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

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2 3 4	1	Association Between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An
5	2	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.

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78 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.

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

111 METHODS

56 112 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

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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, 160-164) [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

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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.

155 Complications were included only when a confirmed diagnosis of the disease was established, and they 156 were mapped using ICD-10 codes. Comorbidities with diagnosis dates before the index date and no end 157 dates were registered until the index date were extracted. Based on this information, concomitant 158 medications and comorbidities were extracted from the MDV database. The explanatory variables included 159 sex, age, comorbidities based on ICD-10 codes, and concomitant medications based on ATC codes.

161 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 (<u>http://www.r-project.org/</u>), and the "clogit" package was used for the conditional logistic regression.

170 Patient and Public Involvement

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

RESULTS

174 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.

Page 7 of 25		BMJ Open	up omjopen-2023-080387 여러 21 d by copyright, includinate for	
2 3 184 4	Table 1. Characteristics of patients with CVD and controls.		.080387	
5		Case group	Cantrel group	
6 7		(n = 39648)	(n = 39648)	Std diff
8		N (%)		
9 10	Age Mean (SD)	78.6 (7.3)	2012 100 100 100 100 100 100 100	
11			emel ed t	
12 13	Sex Male	21551 (54.4)	20 54.4)	
14	Female	18097 (45.6)	13692 (45.6)	
15 16			daur dif	
17	Complication		ata mi	
18 19	Type 2 diabetes mellitus	6322 (15.9)	4513 (11.4)	0.133135
20	Essential (primary) hypertension	13368 (33.7)	2 95 4 (25.1)	0.18983
21 22	Atrial fibrillation and flutter	3256 (8.2)	ā ā [09] (2.8)	0.241354
23	Chronic kidney disease	2711 (6.8)	ā 152 (2.9)	0.183422
24 25	Disorders of lipoprotein metabolism and other			0.11100/
26	lipidemias	6566 (16.6)		0.111926
27 28	Knee osteoarthritis	2416 (6.1)	1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	0.039482
29	Hip osteoarthritis	493 (1.2)	state 490 (1.2)	0.000684
30 31			nola	
32	Concomitant medication		3328 (8.4)	
33 34	Oral antidiabetic drugs	5150 (13.0)	332 (8.4)	0.14913
35	Platelet aggregation inhibitors	6712 (16.9)	2795 (7.0)	0.307715
36 37	Diuretic	5212 (13.1)	188 (4.7)	0.297624
38	Beta blocking agents	4058 (10.2)	106 (2.7)	0.311442
39 40		6	yra	
41		~	nphique	
42			le C	

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Calcium antagonists	10559 (26.6)	6 32 8 (15.9)	0.263247
Agents acting on the renin-angiotensin system	9256 (23.3)	Ē 26 3 (13.3)	0.262641
Lipid-regulating/antiatheroma preparations	7339 (18.5)	4568 (11.5)	0.19651
	7 - http://bmjopen.bmj.com/site/about/guid	025 at Agence Bibliographique d ogies.	

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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).

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		BMJ O	pen	mjopen-2023-080387 on 1 by copyright, including		Pa
5 Table 2. Crude and adjusted ORs and 95% CIs	of CVD in r		-	3-080387 o ıt, includir		
-	Odds ratio	Crude estim Lower 95% CI	uate Upper 95% CI	on 25 March Ense Odds Bass	Adjusted estimated contract Adjusted estimated estimated by CI	upper 95% CI
Type 2 diabetes mellitus	1.482	1.422	1.545	1.18 regine	1.13	1.251
Essential (primary) hypertension	1.515	1.469	1.563	1.022 emen	0.983	1.063
Atrial fibrillation and flutter	3.137	2.923	3.367	2.495 G	2.313	2.693
Chronic kidney disease	2.489	2.317	2.674	1.8239er d	1.685	1.972
Disorders of lipoprotein metabolism and other lipidemias	1.377	1.323	1.433	loaded from hi uperieur (ABE: 1.820 data mir 1.0 mir	0.959	1.064
Knee osteoarthritis	1.189	1.119	1.264		1.108	1.265
Hip osteoarthritis	1.006	0.887	1.141	0.964	0.839	1.102
Oral antidiabetic drugs	1.635	1.561	1.713	1.10	1.045	1.174
Platelet aggregation inhibitors	2.676	2.552	2.806	2.2	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		2.314	2.694
Calcium antagonists	1.918	1.851	1.988	1.2 ב	1.197	1.306
Agents acting on the renin-angiotensin system	1.999	1.925	2.077	2.49 th on June 10, 2 1.2 th tec ¹ 1.2 th tec ² 1.2 th old	1.199	1.317
Lipid-regulating/antiatheroma preparations	1.754	1.684	1.826	1.250 ologie 1.1260 10, 2025 at Agence	1.069	1.188
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207 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.

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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 \geq 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

