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Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies

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ABSTRACT

Background: Knee osteoarthritis (OA) is a major cause of disability in the elderly, however, there are few studies to estimate the global prevalence, incidence, and risk factors of knee OA.

Methods: For this study, we searched PUBMED, EMBASE and SCOPUS from inception to April 4, 2020, without language restriction. We identified eligible studies with information on the prevalence or incidence of knee OA in population-based observational studies and extracted data from published reports. We did random-effects meta-analysis to generate estimates. This study was registered with PROSPERO (CRD42020181035).

Findings: Out of 9570 records identified, 88 studies with 10,081,952 participants were eligible for this study. The pooled global prevalence of knee OA was 16·0% (95% CI, 14·3%-17·8%) in individuals aged 15 and over and was 22·9% (95% CI, 19·8%-26·1%) in individuals aged 40 and over. Correspondingly, there are around 654·1 (95% CI, 565·6–745·6) million individuals (40 years and older) with knee OA in 2020 worldwide. The pooled global incidence of knee OA was 203 per 10,000 person-years (95% CI, 106–331) in individuals aged 20 and over. Correspondingly, there are around annual 86·7 (95% CI, 45·3–141·3) million individuals (20 years and older) with incident knee OA in 2020 worldwide. The prevalence and incidence varied substantially between individual countries and increased with age. The ratios of prevalence and incidence in females and males were 1·69 (95% CI, 1·59–1·80, $p<0·00$) and 1·39 (95% CI, 1·24–1·56, $p<0·00$), respectively.

Interpretation: Our study provides the global prevalence (16·0% [95% CI, 14·3%-17·8%]) and incidence (203 per 10,000 person-years [95% CI, 106–331]) of knee OA. These findings can be used to better assess the global health burden of knee OA. Further prospective cohort studies are warranted to identify modifiable risk factors for providing effectively preventive strategies in the early stages of the disease.

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1. Introduction

Knee osteoarthritis (OA) is a common progressive multifactorial joint disease and is characterized by chronic pain and functional disability [1]. Knee OA accounts for almost four fifths of the burden of OA worldwide and increases with obesity and age [2]. Up to now, knee OA is incurable except knee arthroplasty which is considered as an effective treatment at an advanced stage of the disease, however, which is responsible for substantial health costs [3]. Many researchers have shifted their focus to the prevention and treatment in the early stage of the disease [4]. Accordingly, it is essential to understand the prevalence, incidence, and modifiable risk factors of knee OA for providing effectively preventive strategies.

The World Health Organization, the International League Against Rheumatism, and global OA experts have made substantial efforts over the past few decades, many population-based epidemiological studies of knee OA have been conducted worldwide [5]. Exploring the differences of prevalence, incidence, and risk factors of knee OA in age, gender, region, and others can help us better understand the potential etiology of knee OA. However, there is a paucity of the epidemiologic data of knee OA in the global population. The Global Burden of Disease (GBD) study 2017 and recent several reviews assessed the epidemiological characteristics of knee OA, but they still used data published before 2000 [6,7]. Moreover, the main objective of the GBD study was to assess the burden of OA. Furthermore, the GBD study 2017 only included the symptomatic knee OA which was radiologically confirmed, which tended to collect relatively late cases, because there is discordance between symptomatic and radiographic changes. The early painful patients with knee OA may be not suffer from radiographic changes. On the contrary, the patients with severe

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Research in context

Evidence before this study

To our knowledge, only the Global Burden of Disease Study estimated the global prevalence and incidence of osteoarthritis (OA) from 2000 onwards. The latest estimate was in 2017.

Added value of this study

We included 88 studies for this systematic review and meta-analysis, of which 18 studies were published from 2017 to 2020. We found that the global prevalence of knee OA was 16·0% (95% CI, 14·3%–17·8%) in individuals aged 15 and over and was 22·9% (95% CI, 19·8%–26·1%) in individuals aged 40 and over. Correspondingly, there are around 654·1 (95% CI, 565·6–745·6) million individuals (40 years and older) with knee OA in 2020 worldwide. We found that the global incidence of knee OA was 203 per 10,000 person-years (95% CI, 106–331) in individuals aged 20 and over. Correspondingly, there are around annual 86·7 (95% CI, 45·3–141·3) million individuals (20 years and older) with incident knee OA in 2020 worldwide. The ratios of prevalence and incidence in females and males were 1·69 (95% CI, 1·59–1·80, $p<0{\cdot}00$) and 1·39 (95% CI, 1·24–1·56, $p<0{\cdot}00$), respectively. We also assessed risk factors, the results showed that the prevalence and incidence increased with age, peaked at the advanced age on prevalence and at 70–79 years old on incidence; increasing education attainment was negatively associated with the prevalence of knee OA.

Implications of all the available evidence

Global health-care providers, policy makers, and the general public should be aware of the high prevalence of knee OA and the modifiable risk factors such as obesity, injury, and education. More efforts should be made to explore the cause of the high prevalence and incidence of knee OA in women and elderly and provide effectively preventive strategies in the early stages of the disease.

radiographic changes may not have any symptoms [8]. The possible explanations are that structural changes on radiographs may not have a nociceptive innervation and the experience of pain is related to many factors such as tolerance and susceptibility. In general, the patient with both radiographic changes and symptoms is usually considered to be more severe. Accordingly, only either symptomatic or radiological knee OA may occur earlier than the radiologically confirmed symptomatic knee OA, and the former may provide more opportunities for disease prevention. Even Du H et al. found that almost a quarter of patients with the radiographic OA, but no symptoms, complained of disability [9]. Moreover, with the changes of demographic structure and lifestyle, the epidemiological data of knee OA are also changing. Wallace IJ et al. demonstrated that the prevalence of knee OA has doubled since the mid-20th century in the United States [10]. Consequently, investigating the contemporary epidemiology of knee OA is considerably important. However, it is time-consuming, expensive, and difficult to examine the prevalence or incidence of knee OA in large-scale population.

Therefore, we quantitatively synthesized the published epidemiological data of knee OA in individual country to estimate the global, regional prevalence of knee OA from 2000 to 2020, to estimate the global, regional incidence of knee OA from 1990 to 2020, and to identify risk factors of knee OA, aiming to produce more accurate and up-to-date evidence-based information for health-care providers and policy makers.

2. Methods

2.1. Search strategy and selection criteria

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline, and Guidelines for Accurate and Transparent Health Estimates Reporting: The GATHER Statement [11–13]. The protocol of this study was preregistered in the PROSPERO database (CRD42020181035).

The criteria for study inclusion are as follows: an original study reporting the prevalence or incidence of knee OA; a study examining radiographical (femorotibial), symptomatic, or self-report knee OA; a cross-sectional or longitudinal observational study; a population-based study; on prevalence, a study collecting data from 2000 onwards; on incidence, a study collecting data from 1990 onwards. In addition, several studies reporting register primary care data [14–16] and claims data [17] were included, because those data were a close representation of the national population and had been validated [18,19]. Studies are excluded: examined individuals only with radiographically patellofemoral OA; diagnosed knee OA by MRI and ultrasonography; a hospital-based study; used sample sizes less than 150.

