Association between osteoarthritis and increased risk of dementia
A systemic review and meta-analysis

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Abstract

Objective: To investigate the possible association between osteoarthritis (OA) and the risk of dementia.

Methods: Cohort, case-control, and cross-sectional studies were obtained from wide literature search up to 20 April 2018 from following electronic databases: PubMed, Embase, Cochrane, using the MeSH terms: "osteoarthritis" AND "dementia". The literature search was then expanded to congress abstracts. After screening and selection of relevant studies by two investigators, data was extracted. Estimates were then calculated using a random-effect size model. Sensitivity-analysis was conducted for gender and age adjusted studies and pooled for studies with STROBE quality assessment score ≥75%. Publication bias was assessed by Funnel plot. Analyses were performed using Data Analysis and Statistical Software Version 14.2.

Results: Nearly 1549 publication references were initially retrieved. Twenty-six publications were checked with full-text. Six observational studies with 388,252 individuals were included. OA was associated with a significantly increased risk for dementia (OR = 1.20; 95% confidence interval (CI), 1.03–1.39, I^2 = 95.6%, $P < .05$). After pooling the studies with adjustment of age and gender, the risk increased (OR 1.36; 95% CI, 1.22–1.51, I^2 = 75.6%, $P < .0001$). After pooling the study with a STROBE Quality score ≥75% the risk for dementia was slightly increased (OR 1.33; 95% CI, 1.17–1.5, I^2 = 93.5%, $p < 0.0001$).

Conclusions: There is an association between osteoarthritis and the risk of dementia. This meta-analysis does not provide causality. Further prospective cohort studies are needed to clarify, if knee-, hip-, or hand-OA are independent risk factors for Alzheimer's disease and vascular dementia.

Abbreviations: 3 MS = Modified Mini-Mental State, ACR = American College of Rheumatology, AD = Alzheimer's disease, CI = confidence interval, CIM = cognitive impairment, CRP = C-reactive protein, EULAR = European League Against Rheumatism, HR = hazard risk, ICD = International Classification of Diseases, IL-1beta = interleukin-1-beta, IL-6 = interleukin-6, MMSE = Mini-Mental State Examination, NSAID's = non-steroidal-anti-inflammatory drugs, OA = osteoarthritis, OARSI = Osteoarthritis Research Society International, OR = odds ratio, ox-LDL = oxidized LDL, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, ROS = reactive oxygen species, RR = relative risk, SMR = standard mortality rate, STROBE = Observational Studies in Epidemiology.

Keywords: dementia, meta-analysis, osteoarthritis, systematic review

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1. Introduction

Osteoarthritis (OA) is a debilitating, multi-factorial joint disease which leads to pain and impaired function in the adult population. Its socioeconomic burden increased in the last century[1,2] and is expected to increase in the next decades.[3,4] OA was earlier considered to be a local cartilage problem caused by wear and tear. However, OA is currently broadly accepted as a whole joint disease, which includes synovitis and subchondral bone changes.[5] Bone and synovia are both highly vascularized tissues and can initiate inflammatory responses.[5–7] Beside local peripheral low-grade inflammation, it has been suggested that low-grade systemic inflammation could play a critical role in OA. This relationship has been discussed for patients with systemic inflammatory-associated diseases such as hypertension, obesity, dyslipidemia, and diabetes mellitus.[8–10] This concept of OA as a systemic-associated disease requires more supporting evidence.

A recent nation-wide study from Taiwan brought up that OA is also associated with increased risk for dementia.[11] Alzheimer's disease (AD) and vascular dementia are the most common sub forms of dementia.[12] Dementia is a progressive neurodegenerative brain disorder which leads to cognitive impairment (CIM), disability, and death in the elderly population. The prevalence of dementia is expected to increase rapidly over the next decades.[13] Dementia therefore will have a big impact on the burden of the society. It is of big importance to identify and address potential risk factors. Dementia and OA share similar risk factors, are both age-related and low-grade inflammatory-associated diseases.[5,7,14,15] However, the relationship between OA and dementia is not clear and only very limited data is available.

This is the first meta-analysis synthesizing all observational studies published in peer-reviewed journals up to April 20, 2018 with no lower limitation, investigating the association between OA and the risk of dementia.

