BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080387
Article Type:	Original research
Date Submitted by the Author:	29-Sep-2023
Complete List of Authors:	Uematsu, Takuya; Juntendo University School of Medicine Graduate School of Medicine, Nojiri, Shuko ; Juntendo University School of Medicine Graduate School of Medicine, Clinical Translational Science; Juntendo University Ishijima, Muneaki; Juntendo University, Nishizaki, Yuji; Juntendo University,
Keywords:	EPIDEMIOLOGIC STUDIES, HISTORY (see Medical History), Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Case-Control Studies, Cardiac Epidemiology < CARDIOLOGY

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Association Between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An Administrative Claims Database Analysis

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ABSTRACT

Objective: This study aimed to investigate whether osteoarthritis (OA) is a risk factor for cardiovascular disease (CVD); whether there are differences concerning ischemic heart disease (IHD), congestive heart failure (CHF), and stroke; and whether there are differences between OA sites (knee and hip) in predicting CVD onset.

Design: Population-based matched case–control study.

Setting: Health insurance claims data among Japanese patients.

Participants: Japanese patients aged ≥65 years with newly diagnosed CVD and hospitalized between January 2015 and December 2020 (cases) and age- and sex-matched 1:1 individuals (controls) were included in the study.

Main outcome measures: A conditional logistic regression model was fitted to estimate the adjusted odds ratios (OR) and their 95% confidence intervals (CI) for the risk of CVD, IHD, CHF, and stroke, adjusting for covariates.

Results: A total of 79,296 patients were included, with respect to CVD (39648 patients with newly diagnosed CVD between January 2015 and December 2020 and 39648 controls matched 1:1 by age and sex). After adjustment for covariates, the knee OA (KOA) exposure odds for CVD was 1.184 (95% CI, 1.108–1.265), and the hip OA (HipOA) exposure odds for CVD was 0.961 (95% CI, 0.839–1.102), showing an association only for KOA. The exposure odds of KOA and HipOA for IHD were 1.215 (95% CI, 1.111–1.328) and 0.951 (95% CI, 0.79–1.146), respectively. The exposure odds of KOA and HipOA for stroke were 1.172 (95% CI, 1.057–1.3) and 0.894 (95% CI, 0.708–1.13), respectively. As with CVD, only KOA was found to be associated with both. For CHF, neither KOA nor HipOA was associated with CHF development.

Conclusion: This study confirms the association of KOA with CVD, particularly IHD and stroke, in the Japanese population. The finding that patients with KOA have a higher CVD risk can potentially assist in guiding future treatment strategies.

Strengths and limitations of this study

- This study examined the association between osteoarthritis (OA) and cardiovascular disease (CVD) in a matched case–control study using large real-world data from approximately 80,000 inpatients at various hospitals in Japan.
- The results of this study, which showed an association between KOA and CVD in Japan's super-aging population, may contribute to CVD prevention strategies in the future.
- Data were obtained only from inpatients admitted to hospitals registered in the Japanese administrative database; thus, selection bias and generalizability should be considered.
- Data analyzed were based on health insurance claims and were not generated for research purposes; thus, potential confounding factors that may affect clinical practice, such as environmental and lifestyle factors, cannot be assessed.

INTRODUCTION

Cardiovascular disease (CVD) is composed of diseases related to the heart or blood vessels, such as ischemic heart disease (IHD), congestive heart failure (CHF), and stroke. It accounts for a significant portion of morbidity and mortality rates worldwide, including Japan [1]. Annually, approximately 17 million people globally die from CVD, particularly because of heart attacks and strokes [2]. On the other hand, osteoarthritis (OA), a degenerative disease, typically occurs in middle-aged and older individuals, gradually progressing with the degeneration of joint cartilage [3, 4]. It can potentially affect joints throughout the body, including the knees, hips, lumbar spine, and hands, and is one of the fastest-growing diseases worldwide. In Japan, the number of patients with OA is increasing rapidly because of the aging population, with approximately 25 million people suffering from knee OA (KOA) alone [5]. As the disease progresses, severe pain and other subjective symptoms occur, which not only reduces the quality of life, but also limits treatment options. In Japan, among reasons for requiring caregiving services, the second most common cause is cerebrovascular diseases (16.6%), the fourth is fractures and falls (12.1%), the fifth is joint diseases (10.2%), and the sixth is heart diseases (4.6%), with OA- and CVD-related issues comprising nearly half of the cases [6]. Therefore, early treatment initiation as a preventive measure is considered crucial for extending healthy life expectancy and reducing healthcare costs.

CVD and OA can be prevented through appropriate timing of drug therapy and nonpharmacological interventions. Identifying individuals with a high risk of developing CVD, which contributes significantly to mortality rates, is of utmost importance for public health. Many people who experience CVD have multiple traditional risk factors such as obesity, hypertension, diabetes, chronic kidney disease, dyslipidemia, and smoking. Recent studies have revealed that some of these risk factors are also directly or indirectly involved in the pathogenesis of OA [7]. A recent meta-analysis indicated that individuals with OA have a high CVD risk [8]. However, the interrelationship between OA and CVD and its potential mechanisms are complex, and whether OA increases the risk of CVD independent of the abovementioned risk factors is unclear. Although some studies have investigated the relationship between OA and CVD internationally, to our knowledge, no clinical studies have used large-scale data from Japan. As lifestyle, genetic factors, body type, and population characteristics vary between Japan and other countries, research on this topic, specifically in Japan, is necessary.

Therefore, this study, using data with a high number of variables, such as Medical Data Vision (MDV) data, in Japan, which is experiencing super-aging, aimed to determine whether the presence of OA is a risk factor for CVD development, whether there are differences among IHD, CHF, and stroke, and whether there is any difference between CVD risk and OA sites (hips and knees).

METHODS

Study design and study population

This study employed a population-based case–control matching study design, and a retrospective evaluation was conducted using real-world data from Japanese MDV health insurance claims data. This

dataset covers approximately 22% of diagnosis procedure combination (DPC) hospitals, which include many acute care hospitals across Japan. It is composed of electronic health insurance claims data, DPC claims, and laboratory test results [9].

Approximately one million individuals were randomly selected from 35.23 million older patients who were attending 438 DPC hospitals under contract with MDV among the entire older population in Japan. Disease-related information included the International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis codes, Japanese disease codes, and diagnosis dates. Medication-related data included health insurance claims codes, prescription dates, administration routes, and prescription quantities. All patient data were coded before entry into the database.

Selection of cases and controls

Cases were defined by mapping the disease codes in the dataset to the master codes for CVD, stroke, IHD, and CHF and limiting them to confirmed disease names. Each master code was defined based on the following ICD-10 diagnosis codes: IHD (I20–I25), CHF (I50), stroke (I60–I64), and CVD (I20–I25, I50, I60–I64) [10]. Cases were defined as patients aged ≥65 years who were first diagnosed with the target disease between January 2015 and December 2020, with the diagnosis date serving as the index date. Controls were randomly assigned index dates.

The age of the patients was categorized into 5-year intervals, and 1:1 matching was performed based on age and sex. In cases where there were multiple potential controls for a single case, control individuals were randomly selected from among them.

According to Yamana et al., the validity of diagnoses within the DPC database demonstrated a sensitivity and specificity of 78.9% and 93.2%, respectively. Although variations were observed among different medical conditions, the overall results indicated favorable accuracy without significant diagnostic inaccuracies [11].

Definition of OA and covariates

HipOA (M160–M169) and KOA (M170-M179) were defined as exposure factors. Covariates included common risk factors for CVD, such as type 2 diabetes mellitus, essential (primary) hypertension, atrial fibrillation and flutter, chronic kidney disease, disorders of lipoprotein metabolism and other lipidemias, and medications related to CVD treatment: oral antidiabetic drugs, platelet aggregation inhibitors, diuretics, beta-blocking agents, calcium antagonists, agents acting on the renin–angiotensin system, and lipid-regulating/anti-atheroma preparations (Appendix 1).

The types of medications and comorbidities were obtained from the MDV database. For medications, the unique nine-digit health insurance claims codes, which are assigned to each drug based on its pharmacological properties, were mapped to five-digit codes according to the Anatomical Therapeutic Chemical Classification System managed by the European Pharmaceutical Marketing Research Association [12]. The start date of medication use was set as before the index date, and medications that were being continued at the index date or had an end date within 7 days of the index date were considered. In other

words, a grace period of 7 days was set after the prescription end date, and all medications that were taken at least once within 7 days from the index date were considered to affect the outcome.

Complications were included only when a confirmed diagnosis of the disease was established, and they were mapped using ICD-10 codes. Comorbidities with diagnosis dates before the index date and no end dates were registered until the index date were extracted. Based on this information, concomitant medications and comorbidities were extracted from the MDV database. The explanatory variables included sex, age, comorbidities based on ICD-10 codes, and concomitant medications based on ATC codes.

