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ORIGINAL ARTICLE

# Increased risk of hip fracture among Japanese hemodialysis patients

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**Abstract** Incidence of hip fracture in dialysis patients is significantly higher than that in the general population. As information is lacking about Asian dialysis patients, we compared the incidence of hip fracture in hemodialysis patients with that in the general population in Japan. We conducted a retrospective cohort study using panel data from the Japanese Society for Dialysis Therapy registry. The study included patients without history of hip fracture who received hemodialysis three times per week as of December 31, 2007. We compared the observed number of hip fractures to the expected number derived from a national survey, and calculated standardized incidence ratios (SIRs) and the incidence rate difference. Subgroup analysis was performed according to vintage and diabetic status. During the one-year study period, 1,437 hip fractures were recorded in the 128,141 hemodialysis patients (61.9 % male). The overall incidence was 7.57 and 17.43 per 1,000 person-years in men and women, respectively. The SIRs for male and female patients were 6.2 [95 % confidence interval (CI) 5.7–6.8] and 4.9 (95 % CI 4.6–5.3) compared to the general population, and remained nearly constant until 16 years vintage, but increased steeply thereafter. The incidence rate difference of hip fracture increased with age. The SIRs for diabetics of both genders were higher than those for non-diabetics. Our study provides additional evidence that hip fracture risk among Asian dialysis patients is also significantly higher than in the general population.

**Keywords** General population · Hemodialysis · Hip fracture · Standardized incidence ratio

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## Introduction

Hip fractures lead to considerable mortality and disability among dialysis patients [1, 2]. The number of patients with end-stage renal disease (ESRD) treated with renal replacement therapy is increasing worldwide [3, 4], and hip fracture among these patients is expected to become a larger problem.

Hip fracture is very common in ESRD patients, with an overall age-adjusted incidence that is four to seventeen times greater than in the general population [1, 5]. These studies, however, included no or very few Asians. An international study estimated the overall unadjusted incidence of hip fracture among Japanese hemodialysis (HD) patients [6], but did not compare this with the general population. Race is an important variable in hip fracture incidence among the general population. Incidence of hip fracture among Caucasians in the United States (US) is approximately twice that of Asians [7, 8], although the reasons for this are not well understood [9, 10]. Thus, it is necessary to determine the risk of hip fracture among Asian dialysis patients compared with the general Asian population. The aim of this study is to compare hip fracture incidence of Japanese HD patients with that of the general Japanese population.

## Materials and methods

### Data source

We conducted a retrospective cohort study using two consecutive data panels from the Japanese Society for Dialysis Therapy (JSDT) registry. The registry has conducted an annual questionnaire survey of dialysis facilities throughout Japan since 1968, and several papers based on these surveys have been published [11, 12]. The data collection techniques are described in detail elsewhere [4, 12]. Briefly, year-end survey questionnaires are sent to all dialysis facilities in Japan each year, requesting information on each patient. In each case, the attending nephrologists had determined the primary cause of ESRD [13]. The response rate was 99.0 % for the 2008 survey [4]. This study used data collected as of December 31 of 2007 and 2008.

### Study population

The study included patients without a history of hip fracture who received HD three times per week as of December 31, 2007. Figure 1 summarizes the data extraction process. The 2007 JSDT registry included 275,119 dialysis patients, of which 200,529 were undergoing dialysis three times per week. We excluded 3,540 patients due to history of hip fracture and 68,848 due to incomplete pertinent clinical data. Therefore, we analyzed data from 128,141 HD patients in this study. There were no differences in characteristics such as age, gender, dialysis vintage, primary cause of ESRD, and prevalence of cardiovascular diseases between these 128,141 patients and all dialysis patients as of December 31, 2007 (Table 1).

### Outcome

A question regarding the history of hip fracture as of December 31, 2008, allowed for detection of new hip fracture events. If a patient answered "yes" to the question, the patient was considered to have suffered a hip fracture between January 1 and December 31, 2008.

### Statistical analyses

Incidence was calculated as the total number of hip fractures divided by the total patient time at risk [14]. Since exact dates of fracture incidents were not available in this study, we applied the following estimation method for the total patient time at risk. If a patient did not suffer a hip fracture, the patient's time at risk was calculated as being equal to the patient's survival time during the one-year study period. If a patient suffered a hip fracture, we assumed the patient's time at risk was equal to half of the patient's survival time during the study period. According to our trial calculation, application of this estimation method did not significantly affect the study results (Appendix).

