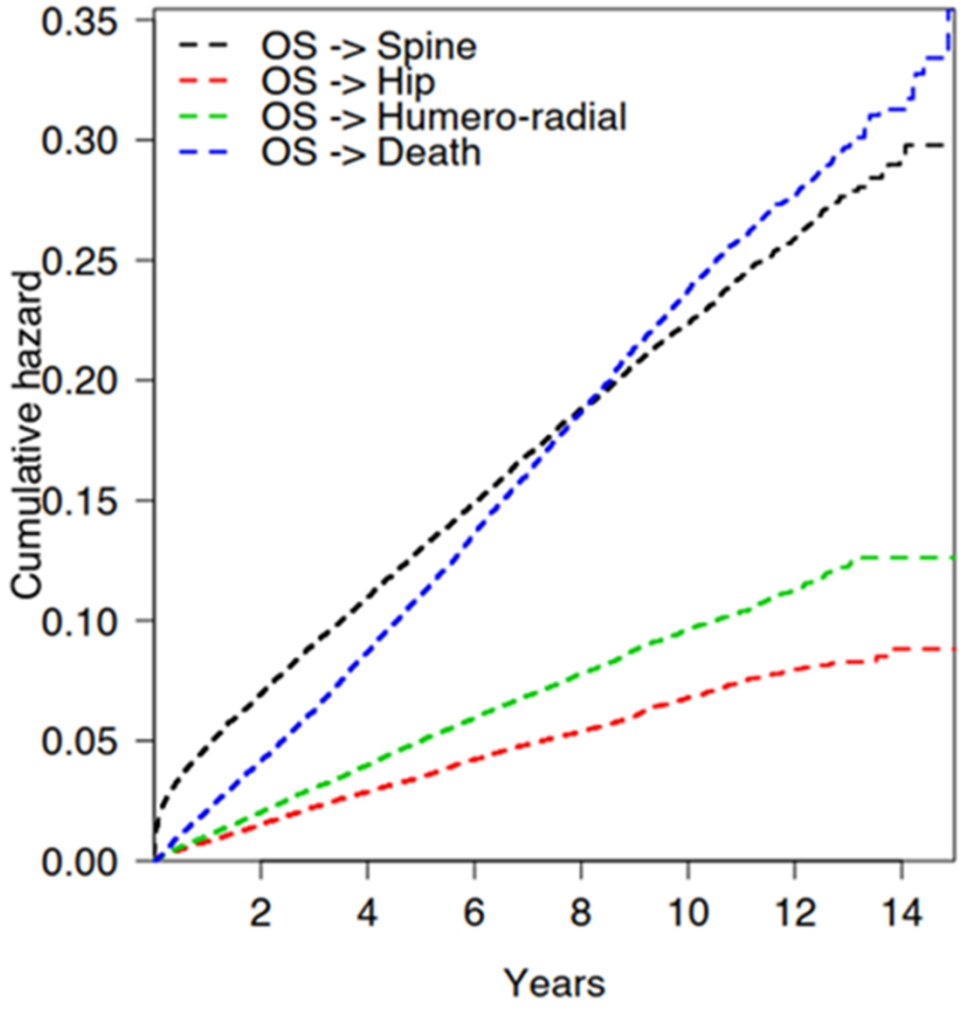

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	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
Introduction			
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
Methods			
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
Results			

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
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations			
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
Other information			
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.

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

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

Running head: Age-related macular degeneration on osteoporosis-related fractures

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Abstract

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

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

Setting: A multicenter study conducted in Taiwan.

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

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

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

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

age, male sex, and all types of co-morbidity ($P < 0.05$) except for hyperthyroidism ($P = 0.200$).

Conclusion: Osteoporotic patients with AMD had a greater risk of spine and hip fractures than did patients without AMD.

Keywords: Age-related macular degeneration; fracture; osteoporosis; population-based, database

Strengths and limitations of this study:

- The current study enrolled a large number of participants 13,548 (AMD group) patients and 54,336 (a non–AMD group) patients.
- Each participant can be followed up to 16 years even when visited to different hospitals.
- The causal relationship between AMD and subsequent bone fracture in patients with OS has not yet been established in the current study.
- The disease severity of OS is inaccessible in the NHIRD because of simply using the ICD-9 diagnostic codes.
- The severity of ocular disease leading to fractures or higher mortality rate has not yet been determined.

Introduction

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

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

fractures, such as those with OS, should be further investigated and identified.