1 2		
3	283	desired to prevent CVD. Our findings may aid in making informed decisions for further management of
4 5	284	KOA.
6	285	
7 8	286	
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26	298	conception, design, or planning of the study. TU, SN, and YN contributed to the data analysis. MI contributed
27 28	299	to data interpretation, commented on expert perspectives, and reviewed and edited the article draft. All
29	300	authors read and provided final approval of the final article to be published. The lead author confirmed that
30 31	301	the manuscript is an integrate, accurate, and transparent description of the reported study.
32	302	
33 34	303	Patient consent for publication
35	304	Not required.
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44	310	Not commissioned; externally peer reviewed.
45 46	311	Data sharing statement
47	312	Although the data are available from Medical Data Vision, the use of data in this study is under license and
48 49	313	not publicly available.
50	314	
51 52	315	Ethics approval
53	316	This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research
54 55	317	Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the
56 57	318	Ministry of Health, Labour and Welfare, Japan. It was approved by the Research Ethics Committee, Faculty
57 58	319	of Medicine, Juntendo University (Research permit no. E21-0264-M01).
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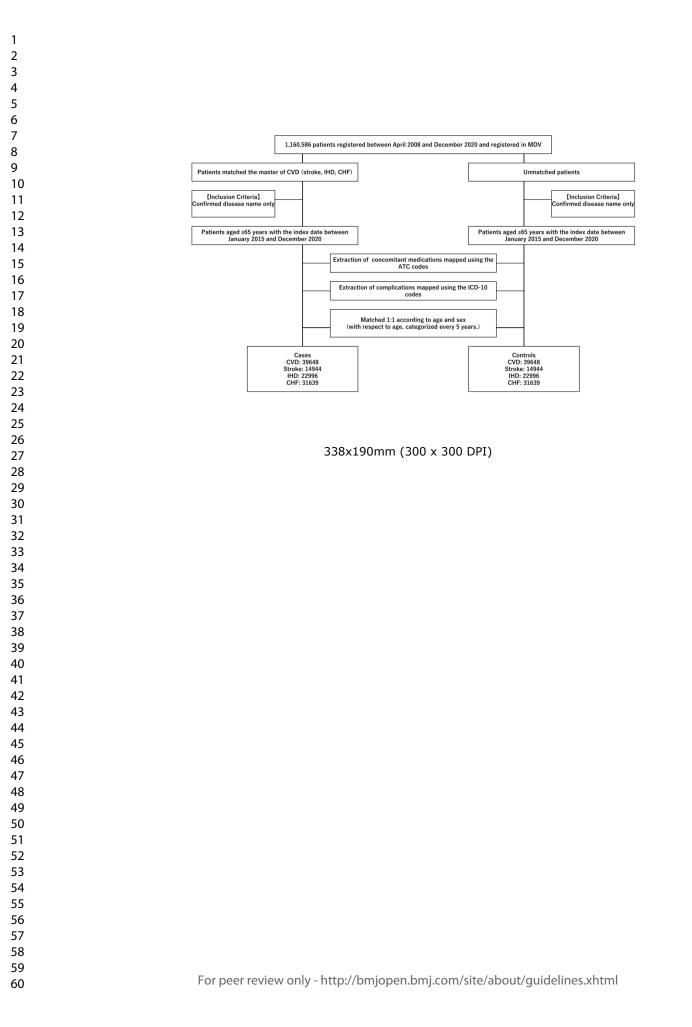
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20	408		
21 22	409	FIGURE LEGEND	
23	410	Figure 1. Flowchart of cases and controls.	
24 25	411	MDV, medical data vision.	
26	412		
27 28	413	TABLES	
29	414	Table 1. Characteristics of patients with CVD and controls.	
30 31	415	SD, standard deviation; Std diff, standardized difference.	
32	416	Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA and HipOA	
33 34	417	CI, confidence interval.	
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36 37			
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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
l10	Essential (primary) hypertension
1480-1489	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

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Page 19 of 25		BMJ Open	d by copyright, Control group, (n =22996)		
1 2 3		Case group (n =22996)	by copyright Control group <u>inclu</u> (n =22996)	Std diff	
4		<u>N (%)</u>	<u>N (%)</u>		
5 Age	Mean (SD)	78.6 (7.2)			
7			78.5 (7.3) for Uses March 12965 (56.4) relationer 10031 (43.6) televicer		
9 Sex	Male	12965 (56.4)			
0 1	Female	10031 (43.6)	10031 (43.6) ar b 24		
2	ination		3742 (16.3) 9191 (40.0) 1538 (6.7)		
-	diabetes mellitus	5676 (24.7)	3742 (16.3) a g g a	0.2096	
5 Essenti	al (primary) hypertension	12321 (53.6)	9191 (40.0) and a	0.2050	
0	"ibrillation and flutter	2945 (12.8)	1538 (6.7) at Am	0.2074	
,	c kidney disease	1914 (8.3)		0.1627	
0	ers of lipoprotein metabolism and other			0.12(7	
1 lipidem	• •	4850 (21.1)	3634 (15.8) ≥ <u></u>	0.1367	
² Knee or	steoarthritis	1376 (6.0)	3634 (15.8) A training 1194 (5.2) and similar 280 (1.2) 2227 (9.7) and similar	0.0345	
Hip ost	eoarthritis	261 (1.1)	280 (1.2) g	-0.0077	
Concor			and		
	nitant medication				
	ntidiabetic drugs	3593 (15.6)	2227 (9.7) 🔤 ר	0.1794	
	t aggregation inhibitors	6357 (27.6)	2669 (11.6) te ha 2287 (9.9) to 5 1425 (6.2) te baseline to 5 2669 (11.6) te ha 5 1425 (6.2) te ha 2669 (11.6) te ha 5 1425 (6.2) te ha 1425 (0.4123	
Diureti		4785 (20.8)	2287 (9.9) ¹⁰ ,0	0.3046	
	ocking agents	4197 (18.3)	1425 (6.2) <u><u>o</u> <u>o</u></u>	0.3744	
	n antagonists	6872 (29.9)	· · · ·	0.235	
	acting on the renin-angiotensin system	6574 (28.6)	4108 (17.9) ♣ 3328 (14.5) ♣	0.256	
₃₆ Lipid-r	egulating/antiatheroma preparations	5579 (24.3)	3328 (14.5) R	0.2496	
37 38 39 40	Characteristics o	Appendix 2. f patients with IHD and contro	ols. Bibliographique ence. Ique		
40 41 42	SD, standard deviati	ion; Std diff, standardized differ	ence. digue		

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		Crude estimate		23-0; yht, i	Adjusted estimate	
-	Odds ratio	Lower 95% CI	Upper 95% CI	Odds Pation	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.694	1.616	1.775	1.3 4	1.284	1.449
Essential (primary) hypertension	1.74	1.676	1.808	1.195 n	1.12	1.233
Atrial fibrillation and flutter	2.056	1.926	2.195	1.49 25	1.384	1.604
Chronic kidney disease	1.973	1.824	2.135	1.196 1.497 Ense 1.414 Ense 1.414 Ense	1.295	1.543
visorders of lipoprotein metabolism and other lipidemias	1.425	1.358	1.494	0.948 0.948 0.948 0.948 0.948 0.958 t	0.892	1.007
Knee osteoarthritis	1.165	1.075	1.262	1.2 \$\$ *	1.111	1.328
Hip osteoarthritis	0.932	0.787	1.103	0.9 5 1 🛱 👂	0.79	1.146
Oral antidiabetic drugs	1.74	1.643	1.842	1.0\$\$\$ <u>22 1</u>	0.977	1.136
Platelet aggregation inhibitors	2.899	2.753	3.053	2.3 10 8 2	2.25	2.516
Diuretic	2.441	2.309	2.582	1.4 🛱 🖥 🖥	1.374	1.562
Beta blocking agents	3.423	3.205	3.656	2.2 招音 1.0 知道	2.115	2.45
Calcium antagonists	1.737	1.662	1.815	1.09 g g 3	1.034	1.152
Agents acting on the renin-angiotensin system	1.851	1.769	1.937	1.0 27 00 2	0.998	1.119
Crude a	and adjusted OR	Appendix 3 s and 95% CIs of IH CI, confidence in	1.937 1.988 3. ID in relation to KOA tterval.	1.29 Al train A and Hip Gg, and similar technologies.		

