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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 ischaemic 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 hospitalised between January 2015 and December 2020 (cases) and age-matched and sex-matched 1:1 individuals (controls).

Main outcome measures A conditional logistic regression model was used to estimate the adjusted ORs and their 95% CIs for CVD, IHD, CHF and stroke risk, adjusting for covariates.

Results A total of 79 296 patients were included, with respect to CVD (39 648 patients with newly diagnosed CVD and 39 648 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 to 1.274), 1.057 (95% CI 0.919 to 1.215) and 1.035 (95% CI 0.684 to 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 to 1.297), 1.078 (95% CI 0.891 to 1.306) and 1.099 (95% CI 0.677 to 1.784), respectively. The exposure odds of KOA, HipOA and HandOA for stroke were 1.221 (95% CI 1.099 to 1.356), 0.918 (95% CI 0.723 to 1.165) and 1.169 (95% CI 0.635 to 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 knee OA and CVD in Japan's super-ageing 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 generalisability should be considered.
⇒ Data analysed 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 ischaemic 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 ageing 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 reduce the quality of life and limit 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-related 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 non-pharmacological 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, dyslipidaemia 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 inter-relationship 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-ageing, 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 1 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 and Related Health Problems, 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 categorised 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 favourable accuracy without significant diagnostic inaccuracies.[11]

Definition of OA and covariates

Hip OA (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 lipidaemias, 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/antiatheroma preparations (online supplemental 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 (ATC) 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 summarised using mean, SD and proportions as descriptive statistics. Furthermore, a conditional logistic regression model was applied to estimate the ORs and their 95% CIs for the risk of developing CVD, IHD, CHF and stroke. Adjustments were made for the covariates mentioned above. All analyses were conducted using R V.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 1 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, totalling 79 296; stroke, 14 944 in each group, totalling 29 888; IHD, 22 996 in each group, totalling 45 992; CHF, 31 639 in each group, totalling 63 278 (figure 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 online supplemental appendices 2–4, respectively.

CVD and OA

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 to 1.28). The ORs for HipOA and HandOA exposures were 1.14 (95% CI 1.001 to 1.298) and 1.06 (95% CI 0.72 to 1.56), respectively, indicating no significant association. After adjusting for covariates, the OR for KOA exposure was 1.192 (95% CI 1.115 to 1.274), indicating a significant association with CVD occurrence. The ORs for HipOA and HandOA exposures were 1.057 (95% CI 0.919 to 1.215) and 1.035 (95% CI 0.684 to 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 to 1.253), while the ORs for HipOA and HandOA exposures were 1.016 (95% CI 0.854 to 1.209) and 0.974 (95% CI 0.623 to 1.523), respectively, with no