Visual impairment is an important risk factor for hip fracture in the elderly population.[20–22] Studies have revealed that macular degeneration and glaucoma suspect would lead to a higher risk of hip fractures.[22] Therefore, it is important to understand the ocular risk factors and take measures to prevent future fractures in osteoporosis patients. However, only a limited number of studies have examined the association between fractures in OS patients and specific ocular disorders.[22–24] Taking AMD as an example, studies focused only on patients with AMD and hip fractures, ignoring spine and humero-radio-ulnar fractures.[22–24] Moreover, the number of participants in previous studies were relatively small ,[22–24] while a population-based study should be conducted to investigate the relationship between AMD and fractures in patients with OS since both disorders affect most population.[1, 14]

Therefore, we used the Taiwan's National Health Insurance Research Database (NHIRD) in this nationwide study with a retrospective cohort and a case-control design to investigate the association between AMD and subsequent fractures in osteoporosis patients.

Methods

Ethics declaration and patient involvement statement

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

Patient and Public Involvement statement

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

Data source

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

Study Population Enrollment and Exclusion Criteria

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

Outcome Definition

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

the expired date recorded in the catastrophic illness registry data files, the discharge date from a patient's insurance coverage within one month after being critical against medical advice discharge or the discharge date from a patient's insurance coverage within one month after emergency department discharge with intravenous epinephrine use. We defined it as such because the National Health Insurance (NHI) is mandatory in Taiwan; therefore, patients, especially sick ones, can rarely stop their own insurance coverage. If the insurance coverage ended, death was the reason. Furthermore, NHI premiums are paid monthly, so coverage can be stopped immediately following a death. The time-to-event outcome was determined as the time from the OS diagnosis date to the date of hip fracture, spine fracture, and humero-radio-ulnar fractures, or all-cause death, respectively.

Covariates

The comorbidities were defined as an outpatient diagnosis listed on two or more visits or a one-time inpatient diagnosis before the index date. Study comorbidities included diabetes mellitus (DM), moderate to severe liver disease, chronic renal disease, hyperthyroidism, rheumatic disease, malignancy, hyperparathyroidism and ocular diseases including cataract, corneal diseases and glaucoma. The Charlson Comorbidity Index score (CCIs) that merges the abovementioned diseases into one numerical score was also recorded.

Statistical Analysis

To compare the AMD and each transition, we performed propensity score matching. The propensity score was the predicted probability of being the

AMD group given the values of covariates including age, sex, rheumatologic diseases, DM with and without complications, malignancy, moderate to severe liver diseases, hyperthyroidism, chronic renal diseases, cataract, corneal disease, glaucoma, hyperparathyroidism, and CCIs. Each patient in the AMD group was matched with four counterparts in the non-AMD group to achieve minimal bias. The cumulative incidence of follow-up outcomes was generated and the comparisons between the two groups for the risk of spine, hip and humero-radio-ulnar fractures were made using the Cox proportional hazards model in which death was considered a competing risk. We checked the proportional hazards assumption using modified Schoenfeld residuals test and residual plots in each Cox model. For the violation of proportional hazards assumption, we demonstrated the interaction between the variable and time using step functions or functions guided from residual plots. To investigate the cumulative incidence of each fracture and cause of death, we engaged in the competing risk model with the hazard ratio (HR) adjusted all the above mentioned covariates to analyze the transitions, including “OS to spine fracture,” “OS to hip fracture,” “OS to humero-radio-ulnar fracture” between AMD and non-AMD subjects, and the transition of “OS to death” for the abovementioned covariates. Finally, to facilitate the interpretation of time-varying coefficients, we conducted post-estimation simulation techniques and graphs with visual weight to demonstrate the results. All reported confidence intervals (CIs) and tests were two-sided with a 5% significance level. All analyses were performed with R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with contributed packages “tableone,” “ReporteRs,” “mstate,” “survival,” “ggplot2,” and “simPH.”

Results

Patient Characteristics

A total of 1,850,205 OS patients were enrolled in this nationwide study. After applying the exclusion criteria, a total of 1,206,247 patients participated, of which 15,128 were in the AMD group, and 18,191,119 were in the non-AMD group. After propensity score matching, 13,548 patients and 54,336 patients were analyzed in the AMD and non-AMD group, respectively (**Figure 1**). The selected characteristics—including age, sex, related covariates, and CCIs—were well balanced between the AMD and non-AMD groups after propensity score matching (**Table 1**).