Two researchers (CAY, LHZ) searched PUBMED, EMBASE, and SCOPUS from inception to April 4, 2020 using search terms defined according to PECOS (participants, exposure, control, outcome, study) principle (Appendix 1.1–3), without limitation in language. We also identified reference lists of relevant systematic reviews and included studies, but we did not search gray literature. To select eligible studies, we firstly used endnote software (version 19·0) to remove duplicates from different bibliographic databases. Then two investigators (CAY, LHZ) independently screened titles and abstracts of remaining literature search records and assessed all potential eligible articles against the inclusion and exclusion criteria. The two researchers (CAY, LHZ) and another professor (LHD) discussed together to resolve any discrepancy in the process of selecting studies.

2.2. Data analysis

Two investigators (CAY, LHZ) extracted data from published reports. We extracted the data related to prevalence and risk factors of knee OA (sample sizes, the number of cases of knee OA) and the data related to incidence of knee OA (sample sizes at risk, the number of cases of incident knee OA, follow-up time, person-years at risk). Where several studies used data from the same study cohort, we only analyzed one study that presented the most comprehensive and latest data.

The primary outcome of this study are the prevalence and incidence of knee OA. The prevalence of knee OA is defined as a proportion, namely, the number of cases of knee OA divided by the sample sizes. The incidence equals the number of cases of incident knee OA divided by the person-years at risk. Concomitantly, we also estimated the global number of individuals with knee OA (40 years and older) and with incident knee OA (20 years and older) in 2020 according to world population prospects obtained from the UN Population Division [20]. The secondary outcome are risk factors (age, gender, area of residence, cigarettes, and education level) of knee OA, and the relationships between risk factors and the prevalence and incidence of knee OA are expressed by risk ratios (RRs).

We assessed the quality of prevalence studies using the risk of bias tool developed by Hoy D et al., which includes 10 items and a summary assessment [21]. And we assessed the quality of incidence studies using risk of bias tool designed by ourselves according to previously validated quality assessment tools, which includes 6 items and a summary assessment. Two raters (CAY, LHZ) independently assessed each item and any discrepancy was resolved by consensus. Finally, we used Revman software (version 5·3) to visualize the results.

We analyzed heterogeneity using the I^2 statistic. To explore the source of heterogeneity, we firstly conducted subgroup analysis according to the characteristics of studies, the classification are as follows: location (continent, country); definition (radiological, symptomatic, and self-report knee OA); sex (female, male); age. Then we performed sensitively analysis to explore the impact of individual study on the overall effects. Univariate meta-regression models were further used to assess the associations between the characteristics of studies and the pooled prevalence and incidence of knee OA. We qualitatively and quantitatively detected publication bias using funnel plots and the Egger linear regression test, respectively [22].

We used R software (version 4·0) and Stata software (version 15·1) to conduct the meta-analysis. Considering the anticipated high heterogeneity of the observational studies, we employed random-effects model to generate estimates. To stabilize variances, study data were transformed using the Freeman-Tukey double arcsine transformation [23]. All results were generated accompanying 95% confidence interval (CI). A 2-sided P value $< 0·05$ was considered statistically significant in all analyses.

2.3. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

In total, 9570 citations were retrieved, of which 4044 were duplicated articles and 5438 were ineligible for inclusion criteria, of 88 remaining articles were included for this meta-analysis. The process of selecting studies was showed in Fig. 1.

We finally conducted the present meta-analysis based on 88 articles with 10,081,952 participants, of those, 73 prevalence studies were showed in Table 1, 17 incidence studies were showed in Table 2. Those studies were from six continents (47 in Asian (144,838 participants), 23 in Europe (9,042,232 participants), 11 in North America (236,263 participants), five in South America (15,670 participants),

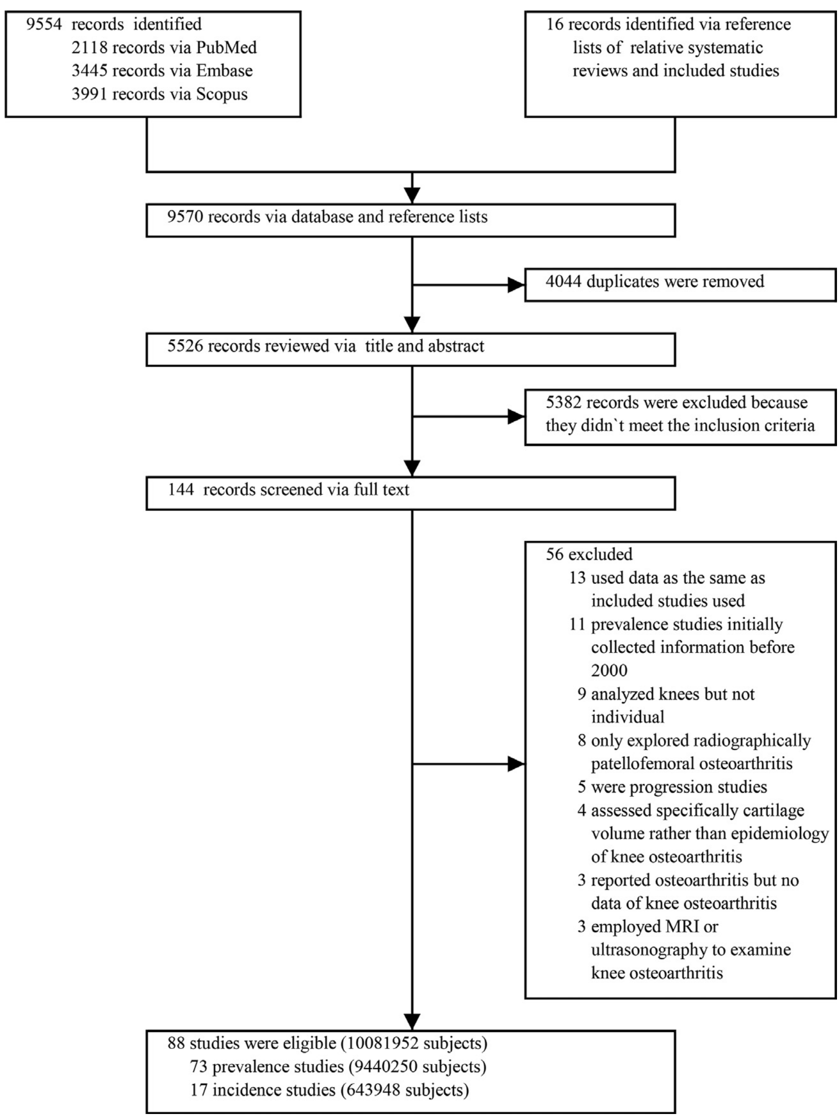

Fig. 1. PRISMA flow diagram.

Table 1
The summary characteristics of included prevalence studies.

