

Association between hypertension and risk of knee osteoarthritis

A meta-analysis of observational studies

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Abstract

Evidence from observational studies shows that hypertension may be a risk factor for knee osteoarthritis (OA). However, the relationship between hypertension and knee OA risk remains controversial. This study aimed to quantitatively assess the relationship between hypertension and risk of knee OA.

Three electronic databases (PubMed, Embase, and Cochrane Library) were searched up to July 25, 2016. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were extracted from the included observational studies. Publication bias, heterogeneity test, and subgroup analyses were performed.

Eight studies including 2 cohort studies and 6 cross-sectional studies with 9762 participants were finally included in this meta-analysis. The results showed that hypertension was significantly associated with higher radiographic knee OA and symptomatic knee OA risks of 2.01 (95% CI, 1.28–3.15, $I^2=90.2\%$, P for heterogeneity $<.001$) and 1.49 (95% CI, 1.26–1.77, $I^2=0\%$, P for heterogeneity $<.412$), respectively. No publication bias was detected. The subgroup analysis showed that the study design did not influence the results (radiographic knee OA: OR=1.42, 95% CI, 1.19–1.71 for cross-sectional studies and OR=2.17, 95% CI, 1.30–3.63 for cohort studies; and symptomatic knee OA: OR=1.85, 95% CI, 1.10–3.13) for cross-sectional studies and OR=2.74, 95% CI, 1.81–4.16 for cohort studies).

This meta-analysis showed that there was a significant relationship between hypertension and knee OA (both radiographic and symptomatic). However, further original studies are needed that use a better design.

Abbreviations: CI = confidence interval, OA = osteoarthritis, OR = odds ratio.

Keywords: hypertension, knee osteoarthritis, meta-analysis, risk

1. Introduction

Osteoarthritis (OA), a severe joint disease, is the 6th leading cause of disability worldwide and a major cause of restricted activity, disability, and low quality of life.^[1] OA is predicted to advance to the 4th leading cause of disability in 2020.^[1–3] The prevalence of knee OA is 3.6% of the total population (nearly 250 million people), while the prevalence of painful disabling knee OA is nearly 35% in adults >60 years of age.^[4–7] Moreover, knee OA may substantially contribute to higher therapeutic costs, the mean of which exceeds \$12,000 annually.^[4–7] However, therapies for knee OA are complicated, and joint replacement is the final choice.^[4–7] Therefore, finding the independent risk factors of knee OA may offer potential preventive insight.

Hypertension, a component of metabolic syndrome and an independent risk factor for cardiovascular and cerebrovascular disease, has been acknowledged as the 3rd leading cause of disability worldwide.^[8,9] In 2005, the National Health and Nutrition Examination Survey revealed that 65 million people in the United States suffered from hypertension.^[8,10] Accordingly, the total number of individuals with hypertension worldwide is predicted to reach 1.56 billion in 2025.^[11]

A new classification for phenotyping OA was recently suggested that includes metabolic syndrome, aging, and posttraumatic-related OA.^[12–14] In metabolic syndrome-related OA, obesity may be the major pathomechanism. However, observational studies have suggested that other components of metabolic syndrome, such as hypertension, may be independent risk factors for knee OA.^[15–22] Because of the conflicting results, the relationship between hypertension and knee OA remains controversial.^[15–22]

To our knowledge, the relationship between hypertension and the risk of knee OA has not been systematically evaluated. Therefore, here we conducted a meta-analysis of observational studies to quantitatively assess the relationship between hypertension and knee OA (radiographic and symptomatic).

2. Methods

We performed a systematic review and meta-analysis of the available studies according to MOOSE guidelines and the PRISMA statement.^[23,24] The ethical approval and written consent are not necessary for the meta-analysis, because the data of meta-analysis are collected from published literature.

Editor: Raouf Hajji.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:32(e7584)

Received: 6 January 2017 / Received in final form: 2 June 2017 / Accepted: 30 June 2017

<http://dx.doi.org/10.1097/MD.0000000000007584>

2.1. Literature search

We searched PubMed, EMBASE, and the Cochrane Library up to July 25, 2016 for observational studies, with no restrictions on language or publication year. All of the relevant observational studies were performed using medical subject headings or free text words. We followed combined medical subject headings and free text words search strategies by using follow search terms: (hypertension OR high blood pressure) AND (degenerative knee OR osteoarthritis OR knee osteoarthritis OR knee joint osteoarthritis). To find additional references, we manually searched the reference lists of all retrieved studies and published reviews and included all identified relevant articles in the analysis.