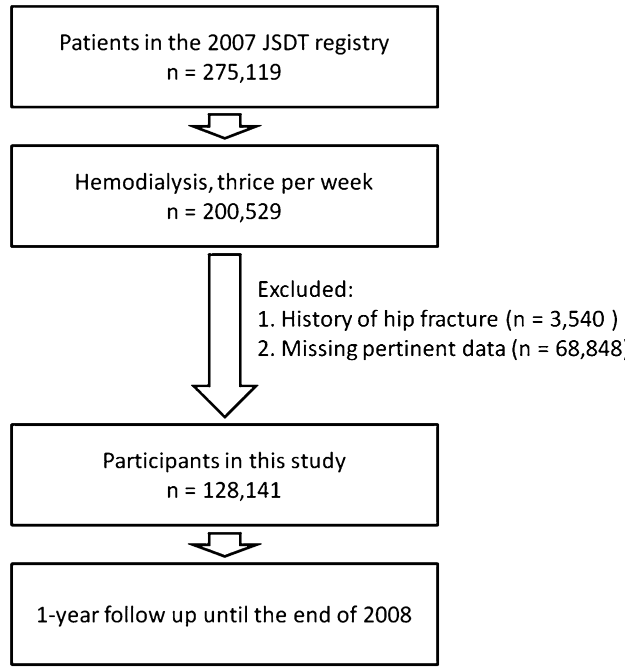


**Fig. 1** Patient selection process. The Japanese Society for Dialysis Therapy (JSDT) registry data from 2007 and 2008 were used

We used an indirect standardization method to compare the incidence of hip fracture among Japanese HD patients with the general population [15]. Incidence of hip fracture in the Japanese general population was extracted from published data collected during a nationwide survey conducted in 2007 [16]. We calculated a standardized incidence ratio (SIR), which can be interpreted as the relative increase in hip fracture incidence among the HD population compared with that of the reference population. Confidence intervals (CIs) were calculated using the normal approximation of the Poisson distribution [14]. The incidence rate difference was calculated as the difference between the observed and expected hip fracture rates, which can be interpreted as the absolute increase in hip fracture incidence among the HD population compared with that of the reference population [17].

We performed subgroup analysis according to diabetic status and vintage. Patients with diabetes mellitus were defined when diabetes was the primary cause of ESRD. Vintage was defined as the duration of dialysis treatment after its initiation. Vintage was categorized with respect to its duration: <1, 1, 2–3 years, 4–7, 8–15, and 16 years or more.

**Table 1** Characteristics of study participants and all dialysis patients as of December 31, 2007

| | Study participants | All dialysis patients |
|---|---|---|
| Number | 128,141 | 275,119 |
| Female (%) | 38.1 | 38.6 |
| Mean age (SD), years | | |
| Male | 63.6 (12.3) | 64.2 (12.5) |
| Female | 65.4 (12.5) | 66.0 (12.9) |
| Vintage (%) | | |
| Less than 5 years | 48.6 | 49.5 |
| 5 through 9 years | 26.2 | 25.0 |
| 10 through 14 years | 12.7 | 12.2 |
| 15 through 19 years | 6.3 | 6.2 |
| 20 through 24 years | 3.4 | 3.6 |
| 25 years or more | 2.7 | 3.5 |
| Primary cause of ESRD | | |
| Chronic glomerulonephritis (%) | 38.8 | 40.4 |
| Diabetic nephropathy (%) | 33.8 | 33.4 |
| History of myocardial infarction (%) | 5.9 | 6.6 |
| History of cerebral infarction (%) | 10.5 | 11.7 |
| History of cerebral bleeding (%) | 3.7 | 4.0 |

*SD* standard deviation, *ESRD* end-stage renal disease

All data were unlinked from patient identifiers. The study was conducted according to Japanese privacy protection laws, and the ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labor and Welfare in 2005. Statistical analyses were performed using SPSS for Windows (Version 18.0; SPSS, Inc., CA, USA).

## Results

During the one-year follow-up, 1,437 hip fractures occurred. The age- and gender- specific incidence of hip fracture are described in Tables 2 and 3. The overall incidences were 7.57 and 17.43 per 1,000 person-years for male and female HD patients, respectively. The incidence rose with increasing age, but was lower among men than women for all age groups. Compared with the general population, the SIR was 6.2 (95 % CI 5.7–6.8) for male and 4.9 (95 % CI 4.6–5.3) for female HD patients. The SIR was highest in the youngest age group for both men and women, and decreased with age. The incidence rate difference of hip fracture increased with age.