	Countries	NO. of Total	NO. of knee OA	Age (Mean (SD); Rang (years))	BMI (kg/m2)	NO. of Female	Methods of Diagnosis	Time of Data Collection	Type of Study	Sampling Method	Type of Article
Zhang Y et al. 2001 [34]	China	1,781	692	≥60	25·7	1,051	KL≥2	2001	Cross-sectional	Random sampling	Full text
Zhang Y et al. 2001 [34]	China	1,781	199	≥60	25·7	1,051	KL≥2 and Symptomatic (pain)	2001	Cross-sectional	Random sampling	Full text
Minh Hoa TT et al. 2003 [35]	Vietnam	2,119	52	40 (17); 16–93	NA	1,138	ACR	2000	Cross-sectional	No random	Full text
Minaur N 2004 [36]	Australia	847	26	35 (13); 15–86	NA	446	Doctor-diagnosed	2002	Cross-sectional	All subjects were interviewed	Full text
Senna ER et al. 2004 [37]	Brazil	3,038	47	36 (16); 16–92	NA	1,929	ACR	2004	Cross-sectional	Probabilistic sampling	Full text
Du H et al. 2005 [9]	China	2,093	934	54; ≥40	22·9	1,099	KL≥2	2001	Cross-sectional	Random sampling	Full text
Du H et al. 2005 [9]	China	2,093	150	54; ≥40	22·9	1,099	KL≥2 and Symptomatic (pain)	2001	Cross-sectional	Random sampling	Full text
Haq SA et al. 2005 [38]	Bangladesh	5,077	441	>15	NA	2,517	ACR	2001	Cross-sectional	Random sampling	Full text
Kaçar C et al. 2005 [39]	Turkey	655	97	60 (8); >50	NA	306	ACR	2005	Cross-sectional	Cluster sampling	Full text
Salaffi F et al. 2005 [40]	Italy	2,155	116	58 (18); 18–91	25·1	1,151	ACR	2004	Cross-sectional	Random sampling	Full text
Wang W et al. 2006 [41]	China	1,450	176	≥40	NA	746	KL≥2	2005	Cross-sectional	Multiple stage cluster sampling	Abstract
Zeng QY et al. 2006 [42]	China	2,188	244	35–64	23·9	1,139	ACR	2005	Cross-sectional	House by house	Full text
Felson DT et al. 2007 [43]	USA	1,128	104	62; 34–90	27·4	NA	KL≥2	2005	Cross-sectional	No random	Full text
Tangtrakulwanich B et al. 2007 [44]	Thailand	506	234	59; >40	24·4	288	KL≥2	2007	Cross-sectional	Cluster stratified sampling	Full text
Davatchi F et al. 2008 [45]	Iran	10,291	1,532	>15	NA	5,413	Doctor-diagnosed	2004–2005	Cross-sectional	Multistage sampling	Full text
Grotle M et al. 2008 [46]	Norway	3,266	232	24–74	NA	1,786	Self-report doctor-diagnosed	2004	Cross-sectional	No random	Full text
Quintana JM et al. 2008 [47]	Spain	7,577	925	71 (7); 60–90	NA	4,264	ACR	2002–2003	Cross-sectional	Stratified random sampling	Full text
Joshi VL et al. 2009 [48]	India	8,145	451	>16	NA	NA	ACR	2004–2008	cross-sectional	House by house	Full text
Kang X et al. 2009 [49]	China	1,025	155	58 (8); >50	22·5	520	KL≥2	2005	Cross-sectional	Compact segment sampling	Full text
Kang X et al. 2009 [49]	China	1,026	109	58 (8); >50	22·5	520	KL≥2 and Symptomatic (pain)	2005	Cross-sectional	Compact segment sampling	Full text
Yoshimura N et al. 2009 [50]	Japan	3,040	1,660	70 (11); >40	23·0	1,979	KL≥2	2005–2007	Cross-sectional	Random sampling	Full text
Kim I et al. 2010 [51]	Korea	504	188	70 (8); >50	24·6	274	KL≥2	2007	Cross-sectional	No random	Full text
Kim I et al. 2010 [51]	Korea	504	121	70 (8); >50	24·6	274	KL≥2 and Symptomatic (pain)	2007	Cross-sectional	No random	Full text
Salve H et al. 2010 [52]	India	260	123	>40	NA	All female	ACR	2009	Cross-sectional	House by house	Full text
Cibere J et al. 2010 [53]	Canada	255	98	40–79	NA	173	K/L ≥ 2	2010	Cross-sectional	Multistage random sampling	Full text
Guillemin F et al. 2011 [54]	France	27,109	1,962	40–75	NA	18,111	KL≥2 and Symptomatic (pain)	2007–2009	Cross-sectional	Random sampling	Full text
Horváth G et al. 2011 [55]	Hungary	672	111	52; 20–67	NA	432	K/L ≥ 2	2011	Cross-sectional	No random	Full text
Namali H et al. 2011 [56]	Sri Lanka	1,750	207	≥50	NA	NA	ACR	2006–2007	Cross-sectional	Stratified cluster sampling	Abstract

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Table 1 (*Continued*)

	Countries	NO. of Total	NO. of knee OA	Age (Mean (SD); Rang (years))	BMI (kg/m2)	NO. of Female	Methods of Diagnosis	Time of Data Collection	Type of Study	Sampling Method	Type of Article
Cakır N et al. 2012 [57]	Turkey	4,952	265	≥40	NA	2,575	ARA	2012	Cross-sectional	No random	Full text
Chaaya M et al. 2012 [58]	Lebanon	3,530	106	38(17); 15–90	NA	1,730	ACR	2007	Cross-sectional	Multistage cluster sampling	Full text
Ajit NE et al. 2012 [59]	India	342	58	43 (17)	NA	NA	ACR	2011–2012	Cross-sectional	Stratified random sampling	Abstract
Jiang L et al. 2012 [60]	China	1,196	193	63 (9); 40–84	NA	623	KL≥2 and Symptomatic (pain)	2005	Cross-sectional	Stagestratified sampling	Full text
Sandoughi M et al. 2013 [61]	Iran	2,100	321	33 (15); >15	NA	1,179	ACR	2008–2009	Cross-sectional	Multistage cluster randomly sampling	Full text
Zhang J et al. 2013 [62]	China	7,126	983	44 (17); 16–90	NA	3,517	KL≥2 and Symptomatic (pain)	2013	Cross-sectional	Stratified multistage cluster sampling	Full text
Yeşil H et al. 2013 [63]	Turkey	522	109	54 (9); ≥40	29·6	390	ACR	2013	Cross-sectional	No random	Full text
Xiang Z et al. 2013 [64]	China	1,499	499	62 (11); ≥40	NA	790	ACR	2010–2011	Cross-sectional	Cluster stratified multistage random sampling	Full text
Turkiewicz A et al. 2013 [65]	Sweden	7,737	1,965	70 (8); 56–84	27·0	947	KL≥2	2007	Cross-sectional	Random sampling	Abstract
Turkiewicz A et al. 2013 [65]	Sweden	7,737	812	70 (8); 56–84	27·0	947	KL≥2 and Symptomatic (pain)	2007	Cross-sectional	Random sampling	Abstract
Turkiewicz A et al. 2013 [65]	Sweden	7,737	696	70 (8); 56–84	27·0	947	ACR	2007	Cross-sectional	Random sampling	Abstract
Thomas E et al. 2014 [66]	England	26,100	8,000	66 (11); ≥50	NA	14,172	Symptomatic OA	2004	Cross-sectional	All subjects were interviewed	Full text
Visser AW et al. 2014 [67]	Netherlands	5,284	991	57; 45–65	29·9	2,794	ACR	2008–2013	Cross-sectional	No random	Full text
Singh AK et al. 2014 [68]	India	496	204	≥60	NA	238	ACR	2009–2010	Cross-sectional	House by house	Full text
Tehrani-Banihashemi A et al. 2014 [69]	Iran	1,565	303	38 (19); >15	NA	862	ACR	2006	Cross-sectional	Random sampling	Full text
Ho-Pham LT et al. 2014 [70]	Vietnam	658	225	56; 40–98	NA	488	KL≥2	2014	Cross-sectional	Simple random sampling	Full text
Haouichat C et al. 2014 [71]	Algeria	400	84	65 (9); ≥50	30·1	All female	KL≥2	2014	Cross-sectional	Stratified sampling	Abstract
Edwards M et al. 2014 [72]	Europe countries	2,904	587	74 (5); 65–85	27·3	1,507	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	Germany	405	45	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	Italy	467	135	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	Netherlands	558	102	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	Spain	535	129	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	Sweden	506	101	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Edwards M et al. 2014 [72]	England	433	69	74 (5); 65–85	27·3	NA	ACR	2010–2011	Cross-sectional	Random sampling	Full text
Ara R et al. 2014 [73]	Bangladesh	4,850	401	56 (13); ≥15	NA	3,502	ACR	2011	Cross-sectional	House by house and census	Abstract
Moghimi N et al. 2015 [74]	Iran	5,830	1,096	>15	NA	3,236	Doctor-diagnosed	2011–2012	Cross-sectional	Clusters randomly sampling	Full text

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Table 1 (*Continued*)

	Countries	NO. of Total	NO. of knee OA	Age (Mean (SD); Rang (years))	BMI (kg/m2)	NO. of Female	Methods of Diagnosis	Time of Data Collection	Type of Study	Sampling Method	Type of Article
Granados Y et al. 2015 [75]	Venezuela	3,973	218	44 (18); >18	NA	2,367	ACR	2011	Cross-sectional	House by house	Full text
Zeng SY et al. 2015 [76]	China	4,056	421	48; ≥16	NA	2,108	ACR	2012	Cross-sectional	Random sampling	Full text
Plotnikoff R et al. 2015 [77]	Canada	4,733	497	≥18	NA	NA	Self-report doctor-diagnosed OA	2015	Cross-sectional	Random sampling	Abstract
Cho HJ et al. 2015 [78]	Korea	696	265	72 (5); 65–91	24·0	398	KL≥2	2005–2006	Cross-sectional	Simple random sampling	Full text
Tang X et al. 2016 [79]	China	17,128	1,387	60; ≥45	NA	8,761	Doctor-diagnosed OA	2011–2012	Cross-sectional	Multistage probability sampling	Full text
Guevara-Pacheco S et al. 2016 [80]	Ecuador	4,877	361	43 (18); >18	NA	2,916	ACR	2014	Cross-sectional	Mixed multistage and random sampling	Full text
Pal CP et al. 2016 [81]	India	4,909	1,412	≥45	NA	NA	KL≥2	2016	Cross-sectional	Simple random sampling	Full text
Branco JC et al. 2016 [82]	Portugal	7,911	981	>18	NA	4,153	ACR	2011–2013	Cross-sectional	Stratified multistage random sampling	Full text
Liu Y et al. 2016 [83]	China	3,428	568	55 (10); ≥40–74	NA	1,767	KL≥2 and Symptomatic (pain)	2010	Cross-sectional	Proportionately stratified random sampling	Full text
Deshpande BR et al. 2016 [84]	USA	198,600	13,750	≥25	NA	103,140	Doctor-diagnosed OA	2007–2008	Cross-sectional	NA	Full text
Al Saleh J et al. 2016 [85]	United Arab Emirates	3,984	1,028	42 (16); 18–85	28·8	3,084	ACR	2009	Cross-sectional	Random sampling	Full text
Murphy LB et al. 2016 [86]	USA	1,246	192	≥51	NA	723	KL≥2	2003	Longitudinal	Stratified simple random sampling	Full text
Murphy LB et al. 2016 [86]	USA	1,342	155	≥51	NA	778	KL≥2 and Symptomatic (pain)	2003	Longitudinal	Stratified simple random sampling	Full text
Kolahi S et al. 2017 [87]	Iran	952	143	50 (9); 35–70	NA	516	ACR	2014–2015	Cross-sectional	Random sampling	Full text
Ahmed S et al. 2017 [88]	Bangladesh	1,843	135	≥18	NA	NA	Doctor-diagnosed OA	2017	Cross-sectional	Clusters sampling	Abstract
Prashansanie Hettihewa A et al. 2018 [89]	Sri Lanka	666	134	63 (9); ≥50	NA	All female	ACR	2013	Cross-sectional	Multistage cluster sampling	Full text
Venkatachalam J et al. 2018 [90]	India	1,986	538	>18	NA	1,260	ACR	2014	Cross-sectional	Random sampling	Full text
Vega-Hinojosa O et al. 2018 [91]	Peru	1,095	17	39; ≥18	NA	614	ARA	2010	Cross-sectional	Probabilistic, stratified random sampling	Full text
Seoane-Mato D et al. 2018 [92]	Spain	4,753	661	≥20	NA	NA	ACR	2016	Cross-sectional	Stratified cluster sampling	Abstract
Kumar P et al. 2018 [93]	India	10,171	766	≥0	NA	NA	Doctor-diagnosed OA	2004–2007	Cross-sectional	Cluster sampling	Full text
Gavali M et al. 2018 [94]	India	647	84	45; 35–57	NA	386	Doctor-diagnosed OA	2017–2018	Cross-sectional	House by house	Abstract
Ananto M et al. 2018 [95]	Indonesia	2,067	296	≥15	NA	NA	Doctor-diagnosed OA	2018	Cross-sectional	Multistage random sampling	Abstract
Leung YY et al. 2018 [96]	Singapore	3,364	370	≥18	NA	1,822	Symptomatic OA	2013–2014	Cross-sectional	A nationally representative sample	Full text
Macías-Hernández SI et al. 2018 [97]	Mexico	204	52	57 (11); ≥40	NA	124	KL≥2	2018	Cross-sectional	No random	Full text
Macías-Hernández SI et al. 2018 [97]	Mexico	204	36	57 (11); ≥40	NA	124	KL≥2 and Symptomatic (pain)	2018	Cross-sectional	No random	Full text

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Table 1 (*Continued*)

