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Risk of knee osteoarthritis in patients with multiple atopic conditions: a nationwide study

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Knee osteoarthritis (OA) and atopic diseases are both characterized by chronic inflammation, yet their potential relationship remains unexplored. This study investigates whether atopic diseases are associated with an increased risk of knee OA in a large nationwide cohort. We conducted a nationwide cohort study using data from the Korean National Health Insurance Service (NHIS), including 880,300 individuals aged ≥ 50 years. Atopic disease was defined as ≥ 3 outpatient visits for asthma, allergic rhinitis, or atopic dermatitis. Knee OA incidence was identified using ICD-10 codes, and hazard ratios (HRs) were estimated using Cox proportional hazards models. Individuals with atopic diseases had a 36% higher risk of developing knee OA compared to those without (HR = 1.36, 95% CI: 1.35–1.37). A dose-response relationship was observed, with risk increasing progressively in individuals with multiple atopic conditions (HR = 1.44 for two conditions; HR = 1.51 for all three conditions). Subgroup analyses indicated that this association was strongest in younger individuals (50–59 years) and males. The results indicate a significant association between atopic diseases and an increased risk of knee OA, which was strongest in younger individuals. Further research is needed to understand the potential role of atopic-specific inflammation on OA development, and any potential implications for targeted therapies.

Keywords Knee osteoarthritis (OA), Atopic disease, Inflammatory pathways, Cohort study, Multimorbidity

Knee osteoarthritis (OA) stands as a formidable challenge in global healthcare, affecting approximately 250 million people worldwide and projected to double in prevalence by 2040[1,2]. Traditionally viewed as wear-and-tear arthritis, emerging evidence suggests that inflammation plays a pivotal role in knee OA's onset and progression[3,4]. This paradigm shift opens new avenues for exploring potential connections with other inflammatory conditions, particularly atopic diseases, which include asthma, eczema, and allergic rhinitis.

Atopic diseases are experiencing a global surge, with prevalence rates increasing significantly, as evidenced by the notable rise in allergic diseases and asthma over the past five decades, particularly in developed countries[5]. These conditions share common inflammatory pathways with knee OA, including the activation of NF-κB and MAPK signaling cascades, which contribute to sustained inflammation and tissue degradation[6–8]. The chronic inflammation driven by pro-inflammatory cytokines in both knee OA and atopic diseases suggests a potential link between these conditions[9–11], a connection that has not been thoroughly explored in the context of knee OA.

Although existing evidence indicates a general link between atopic diseases and various forms of arthritis, the specific connection to knee OA remains under-investigated[9,12]. Immune system dysregulation, particularly the overactivation of Th2 cells, and increased oxidative stress are common features in both conditions, further amplifying the potential link[13,14]. Additionally, some hypothesize that activity limitations due to atopic diseases could lead to weight gain or reduced physical activity, indirectly raising the risk of knee OA[15]. This study is one of the first to systematically explore this link on a large population scale, offering new insights into how atopic multimorbidity may contribute to knee OA. By addressing this gap, our research challenges traditional OA paradigms and introduces a new perspective on the role of systemic inflammation in knee OA development.

Our nationwide cohort study examines the relationship between single and multiple atopic diseases and the risk of incident knee OA over nine years. By analyzing a large cohort of 1,138,904 individuals aged 50 years and above, we aim to provide robust evidence on this potential association. This research not only reassesses traditional OA narratives by highlighting inflammation as a common thread between these conditions but also has the potential to reshape integrated care strategies.

The primary objectives of this study are:

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1. To explore the association between atopic diseases (asthma, atopic dermatitis, and allergic rhinitis) and the risk of developing knee OA.
2. To understand the impact of multiple atopic conditions on the emergence of knee OA.
3. To investigate potential variations in this association across different demographic and clinical subgroups.

By elucidating the interplay between atopic diseases and knee OA, our findings could inform more holistic approaches to patient care, potentially leading to earlier interventions, targeted therapies, and improved quality of life for individuals suffering from these chronic ailments.

Results

Baseline characteristics

The study cohort included 880,300 individuals, with 140,399 (15.9%) having one or more atopic diseases (Table 1). Significant differences were noted across several demographic and clinical variables between atopic and nonatopic groups.