Standardized incidence ratios stratified by diabetic status are shown in Fig. 2. The SIR with and without diabetes was 8.6 (95 % CI 7.6–9.7) and 5.0 (95 % CI 4.5–5.6) for men, and 6.7 (95 % CI 6.0–7.5) and 4.3 (95 % CI 3.9–4.6) for women, respectively. The SIR values for diabetics were higher than for non-diabetics of both genders. SIRs stratified by vintage are shown in Fig. 3. The SIRs were higher than in the general population for patients of both genders with even less than 1 year vintage. SIRs remained nearly constant with increasing vintage, with the exception of patients with vintages exceeding 16 years, whose SIRs increased sharply.

**Table 2** Observed and expected hip fracture incidence among male HD patients

| Age (years) | Patient-years | Observed number of hip fractures | Hip fracture incidence[a] | Hip fracture incidence of general population[a] | Expected number of hip fractures | Standardized incidence ratio (95 % CI) | Incidence rate difference[a] |
|---|---|---|---|---|---|---|---|
| <40 | 3,323 | 4 | 1.20 | 0.032 | 0.11 | 36.4 (9.9, 93.1) | 1.17 |
| 40–49 | 6,815 | 15 | 2.20 | 0.092 | 0.63 | 23.8 (13.3, 39.3) | 2.11 |
| 50–59 | 17,782 | 86 | 4.84 | 0.203 | 3.61 | 23.8 (19.1, 29.4) | 4.63 |
| 60–69 | 23,954 | 157 | 6.55 | 0.481 | 11.52 | 13.6 (11.6, 15.9) | 6.07 |
| 70–79 | 202,06 | 228 | 11.28 | 1.812 | 36.61 | 6.2 (5.4, 7.1) | 9.47 |
| 80–89 | 6,177 | 96 | 15.54 | 6.103 | 37.70 | 2.5 (2.1, 3.1) | 9.44 |
| ≥90 | 358 | 9 | 25.15 | 14.662 | 5.25 | 1.7 (0.7, 3.3) | 10.49 |
| Total | 78,616 | 595 | 7.57 | 0.511 | 95.42 | 6.2 (5.7, 6.8)[b] | |

*HD* hemodialysis, *CI* confidence interval

[a] Data obtained from reference 15. Per 1,000 person-years

[b] Standardized for age

**Table 3** Observed and expected hip fracture incidence among female HD patients

| Age (years) | Patient-years | Observed number of hip fractures | Hip fracture incidence[a] | Hip fracture incidence of general population[a] | Expected number of hip fractures | Standardized incidence ratio (95 % CI) | Incidence rate difference[a] |
|---|---|---|---|---|---|---|---|
| <40 | 1,605 | 3 | 1.87 | 0.015 | 0.02 | 150.0 (30.9, 438.4) | 1.85 |
| 40–49 | 3,483 | 17 | 4.88 | 0.070 | 0.24 | 70.8 (41.3, 113.4) | 4.81 |
| 50–59 | 10,208 | 54 | 5.29 | 0.295 | 3.01 | 17.9 (13.5, 23.4) | 5.00 |
| 60–69 | 14,072 | 186 | 13.22 | 0.811 | 11.41 | 16.3 (14.0, 18.8) | 12.41 |
| 70–79 | 12,706 | 308 | 24.24 | 3.971 | 50.45 | 6.1 (5.4, 6.8) | 20.27 |
| 80–89 | 5,738 | 246 | 42.87 | 15.714 | 90.17 | 2.7 (2.4, 3.1) | 27.16 |
| ≥90 | 484 | 28 | 57.86 | 31.358 | 15.18 | 1.9 (1.2, 2.7) | 26.50 |
| Total | 48,296 | 842 | 17.43 | 1.814 | 170.49 | 4.9 (4.6, 5.3)[b] | |

*HD* hemodialysis, *CI* confidence interval

[a] Data obtained from reference 15. Per 1,000 person-years

[b] Standardized for age

## Discussion

The present study showed that the overall incidence of hip fracture among Japanese HD patients was approximately five-fold greater than in the general population. This is consistent with previous literature from the US, which showed that hip fracture incidence was significantly higher in dialysis patients than in the general population [1, 5]. These studies either included only Caucasians [5] or primarily Blacks, Hispanics, and Caucasians [1]. Our study provides additional evidence that hip fracture risk among Asian dialysis patients is also significantly higher than in the general population.