2.2. Selection criteria

We evaluated all studies independently that presented quantitative evaluations of the relationship between hypertension and the risk of knee OA; the studies that met selection criteria were included in this meta-analysis. Studies were included in the meta-analysis according to PICO's criteria:

- (1) P: adult patients with radiographic or symptomatic knee OA. Kellgren–Lawrence grade is scored on AP view radiograph, joint space narrowing and osteophytes were scored on lateral view radiographs. A knee is defined as having ROA in the tibiofemoral joint if it had Kellgren and Lawrence grade >2 on the AP view, and as having ROA in the patellofemoral joint if it had any osteophyte grade >2, or any osteophyte grade >1 plus joint space narrowing grade >2 in the patellofemoral joint on the lateral view.^[25–27] Symptomatic knee OA defined as the presence of knee pain and at least 1 knee with a K/L grade 2. Adult patients definite age ≥18 years.^[27,28]
- (2) I: any definition of hypertension, the detail definition is given in Table 1.
- (3) C: patients without hypertension.
- (4) O: relative risks, odds ratios (ORs), and their corresponding 95% confidence intervals (CIs) specifically provided or sufficient data present to compute them.

(5) S: study design were observational studies, included the cross-sectional studies, cohort studies, or case–control studies.

If several reports described the same study, we chose the most recent report as the main report, which typically was the latest full-text publication in a peer-reviewed journal.^[29] We excluded letters, comments, reviews, and meta-analyses.

2.3. Data extraction and quality assessment

Two authors extracted the data from each study independently by using a standardized data collection form. The standardized data collection form included the 1st author's name, year of publication, country, study design, age and sex breakdown of the study population, sample size, knee OA type, and hypertension definition. Any disagreements were resolved through consensus.

We utilized the Cross-Sectional/Prevalence Study Quality Scale recommended by the Agency for Healthcare Research and Quality (AHRQ)^[30] to assess cross-sectional study quality. The AHRQ scale is a qualitative 11-item tool that is used to evaluate quality using questions with possible “Yes,” “No,” and “Unclear” answers. It means moderate risk of bias, if a study with more than 3 “YES.”^[31] We also utilized the 9-star Newcastle-Ottawa Scale to assess case–control and cohort study quality; any study with ≥7 stars was considered of high quality.^[32]

2.4. Statistical analysis

ORs were calculated as effect sizes to measure the association between hypertension and the risk of knee OA in the general population. As in prior studies, the multivariable-adjusted relative risks were transformed into ORs.^[33,34] The potential interstudy heterogeneity was examined via Q ^[28] and I^2 statistics.^[35] A P value for heterogeneity of <0.1 or I^2 of >50% indicated that the heterogeneity was statistically significant. Thus, the random-effects model was used to perform the analysis. Otherwise, we computed the summary effect using the fixed-effect model. Subgroup analyses were performed by variables including area, study design, hypertension definition,

Table 1

Characteristics of each included study.