Individuals with atopic diseases were generally older (mean age 59.9 ± 8.0 years vs. 58.9 ± 7.7 years in the nonatopic group) and had a lower proportion of males (53.7% vs. 60.6%). Among those with asthma, 20.42% were in their seventies, compared to 10.08% of those without asthma.

Comorbidities such as hypertension, diabetes mellitus, and dyslipidemia were more prevalent in the atopic group. For instance, hypertension was present in 47.0% of individuals with asthma compared to 39.6% without asthma. Conversely, the nonatopic group had higher proportions of smokers and drinkers.

In the atopic group, allergic rhinitis was the most prevalent condition (89.3%, $n = 125{,}409$), followed by asthma (22.7%, $n = 31{,}936$) and atopic dermatitis (2.4%, $n = 3{,}375$).

Primary outcome: risk for knee OA

During a mean follow-up of 7.7 ± 3.5 years, knee OA was newly diagnosed in 350,995 participants. The incidence rate was higher in the atopic group (69,362 cases; 70.50 per 1000 person-years) compared to the nonatopic group (281,633 cases; 48.58 per 1000 person-years). After adjusting for confounding variables, the atopic group exhibited a significantly increased risk of knee OA compared to the nonatopic group (Hazard Ratio [HR] = 1.36; 95% Confidence Interval [CI]: 1.35–1.37; $P < 0.001$) (Table 2). Kaplan-Meier analysis confirmed that the atopic group had a significantly lower knee OA-free survival rate (log-rank test, $p < 0.001$) (Fig. 1).

A dose-response relationship was observed, where having multiple atopic diseases further elevated the risk of knee OA. Compared to the nonatopic group, the HR for knee OA was:

1. 1.35 (95% CI: 1.34–1.36) in individuals with a single atopic disease;
2. 1.44 (95% CI: 1.41–1.47) in those with two atopic diseases;
3. 1.51 (95% CI: 1.28–1.78) in those with all three atopic diseases.

This trend was statistically significant (P for trend < 0.001) and is illustrated in Fig. 2. The relationship is visually represented in Fig. 2 through both bar graphs showing incidence rates and line graphs depicting hazard ratios.

Among the individual atopic diseases, allergic rhinitis posed the highest risk for knee OA (HR = 1.36; 95% CI: 1.34–1.37). Furthermore, participants with three concurrent atopic conditions had the highest hazard rate for knee OA development (HR = 1.50; 95% CI: 1.28–1.78).

Subgroup analysis

Subgroup analyses revealed that the presence of atopic diseases was associated with an increased risk of knee OA across all examined categories (Table 3). Adjusted HRs with 95% CIs were calculated for various demographic and clinical subgroups.

Significant interactions were observed for age (p for interaction < 0.0001), sex ($p < 0.0001$), and obesity status ($p < 0.0001$). The association between atopic diseases and knee OA risk was strongest in the 50–59 age group (HR = 1.40; 95% CI: 1.38–1.41) and slightly attenuated in older age groups. Males showed a higher risk (HR = 1.41; 95% CI: 1.39–1.42) compared to females (HR = 1.33; 95% CI: 1.31–1.34). Non-obese individuals had a higher HR (1.39; 95% CI: 1.37–1.40) than obese individuals (HR = 1.31; 95% CI: 1.29–1.33).

No significant interaction was found between atopic diseases and diabetes mellitus (p for interaction = 0.2154). Detailed HRs for all subgroups are presented in Table 3.

Discussion

This nationwide cohort study provides robust evidence of a significant association between atopic diseases and an increased risk of developing knee OA. Our results demonstrate that individuals with at least one atopic condition—asthma, atopic dermatitis, or allergic rhinitis—face a higher incidence rate of knee OA compared to those without any atopic diseases. Notably, we observed a dose-response relationship, with the risk escalating progressively in the presence of multiple atopic diseases (HR: 1.36, 1.44, and 1.51 for one, two, and three atopic conditions, respectively).