This study also showed that HD patients were at increased risk for hip fracture as early as the first year following dialysis initiation, which is consistent with a previous study [5]. Patients with moderate to severe chronic kidney disease are at increased risk of hip fracture [18–20], suggesting that fracture risk significantly increases prior to dialysis. In addition, our study showed that the SIR values were higher for diabetics than non-diabetics. More frequent falls probably account for some of this increased risk, because diabetic retinopathy and neuropathy may contribute to a higher propensity for falling in diabetic patients. In addition, it also appears that diabetic bone is more fragile for a given density. Given that the increased risk of hip fracture was even observed in the first year after the initiation of dialysis treatment, the primary causes of renal failure may also affect the bone fragility of HD patients, although it remains controversial whether diabetes is an independent risk factor for fracture in HD patients [6, 21].

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline for Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) does not recommend

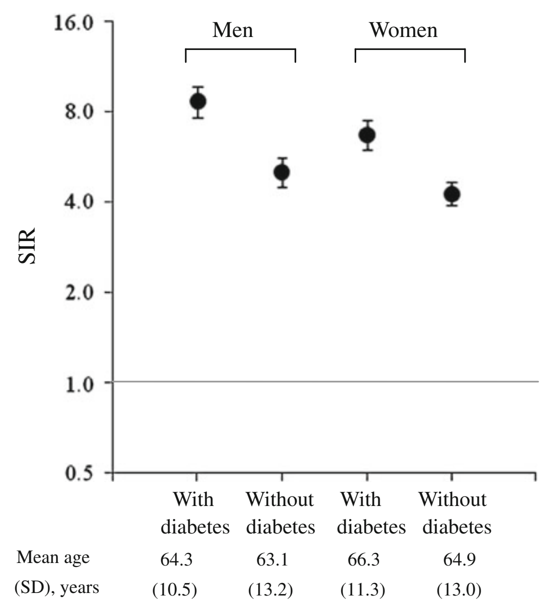


**Fig. 2** Standardized incidence ratios (SIRs) stratified by diabetic status and gender, standardized for age. *Error bars* indicate 95 % confidence intervals

regularly assessing bone mineral density, because such an approach cannot sufficiently predict the risk of fracture [22]. Impaired bone quality has been suggested to play a more important role than mineral density in determining the bone strength of dialysis patients. Thus, the increased incidence of hip fracture among dialysis patients shown here may have resulted from effects of uremia on bone quality, although the etiology of bone quality impairment in dialysis patients remains to be identified. The CKD-MBD may not be the only factor, as suggested by others [2, 6].

Several other factors likely contribute to increased risk of hip fracture in ESRD patients [1, 2, 5, 6, 21, 23, 24].

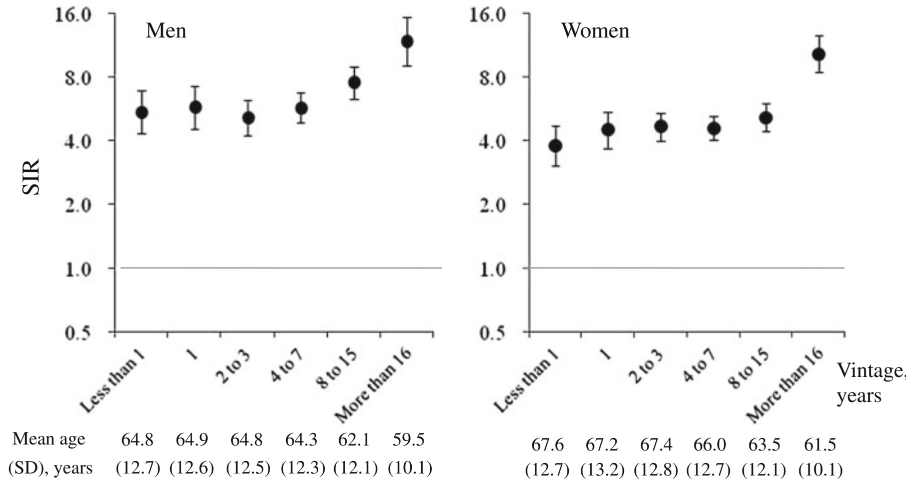


**Fig. 3** Standardized incidence ratios (SIRs) stratified by vintage for men and women, standardized for age. *Error bars* indicate 95 % confidence intervals

Some ESRD-specific factors, such as Abeta-2M-amyloidosis and related osteopathy, may increase the risk. This study showed that the SIR increased steeply after 16 years of dialysis. This steep increase cannot be fully explained by the relatively young age of this group. It is possible that Abeta-2M-amyloidosis and related osteopathy increased the risk in this group since these occur frequently after long-term HD [25, 26]. Abeta-2M-amyloidosis is considered to promote their hip fracture risk, not only through creating physical weak point at hip joints, but also through raising the risk of fall by joint contractions [25, 26].