f 25	BMJ Open	d by copyright, Control group, (n =31639)	
		n-202 pyrig	
	Case group	ې بې کې Control group	
	(n = 31639)	(n = 31639) \vec{c}	Std d
	N (%)	N (%) ing on	
Age Mean (SD)	79.0 (7.3)	78.9 (7.3) 한 <u>원</u>	
		March	
Sex Male	17920 (56.6)	17920 (56.6) ^{د هذي} د الم	
Female	13719 (43.4)	13719 (43.4) and 22	
		d to	
Complication		t Sul	
Type 2 diabetes mellitus	7761 (24.5)	5232 (16.5) and end 12317 (38.9) and end	0.19
Essential (primary) hypertension	19164 (60.6)		0.30
Atrial fibrillation and flutter	4284 (13.5)	1285 (4.1) ^a	0.07
Chronic kidney disease	2739 (8.7)	1061 (3.4) E	0.08
Disorders of lipoprotein metabolism and other lipidemias	8017 (25.3)	1061 (3.4) ning, 5427 (17.2) A training, 1717 (5.4) and similar 370 (1.2) g, 3270 (10.3) and similar 4871 (15.4) technologi 1799 (5.7) nologies 1330 (4.2) gies 6353 (20.1) s, and similar 1061 (3.4) A training, 1717 (5.4) and similar 1717 (5.4) and similar 1719 (5.7) and similar 1729 (5.7) and similar 1730 (4.2) and similar 1	0.11
Knee osteoarthritis	1751 (5.5)	1717 (5.4) 📓 🦉	0.04
Hip osteoarthritis	349 (1.1)	<u>ع</u> ة (1.2) ق	-0.00
		and	
Concomitant medication		sim C	
Oral antidiabetic drugs	4756 (15.0)	3270 (10.3) ar	0.14
Platelet aggregation inhibitors	9219 (29.1)	4871 (15.4) ह ह	0.35
Diuretic	6153 (19.4)	4871 (15.4) te ha 1799 (5.7) to co 1330 (4.2) te ha 6353 (20.1) te ha a	0.13
Beta blocking agents	6412 (20.3)	1330 (4.2) <u>a</u>	0.13
Calcium antagonists	10213 (32.3)		0.18
Agents acting on the renin-angiotensin system	9909 (31.3)	5393 (17.0) ຜູ້	0.21
Lipid-regulating/antiatheroma preparations	8958 (28.3)	5098 (16.1) ਰੋ	0.16
		Bib	
	Appendix 4.	5393 (17.0) Age 5098 (16.1) Bibliographique ntrols. Fference. (rite /shout (swidelings white)) Ge	
	patients with CHF and co	ntrols.	
SD, standard deviatio	n; Std diff, standardized dif	ference.	
		e d	

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		Crude estimate		2023-08 rright, i	Adjusted estimate	
-	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ខ្នាវរេស្ពិ៍	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.649	1.585	1.716	1.32	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	2.8 B	2.682	3.112
Chronic kidney disease	2.719	2.527	2.926	1.85 ⁶ 2 m a	1.685	1.992
Disorders of lipoprotein metabolism and other lipidemias	1.636	1.574	1.701	0.945 land	0.892	0.992
Knee osteoarthritis	1.021	0.953	1.095	1.0 3 63 <u>*</u>	0.975	1.144
Hip osteoarthritis	0.943	0.814	1.092	0.928 g	0.78	1.092
Oral antidiabetic drugs	1.54	1.468	1.616	0.8 🛱 🖸 🛓	0.78	0.893
Platelet aggregation inhibitors	2.25	2.162	2.342	1.5 မြန်စို့ ရွိ	1.442	1.588
Diuretic	4.068	3.839	4.312	2.745 e 8	2.574	2.926
Beta blocking agents	5.877	5.504	6.276	3.3	3.096	3.572
Calcium antagonists	1.893	1.824	1.964	0.995 g =	0.947	1.042
Agents acting on the renin-angiotensin system	2.231	2.146	2.32	1.12.08	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 Hipford and similar technologies. CI, confidence interval. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 23	of 25	BMJ Open	mjopen- d by copy	
1 2 3 4		Case group (n =14944)	d by copyright, includi Control group (n =14944)	Std diff
5		N (%)		
6	Age Mean (SD)	79.1 (7.2)		
7	8		, Υ Υ Υ Υ Υ Υ	
8 9	Sex Male	8657 (57.9)	8657 (57.9) ^{8 ng rch}	
9 10	Female	6287 (42.1)	6287 (42.1) elarge 24	
11	i cinuic			
12	Complication			
13 14	Type 2 diabetes mellitus	3900 (26.1)	2724 (18.2) area	0.1903
15				
16	Essential (primary) hypertension	8830 (59.1)		0.3065
17	Atrial fibrillation and flutter	1605 (10.7)		0.0792
18 19	Chronic kidney disease	1195 (8.0)		0.0816
20 21	Disorders of lipoprotein metabolism and other lipidemias	3605 (24.1)	79.1 (7.2) for uses related to text and similar to text and similar text and sind similar text a	0.1103
22	Knee osteoarthritis	959 (6.4)	799 (5.3) rain p	0.0455
23	Hip osteoarthritis	154 (1.0)	163 (1.1) ¹	-0.0059
24 25	F			
26	Concomitant medication		d sirr	
27 28	Oral antidiabetic drugs	2365 (15.8)	1626 (10.9) ja j	0.1458
20	Platelet aggregation inhibitors	4503 (30.1)	2312 (15.5) 🛱 🚡	0.3549
30	Diuretic	2776 (18.6)	2059 (13.8)	0.1306
31	Beta blocking agents	2340 (15.7)	1651 (11.0) ⁶ / ₉ 8	0.1359
32 33	Calcium antagonists	4404 (29.5)	2312 (15.5) technologi 2059 (13.8) to 1651 (11.0) glies 3213 (21.5) stat	0.1837
34	Agents acting on the renin-angiotensin system	4409 (29.5)		0.2133
35	Lipid-regulating/antiatheroma preparations	3794 (25.4)	2794 (18.7)	0.162
36 27	Lipid-regulating/antiatheroma preparations	5777 (25.7)		0.102
37 38	*	nnondiv 6	Sibli	
39		ppendix 6.	ogr	
40	•	tients with stroke and controls	<u>U</u>	
41	SD, standard deviation;	Std diff, standardized difference	ie. iqu	
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-		Crude estimate		-2023-08 yright, i	Adjusted estimate	
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds ឆ្នាំtiល្លិ៍	Lower 95% CI	Upper 95% C
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	1.564	1.418	1.595
Atrial fibrillation and flutter	1.312	1.214	1.418	1.1 👸	1.08	1.282
Chronic kidney disease	1.378	1.26	1.508	1.1% Ench	0.95	1.154
Disorders of lipoprotein metabolism and other lipidemias	1.309	1.238	1.383	sch 2024. Dow scalanement 9.9 Glated of t 1.1 0.8 of t 0.8 of t	0.841	0.966
Knee osteoarthritis	1.219	1.105	1.344	1.12 3	1.057	1.3
Hip osteoarthritis	0.944	0.757	1.178	0.8954 2 0	0.708	1.13
Oral antidiabetic drugs	1.541	1.44	1.65	1.00522	0.922	1.096
Platelet aggregation inhibitors	2.375	2.24	2.519	2.0868 8	1.956	2.226
Diuretic	1.438	1.35	1.532	2.086 erec 1.064 erec	0.99	1.143
Beta blocking agents	1.495	1.397	1.6	0.9	0.883	1.035
Calcium antagonists	1.527	1.448	1.61		1	1.133
				0.9% (ABE 1.064 BE 1.069 S	1.02	1.163
Lipid-regulating/antiatheroma preparations Crude a	nd adjusted ORs	Appendix 7 and 95% CIs of stro CI, confidence in	7. Oke in relation to KO terval.	0.962 Al train@A. bmj.com A and Hip@G, and s	0.895	1.035
			1.729 1.564 7. Oke in relation to KO terval.	n/ on June 10, 2025 at Aç similar technologies.		
				Jeno		

