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ORIGINAL RESEARCH

Cross-Sectional and Longitudinal Associations of Comorbidities with Knee Symptoms and Radiographic Abnormalities of Osteoarthritis

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ABSTRACT

Introduction: This study aimed to investigate the associations of comorbidities with knee symptoms and radiographic abnormalities of osteoarthritis (OA).

Methods: Participants were from the Osteoarthritis Initiative. Comorbidities were identified at baseline using the modified Charlson Comorbidity Index. For both knees, symptoms were assessed annually from baseline to 48 months using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores (rescaled range 0–100), and radiographic abnormalities using the Kellgren–Lawrence (KL, 0–4) grades. The presence of significant pain and functional disability was defined as a WOMAC score of ≥ 25 and ≥ 22, respectively, and radiographic OA (ROA) as KL ≥ 2. An increase of ≥ 9 in WOMAC scores and ≥ 1 in KL grades were defined as symptomatic and radiographic progression, respectively.

Results: Of 3337 participants, 28% and 9% had one and ≥ 2 comorbidities, respectively. The number of comorbidities was associated with the presence of significant functional disability (odds ratios [ORs] 1.15; 1.46) and predicted the progression of both knee pain and functional disability (ORs 1.11; 1.51). For the type of comorbidities, non-OA musculoskeletal diseases were associated with the presence of ROA and significant functional disability (ORs 1.63; 1.82) and showed a trend to predict incident ROA (OR 1.84, 95% confidence interval 1.00–3.38 $p = 0.051$). Diabetes and kidney diseases were associated with symptomatic progression of OA (ORs 1.38; 2.72).

Conclusions: Having more comorbidities, especially diabetes and kidney diseases, is associated with symptomatic progression of knee OA. Moreover, non-OA musculoskeletal diseases may be associated with the presence and onset of ROA.

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Key Summary Points

Over one in three participants with or at increased risk of symptomatic knee osteoarthritis (OA) had at least one comorbidity.

Participants who had a greater number of comorbidities were more likely to have symptomatic progression of knee OA.

Diabetes and kidney diseases may play a role in the symptomatic progression of knee OA, and non-OA musculoskeletal disorders may be associated with the presence and onset of radiographic OA.

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disease and the leading cause of pain and disability in older adults [1]. Previous studies have found that OA frequently coexists with other diseases (i.e., comorbidities) [2, 3]. A systematic review has shown that having at least one comorbidity was associated with greater deterioration of pain and functional disability in patients with knee and/or hip OA [4]. Moreover, in a recent registry-based study, the authors found that comorbidities were associated with the risk of mortality in patients with OA [5]. Unravelling the association between comorbidities and OA may help to understand the etiology and pathogenesis of OA and to develop a patient-centered management plan [6].

Most studies have focused on the association of the number of comorbidities with the onset and progression of OA, but it is unclear which comorbidities are more important [7]. In a systematic review, the authors found a significant association between diabetes and more severe osteoarthritic pain, and between heart disease and physical impairment [8]. Importantly, the association was stronger in longitudinal studies compared to cross-sectional studies [8]. These findings support that non-mechanical factors, such as cardiometabolic effects, play a role in the progression of OA [9]. Moreover, few studies have discussed the impact of comorbidities on the structural progression of OA. In a cohort study of non-obese patients with symptomatic knee and/or hip OA, cardiovascular disease (CVD) was significantly associated with radiographic changes of knee and hip OA over 5 years [10]. Another study also found that type 2 diabetes but not other metabolic factors or metabolic syndrome was a predictor of joint space narrowing in men with knee OA [11]. No studies have comprehensively evaluated the associations between different types of comorbidities and the presence and progression of symptomatic and structural abnormalities of OA. Therefore, this study aimed to describe the cross-sectional and longitudinal associations of the number and type of comorbidities with knee symptoms and radiographic abnormalities of OA.

MATERIALS AND METHODS

Study Population and Design

The Osteoarthritis Initiative (OAI) study is a prospective longitudinal cohort study of 4796 individuals aged 45–79 years, with or at increased risk of symptomatic knee OA (https://nda.nih.gov/oai/). The OAI database was accessed by the authors with permission.