Factors in common with the general population, such as age and gender, may also increase the risk. This study showed that the incidence rate difference increased with age, which is consistent with a previous study that included only Caucasians [5]. Because the rate difference is an absolute measure of the association between exposure and outcome [14], these results suggest that hip fracture incidence due to ESRD and/or its treatment increases with age regardless of race. It is possible that the rate difference is due to a greater burden of factors in common with the general population. For example, fall risk is higher in the HD population than in the general population [27, 28]. Further studies are necessary to clarify the reasons for differences between HD patients and the general population.

Our study has several limitations. First, we could not confirm the validity of hip fracture diagnoses. However, accurate diagnosis of a hip fracture is typically not difficult, so we consider it unlikely to bias the present results. Second, it is possible that we did not capture some fractures and that our data are limited by recall bias as a consequence of the retrospective nature of our study. If present, then recall bias would result in an underestimation of fracture incidence and the true incidence rate would be greater than our reported incidence rate. Third, the contribution of several risk factors such as serum intact parathyroid hormone concentration and body mass index was not analyzed. However, another group is now conducting analysis pf the several factors that would be associated with hip fracture in the dialysis patient using multivariate logistic regression models. Thus, we showed a descriptive epidemiology of hip fracture in this report. Finally, survival bias may play a role in incidence of hip fracture, especially among patients with a long vintage.

Despite these limitations, to the best of our knowledge, this is the first study to report SIRs for hip fracture among ESRD patients in an Asian country. Because race is an important variable in the incidence of hip fracture, our report is of considerable importance for Asian HD patients. In addition, our study included HD patients with very long vintages. Finally, our study is a nationwide survey of Japanese dialysis facilities with a large sample size.

In conclusion, the overall risk of hip fracture among Japanese HD patients is approximately five-fold greater than that of the general population. Our results provide additional evidence that the risk of hip fracture among Asian dialysis patients is significantly higher than in the general population.

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**Conflict of interest** The authors have no conflicts of interest to declare.

## Appendix

In this Appendix we provide a mathematical basis for the estimation method of the incidence of hip fracture in this study.

If $x$ is the observed number of individuals with the outcome of interest (i.e., hip fracture onset), and Py the number of person-years at risk, the incidence rate (IR) is given by

$$\mathrm{IR} = \frac{x}{\mathrm{Py}}$$

The number of person-years at risk is obtained as a sum of the patient's time at risk who suffered hip fracture (Pfy) and did not (Pny).

$$\mathrm{IR} = \frac{x}{\mathrm{Py}} = \frac{x}{\mathrm{Pny} + \mathrm{Pfy}}$$

If a patient did not suffer a hip fracture, the patient's time at risk of these patients (Pny) is equal to the patient's survival time during the 1-year study period (Psny).

If a patient suffered a hip fracture, we assume the patient's time at risk of these patients (Pfy) is equal to half of Psfy the patient's survival time during the study.

$$\mathrm{IR} = \frac{x}{\mathrm{Py}} = \frac{x}{\mathrm{Pny} + \mathrm{Pfy}} = \frac{x}{\mathrm{Psny} + (0.5 \times \mathrm{Psfy})}$$

This assumption is considered reasonable as no seasonal trends associated with the incidence of hip fractures have been detected in the general Japanese population [ref. 8].