	Countries	NO. of Total	NO. of knee OA	Age (Mean (SD); Rang (years))	BMI (kg/m2)	NO. of Female	Methods of Diagnosis	Time of Data Collection	Type of Study	Sampling Method	Type of Article
Postler A et al. 2018 [17]	Germany	2,700,000	329,216	75; >60	NA	1,884,600	ICD-10 codes	2014	Cross-sectional	De-identified claims data	Full text
Badley EM et al. 2018 [98]	Canada	30,097	4,460	45–85	NA	NA	Self-report doctor-diagnosed OA	2018	Cross-sectional	No random	Abstract
Rodriguez-Veiga D et al. 2019 [99]	Spain	707	207	62; ≥40	NA	398	Doctor-diagnosed OA	2019	Cross-sectional	Random sampling	Abstract
Guevara SV et al. 2019 [100]	Ecuador	2,687	177	44 (20); ≥18	NA	1,690	ACR	2016–2018	Cross-sectional	Random and mixed (stratified and conglomerate)	Full text
Hvidberg MF et al. 2019 [14]	Denmark	4,555,439	177,662	≥16	NA	2,314,163	ICD-10 codes	2013	Longitudinal	NA	Full text
Hong JW et al. 2020 [101]	Korea	12,287	4,313	63; ≥50	NA	7,056	KL≥2	2010–2013	Cross-sectional	Proportional-allocation systematic sampling with multistage stratification	Full text
Sasaki E et al. 2020 [102]	Japan	1,104	282	54; ≥20	22·9	661	KL≥2	2005	Cross-sectional	No random	Full text
Swain S et al. 2020 [15]	England	1,690,618	49,028	≥20	NA	NA	ICD-10 codes	2017	Longitudinal	NA	Full text

NO=numero. OA=osteoarthiritis. SD=standard deviation. BMI=body mass index. KL=the Kellgren and Lawrence. NA=not applicate. ACR=the American College of Rheumatology classification criteria. ARA=the clinical criteria of the American Rheumatism Association. ICD=International Classification of Disease.

one in Oceania (847 participants), one in Africa (400 participants)) and 34 countries. 70 articles were cross-sectional studies, four articles were retrospective cohort studies. 14 articles were prospective cohort studies. On prevalence, 19 studies examined the radiographic knee OA, 56 studies examined the symptomatic knee OA, and 3 studies examined the self-report knee OA; on incidence, ten studies reported the radiological knee OA and seven studies reported the symptomatic knee OA. The number of females was more than that of males in most of the included studies. 16 studies were high risk of bias, 29 were moderate risk of bias, 43 were low risk of bias (Appendix 2.1–4).

We estimated the global prevalence of knee OA based on 9,440,250 participants from 34 countries, most of participants were ≥15 years old (mean 57·2 (standard deviation (SD) 6·5)). The pooled global prevalence of knee OA was 16·0% (95% CI, 14·3%–17·8%) (Fig. 2) in individuals aged 15 and over and was 22·9% (95% CI, 19·8%–26·1%) (Appendix 3) in individuals aged 40 and over. Correspondingly, there are around 654·1 (95% CI, 565·6–745·6) million individuals (40 years and older) with knee OA in 2020 worldwide. The prevalence was 19·2% (95% CI, 15·7%–23·0%) in Asian, 13·4% (95% CI, 10·1%–17·0%) in Europe, 15·8% (95% CI, 11·2%–20·9%) in North America, 4·1% (95% CI, 2·1%–6·9%) in South America, 3·1% (95% CI, 2·0%–4·4%) in Oceania, 21·0% (95% CI, 17·1%–25·1%) in Africa (Fig. 2). The prevalence in individual country ranged from 1·6% (95% CI, 1·1%–2·0%) to 46·3% (95% CI, 41·9%–50·6%) (Fig. 3 and Appendix 4). The radiological knee OA (28·7% [95% CI, 23·6%–34·1%]) (Appendix 5) was more common than the symptomatic (12·5% [95% CI, 10·8%–14·3%]) (Appendix 6) and self-report (10·6% [95% CI, 6·5%–15·6%]) (Appendix 7) knee OA. The prevalence was higher in women (21·7% [95% CI, 19·0%–24·5%]) (Appendix 8) than in men (11·9% [95% CI, 10·2%–13·8%]) (Appendix 9).

We estimated the global incidence of knee OA based on 643,948 participants from 7 countries, most of participants were ≥20 (mean 46·0 (SD 5·7)) years old at baseline. The global incidence of knee OA was 203 per 10,000 person-years (95% CI, 106–331) in individuals aged 20 and over (Fig. 4). Correspondingly, there are around annual 86·7 (95% CI, 45·3–141·3) million individuals (20 years and older) with incident knee OA in 2020 worldwide. The incidence was 130 per 10,000 person-years (95% CI, 59–228) in the United States, 315 per 10,000 person-years (95% CI, 42–824) in the United Kingdom, 525 per 10,000 person-years (95% CI, 245–902) in the Japan, 52 per 10,000 person-years (95% CI, 42–63) in the Finland, 84 per 10,000 person-years (95% CI, 66–106) in the Netherlands, 33 per 10,000 person-years (95% CI, 1–113) in the Norway, 295 per 10,000 person-years (95% CI, 293–296) in the Spain (Appendix 10). The incidence was higher in the radiological knee OA (373 per 10,000 person-years [95% CI, 248–522]) than in the symptomatic knee OA (50 per 10,000 person-years [95% CI, 1–175]) (Fig. 4).

We assessed that the risk factors were age, gender, area of residence, cigarettes, and education level. We found that the risk of prevalence and incidence increased with age, peaked at the advanced age on prevalence (Fig. 5 and Appendix 11) and at 70–79 years old on incidence (Appendix 12 and 13). The risk of prevalence and incidence in females 1·69 (95% CI, 1·59–1·80, $p<0{\cdot}00$) and 1·39 (95% CI, 1·24–1·56, $p<0{\cdot}00$) times as much as males, respectively (Appendix 14 and 15). The risk of prevalence was not significantly different in rural and urban (RRs 0·97, 95% CI, 0·74–1·28, $p<0{\cdot}00$) (Appendix 16). The risk of prevalence was higher in junior and senior high school than in college degree and above (RRs 2·01, 95% CI, 1·28–3·16, $p<0{\cdot}00$) (Appendix 17) and was higher in elementary school and below than in junior and senior high school (RRs 2·14, 95% CI, 1·70–2·69, $p<0{\cdot}00$) (Appendix 18). The risk of prevalence was not significantly different in smoking and no-smoking in cross-sectional studies (RRs 0·81, 95% CI, 0·44–1·51, $p<0{\cdot}51$) (Appendix 19), but the risk of incidence was lower in smoking than in no-smoking in

Table 2
The summary characteristics of included incidence studies.