Participants were recruited from four clinical centers in the US and followed up every 12 months, and those who had bilateral total knee replacements (TKR) at baseline were not eligible for the OAI. The OAI study and public use of clinical and imaging data used in this study were approved by the committee on Human Research at the University of California, San Francisco (IRB approval number, 10–00532). All participants provided written informed consent. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. For this study, we included 3337 participants who had data on

comorbidities, knee symptoms, and radiographic measurements at baseline. Data from baseline to 48 months were analyzed.

Comorbidity

Comorbidities were assessed at baseline using the modified Charlson Comorbidity Index (Katz Questionnaire Adaption) [12]. The following 13 comorbidities were reported in the questionnaire: heart attack, heart failure, unclog or bypass leg arteries, stroke, asthma, obstructive pulmonary disease, polymyalgia rheumatica, rheumatoid arthritis, cancer, peptic ulcer, diabetes, kidney problem, and liver damage (e.g., cirrhosis). Additionally, hypertension was assessed and defined by systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg [13]. The total number of comorbidities was calculated (0–14) and classified into three groups: 0, 1, and $\geq$ 2, because of the small number of participants who had $\geq$ 3 comorbidities (2%).

Seven types of comorbidities were defined for this study: (1) CVD, which included heart attack, heart failure, hypertension, unclog or bypass leg arteries, and stroke; (2) non-OA musculoskeletal disease (MSD), which included polymyalgia rheumatic and rheumatoid arthritis; (3) diabetes; (4) respiratory disease, which included asthma and obstructive pulmonary disease; (5) cancer; (6) digestive and liver diseases (DLD), which included peptic ulcer and liver damage; (7) kidney diseases.

Knee Symptoms and Radiographic Abnormalities

The Western Ontario and McMaster Universities (WOMAC) pain and function subscales (rescaled range 0–100) were used to assess knee pain and functional disability for both knees [14, 15]. In this study, 49% and 54% participants had any knee pain (i.e., WOMAC pain score $>$ 0) in the left and right knees at baseline, respectively, and 58% and 61% had any functional disability. The presence of significant knee pain and functional disability was defined as a WOMAC pain score of $\geq$ 25 and a WOMAC function score of $\geq$ 22, respectively, according to our previous study. [16] Knees with an increase in WOMAC pain and function scores of $\geq$ 9 points from baseline to any follow-up visit until month 48, or had a TKR during the follow-up, were considered symptomatic progression that is clinically important [17–19].

Radiographic OA (ROA) in both knees was assessed using X-rays and defined as a Kellgren–Lawrence (KL; range 0–4) grade of $\geq$ 2. [20] Both increases in KL grade and the implementation of TKR during the 48-month follow-up were considered radiographic progression of knee OA. For knees free of TKR and had KL $<$ 2 at baseline, incident ROA was defined as a KL grade of $\geq$ 2 or the implementation of TKR during the follow-up.

Covariates

Covariates were selected based on previous literature. [21–28] They included the following variables: age (year), sex, race (White, Black, Other), body mass index (BMI), smoking status (never, current, former), alcohol consumption (semi-quantitative assessment, range 0–7), education level (high school or less, some college, college graduate, some graduate school, and graduate degree), income ($<$ \$25,000, \$25,000 $\sim$ 50,000, and $>$ \$50,000), physical activity assessed using the Physical Activity Scale for the Elderly (PASE), history of knee injury, and use of pain-related medications (acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, and intra-articular corticosteroids).

Statistical Analysis

Baseline characteristics of study participants were described using mean (standard deviation) and percentage (%), split by the number of comorbidities (i.e., 0, 1, and $\geq$ 2).

The cross-sectional and longitudinal associations of the number and type of comorbidities with knee symptoms and structural abnormalities or progression were analyzed using generalized estimating equations. The correlation between observations in the left and right knees

was adjusted using the robust estimator of variance and an exchangeable correlation structure [29]. The seven comorbidity types were analyzed in the same model when evaluating the association between the type of comorbidities and OA outcomes. Two adjustment models were built. Model 1 adjusted for age, sex, race, and BMI, and model 2 further adjusted for the remaining covariates, except that the association between comorbidities and structural abnormalities and progression did not adjust for the use of medications given that no disease-modifying drugs are available. Multiple imputations with chained equations were conducted to impute missing data (0.09–7% missing). Five imputations were performed using baseline complete variables and non-missing values of variables being imputed, assuming missing at random. Odds ratio (OR) with 95% confidence interval (CI) were used to describe the associations.

We conducted complete case analyses to test the robustness of the main results. Data analyses were carried out using R software version 4.2.1. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Participants

Of 3337 participants in this study, 28% had at least one comorbidity at baseline. Among participants with comorbidities, the leading comorbidities were hypertension (62%), asthma (24%), and diabetes (17%). Table 1 summarizes the baseline characteristics of the study participants. As the number of comorbidities increased, participants were older, more likely to be Black Americans and smokers, and had higher BMI and lower income and education levels.

Number of Comorbidities and OA

Having more comorbidities was associated with a higher risk of significant functional disability at baseline, in a dose–response manner (one vs. no comorbidity: OR 1.15, 95% CI 1.01–1.32; ≥ 2 vs. no comorbidity: OR 1.46, 95% CI 1.18–1.80; p for trend < 0.001). No statistically significant associations of the number of comorbidities with the presence of significant knee pain and ROA (i.e., KL ≥ 2) were found (Table 2).

In longitudinal analyses, a greater number of comorbidities was associated with the progression of both knee pain and functional disability (≥ 2 vs. no comorbidity: OR for pain = 1.30, 95% CI 1.03–1.64, p for trend < 0.05; OR for functional disability = 1.51, 95% CI 1.17–1.96, p for trend < 0.05). However, the number of comorbidities was not statistically significantly associated with either the incident or progression of ROA (Table 3).

Type of Comorbidities and OA

Only non-OA MSD was associated with the presence of ROA at baseline (OR 1.82, 95% CI 1.07–3.10, $p = 0.027$). Non-OA MSD and DLD were significantly associated with the presence of significant functional disability at baseline (non-OA MSD: OR 1.63, 95% CI 1.03–2.60, $p = 0.038$; DLD: OR 1.50, 95% CI 1.03–2.19, $p = 0.034$) (Table 4).

In longitudinal analysis, diabetes and kidney diseases were associated with symptomatic progression of knee OA over 48 months (diabetes: OR for pain = 1.38, 95% CI 1.05–1.82, $p = 0.023$; OR for functional disability = 1.55, 95% CI 1.16–2.07, $p = 0.003$; kidney: OR for functional disability = 2.72, 95% CI 1.30–5.66, $p = 0.008$) (Table 5). Non-OA MSD showed a trend to be associated with incident ROA (OR 1.84, 95% CI 1.00–3.38, $p = 0.051$).

Sensitivity Analysis

Complete-case analyses did not materially change the main findings (Supplementary Tables 1–4), except that the association between CVD and the presence of significant functional disability at baseline became statistically significant (Supplementary Table 3), and non-OA MSD was statistically significantly associated with the progression but not presence of

Table 1 Baseline characteristics of study participants

	Total (*n* = 3337)	**No comorbidity (*n* = 2074)**	**One comorbidity (*n* = 946)**	**2 or more (*n* = 317)**	***p***
Age, mean (SD)	60.9 (9.2)	59.7 (8.9)	62.1 (9.3)	65.0 (9.1)	< 0.001
Race					< 0.001
White	2803 (84)	1799 (87)	771 (82)	233 (74)	
Black	470 (14)	238 (12)	157 (17)	75 (24)	
Other	61 (2)	35 (2)	17 (2)	9 (3)	
Female	1963 (59)	1241 (60)	538 (57)	184 (58)	0.294
Body mass index, kg/m^2, mean (SD)	28.3 (4.7)	27.6 (4.5)	29.1 (4.8)	30.6 (4.7)	< 0.001
Left knee					
WOMAC pain (> = 25)	764 (23)	438 (21)	223 (24)	103 (33)	< 0.001
WOMAC function (> = 22)	989 (30)	580 (28)	300 (32)	109 (35)	0.014
Kellgren–Lawrence					< 0.001
Grade 0	1343 (40)	897 (43)	345 (37)	101 (32)	
Grade 1	605 (18)	384 (19)	170 (18)	51 (16)	
Grade 2	820 (25)	495 (24)	242 (26)	83 (26)	
Grades 3 and 4	553 (17)	289 (14)	185 (20)	79 (25)	
Right					
WOMAC pain (> = 25)	916 (27)	497 (24)	300 (32)	119 (38)	< 0.001
WOMAC function (> = 22)	1012 (30)	581 (28)	306 (33)	125 (40)	< 0.001
Kellgren–Lawrence					< 0.001
Grade 0	1277 (39)	850 (41)	331 (35)	96 (31)	
Grade 1	609 (18)	384 (19)	172 (18)	53 (17)	
Grade 2	876 (27)	535 (26)	252 (27)	89 (28)	
Grades 3 and 4	545 (17)	288 (14)	180 (19)	77 (24)	
Disease classification					
CVD	777 (23)	0	532 (56)	245 (77)	< 0.001
Respiratory disease	305 (9)	0	180 (19)	125 (39)	< 0.001
Diabetes	212 (6)	0	107 (11)	105 (33)	< 0.001
Cancer	119 (4)	0	51 (5)	68 (22)	< 0.001
DLD	78 (2)	0	37 (4)	41 (13)	< 0.001
non-OA MSD	54 (2)	0	21 (2)	33 (10)	< 0.001

Table 1 continued

	Total (n = 3337)	No comorbidity (n = 2074)	One comorbidity (n = 946)	2 or more (n = 317)	p
Kidney diseases	42 (1)	0	18 (2)	24 (8)	< 0.001
Income					< 0.001
< 25,000$	321 (10)	154 (8)	102 (11)	65 (22)	
25,000–50,000$	752 (24)	419 (21)	238 (27)	95 (32)	
> 50,000$	2074 (66)	1387 (71)	553 (60)	134 (46)	
Education					< 0.001
High school or less	417 (13)	220 (11)	133 (14)	64 (20)	
Some college	748 (22)	424 (20)	232 (25)	92 (29)	
College graduate	747 (22)	510 (25)	189 (20)	48 (15)	
Some graduate school	290 (9)	168 (8)	96 (10)	26 (8)	
Graduate degree	1134 (34)	752 (36)	296 (31)	86 (27)	
Smoking status					0.006
Never	1838 (55)	1176 (57)	519 (55)	143 (46)	
Current	158 (5)	96 (5)	41 (4)	21 (7)	
Former	1319 (40)	786 (38)	384 (41)	149 (48)	
Alcohol intake (0–7), median (IQR)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)	
Use of medication					
NSAID	980 (29)	553 (27)	320 (34)	107 (34)	< 0.001
Acetaminophen	313 (9)	154 (7)	99 (11)	60 (19)	< 0.001
Opioids	69 (2)	36 (2)	19 (2)	14 (4)	0.008
Intra-articular corticosteroids	59 (2)	32 (2)	19 (2)	8 (3)	0.379
PASE score, mean (SD)	164.1 (81.7)	160.0 (81.0)	144.4 (77.4)	169.0 (82.1)	< 0.001
History of knee injury	1362 (41)	843 (41)	400 (43)	119 (38)	0.404

Data were shown as % unless specified otherwise
CVD cardiovascular diseases, *DLD* peptic ulcer and liver damage, digestive and liver diseases, *IQR* interquartile range, *MSD* musculoskeletal diseases, *NSAIDs* non-steroidal anti-inflammatory drugs, *OA* osteoarthritis, *SD* standard deviation, *PASE* Physical Activity Scale for the Elderly, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

significant functional disability (Supplementary Tables 3–4).

DISCUSSION

In this study, we investigated the role of comorbidities in the presence and progression

Table 2 Associations of the number of comorbidities with the presence of radiographic osteoarthritis, knee pain, and functional disability at baseline

	Odds ratio (95% confidence interval)			*p*
	Model 1[†]	*p*	Model 2[‡]	
Presence of radiographic OA				
No comorbidity	Ref.		Ref.	
One comorbidity	1.14 (0.96–1.35)	0.136	1.12 (0.94–1.33)	0.216
≥ 2 comorbidity	1.18 (0.91–1.52)	0.220	1.20 (0.92–1.55)	0.178
P for trend	–	0.109	–	0.109
Presence of knee pain				
No comorbidity	Ref.		Ref.	
One comorbidity	1.16 (0.94–1.44)	0.168	1.08 (0.87–1.33)	0.504
≥ 2 comorbidity	1.39 (1.05–1.84)	0.021	1.13 (0.84–1.53)	0.412
P for trend	–	0.018	–	0.354
Presence of functional disability				
No comorbidity	Ref.		Ref.	
One comorbidity	1.22 (1.07–1.39)	0.004	1.15 (1.01–1.32)	0.036
≥ 2 comorbidity	1.57 (1.28–1.92)	< 0.001	1.46 (1.18–1.80)	0.001
P for trend		< 0.001		< 0.001

OA, osteoarthritis

[†]Model 1: adjusted for age, sex, race, and body mass index

[‡]Model 2: further adjusted for education level, income, smoking, alcohol intake, knee injury, and use of medications (i.e., non-steroid anti-inflammatory drugs, acetaminophen, opioids, and intra-articular corticosteroids)

of knee symptoms and radiographic abnormalities. Our findings revealed that adults who had a greater number of comorbidities were more likely to have functional disability and progression of knee symptoms, in a dose–response manner. Importantly, we found that non-OA MSD was positively associated with the presence and risk but not progression of radiographic OA, and that diabetes, kidney diseases, and DLD were associated with the presence and/or progression of knee symptoms. These findings illustrate that different comorbidities have dissimilar effects in the presence and progression of symptomatic and structural abnormalities of the knee, and that taking account of both the number and the type of comorbidities may be important in OA studies.

We did not find a significant association between the number of comorbidities and the presence or progression of ROA. However, there was a trend, albeit statistically non-significant, that having more comorbidities was associated with a high risk of incident ROA. Further analysis showed that non-OA MSD (i.e., polymyalgia rheumatica and rheumatoid arthritis) played a key role in the risk of ROA. It is possible that rheumatoid arthritis, as a destructive joint disease, directly contributed to the presence of ROA. In a large population-based cohort study, the authors found that patients with rheumatoid arthritis were 2.8 times more likely to develop OA [30]. This may be due to that the increased level of chronic systemic inflammation exhibited by rheumatoid arthritis

Table 3 Associations of the number of comorbidities with incident and progression of radiographic osteoarthritis and progression of knee pain, and functional disability over 48 months

	Odds ratio (95% confidence interval)			*p*
	Model 1[†]	*p*	Model 2[‡]	
Incident ROA				
No comorbidity	Ref.		Ref.	
One comorbidity	1.16 (0.98–1.37)	0.095	1.13 (0.95–1.34)	0.170
≥ 2 comorbidity	1.24 (0.95–1.61)	0.119	1.24 (0.94–1.62)	0.125
P for trend	–	0.047	–	0.066
Progression of ROA				
No comorbidity	Ref.		Ref.	
One comorbidity	0.90 (0.75–1.08)	0.242	0.89 (0.74–1.07)	0.200
≥ 2 comorbidity	1.00 (0.76–1.32)	0.983	1.00 (0.76–1.33)	0.993
P for trend	–	0.570	–	0.551
Progression of knee pain				
No comorbidity	Ref.		Ref.	
One comorbidity	1.16 (1.00–1.34)	0.044	1.11 (0.96–1.28)	0.163
≥ 2 comorbidity	1.40 (1.12–1.76)	0.004	1.30 (1.03–1.64)	0.027
P for trend	–	0.001	–	0.017
Progression of functional disability				
No comorbidity	Ref.		Ref.	
One comorbidity	1.20 (1.02–1.42)	0.032	1.13 (0.95–1.34)	0.162
≥ 2 comorbidity	1.65 (1.29–2.12)	< 0.001	1.51 (1.17–1.96)	0.002
P for trend		< 0.001		0.002

ROA radiographic osteoarthritis

[†]Model 1: adjusted for age, sex, race, and body mass index

[‡]Model 2: further adjusted for education level, income, smoking, alcohol intake, knee injury, and use of medications (i.e., non-steroid anti-inflammatory drugs, acetaminophen, opioids, and intra-articular corticosteroids)

promoted the onset of OA [31]. Additionally, our longitudinal analyses revealed a significant association between the number of comorbidities with the presence of significant functional disability and the progression of both knee pain and functional disability. The association was more evident in participants with ≥ 2 comorbidities. This is consistent with the findings of a systematic review showing that greater comorbidity counts were associated with the severity and deterioration of pain and performance-based physical function outcomes [8]. The association of the number of comorbidities with functional disability was stronger than with knee pain. This is anticipated given that physical function relies more on the conditions of the whole body.

For individual comorbidity, we found that participants with non-OA MSD and DLD, and probably CVD and kidney diseases, were more

Table 4 Associations of the type of comorbidities with the presence of radiographic osteoarthritis, knee pain, and functional disability at baseline

	Odds ratio (95% confidence interval)			*p*
	Model 1[†]	*p*	Model 2[‡]	
Presence of ROA				
CVD	1.09 (0.92–1.31)	0.322	1.08 (0.91–1.30)	0.379
Respiratory disease	1.11 (0.85–1.46)	0.437	1.11 (0.84–1.45)	0.465
Diabetes	0.97 (0.72–1.31)	0.851	0.96 (0.71–1.30)	0.811
Non-OA MSD	1.71 (1.01–2.87)	0.045	1.82 (1.07–3.10)	0.027
Kidney diseases	0.95 (0.52–1.73)	0.869	0.98 (0.53–1.84)	0.956
DLD	1.08 (0.65–1.77)	0.776	1.00 (0.61–1.63)	0.988
Cancer	1.01 (0.70–1.46)	0.939	1.04 (0.73–1.50)	0.817
Presence of knee pain				
CVD	1.11 (0.90–1.37)	0.337	1.05 (0.85–1.30)	0.665
Respiratory disease	1.17 (0.87–1.58)	0.310	1.02 (0.74–1.40)	0.911
Diabetes	1.19 (0.85–1.67)	0.321	1.11 (0.78–1.56)	0.565
Non-OA MSD	1.06 (0.62–1.82)	0.826	0.73 (0.40–1.33)	0.298
Kidney diseases	1.47 (0.72–3.02)	0.294	1.41 (0.71–2.82)	0.326
DLD	1.05 (0.65–1.70)	0.832	0.89 (0.55–1.43)	0.619
Cancer	1.18 (0.77–1.81)	0.444	1.19 (0.77–1.84)	0.431
Presence of functional disability				
CVD	1.18 (1.03–1.36)	0.019	1.14 (0.99–1.31)	0.072
Respiratory disease	1.13 (0.92–1.38)	0.237	1.07 (0.87–1.30)	0.543
Diabetes	1.09 (0.86–1.38)	0.469	1.07 (0.84–1.36)	0.578
Non-OA MSD	1.85 (1.20–2.86)	0.005	1.63 (1.03–2.60)	0.038
Kidney diseases	1.64 (0.98–2.74)	0.063	1.61 (0.92–2.79)	0.093
DLD	1.66 (1.17–2.36)	0.005	1.50 (1.03–2.19)	0.034
Cancer	1.21 (0.89–1.65)	0.221	1.22 (0.89–1.66)	0.224

CVD cardiovascular diseases, *DLD* peptic ulcer, and liver damage, digestive and liver diseases, *MSD* musculoskeletal diseases, *OA* osteoarthritis, *ROA* radiographic osteoarthritis

[†]Model 1: adjusted for age, sex, race, and body mass index

[‡]Model 2: further adjusted for education level, income, smoking, alcohol intake, knee injury, and use of medications (i.e., non-steroid anti-inflammatory drugs, acetaminophen, opioids, and intra-articular corticosteroids)

Table 5 Associations of the type of comorbidities with incident and progression of radiographic osteoarthritis and progression of knee pain, and functional disability over 48 months

	Odds ratio (95% confidence interval)			*p*
	Model 1[†]	*p*	Model 2[‡]	
Incident ROA				
CVD	1.15 (0.96–1.38)	0.127	1.13 (0.95–1.36)	0.171
Respiratory disease	1.13 (0.87–1.46)	0.369	1.11 (0.86–1.45)	0.423
Diabetes	0.99 (0.72–1.36)	0.962	0.95 (0.69–1.31)	0.768
Non-OA MSD	1.75 (0.97–3.19)	0.065	1.84 (1.00–3.38)	0.051
Kidney diseases	0.91 (0.43–1.93)	0.804	0.99 (0.44–2.22)	0.979
DLD	1.11 (0.68–1.81)	0.676	1.06 (0.66–1.69)	0.811
Cancer	1.00 (0.69–1.46)	0.986	1.03 (0.71–1.51)	0.869
Progression of ROA				
CVD	0.94 (0.78–1.14)	0.550	0.93 (0.77–1.12)	0.454
Respiratory disease	1.16 (0.89–1.51)	0.272	1.17 (0.90–1.52)	0.245
Diabetes	0.83 (0.60–1.15)	0.254	0.82 (0.59–1.13)	0.230
Non-OA MSD	1.08 (0.54–2.13)	0.830	1.04 (0.52–2.11)	0.903
Kidney diseases	0.75 (0.34–1.67)	0.483	0.79 (0.34–1.81)	0.572
DLD	1.28 (0.81–2.04)	0.292	1.29 (0.81–2.05)	0.294
Cancer	0.96 (0.62–1.48)	0.849	1.00 (0.65–1.53)	0.983
Progression of knee pain				
CVD	1.17 (1.01–1.37)	0.038	1.14 (0.98–1.32)	0.101
Respiratory disease	1.12 (0.90–1.39)	0.303	1.06 (0.84–1.32)	0.635
Diabetes	1.41 (1.07–1.86)	0.015	1.38 (1.05–1.82)	0.023
Non-OA MSD	1.28 (0.77–2.11)	0.343	1.13 (0.67–1.91)	0.639
Kidney diseases	2.59 (1.29–5.20)	0.008	2.72 (1.30–5.66)	0.008
DLD	1.25 (0.84–1.87)	0.264	1.13 (0.75 to 1.69)	0.569
Cancer	0.88 (0.63–1.23)	0.455	0.87 (0.62–1.21)	0.407
Progression of functional disability				
CVD	1.11 (0.93–1.32)	0.270	1.06 (0.88–1.26)	0.559
Respiratory disease	1.20 (0.94–1.53)	0.154	1.11 (0.86–1.44)	0.433
Diabetes	1.60 (1.20–2.13)	0.001	1.55 (1.16–2.07)	0.003
Non-OA MSD	1.85 (1.07–3.21)	0.028	1.60 (0.90–2.81)	0.113
Kidney diseases	1.76 (0.86–3.60)	0.122	1.76 (0.81–3.81)	0.155
DLD	1.31 (0.85–2.02)	0.217	1.19 (0.75–1.88)	0.465

Table 5 continued

	Odds ratio (95% confidence interval)			*p*
	Model 1[†]	*p*	Model 2[‡]	
Cancer	1.06 (0.72–1.56)	0.775	1.06 (0.72–1.57)	0.770

CVD cardiovascular diseases, *DLD* peptic ulcer, and liver damage, digestive and liver diseases, *MSD* musculoskeletal diseases, *OA* osteoarthritis, *ROA* radiographic osteoarthritis

[†]Model 1: adjusted for age, sex, race, and body mass index

[‡]Model 2: further adjusted for education level, income, smoking, alcohol intake, knee injury, and use of medications (i.e., non-steroid anti-inflammatory drugs, acetaminophen, opioids, and intra-articular corticosteroids)

likely to have significant functional disability. This is consistent with previous studies showing that OA was significantly associated with other MSD [32], DLD, and kidney disease [33]. Moreover, pain-related functional disability can also be directly related to non-OA MSD, given that participants may not be able to determine whether their knee symptoms were due to OA or other MSD. Another study also suggested that cardiovascular comorbidities may have a greater impact on physical dysfunction than joint pain [34]. Our longitudinal analyses showed that diabetes was associated with the progression of both knee pain and functional disability. This is supported by previous studies indicating that diabetes may increase joint pain severity [35] and cause incident functional disability [36]. The mechanism underlying this association may be that diabetes can strongly enhance pain perception in osteoarthritic knee joints [37] and lead to fatigue, blurred vision, and headaches, which can limit physical function [38]. Moreover, 10–20% of patients with diabetes may develop painful neuropathy in the distal extremities, leading to more severe pain symptoms [37, 39]. We also found that kidney diseases were strongly associated with the progression of knee pain and showed a trend to be associated with the progression of functional disability. In a systematic review and meta-analysis, the authors observed that MSD pain was the most common pain symptom in patients with chronic kidney disease (both nondialysis and dialysis subgroups), and this could be related to mineral and bone disorders in chronic kidney disease [40]. Non-OA MSD, predominantly polymyalgia rheumatica and rheumatoid arthritis, also showed a trend to be associated with the progression of functional disability, although statistically non-significant. This is expected given that both diseases are important causes of disability.

This study used data from the well-designed OAI cohort and evaluated the role of not only the number of comorbidities but also individual comorbidity in the presence and progression of both symptomatic and radiographic abnormalities of knee OA. However, our study has some limitations. Firstly, the number of participants in some comorbidity groups was relatively small and may have led to unstable results. Future studies with larger sample sizes are needed to validate our findings. Additionally, some comorbidities, such as metabolic syndrome, were not available in the OAI datasets, and thus their effect on knee OA cannot be examined in our study. Secondly, comorbidities were self-reported without verification from medical records. Despite that there is a high agreement between self-reported comorbidities and those derived from patient medical records [41, 42], the potential for misclassification remains. Thirdly, some patients may have developed comorbidities during the follow-up, but we only used data on baseline comorbidity. This may have underestimated the long-term effects of comorbidities on the outcome measures since patients with OA are more likely to develop comorbidities over time [43, 44]. Lastly, although this study evaluated the associations of both the number and type of comorbidities with the presence and progression of knee

symptoms and radiographic abnormalities, it is unclear whether specific combinations of comorbidities play a more important role. This needs to be assessed in future studies.

In conclusion, more comorbidities, especially diabetes and kidney diseases, are associated with the symptomatic progression of knee OA. Moreover, non-OA musculoskeletal diseases may be associated with the presence and onset of ROA.

Author Contribution. Guoqi Cai had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study design: Xiaoxi Li, and Guoqi Cai. Data clean: Xiaoxi Li, Rui Zhu, Liru Ge, Xiaoyue Zhang, and Guoqi Cai. Analysis and interpretation of data: Xiaoxi Li, Rui Zhu, Liru Ge, Xiaoyue Zhang, Feng Pan, Faming Pan, and Guoqi Cai. Manuscript preparation, revision, and approval: Xiaoxi Li, Xiangrui Wen, Jiantao Zhou, Jiale Cheng, Feng Pan, Faming Pan, and Guoqi Cai.

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Data Availability. The datasets generated during and/or analyzed during the current study are available in the NIH repository (https://nda.nih.gov/oai/).

Declarations

Conflict of Interest. Xiaoxi Li, Feng Pan, Rui Zhu, Liru Ge, Xiaoyue Zhang, Xiangrui Wen, Jiantao Zhou, Jiale Cheng, Faming Pan and Guoqi Cai have nothing to disclose.

Ethical Approval. The OAI study and public use of clinical and imaging data used in this study were approved by the committee on Human Research at the University of California, San Francisco (IRB approval number, 10–00532). All participants provided written informed consent. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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