Author, y	Country	Design	Age, y	Sample size	Sex	Type of knee OA	HT definition	OR (95%CI)	Adjusted factors
Bagge, 1991	Sweden	CSS	79	340	M&F	Radiographic	c	0.96 (0.73, 1.27)	BMI
Hart, 1995	UK	CSS	54.2 (45–64)	979	F	Radiographic	a	1.28 (0.76, 2.16)	Age and BMI
					F	Symptomatic	1.10 (0.53, 2.26)		
Inoue, 2011	Japan	CSS	58.3 (12.0)	295	M	Radiographic	b	2.04 (1.08, 3.84)	Crude
			59.5 (10.4)	500	F	Radiographic		5.09 (3.38, 7.67)	
Liu, 2016	China	CSS	40–74	1661	M	Symptomatic	a	1.48 (1.13, 1.93)	Crude
			40–74	1767	F	Symptomatic		1.42 (1.10, 1.84)	
Maddah, 2015	Iran	CSS	55.46 (11.6)	125	M	Radiographic	a	1.41 (0.54, 3.67)	Crude
			54.44 (12.1)	500	F	Radiographic		3.70 (2.51, 5.44)	
Shin, 2014	Korea	CSS	63.4	2363	M&F	Radiographic	a	1.10 (0.89, 1.36)	Age, sex, income, smoking, alcohol consumption, PA, and BMI
Kim, 2010	Korea	CS	70.2 (8.0)	504	M&F	Radiographic	a	2.74 (1.66, 4.54)	Crude
						Symptomatic		2.17 (1.30, 3.63)	
Yoshimura, 2012	Japan	CS	63.9 (11.8)	728	M&F	Radiographic	b	2.74 (1.30, 5.78)	Age, gender, region, smoking, alcohol, bicycling, exercise, history of knee injuries, overweight, dyslipidaemia, and IGT

a, SBP of ≥140 mm Hg or DBP of ≥90 mm Hg or regular use of antihypertensive medication; b, SBP ≥130 mm Hg or DBP ≥85 mm Hg, or under treatment for hypertension; c, DBP ≥110 mm Hg or regular use of antihypertensive medication. BMI = body mass index, CS = cohort study, CSS = cross-sectional study, DBP = diastolic blood pressure, F = female, HT = hypertension, IGT = impaired glucose tolerance, M = male, OA = osteoarthritis, PA = physical activity, SBP = systolic blood pressure.

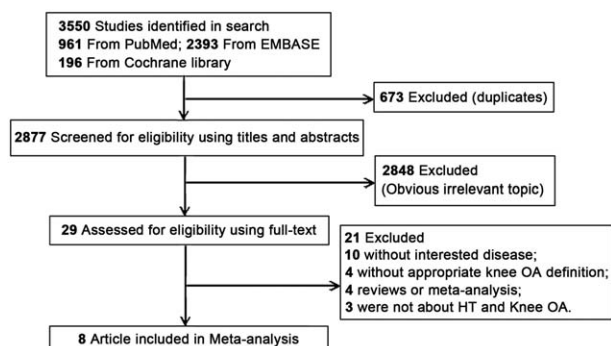


Figure 1. Literature search and study selection.

sex, and whether the data were adjusted (Yes or No). Publication bias was assessed using Egger test.^[36] The meta-analysis was conducted using Stata version 11.0 (Stata Corporation, College Station, TX). Values of $P < .05$ were considered statistically significant.

3. Results

Figure 1 shows the study selection procedure. A total of 3550 studies were included from the primary electronic database search: 961 from PubMed, 393 from EMBASE, and 196 from the Cochrane library. After the assessment for duplicates, 637 studies were excluded. After title and abstract screening, 2848 studies were excluded for obvious irrelevance, while 29 articles remained. After full-text screening, 21 studies were excluded because for not examining the disease of interest ($n=10$), not appropriate knee OA definition ($n=4$), being reviews or meta-analyses ($n=4$), or not examining hypertension and knee OA ($n=3$). Finally, 8 studies^[15–22] with a total of 9762 participants were included in the current meta-analysis.

3.1. Study characteristics

Table 1 shows the characteristics of the included 8 studies: 2 were prospective cohort studies,^[18,22] while the other 6 were cross-sectional studies.^[15–17,19–21] Two of the 8 studies reported data for both radiographic and symptomatic knee OA^[16,18]; 5 reported data for radiographic knee OA only^[15,17,20–22] and only 1 reported data for symptomatic knee OA only.^[19] The studies were performed in 6 different countries (2 each in Japan^[17,22] and Korea^[18,21] and 1 each in China,^[19] Sweden,^[15] the UK,^[16] and Iran^[20]). Seven studies included men and

women,^[15,17–22] while the other included only women.^[16] Five studies^[16,18–21] definite hypertension as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or regular use of antihypertensive medication; 2 studies^[17,22] definite hypertension as a systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or under treatment for hypertension; and only 1 study^[15] definite hypertension as a diastolic blood pressure ≥ 110 mmHg or regular use of antihypertensive medication. All of the included studies were of moderate to high quality (Tables 2 and 3).