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. (%)	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
CCIs, median (IQR)		5.00 (3.00,	5.00 (3.00,	0.22

	7.00)	7.00)

AMD: age-related macular degeneration
No.: number of patients
IQR: interquartile range
DM: diabetes mellitus
CCIs: Charlson comorbidity index score

Estimates of cumulative hazards and probabilities of transition

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

The effect of AMD on transition of fractures

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

and being female are vulnerable to any type of incident fractures is also shown in our results **(Table 2)**. It is also noteworthy that other ocular co-morbidities, including cataract and corneal diseases are associated with a high risk of spine fractures (HR = 1.23; 95% CI = 1.17–1.31; $P < 0.001$ & HR = 1.18; 95% CI = 1.12–1.23; $P < 0.001$) and humero-radio-ulnar fractures (HR = 1.16; 95% CI = 1.06–1.26; $P < 0.001$ & HR = 1.08; 95% CI = 1.00–1.17; $P = 0.041$). However, an OS patient with glaucoma is not associated with a high risk of any incident fractures, which is due to the relatively fewer cases and the heterogeneous disease stages in this study cohort.

Table 2. The effect of AMD on transition of fractures and death.

		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

AMD: age-related macular degeneration

CI: confidential intervals

CCIs: Charlson comorbidity index score

HR: hazard ratio

DM: diabetes mellitus

N/A: the analysis did not perform since it is not necessary for the purpose of the current study

Discussion

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

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

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

analyzing the medicare database.[23, 24, 30] Anastasopoulos et al. found that the risk of hip fractures was significantly higher in cases that were coded with atrophic (dry) AMD.[30] However, the risk was similar in cases that were coded with exudative AMD 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 fractures than patients without a code for AMD in osteoporotic population. The higher risk in this study reflected the fact that OS patients are a potentially vulnerable population to developing fractures secondary to an accidental fall.

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

This study demonstrated that AMD was not associated with a greater risk of humero-radio-ulnar fractures. Primarily because humerus fractures occur in a relatively young population after physical trauma, falls, excess physical stress such as baseball games [34] and even with the presence of AMD, it did not cause significant visual impairment at a relatively younger age. However, proximal humerus fractures occur among elderly patients with OS who fall on an outstretched arm,[35] which corresponded to our

finding in which 70 years or older were associated with an increased risk of humero-radio-ulnar fractures (**Table 2**).

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

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

In conclusion, osteoporosis patients with AMD are at a significantly higher risk of subsequent development of spine and hip fractures, but not humero-radio-ulnar fractures than matched controls. Moreover, older age, male sex and major systemic co-morbidities in OS patients are related to death. Further investigations are needed to clarify if the treatment of AMD, such as

vitrectomy and intravitreal anti-vascular endothelial growth factor injection, would prevent primary fractures in osteoporosis patients.

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Contribution statement:

TSH, FPC, and CCS contributed to the concept and design of the study, CCS-and BYC contributed to analyses of data. CCS, TSF and BYC contributed to interpretation of the data, CYL, FPC and CCS contributed to manuscript writing.

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 analysis. All authors included CCS, TSH, TSF, CYL, BYC and FPC contributed to the critical revision of the study and the approval of submission.

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Conflicts of interest: The authors have no proprietary or commercial interest in any materials discussed in this article.

Patient consent form for publication: not required.

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

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Figures and legends:

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

AMD: age-related macular degeneration

Figure 2. Estimates of cumulative hazards of transition among osteoporosis patients