	Countries	NO. of knee OA	Person- years	Time of Follow-up (years)	Age at baseline, Mean; Range (years)	NO. of Female	Methods of Diagnosis	Time of Data Collection
Oliveria SA et al. 1995 [103]	USA	461	196,990	3·0	20–89	NA	KL≥2 + symptoms	1988-(1991,1992)
Felson DT et al. 1995 [104]	USA	93	4,844	8·1	71; (63–91)	381	K/L grade >2	(1983–1985)-(1992–1993)
Slemenda C et al. 1998 [105]	USA	27	728	2·6	71; (≥65)	113	K/L grade >2	NA
Gelber AC et al. 1999 [106]	USA	62	42,480	36·0	23; (21–25)	All men	Self-report	NA
Murphy LB et al. 2016 [86]	USA	193	6,853	5·5	≥45	723	K/L grade >2	(1991–1997)-(1999–2003)
Cooper C et al. 2000 [107]	England	45	1,234	5·1	70; (≥55)	NA	K/L grade >2	(1990–1991)-(1995–1996)
Duncan R et al. 2011 [108]	England	55	759	3·0	65 (57–73)	NA	K/L grade >2	(2002–2003)-(2005–2006)
Driban JB et al. 2020 [109]	England	93	3,575	15·0	45–64	All female	K/L grade >2	(1988–1989)–2004
Swain S et al. 2020 [15]	England	3,432	1,492,174	1·0	≥20	NA	CDI-10	2007
Prieto-Alhambra D et al. 2014 [16]	Spain	96,222	3,266,826	4·5	≥40	NA	Doctor-diagnosed	2006–2010
Grotle M et al. 2008 [110]	Norway	114	16,750	10·0	42; (24–66)	NA	Self-report	1994–2004
Mork PJ et al. 2012 [111]	Norway	351	329,527	11·0	44; ≥20	15,191	Self-report	(1984–1986)-(1995–1997)
Reijman M et al. 2007 [112]	Netherlands	76	9,055	6·6	66; (≥55)	792	K/L grade >2	(1990–1993)-(1996–1999)
Nishimura A et al. 2011 [113]	Japan	57	1,044	4·0	71; (65–89)	165	K/L grade >2	(1997,1999,2001, 2003)–2007
Muraki S 2012 [114]	Japan	107	3,623	3·3	69; (23–95)	631	K/L grade >2	(2005–2007)-(2008–2010)
Sasaki E et al. 2015 [115]	Japan	129	1,615	5·0	55; (25–85)	NA	K/L grade >2	2008–2013
Toivanen AT et al. 2010 [116]	Finland	94	18,106	22·0	42; (30–72)	454	Doctor-diagnosed	(1978,1980)-(2000,2001)

NO.=numero. OA=osteoarthiritis. KL=the Kellgren and Lawrence. NA=not applicate. ICD=International Classification of Disease.

prospective cohort studies (RRs 0·60, 95% CI, 0·44–0·82, $p<0·00$)) (Appendix 20).

Sensitivity analysis showed that there was no significant change in the estimates of prevalence and incidence after omitting any one of the included studies (Appendix 21 and 22). The univariate meta-regression results could explain some heterogeneity caused by publication year, type of study, sampling method, type of knee OA, mean BMI, but couldn`t explain all heterogeneity (Appendix 23 and 24). The funnel plots showed visually asymmetrical distribution of published studies on prevalence and incidence of knee OA (Appendix 25 and 26). But Egger tests indicated that there was no statistically significant publication bias on prevalence (Egger test: bias=11·98; 95% CI −2·33 to −26·28; p = 0·099) and incidence (Egger test: bias= −17·35; 95% CI −40·45 to 5·74; p = 0·130).

4. Discussion

The present systematic review and meta-analysis is, to our knowledge, the first study pooling the latest data and the largest sample sizes to estimate the epidemiologic characteristics of knee OA at the beginning of the 21st century. Our main findings were that the global prevalence of knee OA was 16·0% (95% CI, 14·3%–17·8%) in individuals aged 15 and over and was 22·9% (95% CI, 19·8%–26·1%) in individuals aged 40 and over; the incidence was 203 per 10,000 person-years (95% CI, 106–331) in individuals aged 20 and over; the prevalence and incidence increased with age, peaked at the advanced age on prevalence and at 70–79 years old on incidence; and the ratios of prevalence and incidence in females and males were 1·69 (95% CI, 1·59–1·80, $p<0·00$) and 1·39 (95% CI, 1·24–1·56, $p<0·00$), respectively.

The prevalence varied with the characteristics of studies (e.g., age, sex, BMI, etc.). In general, the global prevalence of knee OA was high from 2000 to 2020, which may bring a huge burden to global health care system. At continent-level, the prevalence was higher in Asian (19·2% [95% CI, 15·7%–23·0%]) than in Europe (13·4% [95% CI, 10·1%–17·0%]) and North America (15·8% [95% CI, 11·2%–20·9%]). The prevalence was lowest in South America (4·1% [95% CI, 2·1%–6·9%]). There was not adequate data to draw a conclusion in Oceania and Africa. At country-level, the prevalence ranged from 1·6% (95% CI, 1·1%–2·0%) to 46·3% (95% CI, 41·9%–50·6%). Thailand (46·3% [95% CI, 41·9%–50·6%]), Japan (39·6% [95% CI, 14·1%–68·7%]), Korea (36·1% [95% CI, 34·1%–38·1%]) and Indian (21·0% [95% CI, 11·0%–34·%]) had higher prevalence. Given Asian were relatively thinner than others, however, they had higher prevalence in our study. We analyzed that the number of studies examining radiographic knee OA was more in Asian than in other continents in the meta-analysis, which was the main reason why knee OA was more prevalent in Asian. Other possible reasons were that Asian were used to bending knee and squatting and genetic or environmental factors. In conclusion, we failed to determine accurately which country or continent had a higher prevalence of knee OA based on the existing evidence in our study, because there was no comparability of baseline data between studies. We found that the radiographic knee OA (28·7% [95% CI, 23·6%–34·1%]) was more prevalent than the symptomatic knee OA (12·4% [95%CI, 10·8%–14·2%]), which was consistent with a previous systematic review conducted by Pereira D et al. and they concluded that the prevalence of OA depended on definition used [24]. Accordingly, according to the results of our study, we speculated that the radiographic knee OA may be detected earlier, which can provide more opportunities for prevention of knee OA. We found

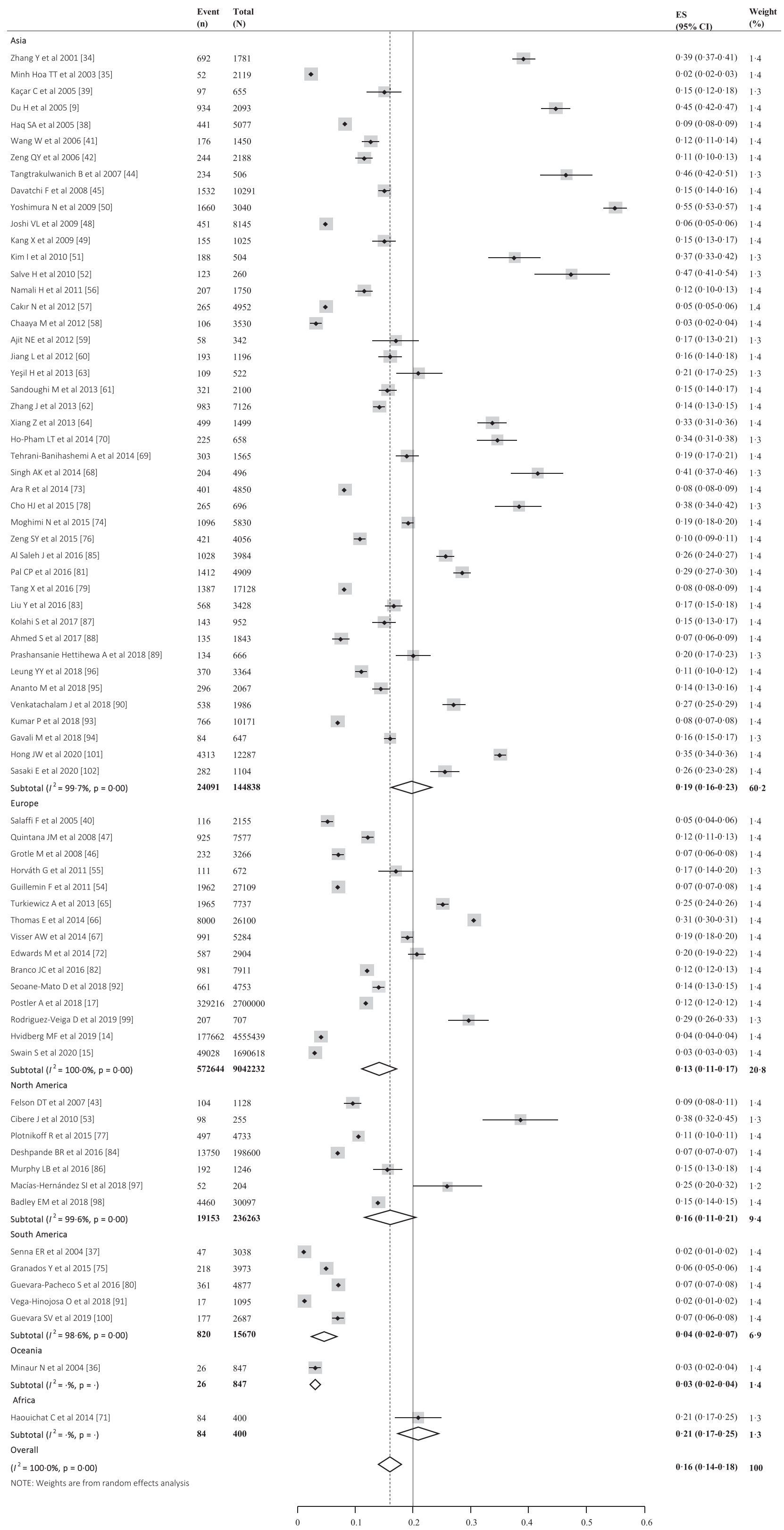

Fig. 2. The forest plot of the global prevalence of knee osteoarthritis.

the positive correlation between the prevalence of knee OA and increased age, similarly, the same result could be seen in GBD 2017 Study [25] and other studies [26,27]. However, the prevalence peaked at around 50 years of age for knee OA in GBD 2014 Study, the potential explanation may be that the GBD 2014 Study used inadequate data. Considering the older people easier encountered with knee OA

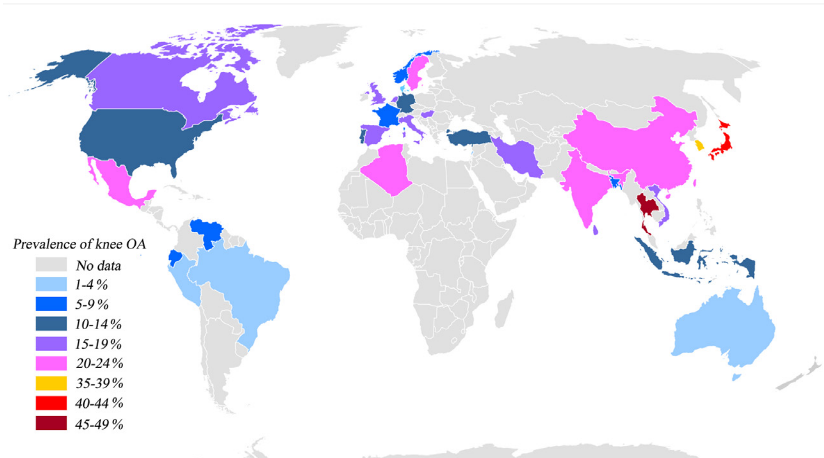

Fig. 3. Global distribution of the prevalence of knee osteoarthritis (OA).

and according to the current consensus, tailored care should be given to them [3]. We pooled a large sample (3,686,544 participants) to explore the ratio of prevalence and incidence of knee OA in women and men, to our knowledge, which was the strongest evidence so far [28]. Consequently, a more accurate estimate can be obtained. The results showed that prevalence and incidence in females 1·69 (95% CI, 1·59–1·80, $p<0{\cdot}00$) and 1·39 (95% CI, 1·24–1·56, $p<0{\cdot}00$) times as much as males, respectively, which was corresponded to established consensus [1,29]. More efforts should be made to explore the cause of the high prevalence of knee OA in women.

There were very rare studies examining the incidence of knee OA, most of the published studies were in Europe and North America. In Asian, only Japan has the published data of incidence of knee OA. The data of incidence was unavailable in South America, Oceania, and Africa. Considering most of whole world population in Asian, Oceania, and Africa, their data may be highly significant to ascertain the etiology and reduce global burden. And in consideration of the economic situation of those areas, initiating new program like Community Oriented for Control of the Rheumatic Diseases (COPCORD) may be a cost-effective strategy for understanding the epidemiological characteristics of knee OA. The data of the United Kingdom and the United States was more comprehensive and the pooled results showed that the incidence was 315 per 10,000 person-years (95% CI, 42–824) in the United Kingdom and 130 per 10,000 person-years (95% CI, 59–228) in the United States. We found that the incidence of knee OA increased with age and peaked at 70–79 years, which was

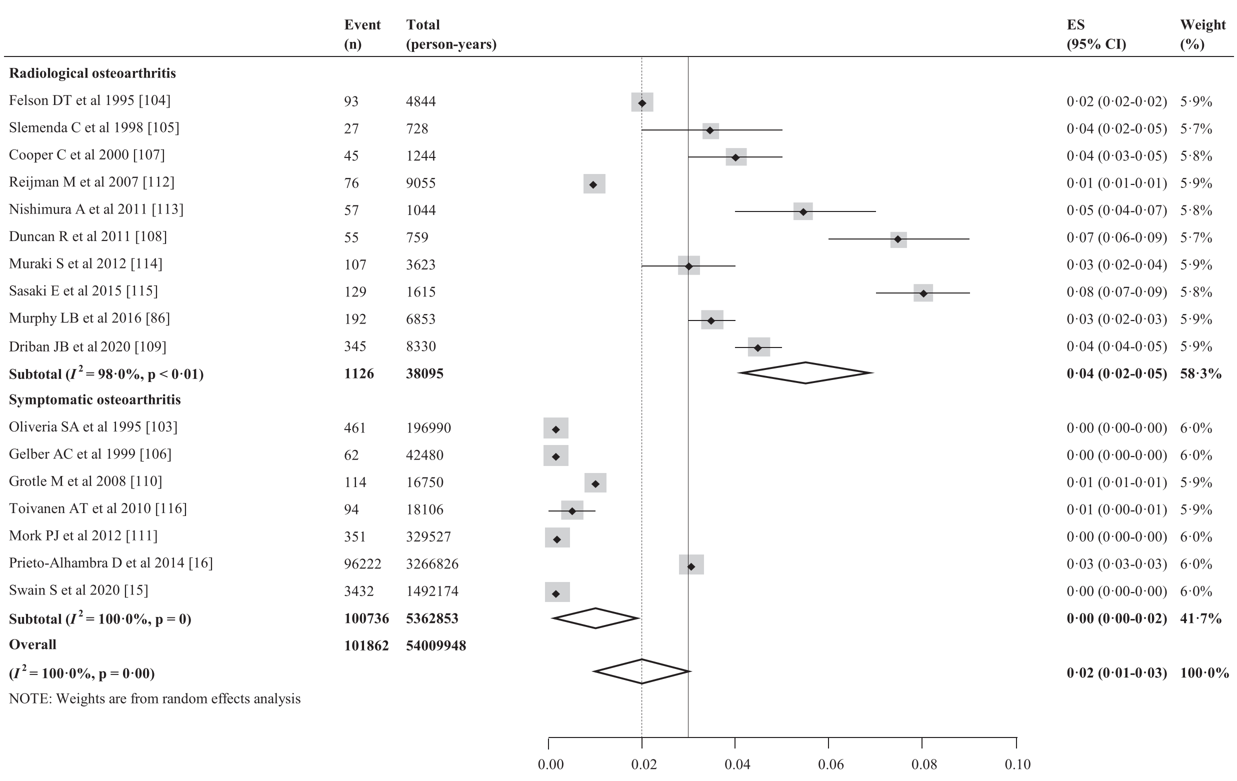

Fig. 4. The forest plot of the global incidence of knee osteoarthritis.

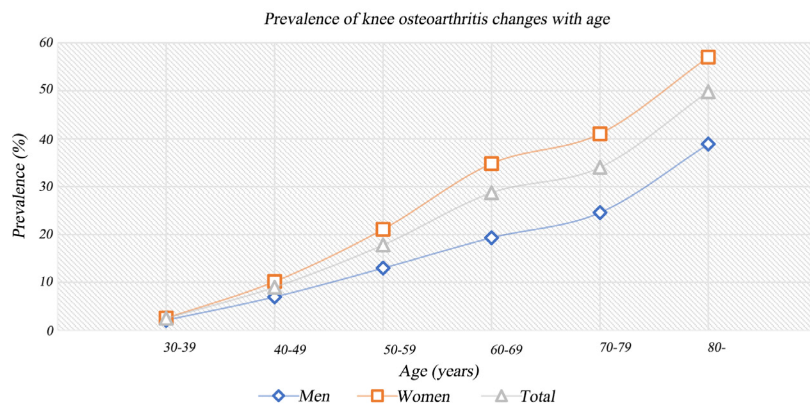

Fig. 5. The trend of the prevalence of knee osteoarthritis changes with age.

consistent with the latest result of the study in the United Kingdom [15]. This may be an interesting topic, the prospective studies are warranted to validate it in future.

It is well known that knee OA is a multiple factors disease, which include modifiable (obesity, knee injury) and unmodifiable (age, sex) factors [30]. In our meta-analysis, the pooled estimates showed that the prevalence of knee OA was negatively associated with education level, which was in agreement with several previous studies [31,32]. This may be because of the fact that individuals with lower education level frequently involved heavy physical activities or accessed to few the knowledge of prevention for knee OA. We found that there was no statistically significant difference in prevalence between rural and urban (RRs 0·97, 95% CI, 0·74–1·28, p = 0·84), which was contradictory to some previous studies included in the meta-analysis. We speculated that the sample size of the individual study may be not enough. However, above estimates should be interpreted with caution because articles included in this meta-analysis were cross-sectional studies, which didn`t allow to draw a causal conclusion. Our pooled estimates showed that the incidence was lower in smokers than in no-smokers in cohort study, which was inconsistent with a previous systematic review and meta-analysis conducted by Hui M et al. [33]. They argued that the relationship between smoking and knee OA may be confounded by body mass index (BMI). Because BMI was a significant risk factor for the occurrence and development of knee OA and smokers were usually thinner than no-smokers. Another possible reason was that smokers often suffered from multiple comorbidities such as lung cancer, cardiovascular disease, so the no-smokers may have a longer life span and they were more likely to develop knee OA. Further prospective studies are needed to verify the dose-response relationship between the incidence of knee OA and cigarettes. Nevertheless, researchers have realized that knee OA is amenable to prevention and treatment at early stages [30]. Increasing education attainment, weight control, injury prevention, improving muscle function, and others may play an important role for early prevention in future.

There are some limitations in our study. Firstly, there is statistically significant heterogeneity in our meta-analysis. However, it is anticipated that the observational studies in epidemiology usually have substantial heterogeneity given established associations between the prevalence and incidence of knee OA and age, sex, BMI, type of knee OA, genetic factors and so on. Secondly, due to included studies had few data directly examining the difference between prevalence of knee OA and ethnicity, we were unable to differentiate it. Thirdly, we couldn`t assess the prevalence of knee OA for individual country accurately owing to the limitations of the number of original studies. Fourthly, despite we assessed the relationships between risk factors (area of residence, cigarettes, and education level) and the prevalence and incidence of knee OA, those evidences were not strong enough because of the limited number of included studies. Fifthly, considering the preference of the journal and individual, the potential publication bias can hardly be excluded.

In conclusion, this study provides the global prevalence (16·0% [95% CI, 14·3%–17·8%]) and incidence (203 per 10,000 person-years [95% CI, 106–331]) of knee OA. These findings can be used to better estimate the global health burden of knee OA. The knee OA is continuing to be prevalent in global adults and over, especially in older and women. Further prospective cohort studies are warranted to identify modifiable risk factors for providing effectively preventive strategies in the early stages of the disease.

Declaration of Competing Interests

We declare that we have no conflicts of interest.

Contributors

LHD, CAY, and LHZ conducted the study protocol. CAY and LHZ searched the databases, selected the literature and extracted the data. CAY and LHZ did the statistical analyses. CAY draw figures, CAY and LHZ prepared the first draft under the guidance of LHD. All authors interpreted the results, reviewed drafts of the Article, and approved the final version. CAY and LHZ contributed equally to this work.

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Data sharing statement

The study protocol is available with this publication. No additional unpublished data are available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100587.

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