3.2. Main analyses

Figure 2 shows the results of the relationship between hypertension and the risk of symptomatic knee OA. Hypertension was significantly associated with a higher symptomatic knee OA risk of 1.49 (95% CI, 1.26–1.77) with no interstudy heterogeneity ($I^2=0\%$, P for heterogeneity $< .412$).

Figure 3 shows the results of the relationship between hypertension and the risk of radiographic knee OA. The results showed that hypertension was significantly associated with a higher radiographic knee OA risk of 2.01 (95% CI, 1.28–3.15), with high interstudy heterogeneity ($I^2=90.2\%$, P for heterogeneity $< .001$).

3.3. Subgroup analyses

Table 4 shows the results of the subgroup analyses of the relationship between hypertension and the risk of radiographic and symptomatic knee OA. For symptomatic knee OA, the subgroup analyses were assessed according to area, design, hypertension definition, sex, and adjusted factors. In the subgroup analysis by area, the OR was 1.52 (95% CI, 1.27–1.81) for Asian countries and 1.10 (95% CI, 0.53–2.27) for Western countries. In the subgroup analysis by study design, the OR was 2.17 (95% CI, 1.30–3.63) for cohort studies and 1.42 (95% CI, 1.19–1.71) for cross-sectional studies. In the subgroup analysis by sex, the OR was 2.17 (95% CI, 1.30–3.63) for both men and women, 1.48 (95% CI, 1.13–1.93) for men only, and 1.38 (95% CI, 1.08–1.76) for women only.

For radiographic knee OA, the subgroup analyses were assessed by area, design, hypertension definition, sex, and adjusted factors. In the subgroup analysis by area, the OR was 2.42 (95% CI, 1.39–4.23) for Asian countries and 1.02 (95% CI, 0.80–1.31) for Western countries. In the subgroup analysis by study design, the ORs were 2.74 (95% CI, 1.81–4.16) for cohort studies and 1.85 (95% CI, 1.10–3.13) for cross-sectional studies. In the subgroup analysis by sex, the OR was 1.53 (95% CI,

Table 2
Methodological quality of cross-sectional studies included in the meta-analysis.

Author	Public Year	1	2	3	4	5	6	7	8	9	10	11
Bagge	1991	+	+	+	+	–	0	+	+	–	0	–
Hart	1995	+	+	–	+	–	–	+	+	–	–	–
Inoue	2011	+	+	+	+	–	–	+	–	–	–	–
Liu	2016	+	+	+	+	–	–	+	–	–	0	–
Maddah	2015	+	+	+	+	–	–	+	–	–	–	–
Shin	2014	+	+	+	+	–	–	+	+	–	–	–

+: Yes; –: No; 0: not clear. 1, Define the source of information (survey, record review); 2, List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; 3, Indicate time period used for identifying patients; 4, Indicate whether or not subjects were consecutive if not population-based; 5, Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; 6, Describe any assessments undertaken for quality assurance purposes (eg, test/retest of primary outcome measurements); 7, Explain any patient exclusions from analysis; 8, Describe how confounding was assessed and/or controlled; 9, If applicable, explain how missing data were handled in the analysis; 10, Summarize patient response rates and completeness of data collection; and 11, Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

Table 3
Methodological quality of case-control studies included in the meta-analysis*.

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor [†]	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts [‡]	Total quality scores
Kim	☆	☆	☆	☆	–	–	–	☆	5
Yoshimura	☆	☆	☆	☆	☆☆	☆	–	☆	8

* A study could be awarded a maximum of one star for each item except for the item control for important factor or additional factor.

[†] A maximum of 2 stars could be awarded for this item.

[‡] A cohort study with a follow-up rate >75% was assigned 1 star.

0.97–2.40) for both men and women, 1.82 (95% CI, 1.07–3.09) for men only, and 2.94 (95% CI, 1.40–6.16) for women only.

3.4. Publication bias

Egger tests suggested nonsignificant publication bias for the association between hypertension and radiographic knee OA ($P=.172$) and symptomatic knee OA ($P=.855$).