These findings challenge the traditional view of knee OA as primarily a wear-and-tear condition[16,17] and contribute to a more nuanced understanding of its etiology[12,18]. Our results indicate that individuals with atopic diseases have an increased risk of knee OA, suggesting that shared factors between atopic conditions and OA warrant further investigation[19,20]. This aligns with emerging literature positioning inflammation as a central element in OA development and progression[12,21,22].

Our research extends previous observations on the link between atopic diseases and arthritis[12,23]. Chang et al. (2021) emphasized the role of immune cells in OA flares[24], which parallels our observations of exacerbated

	Asthma (−)	Asthma (+)		Atopic dermatitis (−)	Atopic dermatitis (+)		Allergic rhinitis (−)	Allergic rhinitis (+)		Atopic disease (−)	Atopic disease (+)	
n	**848,364**	**31,936**	***p*-value**	**876,925**	**3,375**	***p*-value**	**754,891**	**125,409**	***p*-value**	**739,901**	**140,399**	***p*-value**
Age group			< 0.0001			< 0.0001			< 0.0001			< 0.0001
Fifties	505,788 (59.62)	13,259 (41.52)		517,395 (59)	1652 (48.95)		448,372 (59.4)	70,675 (56.36)		442,864 (59.85)	76,183 (54.26)	
Sixties	244,964 (28.87)	11,152 (34.92)		254,998 (29.08)	1118 (33.13)		217,827 (28.86)	38,289 (30.53)		212,481 (28.72)	43,635 (31.08)	
Seventies	85,510 (10.08)	6522 (20.42)		91,517 (10.44)	515 (15.26)		77,271 (10.24)	14,761 (11.77)		73,800 (9.97)	18,232 (12.99)	
Eighties	12,102 (1.43)	1003 (3.14)		13,015 (1.48)	90 (2.67)		11,421 (1.51)	1684 (1.34)		10,756 (1.45)	2349 (1.67)	
Sex, male	506,295 (59.68)	17,441 (54.61)	< 0.0001	521,663 (59.49)	2073 (61.42)	0.0223	457,197 (60.56)	66,539 (53.06)	< 0.0001	448,364 (60.6)	75,372 (53.68)	< 0.0001
Low income 25%	195,948 (23.1)	7361 (23.05)	0.8418	202,494 (23.09)	815 (24.15)	0.146	174,677 (23.14)	28,632 (22.83)	0.0164	171,163 (23.13)	32,146 (22.9)	0.0533
DM	122,533 (14.44)	5358 (16.78)	< 0.0001	127,273 (14.51)	618 (18.31)	< 0.0001	109,512 (14.51)	18,379 (14.66)	0.1677	106,763 (14.43)	21,128 (15.05)	< 0.0001
HP	336,230 (39.63)	15,006 (46.99)	< 0.0001	349,648 (39.87)	1588 (47.05)	< 0.0001	298,478 (39.54)	52,758 (42.07)	< 0.0001	291,127 (39.35)	60,109 (42.81)	< 0.0001
DYS	207,408 (24.45)	9227 (28.89)	< 0.0001	215,606 (24.59)	1029 (30.49)	< 0.0001	180,975 (23.97)	35,660 (28.43)	< 0.0001	176,875 (23.91)	39,760 (28.32)	< 0.0001
Smoking			< 0.0001			< 0.0001			< 0.0001			< 0.0001
Non	498,137 (58.72)	19,751 (61.85)		515,968 (58.84)	1920 (56.89)		437,459 (57.95)	80,429 (64.13)		428,641 (57.93)	89,247 (63.57)	
Ex	160,091 (18.87)	6135 (19.21)		165,490 (18.87)	736 (21.81)		141,270 (18.71)	24,956 (19.9)		138,421 (18.71)	27,805 (19.8)	