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	P2
		the abstract	L44~
		(b) Provide in the abstract an informative and balanced summary of what	P2
		was done and what was found	L39~
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation	P3
5		being reported	L77~
Objectives	3	State specific objectives, including any prespecified hypotheses	P3
5			L105-
Methods			
Study design	4	Present key elements of study design early in the paper	P3
		<u>k</u>	L112-
Setting	5	Describe the setting, locations, and relevant dates, including periods of	P3
		recruitment, exposure, follow-up, and data collection	L113-
Participants	6	(a) Case-control study—Give the eligibility criteria, and the sources and	P4
		methods of case ascertainment and control selection. Give the rationale	L125
		for the choice of cases and controls	
		(b) Case-control study—For matched studies, give matching criteria and	P4
		the number of controls per case	L131
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P4
		confounders, and effect modifiers. Give diagnostic criteria, if applicable	L140
Data sources/	8*	For each variable of interest, give sources of data and details of methods	P4
measurement		of assessment (measurement). Describe comparability of assessment	L113
		methods if there is more than one group	
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
	11		L176 [,] P5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If	L161
	10	applicable, describe which groupings were chosen and why	P5
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for	L161
		confounding	P5
		(b) Describe any methods used to examine subgroups and interactions	L161
		(c) Explain how missing data were addressed	2101
		(d) Case-control study—If applicable, explain how matching of cases	P4
		and controls was addressed	L131-
		(e) Describe any sensitivity analyses	

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	P5
		eligible, examined for eligibility, confirmed eligible, included in the study,	L174~
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	P5
data		and information on exposures and potential confounders	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	Table1
		measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	P4
		and their precision (eg, 95% confidence interval). Make clear which confounders	L139~
		were adjusted for and why they were included	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	P8
		sensitivity analyses	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	P11
		imprecision. Discuss both direction and magnitude of any potential bias	L264~
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	P11
		limitations, multiplicity of analyses, results from similar studies, and other	L278~
		relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11
			L271~
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	P12
		applicable, for the original study on which the present article is based	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

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3 4	1	Association between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An
5	2	Administrative Claims Database Analysis
6 7	3	
8	4	
9 10	5	Takuya Uematsu ^{1,2} , Shuko Nojiri ^{1,3} , Muneaki Ishijima ⁴ , Yuji Nishizaki ^{1,3,5}
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3 4	39	ABSTRACT					
5	40	Objective: To investigate whether osteoarthritis (OA) is a risk factor for cardiovascular disease (CVD);					
6 7	41	whether there are differences concerning ischemic heart disease (IHD), congestive heart failure (CHF), and					
8	42	stroke; and whether there are differences between OA sites (hips, knees, and hand) in predicting CVD onset					
9 10	43	Design: Population-based matched case-control study					
11	44	Setting: Health insurance claims data among Japanese patients					
12 13	45	Participants: Japanese patients aged ≥65 years with newly diagnosed CVD and hospitalized between					
14	46	January 2015 and December 2020 (cases) and age- and sex-matched 1:1 individuals (controls)					
15 16	47	Main outcome measures: A conditional logistic regression model was used to estimate the adjusted odds					
17	48	ratios (OR) and their 95% confidence intervals (CI) for CVD, IHD, CHF, and stroke risk, adjusting for					
18 19	49	covariates.					
20	50	Results: A total of 79,296 patients were included, with respect to CVD (39648 patients with newly					
21 22	51	diagnosed CVD and 39648 controls). After adjustment for covariates, the exposure odds of knee OA (KOA),					
23	52	hip OA (HipOA), and hand OA (HandOA) for CVD were 1.192 (95% CI, 1.115-1.274), 1.057 (95% CI,					
24 25	53	0.919–1.215), and 1.035 (95% CI, 0.684–1.566), respectively, showing an association only for KOA. The					
26	54	exposure odds of KOA, HipOA, and HandOA for IHD were 1.187 (95% CI, 1.086–1.297), 1.078 (95% CI,					
27 28	55	0.891-1.306), and 1.099 (95% CI, 0.677-1.784), respectively. The exposure odds of KOA, HipOA, and					
29	56	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,					
30 31	57	0.635–2.151), respectively. Similar to CVD, only KOA was associated with both. For CHF, neither KOA					
32	58	nor HipOA and HandOA were associated with CHF development.					
33 34	59	Conclusion: This study confirms the association of KOA with CVD, particularly IHD and stroke, in the					
35	60	Japanese population. The finding that patients with KOA have a higher CVD risk can potentially assist in					
36 37	61	guiding future treatment strategies.					
38	62						
39 40	63						
41	64	Strengths and limitations of this study					
42 43	65	• This study examined the association between osteoarthritis (OA) and cardiovascular disease (CVD) in a					
44	66	matched case-control study using large real-world data from approximately 80,000 inpatients at various					
45 46	67	hospitals in Japan.					
47	68	• The results of this study, which showed an association between KOA and CVD in Japan's super-aging					
48 49	69	population, may contribute to CVD prevention strategies in the future.					
50	70	· Data were obtained only from inpatients admitted to hospitals registered in the Japanese administrative					
51 52	71	database; thus, selection bias and generalizability should be considered.					
53	72	• Data analyzed were based on health insurance claims and were not generated for research purposes; thus,					
54 55	73	potential confounding factors that may affect clinical practice, such as environmental and lifestyle factors,					
56	74	cannot be assessed.					
57 58	75						
59	76						
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77 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