OS: osteoporosis

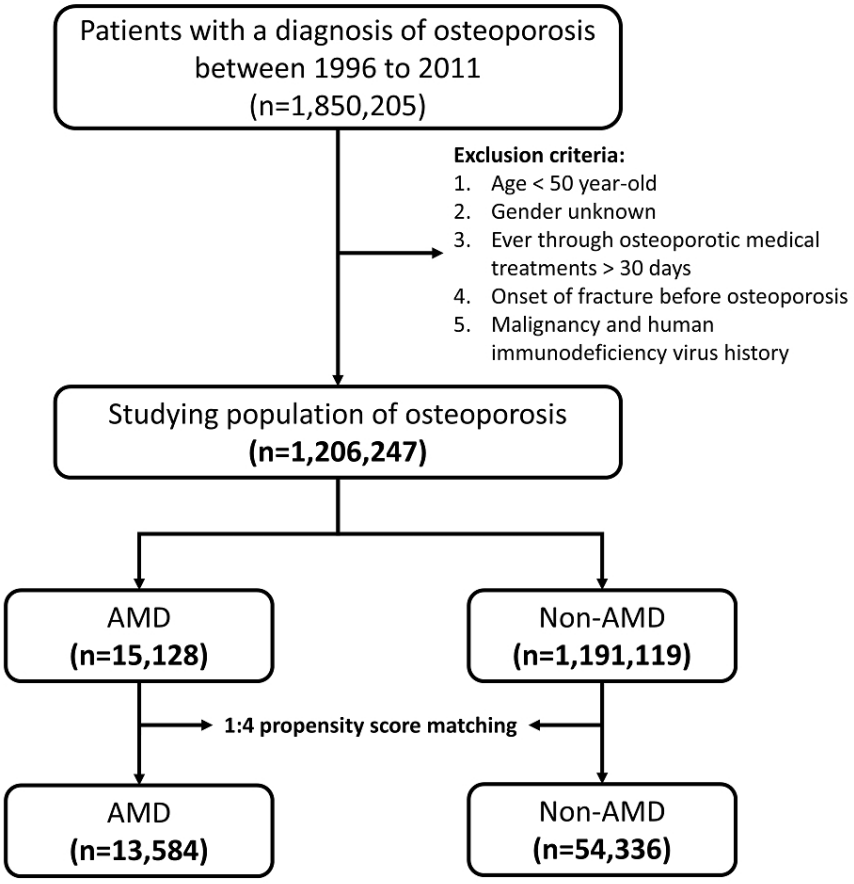

Figure 1

90x90mm (300 x 300 DPI)

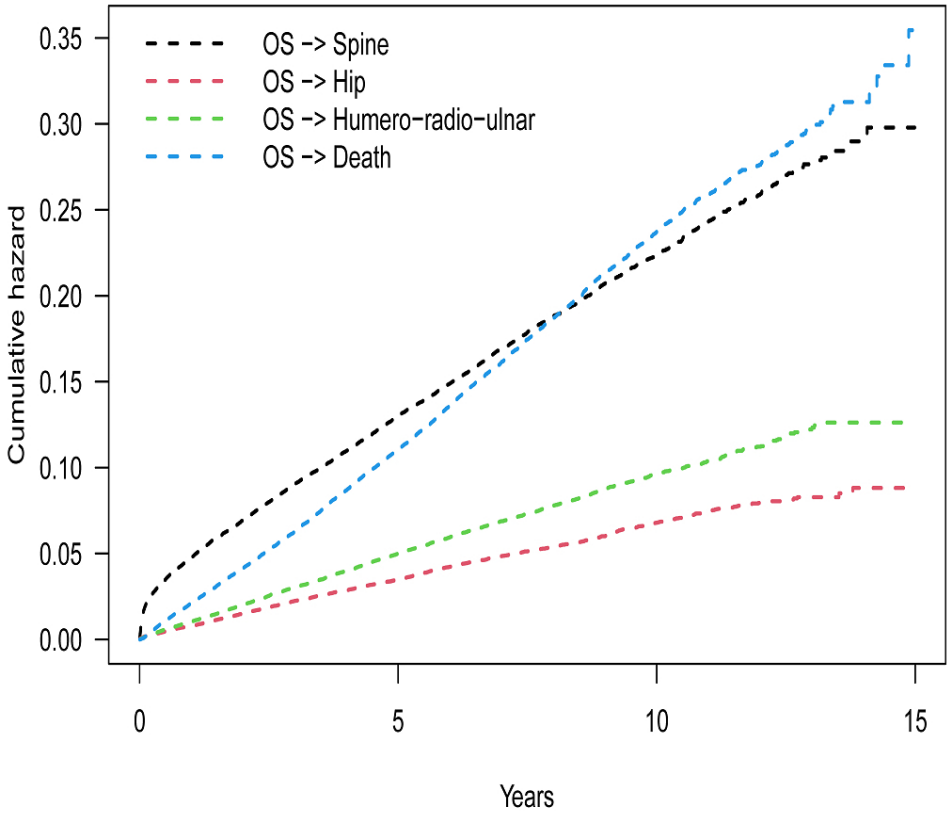

Figure 2

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 #
Title and abstract	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
Introduction			
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
Methods			
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
Results			

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
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations			
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
Other information			
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.