Current	190,136 (22.41)	6050 (18.94)		195,467 (22.29)	719 (21.3)		176,162 (23.34)	20,024 (15.97)		172,839 (23.36)	23,347 (16.63)	
Drinking			< 0.0001			< 0.0001			< 0.0001			< 0.0001
Non	491,864 (57.98)	21,868 (68.47)		511,534 (58.33)	2198 (65.13)		432,891 (57.34)	80,841 (64.46)		422,795 (57.14)	90,937 (64.77)	
Mild	288,199 (33.97)	8292 (25.96)		295,500 (33.7)	991 (29.36)		258,916 (34.3)	37,575 (29.96)		254,962 (34.46)	41,529 (29.58)	
Heavy	68,301 (8.05)	1776 (5.56)		69,891 (7.97)	186 (5.51)		63,084 (8.36)	6993 (5.58)		62,144 (8.4)	7933 (5.65)	
Regular exercise	188,924 (22.27)	6713 (21.02)	< 0.0001	194,824 (22.22)	813 (24.09)	0.009	166,039 (22)	29,598 (23.6)	< 0.0001	163,017 (22.03)	32,620 (23.23)	< 0.0001
Age (years)	58.89 ± 7.66	62.37 ± 8.66	< 0.0001	59.01 ± 7.72	60.89 ± 8.37	< 0.0001	58.95 ± 7.71	59.41 ± 7.78	< 0.0001	58.86 ± 7.66	59.85 ± 8	< 0.0001
Height (cm)	161.86 ± 8.4	160.37 ± 8.42	< 0.0001	161.8 ± 8.4	161.87 ± 8.2	0.6445	161.9 ± 8.41	161.2 ± 8.31	< 0.0001	161.93 ± 8.41	161.12 ± 8.34	< 0.0001
Weight (kg)	62.6 ± 10.17	61.58 ± 10.2	< 0.0001	62.56 ± 10.17	62.85 ± 9.96	0.097	62.59 ± 10.21	62.37 ± 9.97	< 0.0001	62.62 ± 10.2	62.27 ± 10.02	< 0.0001
BMI (kg/m^2)	23.82 ± 2.9	23.89 ± 3.15	< 0.0001	23.82 ± 2.91	23.92 ± 2.88	0.0546	23.8 ± 2.92	23.93 ± 2.85	< 0.0001	23.8 ± 2.92	23.92 ± 2.9	< 0.0001
Waist circumference (cm)	81.89 ± 8.24	82.83 ± 8.59	< 0.0001	81.92 ± 8.25	82.9 ± 8.37	< 0.0001	81.91 ± 8.25	82.03 ± 8.27	< 0.0001	81.88 ± 8.24	82.14 ± 8.32	< 0.0001
Fasting glucose (mg/dL)	102.49 ± 28.34	102.01 ± 27.1	0.0027	102.47 ± 28.28	103.11 ± 31.56	0.1931	102.64 ± 28.65	101.46 ± 26.04	< 0.0001	102.63 ± 28.62	101.66 ± 26.5	< 0.0001
Systolic BP (mm Hg)	126.25 ± 15.86	126.4 ± 15.56	0.0943	126.26 ± 15.85	126.93 ± 15.44	0.0137	126.42 ± 15.95	125.31 ± 15.19	< 0.0001	126.4 ± 15.95	125.51 ± 15.28	< 0.0001
Diastolic BP (mm Hg)	78.1 ± 10.27	77.62 ± 9.97	< 0.0001	78.09 ± 10.26	78.01 ± 10.11	0.6851	78.2 ± 10.31	77.39 ± 9.92	< 0.0001	78.2 ± 10.31	77.45 ± 9.93	< 0.0001
Total cholesterol (mg/dL)	200.25 ± 37.9	198.83 ± 39.05	< 0.0001	200.19 ± 37.94	200.9 ± 39.59	0.2786	200.15 ± 37.92	200.46 ± 38.09	0.0079	200.21 ± 37.89	200.15 ± 38.21	0.584
HDL cholesterol (mg/dL)	55.21 ± 29.54	55.72 ± 32.18	0.0023	55.23 ± 29.65	54.46 ± 28.41	0.1292	55.28 ± 29.9	54.91 ± 28	< 0.0001	55.27 ± 29.78	55.02 ± 28.9	0.0038
LDL cholesterol (mg/dL)	118.11 ± 39.23	117.18 ± 39.74	< 0.0001	118.07 ± 39.22	119.33 ± 45.87	0.0623	117.93 ± 39.33	118.98 ± 38.76	< 0.0001	117.97 ± 39.29	118.66 ± 39.01	< 0.0001
e-GFR (ml/min/1.73 m^2)	83.26 ± 34.57	82.18 ± 36.4	< 0.0001	83.23 ± 34.6	82.18 ± 42.65	0.0791	83.35 ± 34.62	82.47 ± 34.71	< 0.0001	83.37 ± 34.59	82.43 ± 34.85	< 0.0001