2. Materials and methods

2.1. Literature search and inclusion criteria

This systemic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16] and slightly adjusted when necessary. Ethical approval was not necessary, because our meta-analysis is a synthesis of previous studies in which patient's approval has already been obtained. The literature search was conducted using following electronic databases; PubMed, Embase, Cochrane, using the MeSH terms: "osteoarthritis" AND "dementia" without any lower limit of time up to April 20, 2018. Congress abstract were searched in the archives of Osteoarthritis Research Society International (OARSI), American College of Rheumatology (ACR), and European League Against Rheumatism (EULAR).

The literature search was then extended to hand search and for screening of ongoing trials in the registry databases: Open-Grey and the WHO International Clinical Trials. The studies were restricted to human subjects and to studies with English title and abstract. Studies with full text in any translatable language were considered. Only those studies providing sufficient information for the calculation of the odds ratio (OR) of OA associated with the risk of dementia were included in this meta-analysis. Included were all types of observational studies (cohort studies, cross-sectional studies, and case-control studies). There was no restriction on the disease severity or localization (e.g., hip-,

knee-, and hand-osteoarthritis were considered). Both radiographic and symptomatic OA were included. There was no restriction on sub-classification of dementia (e.g., AD and vascular dementia were included). The inclusion of the studies was decided according to the above-mentioned criteria by two investigators (AW and ShM). To qualify for inclusion both investigators had to reach agreement. A third investigator was involved in case of unsolved disagreement (CW).

2.2. Data extraction

The data extraction was conducted by two investigators individually (AW and ShM). The discrepancies in data extraction were all resolved by consensus. The following data was extracted from the included studies: author, year of publication, design, age of population, sample size, gender, definition of OA (International Classification of Diseases (ICD) codes, localization, radiographic or symptomatic), definition of dementia (ICD codes, Mini-Mental State Examination (MMSE), Modified Mini-Mental State (3MS) examination, AD or Vascular dementia, CIM), odds ratios (ORs), relative risk (RR), hazard risk (HR), standard mortality rate (SMR), and adjusted factors. The OR and the respective 95% confidence interval (CI) were directly extracted from the studies when available. OR were calculated from HR, RR, and SMR when OR was not available. OA was considered as the exposure factor. Dementia was considered as the outcome factor. The quality assessment of the included studies was estimated with the Checklist from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[17] The score is expressed as the percentage of included numbers from the checklists.
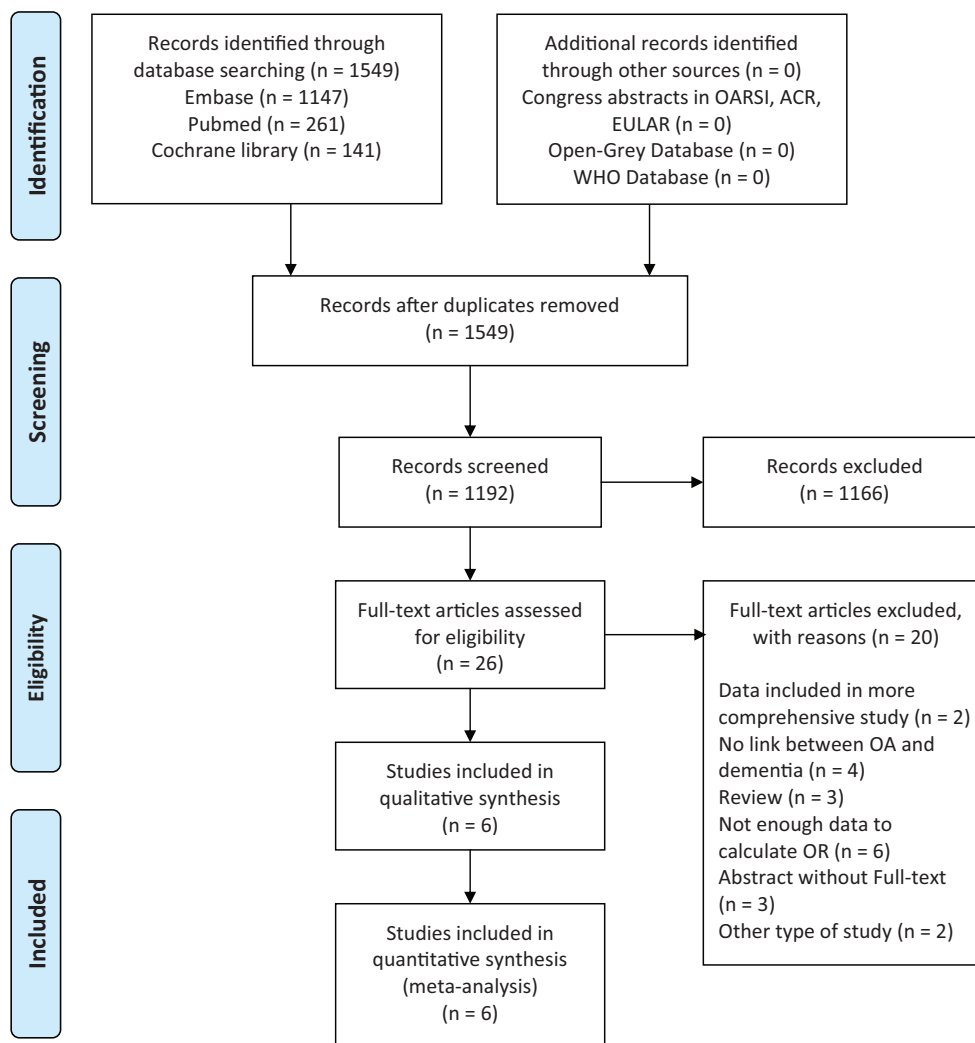
2.3. Statistical analysis

RR, HR and SMR were used to calculate ORs and their 95% CI. The ORs and the calculated summary effects were then used to describe the risk of dementia when exposed to OA. To calculate the overall effect of the OR and their 95% CI, random-effect model was used, because the heterogeneity was high. The study heterogeneity was assessed using I^2-test. $I^2 > 50\%$ was considered as high heterogeneity. The ORs with their corresponding 95% CIs were illustrated with Forrest-plot graphic. $OR > 1$ with a P-value $< .05$ was stated as a statistical significant increased risk of dementia when exposed to OA. The publication bias was assessed by Funnel plot analysis. Analyses were performed using Data Analysis and Statistical Software (STATA) Version 14.2. All statistical tests were two sided and a P-value $< .05$ was considered as a statistically significant outcome. Sensitivity analysis was performed (refer http://links.lww.com/MD/C833 for more details).

3. Results

3.1. Search strategy results

A total of 1549 publication references were initially retrieved using this search strategy. No studies were found in Open-Grey and the WHO International Clinical Trials, nor were any congress abstract received from OARSI, ACR, or EULAR. No further studies were obtained after extended hand search. After removal of 357 duplicates, 1192 publications were screened based on titles and abstracts and 26 publications were identified as potentially eligible. After checking the full text for detailed information and data extraction 6 out of 26 publications were included in this meta-analysis.[11,18–22] Three abstracts without full-text[23–25] were not included in this synthesis (Fig. 1). From

Figure 1. PRISMA flow-chart, result of applied search strategy.

this search strategy three cohort studies, two case control studies, and one cross section study was obtained (Table 1).

3.2. Study characteristics

The 6 independently conducted observational studies included in the meta-analysis were published between 2007 and 2018 including a total of 388,252 individuals. The female rate was remarkably higher (59%–63.2% female) and very high in the study from Fernando et al (84%). Three studies were based in Asia, two in Europe, and one in South America. The 2 studies from Denmark and the 3 studies from Taiwan were conducted with data from national wide databases. The definition of OA is described in Table 1. Four studies defined OA with clinical ICD codes, including hand-, knee-, hip-, shoulder, and ankle/foot OA.[11,19–21] Two studies did not specify OA.[18,22] One study defined the investigation in dementia by CIM and defined it by MMSE <23.[18] One study defined dementia as AD using registered database.[22] Four studies used ICD codes including AD, vascular dementia, or other subforms.[11,19–21] Three studies adjusted for age and gender[11,20] or used age and gender matched

control groups.[22] The median STROBE quality score was 81.7% (range 68%-91%). Five publications had a STROBE quality score ≥75%. The details of the study characteristics are shown in Table 1.

3.3. Osteoarthritis and the risk of dementia

Overall, OA was associated with a significantly increased risk for dementia (OR = 1.20; 95% CI, 1.03–1.39, $I^2 = 95.6\%$, $p < .05$) (Fig. 2). The overall estimate of OR increased after analysis using fixed effects model (OR 1.24; 95% CI, 1.21–1.26, $p < .0001$). The heterogeneity across the studies was very high ($I^2 = 95.6\%$, $P < .0001$). After exclusion of the study with a STROBE Quality score <75% the risk for dementia was slightly increased (OR 1.33; 95% CI, 1.17–1.5, $I^2 = 93.5\%$, $P < .0001$). After pooling the studies that reported adjustment for age and gender, the risk for dementia increased even more (OR 1.36; 95% CI, 1.22–1.51, $I^2 = 75.6\%$, $P < 0.0001$). For further sensitivity analysis, we analyzed the pooled estimates after removing different combinations of the studies which extracted their data from the same databases. Two patterns were seen. Pattern one (Korner 2009,

Table 1

Basic characteristics of included studies.

Author, y	Country	Design	Age, y	Sample size	Gender	Definition of OA	Definition of dementia	OR/RR/HR	Adjusted factors	Case-control-study = CCS, cohort study = CS, cross section study = CSS	Which dementia form	radiographic/symptomatic OA	Localisation OA	STROBE
Fernando, 2014	Ecuador	Cross-sectional study	mean 70.17	391	84% female	OA, not specified	Cognitive impairment: MMSE <23	RR: 1.73 (1.11–2.70), $P=.01$	No adjustment	CSS	n/A, MMSE -> CI	Symptomatic	No specification	84%
Kessing, 2007	Denmark	Danish National Psychiatric Central Register	66.6 (54.8–75.8)	230,208	59.2% female	ICD-8, 713.00–713.09 or ICD-10, DM15–DM19.9	ICD-8, 210.10 and ICD-10, G30–30.9, F00–00.9, ICD-8, 290–290.09, 290.18, 290.19, 291–291.99 and ICD-10, F01.0–01.9, F03.9	SMR: 1.19 (1.16–1.22), P: n.a.	No adjustment	CS	AD, vascular dementia, etc.	Symptomatic	Hand, knee, hip, shoulder, ankle/foot	75%
Korner, 2009	Denmark	Case control study, Danish National Psychiatric Central Register, follow up 4.4 years cohort study	mean 71.8	7301	63% female	ICD-10, M15–M19.9	ICD-10, F00–F01.9, G30, F03	SMR: 0.7 (0.6–0.82), P. n.a.	No adjustment	CS	AD, vascular dementia, etc.	Symptomatic	Hand, knee, hip, shoulder, ankle/foot	68%
Huang, 2015	Taiwan	Retrospective population-based, 4-year follow up cohort study, Taiwan Longitudinal Health Insurance Database 2015 (Identified 2004–2007)	>18	105,447	63.2% female	ICD-9-CM, 715	ICD-9-CM, 290, 294, 331	HR: 1.25 (1.1–1.43), $P<.001$	Age, gender, autoimmune disease, DM, hypertension, hyperlipidaemia, coronary heart disease, stroke, COPD, Parkinson's disease	CS	AD, vascular dementia, etc.	Symptomatic	Hand, knee, hip, shoulder, ankle/foot	86%
Chen, 2017	Taiwan	Retrospective case control study, Taiwan Longitudinal Health Insurance Database 2015, (selected data 2000–2010)	>40	37,051	Men and female	ICD-9-CM, 715	ICD9-CM, 290.0–290.4, 294.1, 331.0	OR: 1.47 (1.4–1.54), $P<0.01$	Age, gender and comorbidities	CCS	AD, vascular dementia, etc.	Symptomatic	Hand, knee, hip, shoulder, ankle/foot	86%
Wang, 2018	Taiwan	Retrospective case control study, Taiwan Longitudinal Health Insurance Database, random 2 million people sample, in year 2000	mean 76.1	7854	59%	OA, not specified	ICD-9, 331.0, 290.0, 290.2, 290.2, 290.21, 290.3	OR: 1.31 (1.19, 1.45)	No adjustment, age and gender-matched control group	CCS	AD	Symptomatic	OA, not specified	91%

AD = Alzheimer's disease, CCS = case-control study, COPD = chronic obstructive pulmonary disease, CS = cohort study, CSS = cross-section -study, DM = diabetes mellitus, ICD = International Classification of Diseases, MMSE = Mini-Mental State Examination, OA = osteoarthritis, OR/RR/HR = odds ratio/risk ratio/hazard ratio, SMR = standardized mortality ratio.
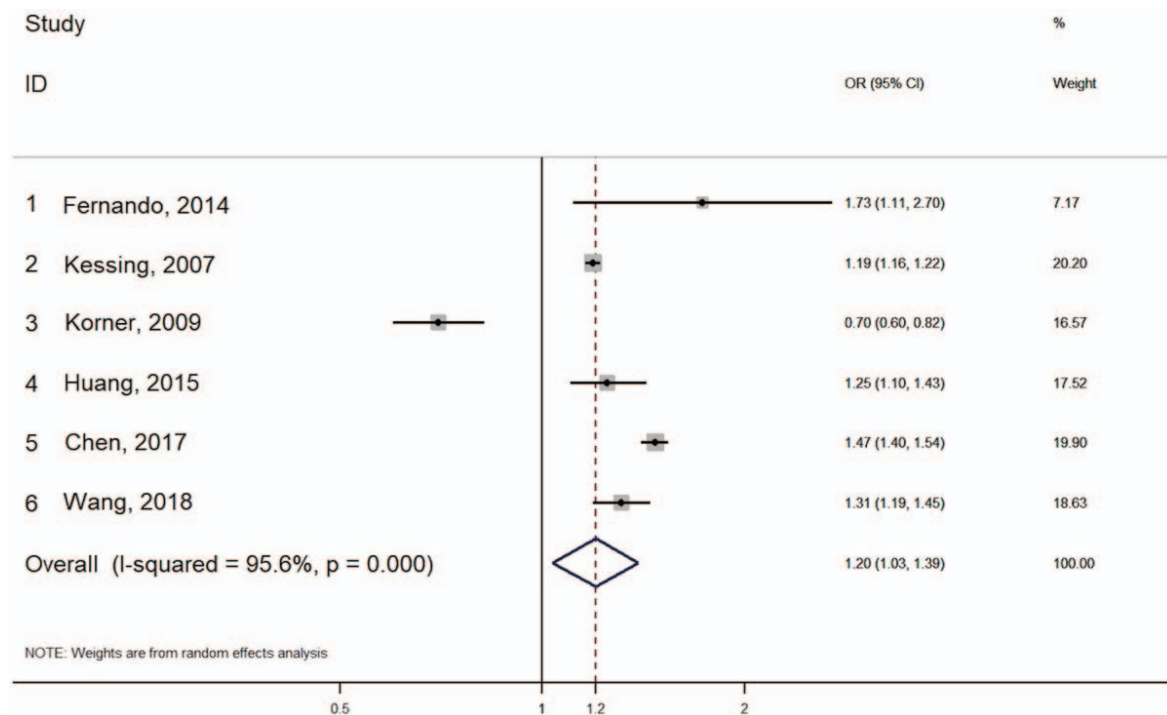
Figure 2. Forrest plot for risk of dementia when OA is diagnosed.

Fernando 2014, including one Taiwanese study) showed a persistent increased risk of dementia (OR 1.22–1.37; 95% CI, (1.12–1.13)–(1.33–1.67), $P < .001$). Pattern two (Kessing 2007, Fernando 2014, including one Taiwanese study) showed a slightly increased risk of dementia without sufficient significant levels (OR 1.11–1.19; 95% CI, (0.67–0.69)–(1.8–1.88), $P = .55$–.66).

There was a moderate asymmetrical distribution in the funnel plot for the studies presenting the association between OA and dementia (Fig. 3).

4. Discussion

This study investigated the potential relationships between OA and the risk of dementia by conducting a systemic review and meta-analysis. The result of our meta-analysis shows an association between OA and increased risk for dementia. The risk slightly increased after pooling for those that adjusted for age and gender, and also after pooling the studies with a STROBE quality score above-equal 75%. Our results provide mounting evidence that OA is not only a local disease but also a systemic-associated disease.

The relationship for the association between OA and increased risk for dementia remains unclear. First, we need to consider possible bias. There are several possible confounders in the relationship between OA and dementia. Firstly, the use of non-steroidal-anti-inflammatory drugs (NSAIDs) is known to increase hypertension and cardiovascular risk, which are both recognized risk factors for dementia and CIM.[12] Second, the population of the included studies contain more female and elderly patients. Female gender and age are not only risk factors for OA but also for dementia. Obesity was not documented in the selected studies but could also be a typical population-based confounder. Our pooled analysis for studies that adjusted for age and gender

showed an increased risk for dementia in OA population. Third, in elderly population we also need to consider the increased prevalence of age-associated common diseases and syndromes such as hypertension, cardiovascular diseases, and insulin resistance. They potentially could bias our demonstrated association between OA and risk for dementia (Fig. 4), as they are well recognized risk factors for dementia.[12] Particularly vascular co-morbidities need to be considered as confounders, because they are highly prevalent in OA population.[26] Two out of six studies included in this meta-analysis adjusted for comorbidities and showed an increased risk for dementia in OA population.[11,20] Another OA population-specific characteristic is physical inactivity when lower limbs are affected. Physical inactivity is broadly accepted to increase systemic inflammation and could therefore play an indirect role for the association between OA and the risk of dementia.[27]

A possible explanation for direct role of OA to increase the risk of dementia and CIM could be through local inflammatory cytokines. An experimental OA animal model supports this view: interleukin-1-beta (IL-1beta) was proposed to be one key mediator to mediate neuroinflammation and promote amyloid-beta-plaques deposition, which is a hallmark of AD[28] (Fig. 4). Beta amyloid is a neurotoxin which potentially induces neuronal loss[29] and also potentially enhances plaque formation in cerebral arteries and promote vascular dementia and CIM[30] (Fig. 4). There is a distinct possibility that local cytokines are released from hypertrophic cartilage, sclerotic subchondral bone, or inflamed synovium in OA joints and reach the brain tissue through the blood circulation and lead to neuroinflammation and cerebrovascular alteration. Different possible shared inflammatory mechanism has been reviewed recently. C-reactive protein (CRP), interleukin-6 (IL-6), oxidized LDL (ox-LDL), and reactive oxygen species (ROS) has been proposed as potential key players.[31]
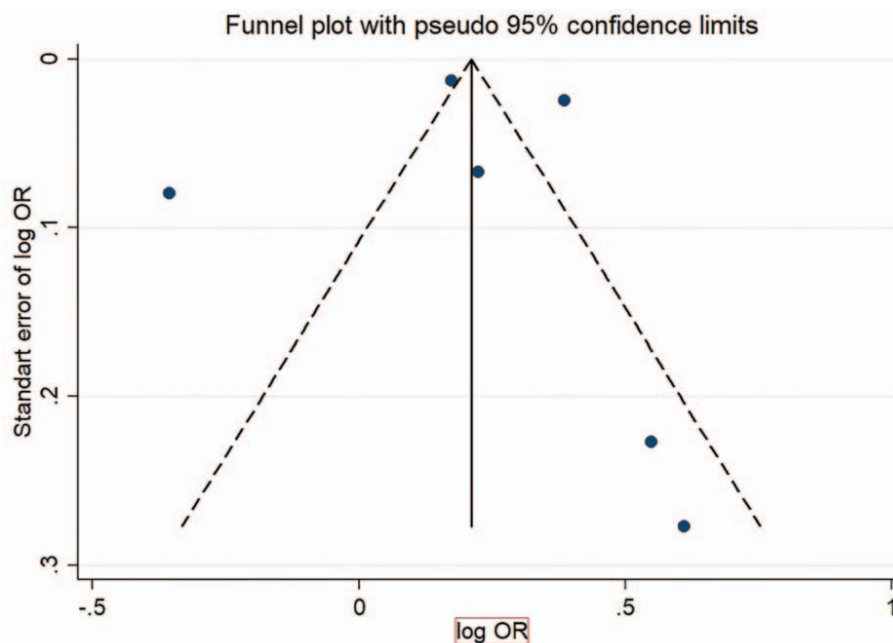
Figure 3. Funnel plot showing association of OA and dementia.

This systemic review and meta-analysis does not claim causal relationship between OA and the pathogenesis of dementia or CIM. However, it points out the importance of further investigations in OA and its associated co-morbidities. Despite our wide literature search, only a few relevant publications were found. There is clearly a lack of studies investigating in this matter.

OA and dementia are both age-associated diseases and because we are facing a growing elderly population, we will face a big burden on our society caused by both diseases. Besides increasing health costs, it has been shown that patients with hip and knee osteoarthritis were found to have a higher risk of death compared to the normal population and the mortality was pronounced with causes of death for dementia.[32] Walking disability has been proposed to be one of the major risk factor in this population.

Another problem within the OA and dementia cohort is that patients with dementia or CIM often be underdiagnosed, because the objectivation of pain and other symptoms are more difficult.[33]

In the literature search we found that OA was often used as a control group, when association between a specific disease and dementia was investigated.[19,21,34,35] The authors legitimize using OA as a control group by claiming that OA does not affect the brain's integrity.[36–38] The result of our meta-analysis suggests that this might not be the case and that the use of OA as a control group could be misleading. This is supported by a clinical study that demonstrated that half of the OA patients were in a depressive state.[39]

This meta-analysis provides a wide search for the very rear data on the link between OA and dementia. However, this study had several limitations. First, due to the lack of published data, we were not able to do subgroup-analyses for different OA localizations. Knee OA might have a different effect than hand OA. Only one abstract found investigating specifically in radiologic knee OA and showed a positive association of

increased risk of CIM.[23] The same limitation counts for dementia subgroups like AD, vascular dementia, or cognitive impairment. This study therefore provides an explorative overview between OA and dementia. To further clarify the relationships between OA and dementia, we suggest that the subgroups of dementia and primary joint-specific OA should be carefully investigated in. Prospective studies with clear disease definition could provide evidence for the increased risk and could further explore the causality. Second, we included only six studies in this meta-analysis and excluded 3 abstracts without full-text. Within these six studies the two studies from Denmark and the three studies from Taiwan, although independently conducted, they used the same databases. There is probably an overlap of data between those studies, as they also used overlapping time periods for the data extraction. In our sensitivity analysis, we can see that our result was altered in two patterns. After removing Korner 2009 and two studies from Taiwan, our result was only slightly affected, whereas the statistical significance of the summarized pooled OR was not sufficiently reached when removing Kessing 2007 and two studies from Taiwan. It suggests that the studies from Taiwan might push towards increased risk, whereas the studies from Denmark use very different data from the register. Given the fact that the number of patients in the Korner 2009 study was very small and no adjustment of gender and age was provided, the result from Korner 2009 should be assessed very carefully. Third, the included studies are observational studies and do not clarify if the association is causal and do not elucidate possible underlying mechanism.

In summary, this meta-analysis supports mounting evidence that OA is a systemic associated disease. There is an association between OA and risk of dementia. However, it does not provide causality, nor can we state that the risk of dementia can be improved by treating OA. Further prospective cohort studies are needed to clarify whether OA is an independent risk factor for dementia.
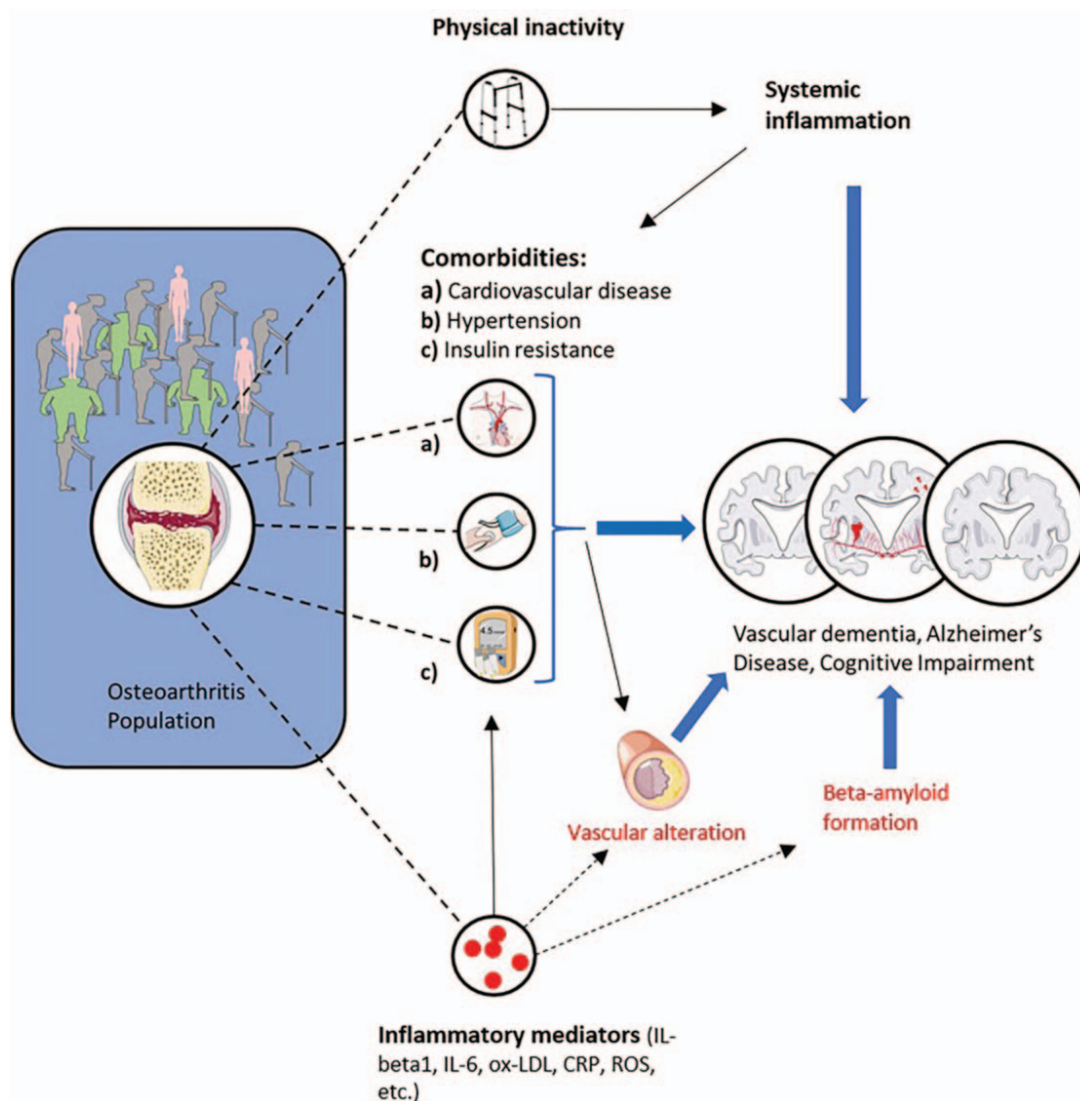
Figure 4. Possible association between osteoarthritis and increased risk for dementia. Frequent age-related comorbidities and physical inactivity in osteoarthritis patients increase risk for Alzheimer's disease, vascular dementia, and cognitive impairment. Local inflammatory mediators can reach the brain through the blood-circulation and directly lead to accelerated beta-amyloid plaques in Alzheimer's disease. Local inflammatory mediators could accelerate vascular alteration and lead to vascular dementia.

Author contributions

AW takes responsibility for the integrity of the work as a whole, from inception to the finished manuscript.
Conception and design: AW, CW, ShM.
Collection and assembly of data: AW, ShM.
Analysis and interpretation of the data: AW, CW, ShM, FB, JS.
Drafting and final approval of the manuscript: AW, CW, ShM, FB, JS, YH, YPZ.
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Formal analysis: Adrian Weber, Shing hung Mak, Chunyi Wen.
Funding acquisition: Chunyi Wen.
Investigation: Adrian Weber, Shing hung Mak, Chunyi Wen.
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Project administration: Adrian Weber, Shing hung Mak, Chunyi Wen.
Resources: Adrian Weber, Shing hung Mak, Chunyi Wen.

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Visualization: Adrian Weber, Shing hung Mak, Chunyi Wen.
Writing – original draft: Adrian Weber, Shing hung Mak, Francis Berenbaum, Jérémie Sellam, Yong-Ping Zheng, Chunyi Wen.
Writing – review & editing: Adrian Weber, Shing hung Mak, Francis Berenbaum, Jérémie Sellam, Yong-Ping Zheng, Yifan Han, Chunyi Wen.

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