In addition, as only a small number of hip fractures were reported, the total patient time at risk estimated using this method did not significantly change when this assumption was changed as below. For male hemodialysis patients, $x = 595$, Psny = 78,319.5388 years, Psfy = 592.75 years,

$$\mathrm{IR} = \frac{x}{\mathrm{Py}} = \frac{x}{\mathrm{Pny} + \mathrm{Pfy}} = \frac{x}{\mathrm{Psny} + (0.5 \times \mathrm{Psfy})} = \frac{595}{78319.5388 + (0.5 \times 592.75)} = 7.57 \times 10^{-3}$$

If we assume that all fractured patients were suffered on the last day (i.e., equal to the patient's survival time during the study), the IR was calculated as below

$$\mathrm{IR} = \frac{x}{\mathrm{Psny} + (1 \times \mathrm{Psfy})} = \frac{595}{78319.5388 + (1 \times 592.75)} = 7.54 \times 10^{-3}$$

If we assume that all fractured patients were suffered on the first study day (i.e., January 1st), the patient's time at risk of these patients (Pfy) is calculated as follow

$$\mathrm{Pfy} = (1 \div 365) \times x$$

Thus, the IR was calculated as below

$$\mathrm{IR} = \frac{x}{\mathrm{Psny} + ((1 \div 365) \times x)} = \frac{595}{78319.5388 + ((1 \div 365) \times 595)} = 7.60 \times 10^{-3}$$

Same as above, for female hemodialysis patients, $x = 842$, Psny = 47,879.5 years, Psfy = 832.58333 years,

$$\mathrm{IR} = \frac{x}{\mathrm{Psny} + (0.5 \times \mathrm{Psfy})} = \frac{842}{47879.5 + (0.5 \times 832.58333)} = 17.43 \times 10^{-3}$$

If we assume that all fractured patients were suffered on the last day (i.e., equal to the patient's survival time during the study), the IR was calculated as below

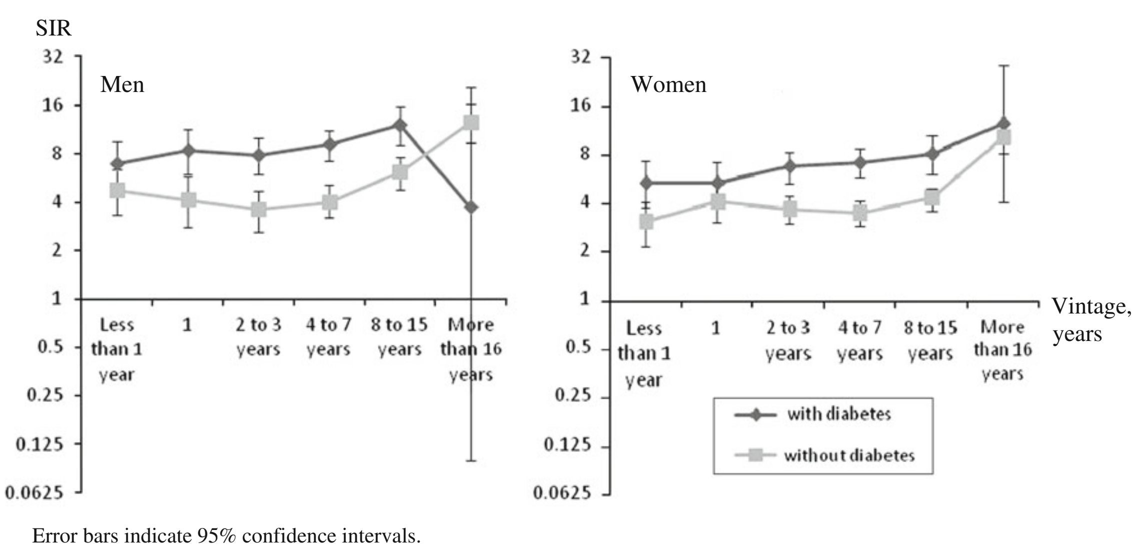


**Fig. 4** Standardized incidence ratios (SIRs) stratified by diabetic status and vintage for men and women, standardized for age

$$\mathrm{IR} = \frac{x}{\mathrm{Psny} + (1 \times \mathrm{Psfy})} = \frac{842}{47879.5 + (1 \times 832.58333)} = 17.29 \times 10^{-3}$$

If we assume that all fractured patients were suffered on the first study day (i.e., January 1st), the patient's time at risk of these patients (Pfy) is calculated as follow

$$\mathrm{Pfy} = (1 \div 365) \times x$$

Thus, the IR was calculated as below

$$\mathrm{IR} = \frac{x}{\mathrm{Psny} + ((1 \div 365) \times x)} = \frac{842}{47879.5 + ((1 \div 365) \times 842)} = 17.58 \times 10^{-3}$$

In conclusion, application of this estimation method did not significantly affect the study results according to our trial calculation. Our assumption is considered reasonable (Fig. 4).

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