Table 1. Baseline characteristics of study population by presence of atopic diseases. Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as numbers and percentages. The *p*-values indicate the statistical significance of differences between groups. Atopic disease is defined as having at least one of the following conditions: asthma, atopic dermatitis, or allergic rhinitis. DM, diabetes mellitus; BP, blood pressure; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate.

Section 1: By Presence of Atopic Diseases							
					HR (95% CI)		
	N	Event	Duration	IR per 1,000	Model 1	Model 2	Model 3
Atopic disease (-)	739,901	281,633	5797298.54	48.58	1 (ref.)	1 (ref.)	1 (ref.)
Atopic disease (+)	140,399	69,362	983901.84	70.50	1.45 (1.44, 1.46)	1.37 (1.35, 1.38)	1.36 (1.35, 1.37)
Asthma	12,891	6055	83804.54	72.25	1.49 (1.45, 1.53)	1.30 (1.27, 1.34)	1.30 (1.27, 1.34)
Atopic dermatitis	1990	861	14646.87	58.78	1.21 (1.13, 1.29)	1.17 (1.10, 1.26)	1.18 (1.10, 1.26)
Allergic rhinitis	105,470	52,088	752154.26	69.25	1.43 (1.41, 1.44)	1.36 (1.35, 1.37)	1.36 (1.34, 1.37)
Asthma & atopic dermatitis	109	53	709.94	74.65	1.54 (1.17, 2.01)	1.42 (1.09, 1.86)	1.43 (1.09, 1.87)
Asthma & allergic rhinitis	18,663	9658	123915.00	77.94	1.60 (1.57, 1.64)	1.44 (1.41, 1.47)	1.44 (1.41, 1.47)
Atopic dermatitis & allergic rhinitis	1003	504	6933.82	72.69	1.50 (1.37, 1.63)	1.44 (1.32, 1.58)	1.44 (1.32, 1.57)
All three conditions	273	143	1737.40	82.31	1.69 (1.44, 2.00)	1.53 (1.30, 1.80)	1.51 (1.28, 1.78)
Section 2: By Number of Atopic Diseases							
Number of atopic disease	N	Event	Duration	IR per 1,000	Model 1	Model 2	Model 3
0	739,901	281,633	5797298.54	48.58	1 (ref.)	1 (ref.)	1 (ref.)
1	120,351	59,004	850605.67	69.37	1.43 (1.42, 1.44)	1.35 (1.34, 1.36)	1.35 (1.34, 1.36)
2	19,775	10,215	131558.76	77.65	1.60 (1.57, 1.63)	1.44 (1.41, 1.47)	1.44 (1.41, 1.47)
3	273	143	1737.40	82.31	1.69 (1.44, 2.00)	1.53 (1.30, 1.80)	1.51 (1.28, 1.78)
Section 2: By Number of Atopic Diseases							
Number of atopic disease	**N**	**Event**	**Duration**	**IR per 1,000**	**Model 1**	**Model 2**	**Model 3**
0	739,901	281,633	5797298.54	48.58	1 (ref.)	1 (ref.)	1 (ref.)
1	120,351	59,004	850605.67	69.37	1.43 (1.42, 1.44)	1.35 (1.34, 1.36)	1.35 (1.34, 1.36)
2	19,775	10,215	131558.76	77.65	1.60 (1.57, 1.63)	1.44 (1.41, 1.47)	1.44 (1.41, 1.47)
3	273	143	1737.40	82.31	1.69 (1.44, 2.00)	1.53 (1.30, 1.80)	1.51 (1.28, 1.78)

Table 2. Incidence rates and hazard ratios for knee osteoarthritis by presence of atopic diseases. Model 1: no adjustment; Model 2: adjusted for age and sex; Model 3 : adjusted for age, sex, income, smoking, drinking, physical activity, diabetes mellitus, dyslipidemia, and hypertension. IR, incidence rate; HR, hazard ratio; CI, confidence interval.

joint pathology in atopic individuals. Moreover, our study uniquely quantifies the impact of different atopic conditions on knee OA risk, addressing a gap in existing research.