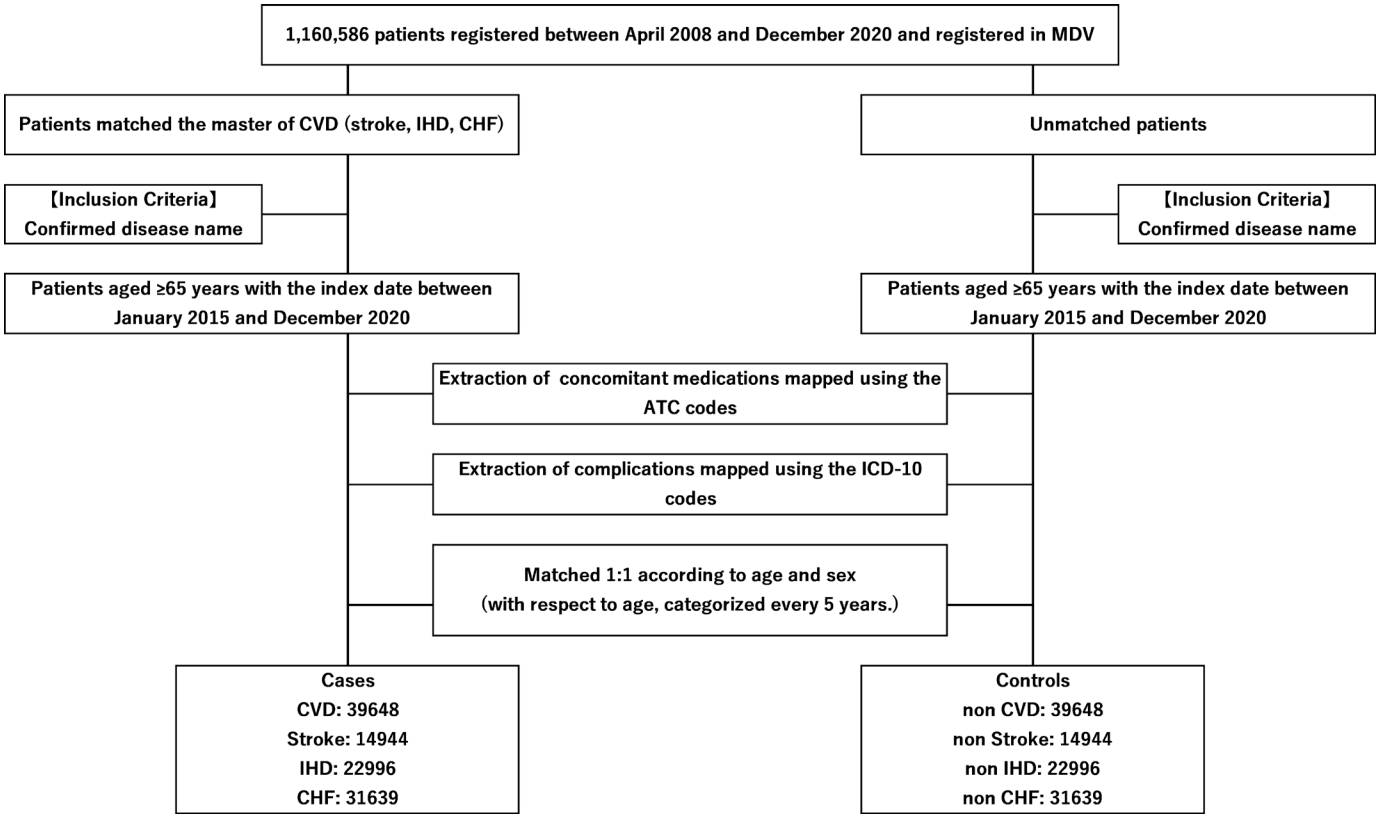

Figure 1 Flow chart of cases and controls. ATC, Anatomical Therapeutic Chemical Classification System; CHF, congestive heart failure; CVD, cardiovascular disease; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; IHD, ischaemic heart disease; MDV, Medical Data Vision.

Table 1 Characteristics of patients with CVD and controls

	Case group (N=39 648) N (%)	Control group (N=39 648) N (%)	Standardised difference
Age			
Mean (SD)	78.6 (7.3)	78.5 (7.3)	
Sex			
Male	21 551 (54.4)	21 551 (54.4)	
Female	18 097 (45.6)	18 097 (45.6)	
Complications			
Type 2 diabetes mellitus	6322 (15.9)	4651 (11.7)	0.122
Essential (primary) hypertension	13 368 (33.7)	9799 (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 lipidaemias	6566 (16.6)	4873 (12.3)	0.122
Knee osteoarthritis	2416 (6.1)	2033 (5.1)	0.042
Hip osteoarthritis	493 (1.2)	433 (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)	1063 (2.7)	0.311
Calcium antagonists	10 559 (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)	4555 (11.5)	0.198

CVD, cardiovascular disease.

significant association. After adjusting for covariates, the OR for KOA exposure was 1.187 (95% CI 1.086 to 1.297), showing a significant association with IHD occurrence; however, the ORs for HipOA and HandOA exposures were 1.078 (95% CI 0.891 to 1.306) and 1.099 (95% CI 0.677 to 1.784), respectively, indicating no significant association (online supplemental appendix 5). For CHF, the unadjusted analysis showed ORs of 1.031 (95% CI 0.962 to 1.104), 0.966 (95% CI 0.834 to 1.12) and 0.911 (95% CI 0.597 to 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 to 1.112), 0.968 (95% CI 0.816 to 1.149) and 1.139 (95% CI 0.705 to 1.841), respectively, indicating no significant association with CHF occurrence (online supplemental appendix 6). Finally, for stroke, the unadjusted analysis showed ORs of 1.26 (95% CI 1.142 to 1.39), 1.013 (95% CI 0.809 to 1.27) and 1.095 (95% CI 0.606 to 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 to 1.356), indicating a significant association with stroke occurrence, while the ORs for HipOA and HandOA exposures were 0.918 (95% CI 0.723 to 1.165) and 1.169 (95% CI 0.635 to 2.151), respectively, showing no significant association (online supplemental appendix 7).

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 Nüesch *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

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

	Crude estimate			Adjusted estimate		
	OR	Lower 95% CI	Upper 95% CI	OR	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 lipidaemias	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

CVD, cardiovascular disease; HandOA, hand osteoarthritis; HipOA, hip osteoarthritis; KOA, knee osteoarthritis.

study, Hoeven *et al* reported no significant association between CVD risk and clinical or radiographic KOA, HipOA and HandOA.[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, dyslipidaemia 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. Nüesch *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, that is, hypertrophy of fat cells, which, in turn, increases the secretion of inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-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 dyslipidaemia.[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 randomisation study by Wang *et al* showed a potential causal relationship between HipOA and CHF along with stroke, but no association of HipOA 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 HandOA 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 KOA 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 generalising 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 emphasises 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.

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 data analysis. MI contributed to data interpretation, commented on expert perspectives and reviewed and edited the article draft. SN acts as guarantor. All authors read and provided final approval of the final article to be published.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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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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	1.2	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	1.37	1.255	1.495
Disorders of lipoprotein metabolism and other lipidemias	1.395	1.33	1.463	0.912	0.858	0.969
Knee osteoarthritis	1.156	1.067	1.253	1.187	1.086	1.297
Hip osteoarthritis	1.016	0.854	1.209	1.078	0.891	1.306
Hand osteoarthritis	0.974	0.623	1.523	1.099	0.677	1.784
Oral antidiabetic drugs	1.681	1.588	1.78	0.987	0.916	1.063
Platelet aggregation inhibitors	2.911	2.763	3.066	2.387	2.257	2.525
Diuretic	2.377	2.249	2.512	1.475	1.384	1.571
Beta blocking agents	3.209	3.009	3.422	2.152	2.002	2.313
Calcium antagonists	1.744	1.669	1.822	1.123	1.065	1.185
Agents acting on the renin-angiotensin system	1.818	1.739	1.901	1.017	0.961	1.076
Lipid-regulating/antiatheroma preparations	1.905	1.815	2	1.264	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	2.759	2.564	2.969
Chronic kidney disease	2.771	2.574	2.984	1.865	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	1.139	0.705	1.841
Oral antidiabetic drugs	1.583	1.508	1.662	0.846	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	3.007	2.816	3.211
Beta blocking agents	5.938	5.559	6.343	3.33	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	1.221	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	1.169	0.635	2.151
Oral antidiabetic drugs	1.503	1.404	1.609	0.986	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	1.107	1.029	1.19
Beta blocking agents	1.473	1.377	1.576	0.931	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.