111 Study design and study population

This study employed a population-based case-control matching study design, and a retrospective
transformation 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

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1 2						
3	115	acute care hospitals across Japan. It is composed of electronic health insurance claims data, DPC claims, and				
4 5 6	116	laboratory test results [9].				
	117	Approximately one million individuals were randomly selected from 35.23 million older patients who were				
7 8	118	attending 438 DPC hospitals under contract with MDV among the entire older population in Japan. Disease-				
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	119	related information included the International Statistical Classification of Diseases, 10th Revision (ICD-10)				
	120	diagnosis codes, Japanese disease codes, and diagnosis dates. Medication-related data included health				
	121	insurance claims codes, prescription dates, administration routes, and prescription quantities. All patient data				
	122	were coded before entry into the database.				
	123					
	124	Selection of cases and controls				
	125	Cases were defined by mapping the disease codes in the dataset to the master codes for CVD, stroke, IHD,				
	126	and CHF and limiting them to confirmed disease names. Each master code was defined based on the				
	127	following ICD-10 diagnosis codes: IHD (I20–I25), CHF (I50), stroke (I60–I64), and CVD (I20–I25, I50,				
	128	I60–I64) [10]. Cases were defined as patients aged \geq 65 years that were first diagnosed with the target disease				
	129	between January 2015 and December 2020, with the diagnosis date serving as the index date. Controls were				
	130	randomly assigned index dates.				
	131	The age of the patients was categorized into 5-year intervals, and 1:1 matching was performed based on				
	132	age and sex. In cases where there were multiple potential controls for a single case, control individuals were				
	133	randomly selected from among them.				
	134	According to Yamana et al., the validity of diagnoses within the DPC database demonstrated a sensitivity				
	135	and specificity of 78.9% and 93.2%, respectively. Although variations were observed among different				
	136	medical conditions, the overall results indicated favorable accuracy without significant diagnostic				
	137	inaccuracies [11].				
38	138					
39 40	139	Definition of OA and covariates				
40 41 42 43 44 45 46	140	HipOA (M160-M169) and KOA (M170-M179) and hand OA (HandOA) (M180-M189) were defined as				
	141	exposure factors. Covariates included common risk factors for CVD, such as type 2 diabetes mellitus,				
	142	essential (primary) hypertension, atrial fibrillation and flutter, chronic kidney disease, disorders of				
	143	lipoprotein metabolism and other lipidemias, and medications related to CVD treatment: oral antidiabetic				
47	144	drugs, platelet aggregation inhibitors, diuretics, beta-blocking agents, calcium antagonists, agents acting on				
48 49	145	the renin-angiotensin system, and lipid-regulating/anti-atheroma preparations (Appendix 1).				
50 51 52 53 54 55 56 57 58	146	The types of medications and comorbidities were obtained from the MDV database. For medications, the				
	147	unique nine-digit health insurance claims codes, which are assigned to each drug based on its				
	148	pharmacological properties, were mapped to five-digit codes according to the Anatomical Therapeutic				
	149	Chemical Classification System managed by the European Pharmaceutical Marketing Research Association				
	150	[12]. The start date of medication use was set as before the index date, and medications that were being				
	151	continued at the index date or had an end date within 7 days of the index date were considered. In other				
59 60	152	words, a grace period of 7 days was set after the prescription end date, and all medications that were taken				

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153 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.

161 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 (<u>http://www.r-project.org/</u>), and the "clogit" package was used for the conditional logistic regression.

Patient and public involvement

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

RESULTS

174 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.

Page 7 of 25			BMJ Open	omjopen-2023-080387 og gr 9 by copyright, including fr		
1 2 3 184 4	Table 1. Characteristics of patients with CVD and controls.			23-080387 ght, includi		
5			Case group	Cantrol group		
6 7			(n = 39648)	ĝn = <u></u> 39648)	Std diff	
8			N (%)			
9 10	Age	Mean (SD)	78.6 (7.3)	en a star (7.3)		
11 12				ated to 2000 (54.4)		
12 13	Sex	Male	21551 (54.4)	کَبَا قَ و َعَظِّ (54.4)		
14 15		Female	18097 (45.6)	B987 (45.6)		
15 16						
17	Complications			ata mi		
18 19	Type 2 diabetes mellitus		6322 (15.9)	je (11.7)	0.122	
20	Essential (primary) hyperte	ension	13368 (33.7)	279 9 (24.7)	0.199	
21 22	Atrial fibrillation and flutte	r	3256 (8.2)	ấ 1 🛱 (2.8)	0.239	
23	Chronic kidney disease		2711 (6.8)	ä 1 d (2.9)	0.182	
24 25	Disorders of lipoprotein me	tabolism and other			0.122	
26 27	lipidemias		6566 (16.6)		0.122	
27 28	Knee osteoarthritis		2416 (6.1)	2033 (5.1)	0.042	
29	Hip osteoarthritis		493 (1.2)	technologies. 10,0025 at	0.014	
30 31	Hand osteoarthritis		53 (0.1)	୍ଟି 5 ପ୍ଟି(0.1)	0.002	
32				gies		
33 34	Concomitant medication			· at Ag		
35	Oral antidiabetic drugs		5150 (13.0)	34 2 8 (8.6)	0.14	
36 37	Platelet aggregation inhibit	ors	6712 (16.9)	28 🛱 (7.1)	0.307	
38	Diuretic		5212 (13.1)	19 5 (4.9)	0.29	
39 40			6	yrap		
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Beta blocking agents	4058 (10.2)	d by copyright, includin	0.311
Calcium antagonists	10559 (26.6)	3 183 (15.6)	0.273
Agents acting on the renin-angiotensin system	9256 (23.3)	189 (15.6) 1926 (13.3)	0.263
Linid-regulating/antiatheroma preparations	7339 (18 5)		0.198
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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).