The chronic inflammatory state induced by atopic diseases may accelerate joint degradation through mechanisms similar to those observed in age-related OA progression[25,26]. This parallelism with the concept of "inflammaging" suggests that atopic diseases could potentially exacerbate age-related changes in joint tissues. Inflammaging, a term combining "inflammation" and "aging," describes the chronic, low-grade inflammation that typically develops as individuals age and is associated with various age-related diseases.

Our study suggests that atopic diseases may predispose individuals to knee OA through systemic inflammation and immune dysregulation. Although our observational study design limits direct causal inference, our findings align with recent research. Koo et al. (2021) and Kim et al. (2024) have identified increased OA incidence in patients with atopic conditions, suggesting that chronic inflammatory states associated with these conditions could detrimentally impact joint health[27,28]. Yao et al. (2023) further emphasize the need to explore shared inflammatory pathways as potential contributors to joint disease in atopic dermatitis patients[29].

These results highlight the need to consider atopic status when assessing OA risk. Further research is necessary to determine whether inflammatory pathways play a direct role in OA development in individuals with atopic diseases. Our findings emphasize the need for an integrated treatment approach for patients with both atopic diseases and OA, potentially involving coordinated care between rheumatologists, allergists, and primary care physicians.

Furthermore, our study opens up new possibilities for novel treatment strategies. Biologics used in severe atopic diseases that target specific inflammatory pathways (e.g., IL-4, IL-13 inhibitors) could be investigated for their potential benefits in preventing or slowing OA progression[30].

This nationwide cohort study's key strengths lie in its large, representative sample of the Korean population and its longitudinal design spanning nine years. This approach provides robust statistical power and allows for observing the development of knee osteoarthritis over a significant period, crucial for understanding the temporal relationships between atopic diseases and knee OA onset. Our statistical analysis, using the Cox proportional hazards regression model, adjusted for a wide range of confounders, enhancing the reliability of our findings by minimizing the influence of external factors.

Despite its strengths, our study has several limitations. First, surveillance bias may have influenced our findings, as individuals with atopic diseases tend to have more frequent healthcare visits, increasing the likelihood of OA diagnosis. However, this does not fully explain our results, given the dose-response relationship and adjustment for comorbidities. Second, we adjusted for obesity status (obese vs. non-obese) to mitigate collinearity, but BMI as a continuous variable could not be incorporated due to data access limitations. Future research with