4. Discussion

The new classification for phenotyping OA, including metabolic syndrome, aging, and posttraumatic-related OA, has been certified by epidemiological studies.^[12–14] However, the relationship between each component, such as hypertension, of metabolic syndrome and OA requires further investigation. Therefore, this meta-analysis has systematically gathered the peer-reviewed evidence regarding the role of hypertension in the development of knee OA. Eight studies including 2 cohort studies and 6 cross-sectional studies with a total of 9762 participants were finally included in this meta-analysis.

Regarding the explanation for the associations between hypertension and knee OA risk, Hart et al^[16] found that metabolic factors such as hypertension, blood glucose, and

hypercholesterolemia were associated with knee OA independent of obesity. Puenpatom and Victor^[37] reported that the component factors of metabolic syndrome (MetS), including hypertension, abdominal obesity, and hyperglycemia, were more prevalent in the population with OA than in that without OA.^[38] OA and MetS share the same mechanisms of inflammation, obesity increased mass and joint load and altered proinflammatory factor adipokines secretion, leading to the chronic low grade inflammatory status in joint tissues. Additionally, cholesterol accumulation in the cartilage can impair the efflux function of cartilage, hence inducing OA.^[39,40]

In order to found the confound factors, the subgroup analysis of studies included in the meta-analysis were performed. Subgroup analysis shown that the area (Asian vs Western), the definition of hypertension, and adjusted analysis might confounded the association between hypertension and knee OA.

However, the precise mechanism of this relationship is unclear. Hypertension and OA are both highly prevalent diseases. Some studies suggest that there may be several shared risk factors implicated in the plausible mechanisms of the relationship between hypertension and knee OA.^[41,42] One possible explanation for the relationship between hypertension and knee OA is shared traditional risk factors, such as aging, obesity, and chronic

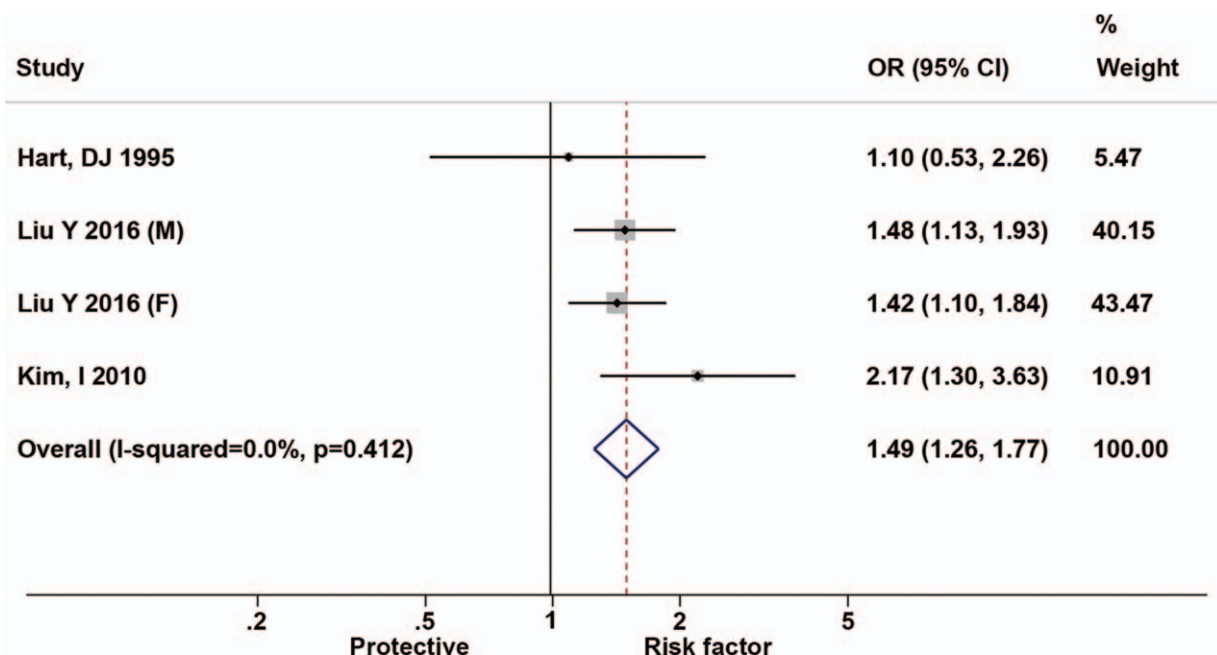


Figure 2. Forest plots for odds ratios of the association between hypertension and risk of symptomatic knee osteoarthritis.

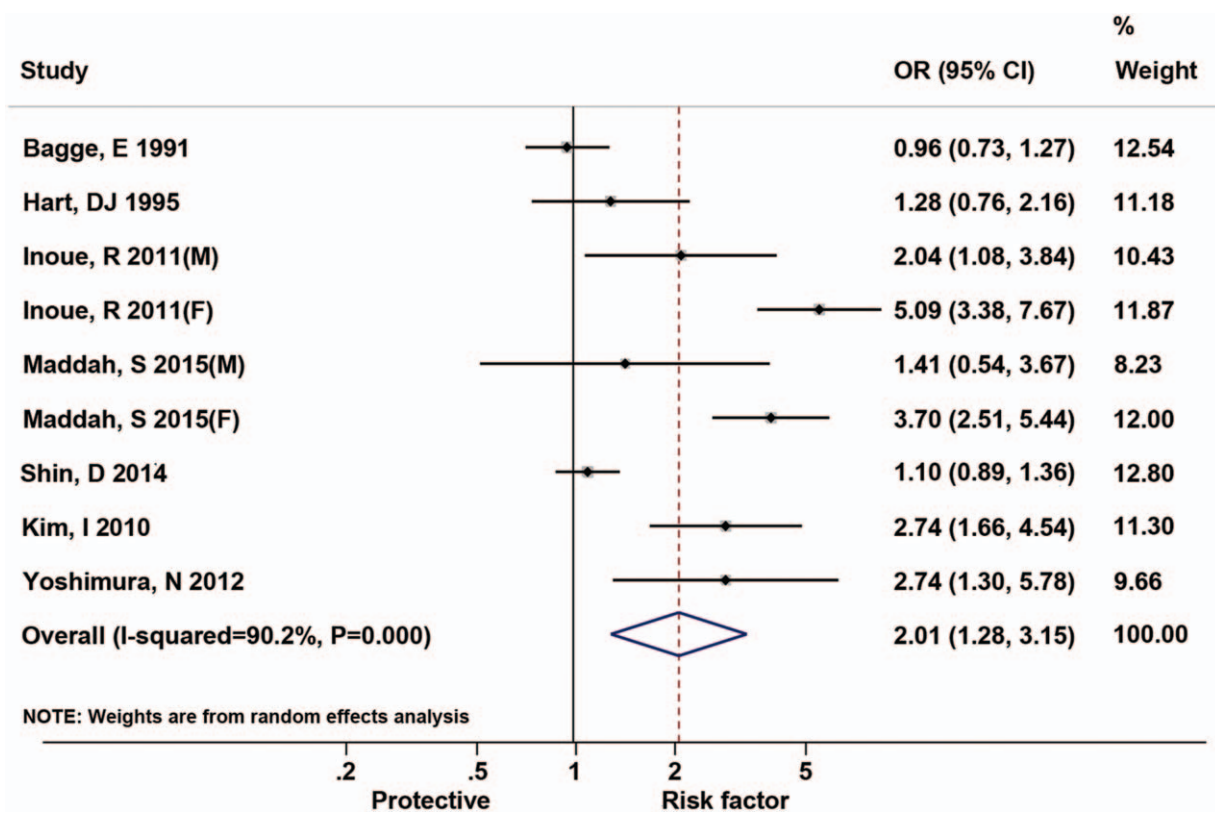


Figure 3. Forest plots for odds ratios of the association between hypertension and risk of radiographic knee osteoarthritis.

inflammation.^[2,9,43,44] Moreover, some studies have proven that multiple genes are involved in both hypertension and knee OA. The proinflammatory cytokine interleukin-6 plays an important role in hypertension and knee OA.^[45-48] During bone resorption and formation, OPG and LDL Receptor Related Protein 6 play an

important role in the OPG/receptor activator of nuclear factor kappa-B ligand (RANKL) and Wnt signaling pathways.^[48,49] Both OPG and LDL Receptor Related Protein 6 were shown to be associated with hypertension as well.^[49] In addition, some studies showed that polymorphisms in the vitamin D receptor

Table 4

Subgroup analysis of studies included in the meta-analysis.

Subgroup	Symptomatic knee OA					Radiographic knee OA				
	n	OR (95%CI)	P_H	I^2 , %	P_A	n	OR (95%CI)	P_H	I^2 , %	P_A
Total	4	1.49 (1.26, 1.77)	.412	0.0	<.001	9	2.01 (1.28, 3.15)	<.001	90.2	.002
Area										
Asian	3	1.52 (1.27, 1.81)	.341	7.1	<.001	7	2.42 (1.39, 4.23)	<.001	90.4	.002
Western	1	1.10 (0.53, 2.27)	-	-	.797	2	1.02 (0.80, 1.31)	.340	0.0	.858
Design										
CSS	3	1.42 (1.19, 1.71)	.753	0.0	<.001	7	1.85 (1.10, 3.13)	<.001	92.0	.021
CS	1	2.17 (1.30, 3.63)	-	-	.003	2	2.74 (1.81, 4.16)	1.0	0.0	<.001
HT definition										
a	4	1.49 (1.26, 1.77)	.412	0.0	<.001	5	1.84 (1.04, 3.28)	<.001	88.6	.038
b	0	-	-	-	-	3	3.20 (1.75, 5.84)	.042	68.4	<.001
c	0	-	-	-	-	1	0.96 (0.73, 1.27)	-	-	.773
Gender										
M&F	1	2.17 (1.30, 3.63)	-	-	.003	4	1.53 (0.97, 2.40)	<.001	83.5	.065
F	2	1.38 (1.08, 1.76)	.515	0.0	.009	3	2.94 (1.40, 6.16)	<.001	88.4	.004
M	1	1.48 (1.13, 1.93)	-	-	.004	2	1.82 (1.07, 3.09)	.529	0.0	.026
Adjusted										
Yes	1	1.10 (0.53, 2.27)	-	-	.797	4	1.20 (0.90, 1.59)	.072	57.0	.215
No	3	1.52 (1.27, 1.81)	.341	7.1	<.001	5	3.04 (2.08, 4.45)	.035	61.3	<.001

a, SBP of ≥ 140 mm Hg or DBP of ≥ 90 mm Hg or regular use of antihypertensive medication; b, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, or under treatment for hypertension; c, DBP ≥ 110 mm Hg or regular use of antihypertensive medication. CI=confidence interval, CS=cohort study, CSS=cross-sectional study, DBP=diastolic blood pressure, F=female, HT=hypertension, M=male, n=number of study, OA=osteoarthritis, OR=odds ratio, P_A =P value of association, P_H =P value of heterogeneity, SBP=systolic blood pressure.

may be associated with low bone mineral density, OA, and hypertension.^[27,50–53]

Our study has several advantages. First, this is the 1st meta-analysis to evaluate the relationship between hypertension and the risk of knee OA. We did a comprehensive search and included a large number of participants (9762 total). Therefore, the statistical power of this study is sufficient. Second, we extracted the data, preformed the analysis, independently evaluated study quality, and resolved disagreements by consensus to minimize bias. Third, all types of observational studies were included in the meta-analysis, and the result of publication bias test was nonsignificant.

Our meta-analysis has some limitations. First, due to the inclusion of observational studies, confounding factors were inherent and the risk estimates may be exaggerated or underestimated. Second, the use of medicine (s) for hypertension were not described in the included studies, whether antihypertension or diuretic drugs, which might offer a further explanation for the relationship. Third, we did not conduct a subgroup analysis of knee OA stage, so a further study is required to investigate the relationship between hypertension and the risk of different knee OA stages. Finally, heterogeneity may have been introduced in this meta-analysis by the methodological differences among the included studies, which may reduce the strength of our conclusions.

In conclusion, this meta-analysis showed a significant relationship between hypertension and knee OA (radiographic and symptomatic). However, a study that is community-based, well-powered, and primarily designed for the target question should be considered in the future to identify true association.

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