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Γable 2. Crude and adjusted ORs and 95% C –	Is of CVD i			mjopen-zuz3-u80387 on I by copyright, including	•			
_		Crude estin	nate		~ % ″			
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds us naro ratio s and ratio s and	Lower 95% CI	Upper 95% CI		
Type 2 diabetes mellitus	1.426	1.369	1.486	1.147 1.049 to	1.091	1.206		
Essential (primary) hypertension	1.547	1.499	1.595		1.009	1.09		
Atrial fibrillation and flutter	3.103	2.892	3.33	2.521 to 1	2.337	2.72		
Chronic kidney disease	2.418	2.253	2.595	1.712 no page	1.585	1.85		
Disorders of lipoprotein metabolism and other lipidemias	1.42	1.364	1.478	o trom a control of the second	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 E	0.919	1.215		
Hand osteoarthritis	1.06	0.72	1.56	1.192 ning, 1.057 A 1.035 training, 1.077 an 1.077 an	0.684	1.566		
Oral antidiabetic drugs	1.58	1.509	1.655	1.077 a	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 art	1.892	2.131		
Beta blocking agents	4.126	3.845	4.428	2.008 milar technologie	2.337	2.72		
Calcium antagonists	1.973	1.903	2.045	1.292 e	1.237	1.349		
Agents acting on the renin- angiotensin system	1.972	1.9	2.048	1.234 ^{.9} a	1.178	1.292		
Lipid-regulating/antiatheroma preparations	1.755	1.686	1.828	Agence 1.132 Bibliographique delines.xhtml		1.194		

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 \geq 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

1 2		
3	287	desired to prevent CVD. Our findings may aid in making informed decisions for further management of
4 5	288	KOA.
6	289	
7 8	290	
9	291	
10 11	292	Competing interests
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18	297	commercial, or not-for-profit sectors.
19 20	298	
21	299	Contributors
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27	303	authors read and provided final approval of the final article to be published. The lead author confirmed that
28 29	304	the manuscript is an integrate, accurate, and transparent description of the reported study.
30	305	
31 32	306	Patient consent for publication
33	307	Not required.
34 35	308	
36	309	Disclaimer
37 38	310	No endorsement by MDV is intended nor should be inferred. The papers reported are those of the authors.
39	311	
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42	313	Not commissioned; externally peer reviewed.
43 44	314	Provenance and peer review Not commissioned; externally peer reviewed. Data sharing statement
45	315	Although the data are available from Medical Data Vision, the use of data in this study is under license and
46 47	316	not publicly available.
48	317	
49 50	318	Ethics approval
51	319	This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research
52 53	320	Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the
54 55	321	Ministry of Health, Labour and Welfare, Japan. It was approved by the Research Ethics Committee, Faculty
55 56	322	of Medicine, Juntendo University (Research permit no. E21-0264-M01).
57 58	323	
58 59	324	References
60		12

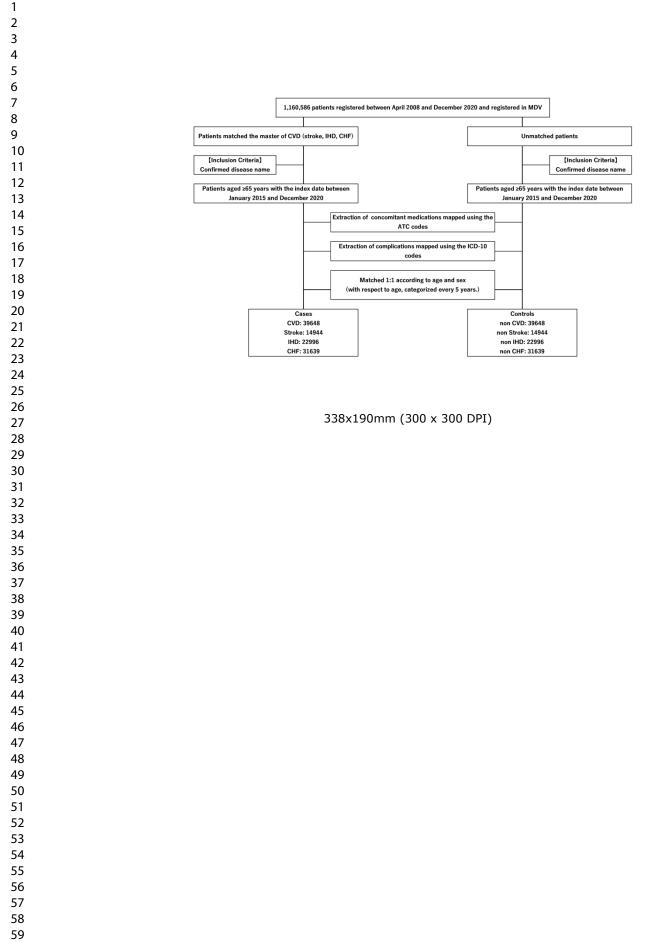
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18 19	411	
20	412	FIGURE LEGEND
21 22	413	Figure 1. Flowchart of cases and controls.
23	414	MDV, medical data vision.
24 25	415	
26	416	TABLES
27 28	417	Table 1. Characteristics of patients with CVD and controls.
29	418	SD, standard deviation; Std diff, standardized difference.
30 31	419	Table 2. Crude and adjusted ORs and 95% CIs of CVD in relation to KOA, HipOA, and HandOA.
32 33	420	CI, confidence interval.
33 34		
35 36		
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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
l10	Essential (primary) hypertension
1480-1489	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

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Page 19 of 25		BMJ Open		mjopen-2023- d by copyright	
		Case group (n =22996)	Control group (n =22996)	2023-08038 right, inclu	Std diff
		N (%)	N (%)	7 or din	
Age	Mean (SD)	78.6 (7.2)	78.5 (7.3)	125	
				March Ense r uses r	ł
Sex	Male	12965 (56.4)	12965 (56.4)	nse es r	
	Female	10031 (43.6)	10031 (43.6)	2024. ignem elated	
Compli	ications			2024. Downl ignement Su elated to tex	
-	diabetes mellitus	5676 (24.7)	3818 (16.6)	Sup Sup	0.201
	ial (primary) hypertension	12321 (53.6)	9133 (39.7)	loaded uperieu xt and c	0.201
	fibrillation and flutter	2945 (12.8)	1651 (7.2)	data	0.188
	ic kidney disease	1914 (8.3)	1023 (4.4)	a mi	0.159
	ers of lipoprotein metabolism and other	4850 (21.1)	. ,	l from http://bmj ur (ABES) . data mining, Al t	0.129
-	steoarthritis	1376 (6.0)	1202 (5.2)	njop VI tra	0.033
	teoarthritis	261 (1.1)	257 (1.1)	jopen.brr training,	0.002
_	osteoarthritis	38 (0.2)			
		50 (0.2)	37 (0.2)	mj.com/ on June 10, 2025 a y, and similar technologies.	0.001
	mitant medication			on ,	
	ntidiabetic drugs	3593 (15.6)	2305 (10.0)	June ar tech	0.168
	t aggregation inhibitors	6357 (27.6) 4785 (20.8)	2700 (11.7)	e 10	
Diureti Bata bl		4785 (20.8)	2334 (10.1)	nologie:	0.298
	locking agents	4197 (18.3)	1509 (6.6)	25 a jies.	
	m antagonists	6872 (29.9) (574 (28.6)	4520 (19.7)	at Age s.	
	acting on the renin-angiotensin system	6574 (28.6) 5570 (24.2)	4126 (17.9)	gence	0.254
Lipia-r	regulating/antiatheroma preparations	5579 (24.3)	3316 (14.4)		
		Appendix 2. patients with IHD and con on; Std diff, standardized diff		Bibliographique de I	
	For peer re	view only - http://bmjopen.bmj.co	m/site/about/guidelines.xhtm	nl de	

Appendix 2.

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			mjopen-2023-080387 or by copyright, including
	Case group	Control group	3-08 nt, ir
	(n = 31639)	(n = 31639)	ੇ ਛੈ Std diff
_	N (%)	N (%)	7 or ding
Age Mean (SD)	79.0 (7.3)	78.9 (7.3)	25 I for
			25 March 2024. Downloaded fr Enseignement Superieur for uses related to text and da
Sex Male	17920 (56.6)	17920 (56.6)	ch) nsei es re
Female	13719 (43.4)	13719 (43.4)	2024. Pignen related
			ed to
Complications			Down nent Si d to te
Type 2 diabetes mellitus	7761 (24.5)	5164 (16.3)	
Essential (primary) hypertension	19164 (60.6)	12085 (38.2)	t and construction of the second seco
Atrial fibrillation and flutter	4284 (13.5)	1304 (4.1)	at⊋g 0.33/
Chronic kidney disease	2739 (8.7)	1044 (3.3)	
Disorders of lipoprotein metabolism and other	8017 (25.3)	5355 (16.9)	ing
lipidemias	0017 (23.3)	5555 (10.7)	
Knee osteoarthritis	1751 (5.5)	• 1702 (5.4)	training 0.007
Hip osteoarthritis	349 (1.1)	361 (1.1)	nin 6 0.004
Hand osteoarthritis	41 (0.1)	45 (0.1)	BEST 0.227 New York Constraints of the second seco
			ld si
Concomitant medication			mili
Oral antidiabetic drugs	4756 (15.0)	3197 (10.1)	ar tech 0.346
Platelet aggregation inhibitors	9219 (29.1)	4751 (15.0)	
Diuretic	6153 (19.4)	1682 (5.3)	nologie: 0.508
Beta blocking agents	6412 (20.3)	1311 (4.1)	gie 25 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)	Gence 0.303
Lipid-regulating/antiatheroma preparations	8958 (28.3)	5031 (15.9)	<u>a</u> 0.303
Characteristics of p	Appendix 3. Datients with CHF and control of the stand read of the standardized difter the standardize		Bibliographique de I
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Appendix 3.

age 21 of 25	BMJ Open		mjopen-2023-(d by copyright,	
	Case group (n =14944)	Control group (n =14944)	2023-08038 7right, inclu	d diff
	N (%)	N (%)	7 ol	
Age Mean (SD)	79.1 (7.2)	79.1 (7.2)	r 25 I g for	
Sex Male	8657 (57.9)	8657 (57.9)	25 March 2 Ensei for uses re	
Female	6287 (42.1)	6287 (42.1)	2024 gnei elate	
Complications			0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
Type 2 diabetes mellitus	3900 (26.1)	2781 (18.6)	upe training 0).18
Essential (primary) hypertension	8830 (59.1)	6490 (43.4)	nd of the ded	.317
Atrial fibrillation and flutter	1605 (10.7)	1221 (8.2)	froi froi froi	.088
Chronic kidney disease	1195 (8.0)	824 (5.5)		.099
Disorders of lipoprotein metabolism and other lipidemias	3605 (24.1)	2851 (19.1)	0. 0. 0. 0. ed from http://bmj eur (ABES) . d data mining, AI	.123
Knee osteoarthritis	959 (6.4)	• 774 (5.2)	traj <mark>9</mark> 0.	.053
Hip osteoarthritis	154 (1.0)	152 (1.0)	open.brr training,	.001
Hand osteoarthritis	23 (0.2)	21 (0.1)	nj.com/ and si	.003
Concomitant medication	2265 (15.8)	1671 (11.2)	milar	126
Oral antidiabetic drugs Platelet aggregation inhibitors	2365 (15.8) 4503 (30.1)	1671 (11.2) 2333 (15.6)	June ar tech	.136 .351
Diuretic	2776 (18.6)	2002 (13.4)	10, 0,	.142
Beta blocking agents	2340 (15.7)	1671 (11.2)	2025 Jogie	.132
Calcium antagonists	4404 (29.5)	3165 (21.2)	es. at 0.	.192
Agents acting on the renin-angiotensin system	4409 (29.5)	3094 (20.7)	> ``	.204
Lipid-regulating/antiatheroma preparations	3794 (25.4)	2767 (18.5)		.167
Characteristics of	Appendix 4. Patients with stroke and con ion; Std diff, standardized diffe	trols.	Bibliographique de I	
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Appendix 4.

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		Crude estimate		23-08 Jht, i	Adjusted estimate	
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds eation	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.659	1.584	1.739	1.3 📴 🎽	1.283	1.446
Essential (primary) hypertension	1.751	1.686	1.818	1.9 n	1.144	1.259
Atrial fibrillation and flutter	1.902	1.784	2.027	1.379 25	1.283	1.482
Chronic kidney disease	1.96	1.811	2.121	1.37 March	1.255	1.495
Disorders of lipoprotein metabolism and other lipidemias	1.395	1.33	1.463	ch 2024. [s: 窟latem 1.1智	0.858	0.969
Knee osteoarthritis	1.156	1.067	1.253	1.1 & *	1.086	1.297
Hip osteoarthritis	1.016	0.854	1.209	1.0 7 8 🚆 🎽	0.891	1.306
Hand osteoarthritis	0.974	0.623	1.523	1.0 to an	0.677	1.784
Oral antidiabetic drugs	1.681	1.588	1.78	0.987 ried	0.916	1.063
Platelet aggregation inhibitors	2.911	2.763	3.066	2.3	2.257	2.525
Diuretic	2.377	2.249	2.512	2.3% from 1.475 ABE	1.384	1.571
Beta blocking agents	3.209	3.009	3.422	2.1	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	1.0 🛱 🧵	0.961	1.076
Lipid-regulating/antiatheroma preparations	1.905	1.815	2	1.0 ¹ 7 ^m jopen.bm	1.187	1.346
Crude and	l adjusted ORs and	Appendix 5 95% CIs of IHD in 1 CI, confidence in	relation to KOA, Hip	ພ 📮	Δ.	
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BMJ Open

ıf 25	BMJ Open			mjopen-2023-0; 1 by copyright, i		
		Crude estimate		i De	Adjusted estimate	
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds Batio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.676	1.61	1.744		1.253	1.398
Essential (primary) hypertension	2.495	2.413	2.581		1.577	1.723
Atrial fibrillation and flutter	3.603	3.374	3.846	2.7 9 95	2.564	2.969
Chronic kidney disease	2.771	2.574	2.984	1.860 Ens	1.713	2.029
Disorders of lipoprotein metabolism and other lipidemias	1.675	1.611	1.743	0.945 eign	0.891	0.993
Knee osteoarthritis	1.031	0.962	1.104	1.02/3	0.948	1.112
Hip osteoarthritis	0.966	0.834	1.12		0.816	1.149
Hand osteoarthritis	0.911	0.597	1.391	1.1% and the superieur 0.84 dat 0.84 dat	0.705	1.841
Oral antidiabetic drugs	1.583	1.508	1.662	0.84 6 2 2	0.79	0.905
Platelet aggregation inhibitors	2.343	2.25	2.44	1.574 (ABE 3.067/88	1.496	1.65
Diuretic	4.374	4.121	4.643	3.0 6 7 🛱 🗎	2.816	3.211
Beta blocking agents	5.938	5.559	6.343	3.3 <u>3</u> .00	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	1.0 🏝 💆	1.021	1.133
Lipid-regulating/antiatheroma preparations	2.104	2.021	2.189	1.22 ming,	1.149	1.286
Crude an	d adjusted ORs and	Appendix 6 95% CIs of CHF in a CI, confidence in	relation to KOA, Hip		A .	
				n/ on June 10, 2025 at Agence Bibliographique de I similar technologies.		

		BMJ Oper	1	omjopen-2023-0; 1 by copyright, i		Pa
		Crude estimate		_ //	Adjusted estimate	
	Odds ratio	Lower 95% CI	Upper 95% CI	Odds eatio	Lower 95% CI	Upper 95% CI
Type 2 diabetes mellitus	1.555	1.47	1.644	1.254 ⁷⁷ 1.564 ⁹	1.17	1.344
Essential (primary) hypertension	1.913	1.824	2.007	N)	1.472	1.656
Atrial fibrillation and flutter	1.355	1.252	1.465	1.178 5	1.08	1.284
Chronic kidney disease	1.489	1.358	1.632	1.14 March	1.034	1.259
Disorders of lipoprotein metabolism and other lipidemias	1.357	1.283	1.435		0.875	1.005
Knee osteoarthritis	1.26	1.142	1.39	1.2 2	1.099	1.356
Hip osteoarthritis	1.013	0.809	1.27		0.723	1.165
Hand osteoarthritis	1.095	0.606	1.979	1.18 angle 1.18 angle 0.98 du	0.635	2.151
Oral antidiabetic drugs	1.503	1.404	1.609	0.98 ge e	0.904	1.074
Platelet aggregation inhibitors	2.323	2.193	2.462	2.0 ² (Am from 1.10 ⁴ (Bm h	1.903	2.162
Diuretic	1.498	1.405	1.597	1.10 m =	1.029	1.19
Beta blocking agents	1.473	1.377	1.576	0.9 편이문	0.86	1.008
Calcium antagonists	1.564	1.483	1.65	1.094. 岌	1.027	1.165
Agents acting on the renin-angiotensin system Lipid-regulating/antiatheroma preparations	1.599 1.498	1.516 1.417	1.686 1.584	1.0赛 <u>m</u> 0.9函 p	0.969 0.908	1.105 1.05
Crude and a	djusted ORs and 9	Appendix 7 25% CIs of stroke in CI, confidence in	relation to KOA, Hi		А.	
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Fo	or peer review only	- http://bmjopen.bmj	.com/site/about/guide	elines.xhtml		

STROBE Statement-checklist of items that should be included in reports of observational studies	es
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	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or	P2
		the abstract	L44~
		(b) Provide in the abstract an informative and balanced summary of what	P2
		was done and what was found	L39~
Introduction			-
Background/rationale	2	Explain the scientific background and rationale for the investigation	P3
		being reported	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	P3
		recruitment, exposure, follow-up, and data collection	L113-
Participants	6	(a) Case-control study—Give the eligibility criteria, and the sources and	P4
		methods of case ascertainment and control selection. Give the rationale	L125-
		for the choice of cases and controls	
		(b) Case-control study—For matched studies, give matching criteria and	P4
		the number of controls per case	L131-
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P4
		confounders, and effect modifiers. Give diagnostic criteria, if applicable	L140-
Data sources/	8*	For each variable of interest, give sources of data and details of methods	P4
measurement		of assessment (measurement). Describe comparability of assessment	L113-
		methods if there is more than one group	
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	P5
		applicable, describe which groupings were chosen and why	L161-
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	P5
		confounding	L161-
		(b) Describe any methods used to examine subgroups and interactions	P5
		(a) Europain have missing data seems addressed	L161-
		(c) Explain how missing data were addressed	P4
		(<i>d</i>) <i>Case-control study</i> —If applicable, explain how matching of cases	L131
		and controls was addressed	

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	P5
		eligible, examined for eligibility, confirmed eligible, included in the study,	L174~
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	P5
data		and information on exposures and potential confounders	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	Table1
		measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	P4
		and their precision (eg, 95% confidence interval). Make clear which confounders	L139~
		were adjusted for and why they were included	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	P8
		sensitivity analyses	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	P11
		imprecision. Discuss both direction and magnitude of any potential bias	L264~
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	P11
		limitations, multiplicity of analyses, results from similar studies, and other	L278~
		relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11
			L271~
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	P12
		applicable, for the original study on which the present article is based	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.