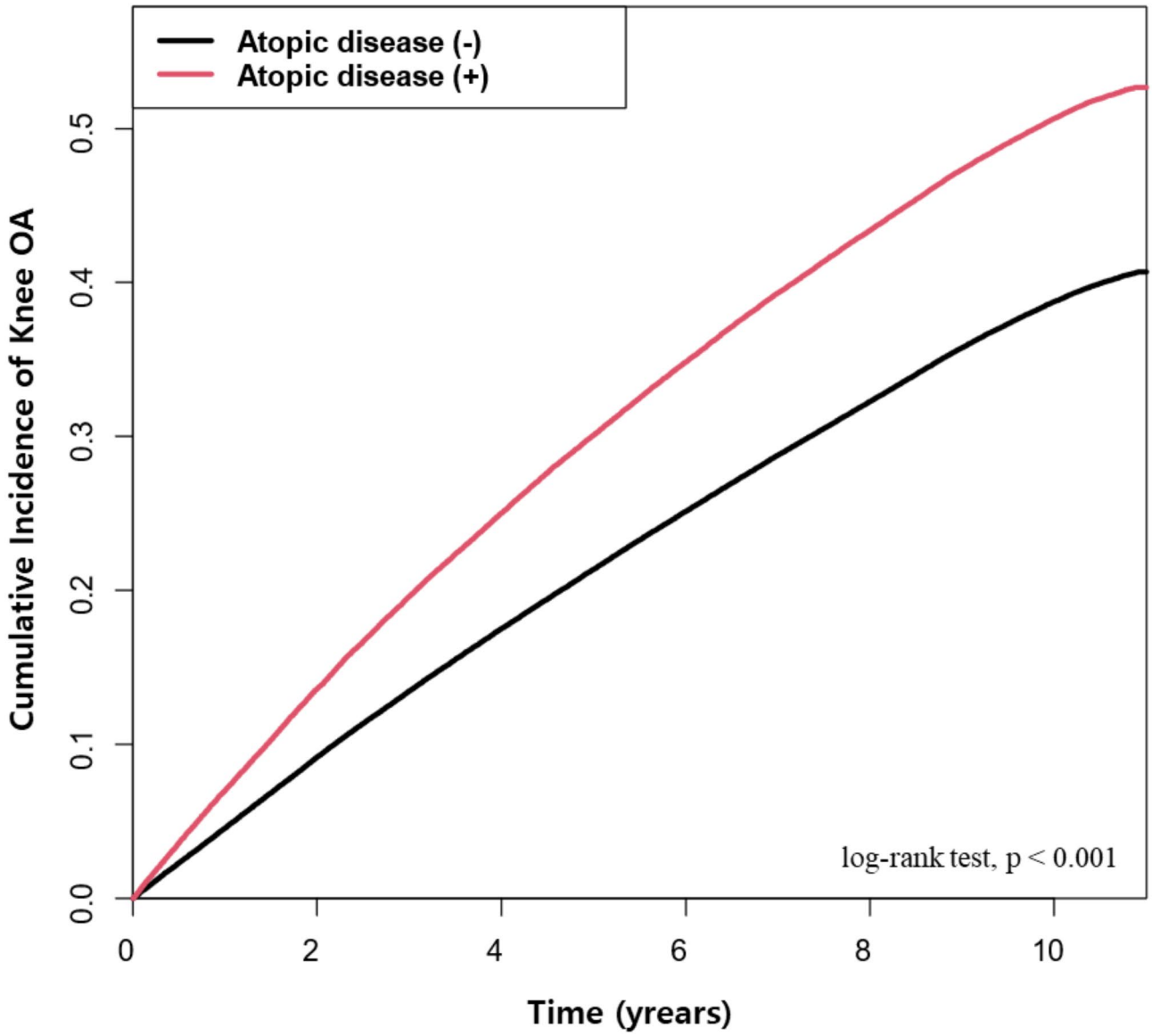

Fig. 1. Kaplan-Meier Curve for Knee Osteoarthritis Incidence by Atopic Disease Status. The Kaplan-Meier curves show the cumulative incidence probability of knee osteoarthritis (OA) over the 9-year follow-up period, stratified by atopic disease status. The black line represents individuals without atopic diseases, while the red line represents those with one or more atopic conditions (asthma, atopic dermatitis, or allergic rhinitis).

more granular BMI data could help refine these findings. Third, our definition of atopic diseases required ≥ 3 outpatient visits per year, which ensured sustained disease activity but may have excluded milder or episodic cases, limiting generalizability. Further studies should explore associations across different disease severities. Fourth, we lacked medication data, making it unclear whether anti-inflammatory treatments for atopic diseases influence OA risk. Given the distinct immune pathways of atopic diseases (Th2-driven) and OA (Th1/Th17-driven), IL-4/IL-13 blockade has been explored in inflammatory diseases[31,32], warranting further investigation into its potential effects on OA progression. Finally, misclassification bias is possible due to reliance on ICD-10 codes, which may not fully capture disease severity. However, our use of a large, nationally representative cohort and rigorous case definitions helps mitigate this concern.

Despite these limitations, our study provides valuable insights into the link between atopic diseases and OA, underscoring the need for integrated OA risk assessment. Future research incorporating prospective designs, biomarker analyses, and genetic data could further clarify underlying mechanisms.

Future research should prioritize longitudinal cohort studies to track knee OA progression in individuals with atopic diseases, strengthening evidence for a causal relationship. