

Review Article

Increased risk of hip fracture related to cardiovascular disease: a meta-analysis

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Abstract: Cardiovascular diseases (CVDs) might have a relationship to hip fracture risk. Many studies have investigated this hypothesis but provided conflicting and inconclusive findings. In this study, we aim to validate the potential association between CVD and hip fracture risk by pooling all available publications. After a comprehensive literature search in PubMed, Embase, Wanfang and CNKI databases from their inception up to June 20, 2017, a total of 13 independent studies were identified and included in our study. The pooled relative risks (RRs) with 95% confidence intervals (95% CIs) were calculated to assess the strength of the association. The results from this meta-analysis showed that CVD is positively associated with the risk of hip fracture, suggesting a risk role of CVD in the development of hip fracture (RR = 1.67, 95% CI 1.39-1.99, $P < 0.001$). Stratified analyses by study design further confirmed the pooled findings. CVD is related to increased risk of hip fracture among Caucasians but not Asians. Our pioneering findings provide strong evidence for a risk effect of CVD on hip fracture, particularly in the Caucasian population.

Keywords: Hip fracture, cardiovascular disease, meta-analysis

Introduction

Cardiovascular disease (CVD) and osteoporotic fracture are major diseases causing marked morbidity, disability, and mortality worldwide, especially in the elderly [1-3]. Both share many common risk factors and pathophysiologic pathways [4-6]. Hip fracture is one of the most common osteoporotic fractures, which is a very large socioeconomic burden in the world. Although the evident link between CVD and osteoporosis has been established in postmenopausal women [7-9], the data currently available for hip fracture yielded contradictory conclusions. The strength of the link between CVD and hip fracture risk varies among different studies, probably due to diverse race, study design, kinds of CVD, disease severity, and fracture outcomes. In this paper, we made a pioneering effort to carry out a meta-analysis of all published studies to provide a better estimate for the association between CVD and hip fracture risk.

Materials and methods

Search strategy

An extensive literature search in PubMed, Embase, Wanfang and CNKI databases from their inception up to June 20, 2017 was performed to identify eligible studies on the association of CVD and hip fracture risk. We used the terms “cardiovascular disease” or “coronary heart disease” or “hypertension” or “heart failure” or “ischemic heart disease” or “atherosclerosis” or “aortic calcification” or “myocardial infarction” and “hip fracture” and “risk”. The reference lists of all retrieved studies were also screened for additional studies.

Inclusion criteria

Studies were included in our study if they conformed to the following criteria: (1) Studies on the relationship between CVD and hip fracture risk; (2) Studies in case-control designs or

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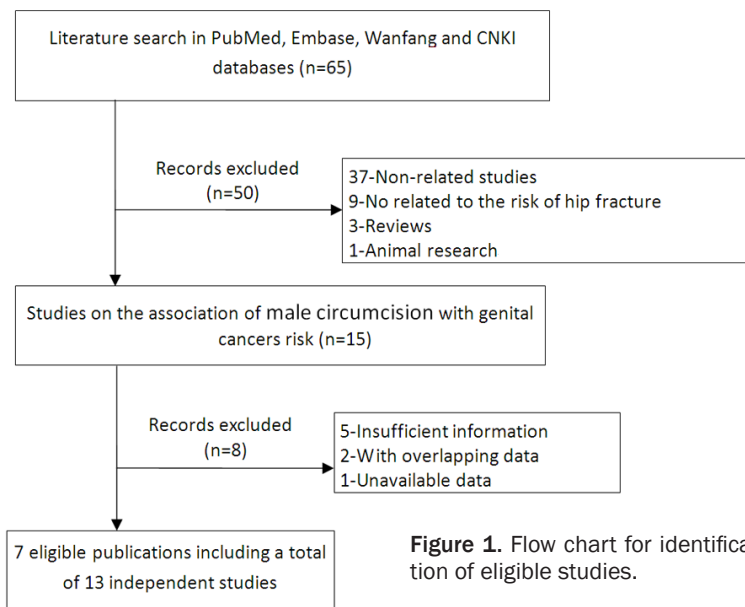


Figure 1. Flow chart for identification of eligible studies.

cohort designs; (3) Studies providing enough information for calculating odds ratio (ORs), relative risks (RRs), or hazard ratios (HRs) and 95% confidence intervals (95% CIs). Reviews, irrelevant studies and studies with overlapping data were all excluded. The qualities of all included studies were assessed using the Newcastle-Ottawa Scale (NOS). Studies were graded as good quality if they awarded 6 to 9 stars; fair if they awarded 3 to 5 stars; and poor if they awarded less than 3 stars.

Data extraction

All data were extracted by two investigators independently using a standardized data extraction form. Discrepancies were solved by consensus. The following data were extracted: first author, year of publication, study design, country, location, ethnicity, number of cases and controls, follow-up period, matching factors, adjusted factors, RRs or HRs or ORs with 95% CIs.

Statistical analysis

The strength for the relationship between CVD and hip fracture risk was estimated by calculating the pooled RRs with 95% CIs. All *P* values were two-sided. The between-study heterogeneity was determined by the Cochran's *Q* and *I*² statistic tests [10, 11]. The random-effects model was applied when the between-study

heterogeneity was significant [12]; otherwise, the fixed-effects model was used when the between-study heterogeneity was not significant [13]. We conducted stratified analyses by study design and ethnicity for further investigation. Sensitivity analysis was also carried out by sequential omission of individual studies. Begg's funnel plot and Egger's test were adopted to assess the publication bias in the present meta-analysis [14, 15]. All analyses were performed using STATA 12.0 software.

Results

Identification and characteristics of studies included in the meta-analysis

After a comprehensive search in PubMed, Embase, Wanfang and CNKI databases up to June 20, 2017, a total of 7 studies were retrieved regarding the association between CVD and hip fracture risk [16-22]. Among them, 3 publications were regarded as 9 independent studies according to different CVD [16-18]. As a result, there were 13 individual studies totally. **Figure 1** showed details for the inclusion of all eligible studies. Characteristics of all included studies were shown in **Table 1**. Among the 13 studies, 8 of them were in case-control design, while 5 were in cohort design. Eleven independent studies were conducted among Caucasians, and still 2 were among Asians. The modifying effect on hip fracture development was mainly estimated related to CVDs including coronary heart disease, hypertension, heart failure, ischemic heart disease, atherosclerosis, aortic calcification, and myocardial infarction.

Increased risk of hip fracture associated with CVD

Overall, the pooled RR suggested that CVD was significantly associated with elevated risk of hip fracture (RR = 1.67, 95% CI 1.39-1.99, *P* < 0.001) (**Table 2, Figures 2 and 3**). Sensitivity analysis by omitting each study did not

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Table 1. Descriptive characteristic of all studies

Study	Year	Location	Ethnicity	Disease	Study design	Hip Fracture				Control				Quality assessment score	Adjusted or Matching factors
						Number	Number (Percentage) of Cardiovascular disease	Age (year)	Gender (male/female)	Number	Number (Percentage) of Cardiovascular disease	Age (year)	Gender (male/female)		
Szulc P	2014	USA	Caucasians	Aortic calcification	Cohort	178	NR	> 65	178/0	5816	NR	> 65	5816/0	7	Age, BMI, total hip BMD, fall history, prior fracture, smoking status, comorbidities, race, and clinical center
Xu B	2013	China	Asians	Cardiovascular disease	CC	13071	7101	> 55	4720/8351	851337	448397	> 55	476719/374618	6	Sex, age, and number of diagnosis
Gerber Y (1)	2013	USA	Caucasians	Coronary heart disease	CC	1,904	39%	> 50	NR	1,904	61%	> 50	NR	6	Age, sex, and index year
Gerber Y (2)	2013	USA	Caucasians	Hypertension	CC	1,904	66%	> 50	NR	1,904	34%	> 50	NR	6	Age, sex, and index year
Lai SW	2013	Taiwan	Asians	Cardiovascular disease	Cohort	1710	990	> 50	NR	86038	42884	> 50	NR	7	Sex, age, and date selected
Sennerby U (1)	2009	Sweden	Caucasians	Heart failure	Cohort	639	113	> 50	NR	20720	2157	> 50	NR	7	Sex
Sennerby U (2)	2009	Sweden	Caucasians	Ischemic heart disease	Cohort	711	185	> 50	NR	23247	4684	> 50	NR	7	Sex
Sennerby U (3)	2009	Sweden	Caucasians	Peripheral atherosclerosis	Cohort	571	45	> 50	NR	19579	1016	> 50	NR	7	Sex
Sennerby U (1)	2007	Sweden	Caucasians	Heart failure	CC	1327	87	> 40	NR	3170	82	> 40	NR	6	Age, BMI, smoke, alcohol, physical activity, use of HRT, and disease history
Sennerby U (2)	2007	Sweden	Caucasians	Ischemic heart disease	CC	1327	120	> 40	NR	3170	181	> 40	NR	6	Age, BMI, smoke, alcohol, physical activity, use of HRT, and disease history
Sennerby U (3)	2007	Sweden	Caucasians	Hypertension	CC	1327	142	> 40	NR	3170	124	> 40	NR	6	Age, BMI, smoke, alcohol, physical activity, use of HRT, and disease history
Sennerby U (4)	2007	Sweden	Caucasians	Atherosclerosis	CC	1327	36	> 40	NR	3170	34	> 40	NR	6	Age, BMI, smoke, alcohol, physical activity, use of HRT, and disease history
Kanis J	1999	Europe	Caucasians	Myocardial infarction	CC	730	NR	> 50	730/0	1132	NR	> 50	1,132/0	5	Age

CC, case-control study; Cohort, cohort study; NR, not reported.

Table 2. Summary meta-analysis results

Contrasts	Study number	RR (95% CI)	P value	Model	Heterogeneity analysis	
					I ² (%)	P value
Overall	13	1.67 (1.39-1.99)	< 0.001	R	96.9	< 0.001
Caucasians	11	1.78 (1.35-2.33)	< 0.001	R	96.3	< 0.001
Asians	2	1.25 (0.84-1.86)	0.266	R	98.0	< 0.001
Cohort	5	1.62 (1.18-2.22)	0.003	R	97.0	< 0.001
CC	8	1.71 (1.42-2.07)	< 0.001	R	87.4	< 0.001

RR, relative risk; 95% CI, 95% confidence interval; CC, case-control study; Cohort, cohort study; R, random-effects model.

materially modify the pooled results (data not shown).

Stratified analysis by ethnicity

We performed stratified analysis among Asians and Caucasians. Increased risk of hip fracture was observed related to CVD among the Caucasians (RR = 1.78, 95% CI 1.35-2.33, $P < 0.001$), but not the Asians (RR = 1.25, 95% CI 0.84-1.86, $P = 0.226$) (Table 2 and Figure 2).

Stratified analysis by study design

The pooled results in case-control (CC) studies and cohort studies showed that CVD could increase the risk of hip fracture (CC: RR = 1.71, 95% CI 1.42-2.07, $P < 0.001$; Cohort: RR = 1.62, 95% CI 1.18-2.22, $P = 0.003$) (Table 2 and Figure 3).

Heterogeneity analysis and publication bias risk

As shown in Table 2, significant between-study heterogeneity was observed in all contrasts, including Caucasians subgroup ($I^2 = 96.3$, $P < 0.001$), Asians subgroup ($I^2 = 98.0$, $P < 0.001$), Cohort study subgroup ($I^2 = 97.0$, $P < 0.001$), case-control study subgroup ($I^2 = 87.4$, $P < 0.001$) and Overall ($I^2 = 96.9$, $P < 0.001$). Therefore, the pooled findings should be interpreted with caution. As shown in Figure 4, no publication bias risk was found in the present meta-analysis according to symmetrical Begg's funnel plot and insignificant Egger's test ($P = 0.6$).

Discussion

Currently published studies on the association between cardiovascular diseases and hip frac-

ture risk have yielded conflicting and inconclusive findings. The link between CVD and hip fracture risk is still questionable. Our data expand on the previous findings evaluating the association between CVD and hip fracture risk and suggest that cardiovascular disease confers risk effect on hip fracture development, particularly among the Caucasian population.

Hip fracture is a common consequence of osteoporosis. It has been suggested in multiple comorbidities including cardiovascular disease [23, 24]. The incidence rate of hip fracture is approximately 13 per 1000 person-year in patients with a diagnosis of cardiovascular disease, which was demonstrated in a previous European study [17]. Bone mineralization and vascular calcification share common pathologic pathways and medications [25]; thus, CVD may modify the risk factors of hip fracture. The relationship of CVD and hip fracture risk varies with different CVDs or even one specific disease, such as coronary heart disease, hypertension, heart failure, ischemic heart disease, atherosclerosis, aortic calcification, and myocardial infarction. Kanis J and the colleagues firstly demonstrated that individuals with myocardial infarction were at lower risk of hip fracture [19]. Reversely, a recent case-control study revealed that CVD was positively related to the development of hip fracture, indicating a risk role of CVD [21]. Similarly, a diagnosis of CVD was significantly associated with risk of subsequent hip fracture, which was implicated in a cohort study [17]. Taken together, the modifying effect of cardiovascular disease on hip fracture risk is largely different, probably owing to diverse ethnic populations, study design as well as different statistical power in independent studies. Meta-analysis can shed some light on the conflicting findings across individual studies. The current meta-analysis is based on 13 independent published studies and for the first time shows strong evidence that CVD can increase the risk of hip fracture.

The effect of CVD on the susceptibility to hip fracture differs by race. Elevated risk of hip fracture was associated with CVD among Asians [21], while the reduced risk of hip frac-

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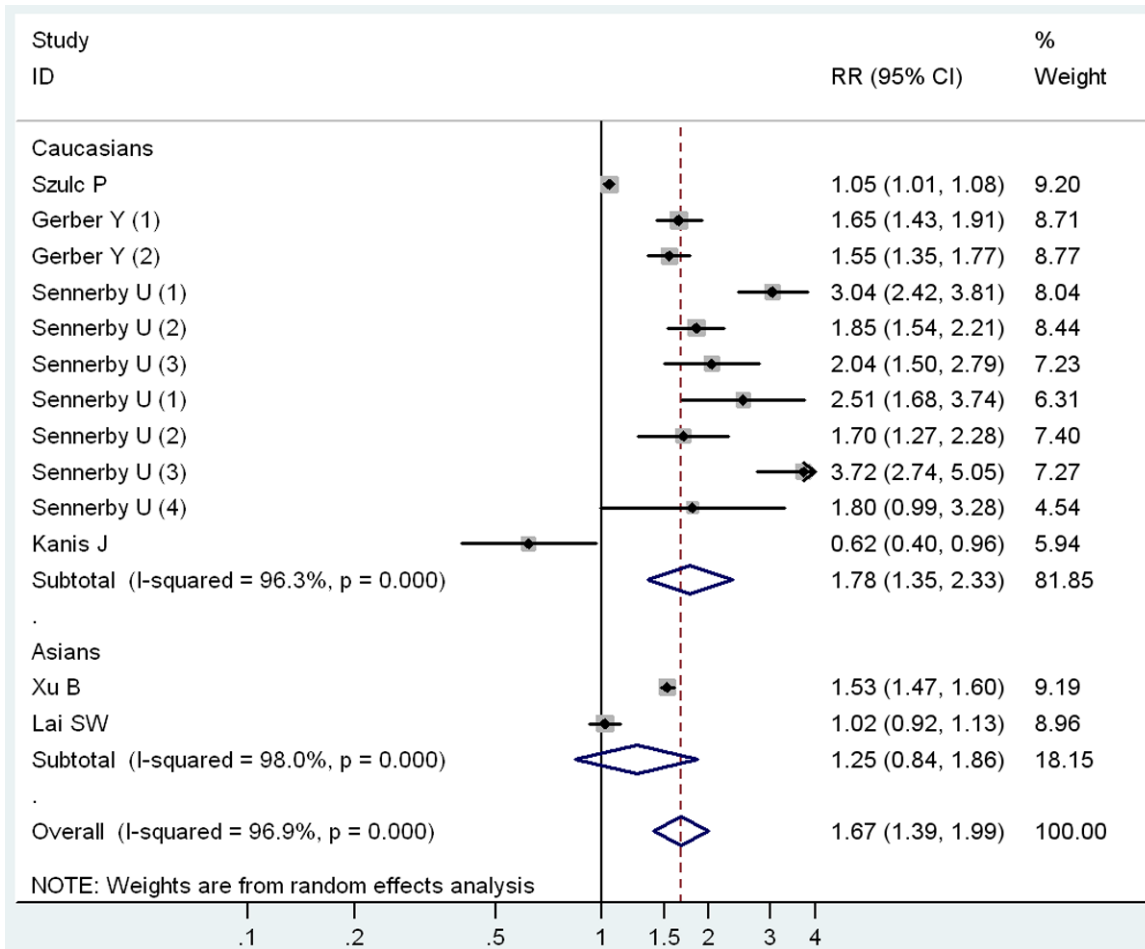


Figure 2. Increased risk of hip fracture associated with cardiovascular disease among Caucasians but not Asians.

ture was related to this kind of disease among Caucasians. However, significantly positive association was observed between CVD and the risk of hip fracture in another Caucasian population [16]. We found that CVD conferred risk effect on the development of hip fracture among Caucasians but not Asians. Nonetheless, there were only two eligible studies estimating the relationship of CVD with hip fracture risk among Asians. At all events, genetic backgrounds, specific environmental exposures and other racial discrepancies should be widely considered. Aside from ethnicity, the role of CVD in hip fracture development may be influenced by gender, which is an underlying confounding factor since gender discrepancy is large in the incidence rates of CVD and hip fracture. Although Gerber Y et al. supported the hypothesis that the risk of hip fracture was not specific to CVD [16], it should be interpreted with caution when determining the modifying

effects of different CVD on subsequent hip fracture risk. More future studies are warranted to further elucidate these questions.

Some limitations must be taken into account when interpreting the pooled results in the present meta-analysis. First, as mentioned above, studies conducted among the Asian population were insufficient for a precise estimate. More studies with large sample size are warranted for better elucidation. Second, the adjusted or matching factors in each study were diverse, which might be confusing for evaluation. Third, there was significant heterogeneity in this study. The source of between-study heterogeneity might be attributed to the different ethnicity of study subjects and study design in independent studies. Therefore, more studies with high quality are warranted for further investigation. Last but not least, confounding factors including sex, age, and specific CVD,

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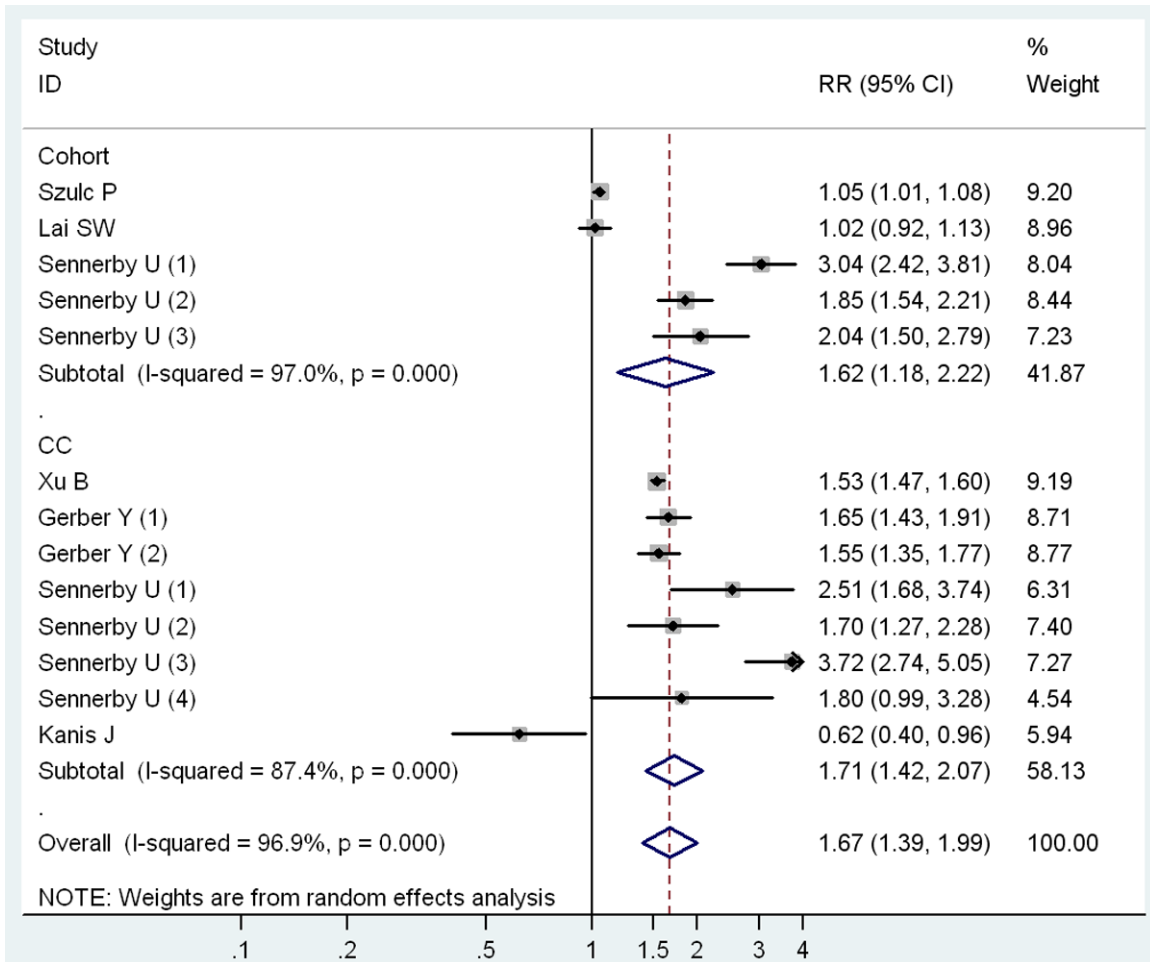


Figure 3. Increased risk of hip fracture associated with cardiovascular disease in both case-control and cohort studies.

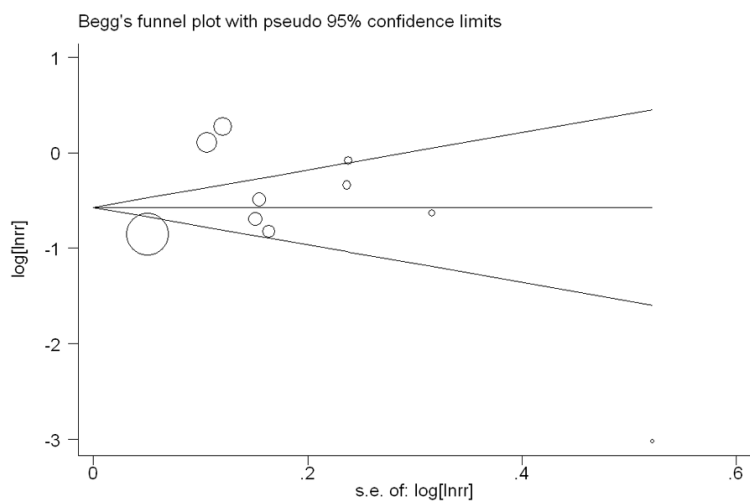


Figure 4. Begg's funnel plots for the determination of publication bias risk ($P_{\text{Egger's test}} = 0.6$).

should be considered when investigating the influence of CVD on hip fracture development in future studies.

In summary, the current meta-analysis firstly provides strong evidence for a risk effect of cardiovascular disease on hip fracture, particularly in the Caucasian population. Nevertheless, the association between specific CVD and the risk of hip fracture warrants close attention. More relevant studies with high quality are needed for further investigation in the future.

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Disclosure of conflict of interest

None.

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