Statistical analysis

Sex, concomitant medications, and comorbidities were treated as binary variables. The characteristics of the case and control groups regarding age, sex, comorbidities, and concomitant medications were summarized using mean, standard deviation, and proportions as descriptive statistics. Furthermore, a conditional logistic regression model was applied to estimate the odds ratios (OR) and their 95% confidence intervals (CI) for the risk of developing CVD, IHD, CHF, and stroke. Adjustments were made for the covariates mentioned above. All analyses were conducted using R version 4.1.0 (http://www.r-project.org/), and the "clogit" package was used for the conditional logistic regression.

Patient and Public Involvement

This study will not have any patient or public involvement because it is health insurance claims data.

RESULTS

Characteristics of the study population

The study population was based on approximately one million MDV data; initially, cases and controls meeting the selection criteria were extracted, followed by those meeting the criteria for "Definition of OA and covariates." Finally, 1:1 matching based on age and sex was conducted. The total number of participants, including the case and control groups for each condition, is as follows: CVD (IHD, CHF, and stroke), 39,648 in each group, totaling 79,296; stroke, 14,944 in each group, totaling 29,888; IHD, 22,996 in each group, totaling 45,992; CHF, 31,639 in each group, totaling 63,278 (Fig. 1). The mean age of CVD occurrence was 78.6 (SD 7.3) years, and 54.4% were males and 45.6% were females. In addition, Table 1 shows the percentage of patients with comorbidities and concomitant medications. IHD, CHF, and stroke are shown in Appendices 2, 4, and 6, respectively.

184 **Table 1. Characteristics of patients with CVD and controls.**

		Case group (n = 39648) N (%)	Control group (n = 39648) N (%)	Std diff
Age	**Mean (SD)**	**78.6 (7.3)**	**78.6 (7.3)**	
Sex	**Male**	**21551 (54.4)**	**21551 (54.4)**	
	Female	**18097 (45.6)**	**18097 (45.6)**	
Complication				
Type 2 diabetes mellitus		**6322 (15.9)**	**4511 (11.4)**	**0.133135**
Essential (primary) hypertension		**13368 (33.7)**	**9954 (25.1)**	**0.18983**
Atrial fibrillation and flutter		**3256 (8.2)**	**1093 (2.8)**	**0.241354**
Chronic kidney disease		**2711 (6.8)**	**1151 (2.9)**	**0.183422**
Disorders of lipoprotein metabolism and other lipidemias		**6566 (16.6)**	**5002 (12.6)**	**0.111926**
Knee osteoarthritis		**2416 (6.1)**	**2052 (5.2)**	**0.039482**
Hip osteoarthritis		**493 (1.2)**	**496 (1.2)**	**0.000684**
Concomitant medication				
Oral antidiabetic drugs		**5150 (13.0)**	**3328 (8.4)**	**0.14913**
Platelet aggregation inhibitors		**6712 (16.9)**	**2796 (7.0)**	**0.307715**
Diuretic		**5212 (13.1)**	**1884 (4.7)**	**0.297624**
Beta blocking agents		**4058 (10.2)**	**1068 (2.7)**	**0.311442**

Calcium antagonists	**10559 (26.6)**	**6328 (15.9)**	**0.263247**
Agents acting on the renin-angiotensin system	**9256 (23.3)**	**5263 (13.3)**	**0.262641**
Lipid-regulating/antiatheroma preparations	**7339 (18.5)**	**4566 (11.5)**	**0.19651**

CVD and osteoarthritis

In the unadjusted analysis for CVD, the OR for KOA exposure in the case group compared with the control group was 1.189 (95% CI, 1.119–1.264). The OR for HipOA exposure was 1.006 (95% CI, 0.887–1.141), indicating no significant association. After adjusting for covariates, the OR for KOA exposure was 1.184 (95% CI, 1.108–1.265), showing a significant association with CVD occurrence. The OR for HipOA exposure was 0.961 (95% CI, 0.839–1.102), still showing no significant association (Table 2). Similarly, in the unadjusted analysis for IHD, the OR for KOA exposure was 1.165 (95% CI, 1.075–1.262), whereas the OR for HipOA exposure was 0.932 (95% CI, 0.787–1.103), with no significant association. After adjusting for covariates, the OR for KOA exposure was 1.215 (95% CI, 1.111–1.328), showing a significant association with IHD occurrence; however, the OR for HipOA exposure was 0.951 (95% CI, 0.79–1.146), indicating no significant association (Appendix 3). For CHF, the unadjusted analysis showed ORs of 1.021 (95% CI, 0.953–1.095) and 0.943 (95% CI, 0.814–1.092) for KOA and HipOA exposures, respectively. After adjusting for covariates, the ORs for KOA and HipOA exposures were 1.056 (95% CI, 0.975–1.144) and 0.923 (95% CI, 0.78–1.092), respectively, indicating that neither had a significant association with CHF occurrence (Appendix 5). Finally, for stroke, the unadjusted analysis showed ORs of 1.219 (95% CI, 1.105–1.344) and 0.944 (95% CI, 0.757–1.178) for KOA and HipOA exposures, respectively. After adjusting for covariates, the OR for KOA exposure was 1.172 (95% CI, 1.057–1.3), indicating a significant association with stroke occurrence, whereas the OR for HipOA exposure was 0.894 (95% CI, 0.708–1.13), showing no significant association (Appendix 7).

205 **Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA and HipOA.**

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.482	1.422	1.545	1.18	1.13	1.251
Essential (primary) hypertension	1.515	1.469	1.563	1.02	0.983	1.063
Atrial fibrillation and flutter	3.137	2.923	3.367	2.49	2.313	2.693
Chronic kidney disease	2.489	2.317	2.674	1.82	1.685	1.972
Disorders of lipoprotein metabolism and other lipidemias	1.377	1.323	1.433	1.01	0.959	1.064
Knee osteoarthritis	1.189	1.119	1.264	1.18	1.108	1.265
Hip osteoarthritis	1.006	0.887	1.141	0.96	0.839	1.102
Oral antidiabetic drugs	1.635	1.561	1.713	1.08	1.045	1.174
Platelet aggregation inhibitors	2.676	2.552	2.806	2.21	2.105	2.331
Diuretic	3.061	2.894	3.238	2.13	2.008	2.268
Beta blocking agents	4.143	3.86	4.446	2.49	2.314	2.694
Calcium antagonists	1.918	1.851	1.988	1.24	1.197	1.306
Agents acting on the renin-angiotensin system	1.999	1.925	2.077	1.25	1.199	1.317
Lipid-regulating/antiatheroma preparations	1.754	1.684	1.826	1.12	1.069	1.188

Discussion

To our knowledge, this study is the first large-scale population-based case–control study conducted on Japanese individuals, evaluating the relationship between OA and CVD risk using administrative claims database. In this study, after adjusting for various potential confounding factors, KOA was found to be associated with an increased risk of CVD. Furthermore, the subgroup analysis revealed that patients with KOA had an increased risk of IHD and stroke.

According to the population-based study by Nuesch et al., patients with KOA and HipOA have higher overall mortality rates than the general population, particularly with a significant association with CVD and dementia-associated mortality [13]. Goel et al. found a strong relationship between KOA and CVD, and the cardiovascular risk score positively correlated with the OA severity [14]. On the contrary, in their prospective population-based cohort study, Hoeven et al. reported no significant association between CVD risk and clinical or radiographic knee, hip, and hand OA [15]. While the relationship between OA and CVD remains debatable, many studies have suggested that a potential increase in CVD risk is associated with OA [16].

The underlying fundamental mechanisms linking the risks of OA and CVD remain unclear; however, several mechanisms have been proposed to explain the association between OA and CVD. First and foremost, a shared risk factor aspect involves metabolic syndrome components such as diabetes, dyslipidemia, and hypertension, which are common to both OA and CVD [17-21]. However, these factors may act as confounding variables. Therefore, if the increased risk of CVD persists even after conducting multivariate analysis accounting for these factors, it can imply an independent association between OA and CVD. Second, the induction of inflammatory responses associated with cytokines is another point of consideration. Nuesch et al. reported that walking disability, along with OA, was associated with high CVD-related mortality, and Hoeven et al. reported that some forms of disability in daily activities, rather than OA itself, were associated with CVD onset [13, 15]. OA development can lead to severe joint pain, ultimately resulting in walking disability and decreased physical activity over time. Reduced physical activity can lead to the accumulation of visceral fat, i.e., hypertrophy of fat cells, which, in turn, increases the secretion of inflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6). Many of these inflammatory processes and cytokines also contribute to the development of vascular inflammation underlying conditions such as hypertension, myocardial infarction, heart failure, and cerebrovascular disorders, which are components of many CVDs [22-24]. Moreover, Yoshimura et al. reported that the risk of KOA development increases with the presence of hypertension and impaired glucose tolerance; conversely, the coexistence of KOA increases the risk of developing hypertension and dyslipidemia [25]. These findings indicate a mutual relationship between the development and coexistence of KOA and metabolic syndrome components.

The study found associations of KOA with IHD and stroke, but no association of KOA with CHF. In a meta-analysis, Hall et al. found that patients with OA had a significantly increased CHF and IHD risk compared with patients without OA; however, no significant difference was observed in stroke risk [8]. A Mendelian randomization study by Wang et al. showed a potential causal relationship between hip OA and CHF along with stroke, but no association of hip OA with IHD. Although no significant associations were observed in all aspects with KOA, IHD strongly correlated with KOA onset [26]. Rahman et al. reported a

significant association of OA with IHD and CHF in individuals aged ≥65 years, but no association of OA with myocardial infarction or stroke [27]. Overall, results regarding the association with stroke, IHD, and CHF vary among studies, and why only CHF among CVDs showed no association with OA in the present study remains unclear. However, one hypothesis could be that patients with OA generally have reduced physical activity [28, 29] and are less likely to experience overexertion in daily life. Consequently, there may be less strain on the heart, which does not increase the CHF risk.

In this study, no associations were observed in HipOA. Macêdo et al. found that both HipOA and KOA increase the risk of subclinical atherosclerosis and CVD, whereas hand OA showed no association with CVD [30]. Tsuboi et al. reported that when KOA coexists, the odds of death after 10 years significantly increased; however, no significant difference was observed when coexisting with lower back abnormalities [31]. These authors explain this phenomenon from the perspective of weight-bearing joints. In the present study, KOA showed a significant association; however, hip OA did not. One possible reason is that the knee is a weight-bearing joint more than the hip, which may lead to excessive stress on the bones and cartilage because of biomechanical load caused by the body weight, increasing the risk for KOA development and leading to more significant inflammatory reactions and a more pronounced association with CVD. Moreover, a strong correlation was found between KOA and physical activity; however, the association with HipOA is weaker than that with KOA, as suggested by previous studies [32, 33]. This indicates that the knee is more susceptible to physical stress than the hip.

Strengths and limitations

This study has some limitations. First, the case–control study design allows us to establish an association between knee OA and CVD; however, a causal relationship could not be established. Second, the diagnosis of OA was based solely on cases diagnosed by physicians, which may have underestimated the results by not considering patients with asymptomatic OA who do not exhibit symptoms such as pain. Third, the data used in this study only included acute care hospital data from the MDV database, which may have a higher likelihood of including patients with more severe conditions and multiple comorbidities than the general population. Fourth, lifestyle factors such as alcohol consumption, smoking, and exercise habits were not considered. Finally, this study was conducted using Japanese insurance claims data, and there may be limitations in generalizing our research findings to other ethnic groups.

Despite these limitations, this study has several strengths that outweigh them. First, the study has a large sample size, and a case–control study design was employed while adjusting for multiple important confounding factors. In addition, health administrative data were used to verify the outcomes, providing more robust evidence in a real clinical setting.

Conclusion

This study research emphasizes the potential association between KOA and increased CVD risk in real-world data of older Japanese individuals. Furthermore, KOA is associated with an increased risk of IHD and stroke. Given that KOA and CVD are both significant public health issues, early intervention for KOA is

desired to prevent CVD. Our findings may aid in making informed decisions for further management of KOA.

Acknowledgments

Competing interests

None declared.

Funding

The authors did not receive a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Contributors

All authors are responsible for the work described in this paper. TU, SN, and YN contributed to the conception, design, or planning of the study. TU, SN, and YN contributed to the data analysis. MI contributed to data interpretation, commented on expert perspectives, and reviewed and edited the article draft. All authors read and provided final approval of the final article to be published. The lead author confirmed that the manuscript is an integrate, accurate, and transparent description of the reported study.

Patient consent for publication

Not required.

Disclaimer

No endorsement by MDV is intended nor should be inferred. The papers reported are those of the authors.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

Although the data are available from Medical Data Vision, the use of data in this study is under license and not publicly available.

Ethics approval

This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare, Japan. It was approved by the Research Ethics Committee, Faculty of Medicine, Juntendo University (Research permit no. E21-0264-M01).

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FIGURE LEGEND

Figure 1. Flowchart of cases and controls.

MDV, medical data vision.

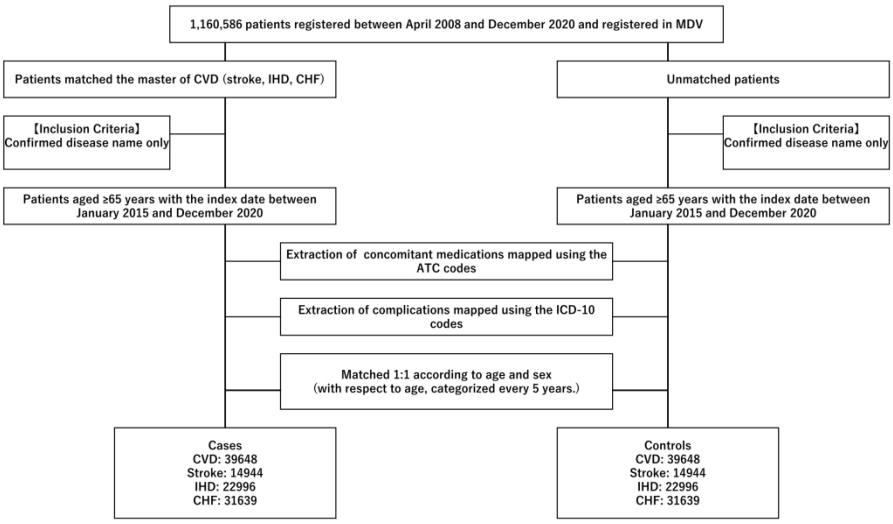
TABLES

Table 1. Characteristics of patients with CVD and controls.

SD, standard deviation; Std diff, standardized difference.

Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA and HipOA

CI, confidence interval.



338x190mm (300 x 300 DPI)

Indexed according to the ICD-10 codes	Category of complications
E110-E119	Type 2 diabetes mellitus
E780-E789	Disorders of lipoprotein metabolism and other lipidemias
I10	Essential (primary) hypertension
I480-I489	Atrial fibrillation and flutter
N180-N189	Chronic kidney disease

Indexed according to ATC codes	Category of concomitant medications
A10H0-A10P5	Oral antidiabetic drugs
B01C1-B01C9	Platelet aggregation inhibitors
C03A1-C03A9	Diuretic
C07A0	Beta blocking agents
C08A0	Calcium antagonists
C09A0-C09X0	Agents acting on the renin-angiotensin system
C10A1-C10C0	Lipid-regulating/antiatheroma preparations

Appendix 1.

Covariates classification based on ICD-10 codes and ATC codes.

ICD-10, International Classification of Diseases, 10th Revision

ATC, Anatomical Therapeutic Chemical Classification System

		Case group (n =22996)	Control group (n =22996)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**78.6 (7.2)**	**78.5 (7.3)**	
Sex	**Male**	**12965 (56.4)**	**12965 (56.4)**	
	Female	**10031 (43.6)**	**10031 (43.6)**	
Complication				
Type 2 diabetes mellitus		**5676 (24.7)**	**3742 (16.3)**	**0.2096**
Essential (primary) hypertension		**12321 (53.6)**	**9191 (40.0)**	**0.2754**
Atrial fibrillation and flutter		**2945 (12.8)**	**1538 (6.7)**	**0.2074**
Chronic kidney disease		**1914 (8.3)**	**1005 (4.4)**	**0.1627**
Disorders of lipoprotein metabolism and other lipidemias		**4850 (21.1)**	**3634 (15.8)**	**0.1367**
Knee osteoarthritis		**1376 (6.0)**	**1194 (5.2)**	**0.0345**
Hip osteoarthritis		**261 (1.1)**	**280 (1.2)**	**-0.0077**
Concomitant medication				
Oral antidiabetic drugs		**3593 (15.6)**	**2227 (9.7)**	**0.1794**
Platelet aggregation inhibitors		**6357 (27.6)**	**2669 (11.6)**	**0.4123**
Diuretic		**4785 (20.8)**	**2287 (9.9)**	**0.3046**
Beta blocking agents		**4197 (18.3)**	**1425 (6.2)**	**0.3744**
Calcium antagonists		**6872 (29.9)**	**4553 (19.8)**	**0.235**
Agents acting on the renin-angiotensin system		**6574 (28.6)**	**4108 (17.9)**	**0.256**
Lipid-regulating/antiatheroma preparations		**5579 (24.3)**	**3328 (14.5)**	**0.2496**

Appendix 2.

Characteristics of patients with IHD and controls.

SD, standard deviation; Std diff, standardized difference.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.694	1.616	1.775	1.364	1.284	1.449
Essential (primary) hypertension	1.74	1.676	1.808	1.195	1.12	1.233
Atrial fibrillation and flutter	2.056	1.926	2.195	1.49	1.384	1.604
Chronic kidney disease	1.973	1.824	2.135	1.414	1.295	1.543
Disorders of lipoprotein metabolism and other lipidemias	1.425	1.358	1.494	0.946	0.892	1.007
Knee osteoarthritis	1.165	1.075	1.262	1.215	1.111	1.328
Hip osteoarthritis	0.932	0.787	1.103	0.953	0.79	1.146
Oral antidiabetic drugs	1.74	1.643	1.842	1.051	0.977	1.136
Platelet aggregation inhibitors	2.899	2.753	3.053	2.375	2.25	2.516
Diuretic	2.441	2.309	2.582	1.462	1.374	1.562
Beta blocking agents	3.423	3.205	3.656	2.272	2.115	2.45
Calcium antagonists	1.737	1.662	1.815	1.093	1.034	1.152
Agents acting on the renin-angiotensin system	1.851	1.769	1.937	1.053	0.998	1.119
Lipid-regulating/antiatheroma preparations	1.895	1.805	1.988	1.209	1.135	1.287

Appendix 3.

Crude and adjusted ORs and 95% CIs of IHD in relation to KOA and HipOA.

CI, confidence interval.

		Case group (n =31639)	Control group (n =31639)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**79.0 (7.3)**	**78.9 (7.3)**	
Sex	**Male**	**17920 (56.6)**	**17920 (56.6)**	
	Female	**13719 (43.4)**	**13719 (43.4)**	
Complication				
Type 2 diabetes mellitus		**7761 (24.5)**	**5232 (16.5)**	**0.1903**
Essential (primary) hypertension		**19164 (60.6)**	**12317 (38.9)**	**0.3065**
Atrial fibrillation and flutter		**4284 (13.5)**	**1285 (4.1)**	**0.0792**
Chronic kidney disease		**2739 (8.7)**	**1061 (3.4)**	**0.0816**
Disorders of lipoprotein metabolism and other lipidemias		**8017 (25.3)**	**5427 (17.2)**	**0.1103**
Knee osteoarthritis		**1751 (5.5)**	**1717 (5.4)**	**0.0455**
Hip osteoarthritis		**349 (1.1)**	**370 (1.2)**	**-0.0059**
Concomitant medication				
Oral antidiabetic drugs		**4756 (15.0)**	**3270 (10.3)**	**0.1458**
Platelet aggregation inhibitors		**9219 (29.1)**	**4871 (15.4)**	**0.3549**
Diuretic		**6153 (19.4)**	**1799 (5.7)**	**0.1306**
Beta blocking agents		**6412 (20.3)**	**1330 (4.2)**	**0.1359**
Calcium antagonists		**10213 (32.3)**	**6353 (20.1)**	**0.1837**
Agents acting on the renin-angiotensin system		**9909 (31.3)**	**5393 (17.0)**	**0.2133**
Lipid-regulating/antiatheroma preparations		**8958 (28.3)**	**5098 (16.1)**	**0.162**

Appendix 4.
Characteristics of patients with CHF and controls.
SD, standard deviation; Std diff, standardized difference.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.649	1.585	1.716	1.326	1.256	1.4
Essential (primary) hypertension	2.415	2.335	2.497	1.564	1.497	1.634
Atrial fibrillation and flutter	3.769	3.525	4.03	2.889	2.682	3.112
Chronic kidney disease	2.719	2.527	2.926	1.832	1.685	1.992
Disorders of lipoprotein metabolism and other lipidemias	1.636	1.574	1.701	0.941	0.892	0.992
Knee osteoarthritis	1.021	0.953	1.095	1.053	0.975	1.144
Hip osteoarthritis	0.943	0.814	1.092	0.923	0.78	1.092
Oral antidiabetic drugs	1.54	1.468	1.616	0.837	0.78	0.893
Platelet aggregation inhibitors	2.25	2.162	2.342	1.515	1.442	1.588
Diuretic	4.068	3.839	4.312	2.744	2.574	2.926
Beta blocking agents	5.877	5.504	6.276	3.334	3.096	3.572
Calcium antagonists	1.893	1.824	1.964	0.993	0.947	1.042
Agents acting on the renin-angiotensin system	2.231	2.146	2.32	1.119	1.064	1.179
Lipid-regulating/antiatheroma preparations	2.058	1.979	2.141	1.197	1.132	1.266

Appendix 5.

Crude and adjusted ORs and 95% CIs of CHF in relation to KOA and HipOA.

CI, confidence interval.

		Case group (n =14944)	Control group (n =14944)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**79.1 (7.2)**	**79.1 (7.2)**	
Sex	**Male**	**8657 (57.9)**	**8657 (57.9)**	
	Female	**6287 (42.1)**	**6287 (42.1)**	
Complication				
Type 2 diabetes mellitus		**3900 (26.1)**	**2724 (18.2)**	**0.1903**
Essential (primary) hypertension		**8830 (59.1)**	**6567 (44.0)**	**0.3065**
Atrial fibrillation and flutter		**1605 (10.7)**	**1257 (8.4)**	**0.0792**
Chronic kidney disease		**1195 (8.0)**	**885 (6.0)**	**0.0816**
Disorders of lipoprotein metabolism and other lipidemias		**3605 (24.1)**	**2925 (19.6)**	**0.1103**
Knee osteoarthritis		**959 (6.4)**	**799 (5.3)**	**0.0455**
Hip osteoarthritis		**154 (1.0)**	**163 (1.1)**	**-0.0059**
Concomitant medication				
Oral antidiabetic drugs		**2365 (15.8)**	**1626 (10.9)**	**0.1458**
Platelet aggregation inhibitors		**4503 (30.1)**	**2312 (15.5)**	**0.3549**
Diuretic		**2776 (18.6)**	**2059 (13.8)**	**0.1306**
Beta blocking agents		**2340 (15.7)**	**1651 (11.0)**	**0.1359**
Calcium antagonists		**4404 (29.5)**	**3213 (21.5)**	**0.1837**
Agents acting on the renin-angiotensin system		**4409 (29.5)**	**3038 (20.3)**	**0.2133**
Lipid-regulating/antiatheroma preparations		**3794 (25.4)**	**2794 (18.7)**	**0.162**

Appendix 6.

Characteristics of patients with stroke and controls.

SD, standard deviation; Std diff, standardized difference.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.594	1.507	1.686	1.285	1.198	1.378
Essential (primary) hypertension	1.848	1.763	1.937	1.504	1.418	1.595
Atrial fibrillation and flutter	1.312	1.214	1.418	1.117	1.08	1.282
Chronic kidney disease	1.378	1.26	1.508	1.045	0.95	1.154
Disorders of lipoprotein metabolism and other lipidemias	1.309	1.238	1.383	0.903	0.841	0.966
Knee osteoarthritis	1.219	1.105	1.344	1.112	1.057	1.3
Hip osteoarthritis	0.944	0.757	1.178	0.894	0.708	1.13
Oral antidiabetic drugs	1.541	1.44	1.65	1.063	0.922	1.096
Platelet aggregation inhibitors	2.375	2.24	2.519	2.086	1.956	2.226
Diuretic	1.438	1.35	1.532	1.061	0.99	1.143
Beta blocking agents	1.495	1.397	1.6	0.958	0.883	1.035
Calcium antagonists	1.527	1.448	1.61	1.061	1	1.133
Agents acting on the renin-angiotensin system	1.639	1.553	1.729	1.088	1.02	1.163
Lipid-regulating/antiatheroma preparations	1.479	1.399	1.564	0.962	0.895	1.035

Appendix 7.

Crude and adjusted ORs and 95% CIs of stroke in relation to KOA and HipOA.

CI, confidence interval.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P2 L44~
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2 L39~
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3 L77~
Objectives	3	State specific objectives, including any prespecified hypotheses	P3 L105~
Methods			
Study design	4	Present key elements of study design early in the paper	P3 L112~
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3 L113~
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	P4 L125~
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P4 L131~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P4 L140~
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4 L113~
Bias	9	Describe any efforts to address potential sources of bias	P4 L131~
Study size	10	Explain how the study size was arrived at	P5 L176~
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P5 L161~
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P5 L161~
		(*b*) Describe any methods used to examine subgroups and interactions	P5 L161~
		(*c*) Explain how missing data were addressed	
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	P4 L131~
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P5 L174~
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P5 L179~
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Table1
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P4 L139~ P8 L185~
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8 L190~
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10 L207~
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P11 L264~
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11 L278~
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11 L271~
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P12 L291~

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An Administrative Claims Database Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080387.R1
Article Type:	Original research
Date Submitted by the Author:	13-Feb-2024
Complete List of Authors:	Uematsu, Takuya; Juntendo University School of Medicine Graduate School of Medicine, Nojiri, Shuko ; Juntendo University School of Medicine Graduate School of Medicine, Clinical Translational Science; Juntendo University Ishijima, Muneaki; Juntendo University, Nishizaki, Yuji; Juntendo University,
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Research methods
Keywords:	EPIDEMIOLOGIC STUDIES, HISTORY (see Medical History), Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Case-Control Studies, Cardiac Epidemiology < CARDIOLOGY

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Association between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An Administrative Claims Database Analysis

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ABSTRACT

Objective: To investigate whether osteoarthritis (OA) is a risk factor for cardiovascular disease (CVD); whether there are differences concerning ischemic heart disease (IHD), congestive heart failure (CHF), and stroke; and whether there are differences between OA sites (hips, knees, and hand) in predicting CVD onset

Design: Population-based matched case–control study

Setting: Health insurance claims data among Japanese patients

Participants: Japanese patients aged ≥65 years with newly diagnosed CVD and hospitalized between January 2015 and December 2020 (cases) and age- and sex-matched 1:1 individuals (controls)

Main outcome measures: A conditional logistic regression model was used to estimate the adjusted odds ratios (OR) and their 95% confidence intervals (CI) for CVD, IHD, CHF, and stroke risk, adjusting for covariates.

Results: A total of 79,296 patients were included, with respect to CVD (39648 patients with newly diagnosed CVD and 39648 controls). After adjustment for covariates, the exposure odds of knee OA (KOA), hip OA (HipOA), and hand OA (HandOA) for CVD were 1.192 (95% CI, 1.115–1.274), 1.057 (95% CI, 0.919–1.215), and 1.035 (95% CI, 0.684–1.566), respectively, showing an association only for KOA. The exposure odds of KOA, HipOA, and HandOA for IHD were 1.187 (95% CI, 1.086–1.297), 1.078 (95% CI, 0.891–1.306), and 1.099 (95% CI, 0.677–1.784), respectively. The exposure odds of KOA, HipOA, and HandOA for stroke were 1.221 (95% CI, 1.099–1.356), 0.918 (95% CI, 0.723–1.165), and 1.169 (95% CI, 0.635–2.151), respectively. Similar to CVD, only KOA was associated with both. For CHF, neither KOA nor HipOA and HandOA were associated with CHF development.

Conclusion: This study confirms the association of KOA with CVD, particularly IHD and stroke, in the Japanese population. The finding that patients with KOA have a higher CVD risk can potentially assist in guiding future treatment strategies.

Strengths and limitations of this study

- This study examined the association between osteoarthritis (OA) and cardiovascular disease (CVD) in a matched case–control study using large real-world data from approximately 80,000 inpatients at various hospitals in Japan.
- The results of this study, which showed an association between KOA and CVD in Japan's super-aging population, may contribute to CVD prevention strategies in the future.
- Data were obtained only from inpatients admitted to hospitals registered in the Japanese administrative database; thus, selection bias and generalizability should be considered.
- Data analyzed were based on health insurance claims and were not generated for research purposes; thus, potential confounding factors that may affect clinical practice, such as environmental and lifestyle factors, cannot be assessed.

INTRODUCTION

Cardiovascular disease (CVD) is composed of diseases related to the heart or blood vessels, such as ischemic heart disease (IHD), congestive heart failure (CHF), and stroke. It accounts for a significant portion of morbidity and mortality rates worldwide, including Japan [1]. Annually, approximately 17 million people globally die from CVD, particularly because of heart attacks and strokes [2]. On the other hand, osteoarthritis (OA), a degenerative disease, typically occurs in middle-aged and older individuals, gradually progressing with the degeneration of joint cartilage [3, 4]. It can potentially affect joints throughout the body, including the knees, hips, lumbar spine, and hands, and is one of the fastest-growing diseases worldwide. In Japan, the number of patients with OA is increasing rapidly because of the aging population, with approximately 25 million people suffering from knee OA (KOA) alone [5]. As the disease progresses, severe pain and other subjective symptoms occur, which not only reduces the quality of life, but also limits treatment options. In Japan, among reasons for requiring caregiving services, the second most common cause is cerebrovascular diseases (16.6%), the fourth is fractures and falls (12.1%), the fifth is joint diseases (10.2%), and the sixth is heart diseases (4.6%), with OA- and CVD-related issues comprising nearly half of the cases [6]. Therefore, early treatment initiation as a preventive measure is considered crucial for extending healthy life expectancy and reducing healthcare costs.

CVD and OA can be prevented through appropriate timing of drug therapy and nonpharmacological interventions. Identifying individuals with a high risk of developing CVD, which contributes significantly to mortality rates, is of utmost importance for public health. Many people who experience CVD have multiple traditional risk factors such as obesity, hypertension, diabetes, chronic kidney disease, dyslipidemia, and smoking. Recent studies have revealed that some of these risk factors are also directly or indirectly involved in the pathogenesis of OA [7]. A recent meta-analysis indicated that individuals with OA have a high CVD risk [8]. However, the interrelationship between OA and CVD and its potential mechanisms are complex, and whether OA increases the risk of CVD independent of the abovementioned risk factors is unclear. Although some studies have investigated the relationship between OA and CVD internationally, to our knowledge, no clinical studies have used large-scale data from Japan. As lifestyle, genetic factors, body type, and population characteristics vary between Japan and other countries, research on this topic, specifically in Japan, is necessary.

Therefore, this study, using data with a high number of variables, such as Medical Data Vision (MDV) data, in Japan, which is experiencing super-aging, aimed to determine whether the presence of OA is a risk factor for CVD development, whether there are differences among IHD, CHF, and stroke, and whether there is any difference between CVD risk and OA sites (hips, knees, and hand).

METHODS

Study design and study population

This study employed a population-based case–control matching study design, and a retrospective evaluation was conducted using real-world data from Japanese MDV health insurance claims data. This dataset covers approximately 22% of diagnosis procedure combination (DPC) hospitals, which include many

acute care hospitals across Japan. It is composed of electronic health insurance claims data, DPC claims, and laboratory test results [9].

Approximately one million individuals were randomly selected from 35.23 million older patients who were attending 438 DPC hospitals under contract with MDV among the entire older population in Japan. Disease-related information included the International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis codes, Japanese disease codes, and diagnosis dates. Medication-related data included health insurance claims codes, prescription dates, administration routes, and prescription quantities. All patient data were coded before entry into the database.

Selection of cases and controls

Cases were defined by mapping the disease codes in the dataset to the master codes for CVD, stroke, IHD, and CHF and limiting them to confirmed disease names. Each master code was defined based on the following ICD-10 diagnosis codes: IHD (I20–I25), CHF (I50), stroke (I60–I64), and CVD (I20–I25, I50, I60–I64) [10]. Cases were defined as patients aged ≥65 years that were first diagnosed with the target disease between January 2015 and December 2020, with the diagnosis date serving as the index date. Controls were randomly assigned index dates.

The age of the patients was categorized into 5-year intervals, and 1:1 matching was performed based on age and sex. In cases where there were multiple potential controls for a single case, control individuals were randomly selected from among them.

According to Yamana et al., the validity of diagnoses within the DPC database demonstrated a sensitivity and specificity of 78.9% and 93.2%, respectively. Although variations were observed among different medical conditions, the overall results indicated favorable accuracy without significant diagnostic inaccuracies [11].

Definition of OA and covariates

HipOA (M160–M169) and KOA (M170-M179) and hand OA (HandOA) (M180-M189) were defined as exposure factors. Covariates included common risk factors for CVD, such as type 2 diabetes mellitus, essential (primary) hypertension, atrial fibrillation and flutter, chronic kidney disease, disorders of lipoprotein metabolism and other lipidemias, and medications related to CVD treatment: oral antidiabetic drugs, platelet aggregation inhibitors, diuretics, beta-blocking agents, calcium antagonists, agents acting on the renin–angiotensin system, and lipid-regulating/anti-atheroma preparations (Appendix 1).

The types of medications and comorbidities were obtained from the MDV database. For medications, the unique nine-digit health insurance claims codes, which are assigned to each drug based on its pharmacological properties, were mapped to five-digit codes according to the Anatomical Therapeutic Chemical Classification System managed by the European Pharmaceutical Marketing Research Association [12]. The start date of medication use was set as before the index date, and medications that were being continued at the index date or had an end date within 7 days of the index date were considered. In other words, a grace period of 7 days was set after the prescription end date, and all medications that were taken

at least once within 7 days from the index date were considered to affect the outcome.

Complications were included only when a confirmed diagnosis of the disease was established, and they were mapped using ICD-10 codes. Comorbidities with diagnosis dates before the index date and no end dates were registered until the index date was extracted. Based on this information, concomitant medications and comorbidities were extracted from the MDV database. The explanatory variables included sex, age, comorbidities based on ICD-10 codes, and concomitant medications based on the Anatomical Classification of Pharmaceutical Products (ATC) codes.

Statistical analysis

Sex, concomitant medications, and comorbidities were treated as binary variables. The characteristics of the case and control groups regarding age, sex, comorbidities, and concomitant medications were summarized using mean, standard deviation, and proportions as descriptive statistics. Furthermore, a conditional logistic regression model was applied to estimate the odds ratios (OR) and their 95% confidence intervals (CI) for the risk of developing CVD, IHD, CHF, and stroke. Adjustments were made for the covariates mentioned above. All analyses were conducted using R version 4.1.0 (http://www.r-project.org/), and the "clogit" package was used for the conditional logistic regression.

Patient and public involvement

This study will not have any patient or public involvement because it is health insurance claims data.

RESULTS

Characteristics of the study population

The study population was based on approximately one million MDV data; initially, cases and controls meeting the selection criteria were extracted, followed by those meeting the criteria for "Definition of OA and covariates." Finally, 1:1 matching based on age and sex was conducted. The total number of participants, including the case and control groups for each condition, is as follows: CVD (IHD, CHF, and stroke), 39,648 in each group, totaling 79,296; stroke, 14,944 in each group, totaling 29,888; IHD, 22,996 in each group, totaling 45,992; CHF, 31,639 in each group, totaling 63,278 (Fig. 1). The mean age of CVD occurrence was 78.6 (SD 7.3) years, and 54.4% were males and 45.6% were females. In addition, Table 1 shows the percentage of patients with comorbidities and concomitant medications. IHD, CHF, and stroke are shown in Appendices 2, 3, and 4, respectively.

184 **Table 1. Characteristics of patients with CVD and controls.**

		Case group (n = 39648) N (%)	Control group (n = 39648) N (%)	Std diff
Age	**Mean (SD)**	**78.6 (7.3)**	**78.6 (7.3)**	
Sex	**Male**	**21551 (54.4)**	**21571 (54.4)**	
	Female	**18097 (45.6)**	**18077 (45.6)**	
Complications				
Type 2 diabetes mellitus		**6322 (15.9)**	**4666 (11.7)**	**0.122**
Essential (primary) hypertension		**13368 (33.7)**	**9791 (24.7)**	**0.199**
Atrial fibrillation and flutter		**3256 (8.2)**	**1113 (2.8)**	**0.239**
Chronic kidney disease		**2711 (6.8)**	**1164 (2.9)**	**0.182**
Disorders of lipoprotein metabolism and other lipidemias		**6566 (16.6)**	**4887 (12.3)**	**0.122**
Knee osteoarthritis		**2416 (6.1)**	**2033 (5.1)**	**0.042**
Hip osteoarthritis		**493 (1.2)**	**435 (1.1)**	**0.014**
Hand osteoarthritis		**53 (0.1)**	**50 (0.1)**	**0.002**
Concomitant medication				
Oral antidiabetic drugs		**5150 (13.0)**	**3428 (8.6)**	**0.14**
Platelet aggregation inhibitors		**6712 (16.9)**	**2807 (7.1)**	**0.307**
Diuretic		**5212 (13.1)**	**1951 (4.9)**	**0.29**

Beta blocking agents	**4058 (10.2)**	**1067 (2.7)**	**0.311**
Calcium antagonists	**10559 (26.6)**	**6183 (15.6)**	**0.273**
Agents acting on the renin-angiotensin system	**9256 (23.3)**	**5263 (13.3)**	**0.263**
Lipid-regulating/antiatheroma preparations	**7339 (18.5)**	**4545 (11.5)**	**0.198**

CVD and osteoarthritis

In the unadjusted analysis for CVD, the OR for KOA exposure in the case group compared with the control group was 1.204 (95% CI, 1.133–1.28). The ORs for HipOA and HandOA exposures were 1.14 (95% CI, 1.001–1.298) and 1.06 (95% CI, 0.72–1.56), respectively, indicating no significant association. After adjusting for covariates, the OR for KOA exposure was 1.192 (95% CI, 1.115–1.274), indicating a significant association with CVD occurrence. The ORs for HipOA and HandOA exposures were 1.057 (95% CI, 0.919–1.215) and 1.035 (95% CI, 0.684–1.566), respectively, indicating no significant association (Table 2). Similarly, in the unadjusted analysis for IHD, the OR for KOA exposure was 1.156 (95% CI, 1.067–1.253), while the ORs for HipOA and HandOA exposures were 1.016 (95% CI, 0.854–1.209) and 0.974 (95% CI, 0.623–1.523), respectively, with no significant association. After adjusting for covariates, the OR for KOA exposure was 1.187(95% CI, 1.086–1.297), showing a significant association with IHD occurrence; however, the ORs for HipOA and HandOA exposures were 1.078 (95% CI, 0.891–1.306) and 1.099 (95% CI, 0.677–1.784), respectively, indicating no significant association (Appendix 5). For CHF, the unadjusted analysis showed ORs of 1.031 (95% CI, 0.962–1.104), 0.966(95% CI, 0.834–1.12), and 0.911(95% CI, 0.597–1.391) for KOA, HipOA, and HandOA exposures, respectively. After adjusting for covariates, the ORs for KOA, HipOA, and HandOA exposures were 1.027(95% CI, 0.948–1.112), 0.968(95% CI, 0.816–1.149), and 1.139(95% CI, 0.705–1.841), respectively, indicating no significant association with CHF occurrence (Appendix 6). Finally, for stroke, the unadjusted analysis showed ORs of 1.26 (95% CI, 1.142–1.39), 1.013 (95% CI, 0.809–1.27), and 1.095(95% CI, 0.606–1.979) for KOA, HipOA, and HandOA exposures, respectively. After adjusting for covariates, the OR for KOA exposure was 1.221 (95% CI, 1.099–1.356), indicating a significant association with stroke occurrence, while the ORs for HipOA and HandOA exposures were 0.918 (95% CI, 0.723–1.165) and 1.169 (95% CI, 0.635–2.151), respectively, showing no significant association (Appendix 7).

209 **Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA, HipOA, and HandOA.**

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.426	1.369	1.486	1.147	1.091	1.206
Essential (primary) hypertension	1.547	1.499	1.595	1.049	1.009	1.09
Atrial fibrillation and flutter	3.103	2.892	3.33	2.521	2.337	2.72
Chronic kidney disease	2.418	2.253	2.595	1.712	1.585	1.85
Disorders of lipoprotein metabolism and other lipidemias	1.42	1.364	1.478	1.02	0.968	1.075
Knee osteoarthritis	1.204	1.133	1.28	1.192	1.115	1.274
Hip osteoarthritis	1.14	1.001	1.298	1.057	0.919	1.215
Hand osteoarthritis	1.06	0.72	1.56	1.035	0.684	1.566
Oral antidiabetic drugs	1.58	1.509	1.655	1.077	1.017	1.141
Platelet aggregation inhibitors	2.69	2.565	2.822	2.219	2.108	2.336
Diuretic	2.923	2.766	3.088	2.008	1.892	2.131
Beta blocking agents	4.126	3.845	4.428	2.521	2.337	2.72
Calcium antagonists	1.973	1.903	2.045	1.292	1.237	1.349
Agents acting on the renin-angiotensin system	1.972	1.9	2.048	1.234	1.178	1.292
Lipid-regulating/antiatheroma preparations	1.755	1.686	1.828	1.132	1.074	1.194

Discussion

To our knowledge, this study is the first large-scale population-based case–control study conducted on Japanese individuals, evaluating the relationship between OA and CVD risk using administrative claims database. In this study, after adjusting for various potential confounding factors, KOA was found to be associated with an increased risk of CVD. Furthermore, the subgroup analysis revealed that patients with KOA had an increased risk of IHD and stroke.

According to the population-based study by Nuesch et al., patients with KOA and HipOA have higher overall mortality rates than the general population, particularly with a significant association with CVD and dementia-associated mortality [13]. Goel et al. found a strong relationship between KOA and CVD, and the cardiovascular risk score positively correlated with the OA severity [14]. On the contrary, in their prospective population-based cohort study, Hoeven et al. reported no significant association between CVD risk and clinical or radiographic knee, hip, and hand OA [15]. While the relationship between OA and CVD remains debatable, many studies have suggested that a potential increase in CVD risk is associated with OA [16].

The underlying fundamental mechanisms linking the risks of OA and CVD remain unclear; however, several mechanisms have been proposed to explain the association between OA and CVD. First and foremost, a shared risk factor aspect involves metabolic syndrome components such as diabetes, dyslipidemia, and hypertension, which are common to both OA and CVD [17-21]. However, these factors may act as confounding variables. Therefore, if the increased risk of CVD persists even after conducting multivariate analysis accounting for these factors, it can imply an independent association between OA and CVD. Second, the induction of inflammatory responses associated with cytokines is another point of consideration. Nuesch et al. reported that walking disability, along with OA, was associated with high CVD-related mortality, and Hoeven et al. reported that some forms of disability in daily activities, rather than OA itself, were associated with CVD onset [13, 15]. OA development can lead to severe joint pain, ultimately resulting in walking disability and decreased physical activity over time. Reduced physical activity can lead to the accumulation of visceral fat, i.e., hypertrophy of fat cells, which, in turn, increases the secretion of inflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6). Many of these inflammatory processes and cytokines also contribute to the development of vascular inflammation underlying conditions such as hypertension, myocardial infarction, heart failure, and cerebrovascular disorders, which are components of many CVDs [22-24]. Moreover, Yoshimura et al. reported that the risk of KOA development increases with the presence of hypertension and impaired glucose tolerance; conversely, the coexistence of KOA increases the risk of developing hypertension and dyslipidemia [25]. These findings indicate a mutual relationship between the development and coexistence of KOA and metabolic syndrome components.

The study found associations of KOA with IHD and stroke, but no association of KOA with CHF. In a meta-analysis, Hall et al. found that patients with OA had a significantly increased CHF and IHD risk compared with patients without OA; however, no significant difference was observed in stroke risk [8]. A Mendelian randomization study by Wang et al. showed a potential causal relationship between hip OA and CHF along with stroke, but no association of hip OA with IHD. Although no significant associations were observed in all aspects with KOA, IHD strongly correlated with KOA onset [26]. Rahman et al. reported a

significant association of OA with IHD and CHF in individuals aged ≥65 years, but no association of OA with myocardial infarction or stroke [27]. Overall, results regarding the association with stroke, IHD, and CHF vary among studies, and why only CHF among CVDs showed no association with OA in the present study remains unclear. However, one hypothesis could be that patients with OA generally have reduced physical activity [28, 29] and are less likely to experience overexertion in daily life. Consequently, there may be less strain on the heart, which does not increase the CHF risk.

In this study, no associations were observed in HipOA and HandOA. Macêdo et al. found that both HipOA and KOA increase the risk of subclinical atherosclerosis and CVD, whereas hand OA showed no association with CVD [30]. Tsuboi et al. reported that when KOA coexists, the odds of death after 10 years significantly increased; however, no significant difference was observed when coexisting with lower back abnormalities [31]. These authors explain this phenomenon from the perspective of weight-bearing joints. In the present study, KOA showed a significant association; however, HipOA and HandOA did not. One possible reason is that the knee and hand are weight-bearing joints more than the hip, which may lead to excessive stress on the bones and cartilage because of biomechanical load caused by the body weight, increasing the risk for KOA development and leading to more significant inflammatory reactions and a more pronounced association with CVD. Moreover, a strong correlation was found between KOA and physical activity; however, the association with HipOA is weaker than that with KOA, as suggested by previous studies [32, 33]. This indicates that the knee is more susceptible to physical stress than the hip.

Strengths and limitations

This study has some limitations. First, the case–control study design allows us to establish an association between knee OA and CVD; however, a causal relationship could not be established. Second, the diagnosis of OA was based solely on cases diagnosed by physicians, which may have underestimated the results by not considering patients with asymptomatic OA who do not exhibit symptoms such as pain. Third, the data used in this study only included acute care hospital data from the MDV database, which may have a higher likelihood of including patients with more severe conditions and multiple comorbidities than the general population. Fourth, lifestyle factors such as alcohol consumption, smoking, and exercise habits were not considered. Finally, this study was conducted using Japanese insurance claims data, and there may be limitations in generalizing our research findings to other ethnic groups.

Despite these limitations, this study has several strengths that outweigh them. First, the study has a large sample size, and a case–control study design was employed while adjusting for multiple important confounding factors. In addition, health administrative data were used to verify the outcomes, providing more robust evidence in a real clinical setting.

Conclusion

This study research emphasizes the potential association between KOA and increased CVD risk in real-world data of older Japanese individuals. Furthermore, KOA is associated with an increased risk of IHD and stroke. Given that KOA and CVD are both significant public health issues, early intervention for KOA is

desired to prevent CVD. Our findings may aid in making informed decisions for further management of KOA.

Competing interests

None declared.

Funding

The authors did not receive a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Contributors

All authors are responsible for the work described in this paper. TU, SN, and YN contributed to the conception, design, or planning of the study. TU, SN, and YN contributed to the data analysis. MI contributed to data interpretation, commented on expert perspectives, and reviewed and edited the article draft. All authors read and provided final approval of the final article to be published. The lead author confirmed that the manuscript is an integrate, accurate, and transparent description of the reported study.

Patient consent for publication

Not required.

Disclaimer

No endorsement by MDV is intended nor should be inferred. The papers reported are those of the authors.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

Although the data are available from Medical Data Vision, the use of data in this study is under license and not publicly available.

Ethics approval

This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare, Japan. It was approved by the Research Ethics Committee, Faculty of Medicine, Juntendo University (Research permit no. E21-0264-M01).

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FIGURE LEGEND

Figure 1. Flowchart of cases and controls.

MDV, medical data vision.

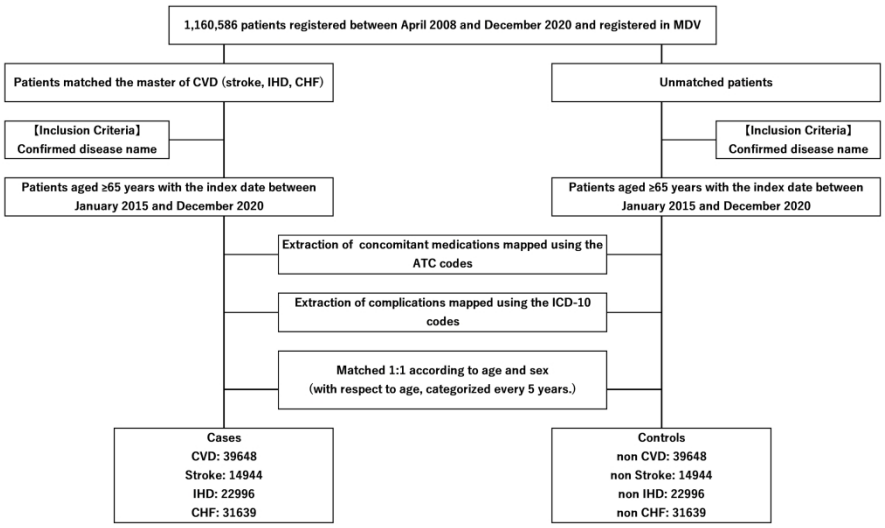
TABLES

Table 1. Characteristics of patients with CVD and controls.

SD, standard deviation; Std diff, standardized difference.

Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA, HipOA, and HandOA.

CI, confidence interval.



338x190mm (300 x 300 DPI)

Indexed according to the ICD-10 codes	Category of complications
E110-E119	Type 2 diabetes mellitus
E780-E789	Disorders of lipoprotein metabolism and other lipidemias
I10	Essential (primary) hypertension
I480-I489	Atrial fibrillation and flutter
N180-N189	Chronic kidney disease

Indexed according to ATC codes	Category of concomitant medications
A10H0-A10P5	Oral antidiabetic drugs
B01C1-B01C9	Platelet aggregation inhibitors
C03A1-C03A9	Diuretic
C07A0	Beta blocking agents
C08A0	Calcium antagonists
C09A0-C09X0	Agents acting on the renin-angiotensin system
C10A1-C10C0	Lipid-regulating/antiatheroma preparations

Appendix 1.

Covariates classification based on ICD-10 codes and ATC codes.

ICD-10, International Classification of Diseases, 10th Revision

ATC, Anatomical Therapeutic Chemical Classification System

		Case group (n =22996)	Control group (n =22996)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**78.6 (7.2)**	**78.5 (7.3)**	
Sex	**Male**	**12965 (56.4)**	**12965 (56.4)**	
	Female	**10031 (43.6)**	**10031 (43.6)**	
Complications				
Type 2 diabetes mellitus		**5676 (24.7)**	**3818 (16.6)**	**0.201**
Essential (primary) hypertension		**12321 (53.6)**	**9133 (39.7)**	**0.281**
Atrial fibrillation and flutter		**2945 (12.8)**	**1651 (7.2)**	**0.188**
Chronic kidney disease		**1914 (8.3)**	**1023 (4.4)**	**0.159**
Disorders of lipoprotein metabolism and other lipidemias		**4850 (21.1)**	**3702 (16.1)**	**0.129**
Knee osteoarthritis		**1376 (6.0)**	**1202 (5.2)**	**0.033**
Hip osteoarthritis		**261 (1.1)**	**257 (1.1)**	**0.002**
Hand osteoarthritis		**38 (0.2)**	**39 (0.2)**	**0.001**
Concomitant medication				
Oral antidiabetic drugs		**3593 (15.6)**	**2305 (10.0)**	**0.168**
Platelet aggregation inhibitors		**6357 (27.6)**	**2700 (11.7)**	**0.408**
Diuretic		**4785 (20.8)**	**2334 (10.1)**	**0.298**
Beta blocking agents		**4197 (18.3)**	**1509 (6.6)**	**0.36**
Calcium antagonists		**6872 (29.9)**	**4520 (19.7)**	**0.239**
Agents acting on the renin-angiotensin system		**6574 (28.6)**	**4126 (17.9)**	**0.254**
Lipid-regulating/antiatheroma preparations		**5579 (24.3)**	**3316 (14.4)**	**0.251**

Appendix 2.
Characteristics of patients with IHD and controls.
SD, standard deviation; Std diff, standardized difference.

		Case group (n =31639)	Control group (n =31639)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**79.0 (7.3)**	**78.9 (7.3)**	
Sex	**Male**	**17920 (56.6)**	**17920 (56.6)**	
	Female	**13719 (43.4)**	**13719 (43.4)**	
Complications				
Type 2 diabetes mellitus		**7761 (24.5)**	**5164 (16.3)**	**0.205**
Essential (primary) hypertension		**19164 (60.6)**	**12085 (38.2)**	**0.459**
Atrial fibrillation and flutter		**4284 (13.5)**	**1304 (4.1)**	**0.337**
Chronic kidney disease		**2739 (8.7)**	**1044 (3.3)**	**0.227**
Disorders of lipoprotein metabolism and other lipidemias		**8017 (25.3)**	**5355 (16.9)**	**0.207**
Knee osteoarthritis		**1751 (5.5)**	**1702 (5.4)**	**0.007**
Hip osteoarthritis		**349 (1.1)**	**361 (1.1)**	**0.004**
Hand osteoarthritis		**41 (0.1)**	**45 (0.1)**	**0.003**
Concomitant medication				
Oral antidiabetic drugs		**4756 (15.0)**	**3197 (10.1)**	**0.149**
Platelet aggregation inhibitors		**9219 (29.1)**	**4751 (15.0)**	**0.346**
Diuretic		**6153 (19.4)**	**1682 (5.3)**	**0.439**
Beta blocking agents		**6412 (20.3)**	**1311 (4.1)**	**0.508**
Calcium antagonists		**10213 (32.3)**	**6314 (20.0)**	**0.283**
Agents acting on the renin-angiotensin system		**9909 (31.3)**	**5390 (17.0)**	**0.338**
Lipid-regulating/antiatheroma preparations		**8958 (28.3)**	**5031 (15.9)**	**0.303**

Appendix 3.
Characteristics of patients with CHF and controls.
SD, standard deviation; Std diff, standardized difference.

		Case group (n =14944)	Control group (n =14944)	Std diff
		N (%)	N (%)	
Age	**Mean (SD)**	**79.1 (7.2)**	**79.1 (7.2)**	
Sex	**Male**	**8657 (57.9)**	**8657 (57.9)**	
	Female	**6287 (42.1)**	**6287 (42.1)**	
Complications				
Type 2 diabetes mellitus		**3900 (26.1)**	**2781 (18.6)**	**0.18**
Essential (primary) hypertension		**8830 (59.1)**	**6490 (43.4)**	**0.317**
Atrial fibrillation and flutter		**1605 (10.7)**	**1221 (8.2)**	**0.088**
Chronic kidney disease		**1195 (8.0)**	**824 (5.5)**	**0.099**
Disorders of lipoprotein metabolism and other lipidemias		**3605 (24.1)**	**2851 (19.1)**	**0.123**
Knee osteoarthritis		**959 (6.4)**	**774 (5.2)**	**0.053**
Hip osteoarthritis		**154 (1.0)**	**152 (1.0)**	**0.001**
Hand osteoarthritis		**23 (0.2)**	**21 (0.1)**	**0.003**
Concomitant medication				
Oral antidiabetic drugs		**2365 (15.8)**	**1671 (11.2)**	**0.136**
Platelet aggregation inhibitors		**4503 (30.1)**	**2333 (15.6)**	**0.351**
Diuretic		**2776 (18.6)**	**2002 (13.4)**	**0.142**
Beta blocking agents		**2340 (15.7)**	**1671 (11.2)**	**0.132**
Calcium antagonists		**4404 (29.5)**	**3165 (21.2)**	**0.192**
Agents acting on the renin-angiotensin system		**4409 (29.5)**	**3094 (20.7)**	**0.204**
Lipid-regulating/antiatheroma preparations		**3794 (25.4)**	**2767 (18.5)**	**0.167**

Appendix 4.
Characteristics of patients with stroke and controls.
SD, standard deviation; Std diff, standardized difference.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.659	1.584	1.739	1.362	1.283	1.446
Essential (primary) hypertension	1.751	1.686	1.818	1.5	1.144	1.259
Atrial fibrillation and flutter	1.902	1.784	2.027	1.379	1.283	1.482
Chronic kidney disease	1.96	1.811	2.121	1.3	1.255	1.495
Disorders of lipoprotein metabolism and other lipidemias	1.395	1.33	1.463	0.91	0.858	0.969
Knee osteoarthritis	1.156	1.067	1.253	1.18	1.086	1.297
Hip osteoarthritis	1.016	0.854	1.209	1.07	0.891	1.306
Hand osteoarthritis	0.974	0.623	1.523	1.09	0.677	1.784
Oral antidiabetic drugs	1.681	1.588	1.78	0.98	0.916	1.063
Platelet aggregation inhibitors	2.911	2.763	3.066	2.38	2.257	2.525
Diuretic	2.377	2.249	2.512	1.47	1.384	1.571
Beta blocking agents	3.209	3.009	3.422	2.15	2.002	2.313
Calcium antagonists	1.744	1.669	1.822	1.12	1.065	1.185
Agents acting on the renin-angiotensin system	1.818	1.739	1.901	1.01	0.961	1.076
Lipid-regulating/antiatheroma preparations	1.905	1.815	2	1.26	1.187	1.346

Appendix 5.

Crude and adjusted ORs and 95% CIs of IHD in relation to KOA, HipOA, and HandOA.

CI, confidence interval.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.676	1.61	1.744	1.324	1.253	1.398
Essential (primary) hypertension	2.495	2.413	2.581	1.648	1.577	1.723
Atrial fibrillation and flutter	3.603	3.374	3.846	2.739	2.564	2.969
Chronic kidney disease	2.771	2.574	2.984	1.862	1.713	2.029
Disorders of lipoprotein metabolism and other lipidemias	1.675	1.611	1.743	0.941	0.891	0.993
Knee osteoarthritis	1.031	0.962	1.104	1.027	0.948	1.112
Hip osteoarthritis	0.966	0.834	1.12	0.968	0.816	1.149
Hand osteoarthritis	0.911	0.597	1.391	1.137	0.705	1.841
Oral antidiabetic drugs	1.583	1.508	1.662	0.844	0.79	0.905
Platelet aggregation inhibitors	2.343	2.25	2.44	1.571	1.496	1.65
Diuretic	4.374	4.121	4.643	3.008	2.816	3.211
Beta blocking agents	5.938	5.559	6.343	3.317	3.099	3.579
Calcium antagonists	1.92	1.85	1.993	0.999	0.952	1.048
Agents acting on the renin-angiotensin system	2.243	2.157	2.333	1.076	1.021	1.133
Lipid-regulating/antiatheroma preparations	2.104	2.021	2.189	1.215	1.149	1.286

Appendix 6.

Crude and adjusted ORs and 95% CIs of CHF in relation to KOA, HipOA, and HandOA.

CI, confidence interval.

	Crude estimate			Adjusted estimate		
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ratio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.555	1.47	1.644	1.254	1.17	1.344
Essential (primary) hypertension	1.913	1.824	2.007	1.561	1.472	1.656
Atrial fibrillation and flutter	1.355	1.252	1.465	1.178	1.08	1.284
Chronic kidney disease	1.489	1.358	1.632	1.141	1.034	1.259
Disorders of lipoprotein metabolism and other lipidemias	1.357	1.283	1.435	0.938	0.875	1.005
Knee osteoarthritis	1.26	1.142	1.39	1.224	1.099	1.356
Hip osteoarthritis	1.013	0.809	1.27	0.918	0.723	1.165
Hand osteoarthritis	1.095	0.606	1.979	1.161	0.635	2.151
Oral antidiabetic drugs	1.503	1.404	1.609	0.98	0.904	1.074
Platelet aggregation inhibitors	2.323	2.193	2.462	2.028	1.903	2.162
Diuretic	1.498	1.405	1.597	1.161	1.029	1.19
Beta blocking agents	1.473	1.377	1.576	0.937	0.86	1.008
Calcium antagonists	1.564	1.483	1.65	1.094	1.027	1.165
Agents acting on the renin-angiotensin system	1.599	1.516	1.686	1.035	0.969	1.105
Lipid-regulating/antiatheroma preparations	1.498	1.417	1.584	0.976	0.908	1.05

Appendix 7.

Crude and adjusted ORs and 95% CIs of stroke in relation to KOA, HipOA, and HandOA.

CI, confidence interval.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P2 L44~
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2 L39~
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3 L77~
Objectives	3	State specific objectives, including any prespecified hypotheses	P3 L105~
Methods			
Study design	4	Present key elements of study design early in the paper	P3 L112~
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3 L113~
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	P4 L125~
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P4 L131~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P4 L140~
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4 L113~
Bias	9	Describe any efforts to address potential sources of bias	P4 L131~
Study size	10	Explain how the study size was arrived at	P5 L176~
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P5 L161~
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P5 L161~
		(*b*) Describe any methods used to examine subgroups and interactions	P5 L161~
		(*c*) Explain how missing data were addressed	
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	P4 L131~
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P5 L174~
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P5 L179~
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Table1
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P4 L139~ P8 L185~
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8 L190~
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10 L207~
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P11 L264~
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11 L278~
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11 L271~
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P12 L291~

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.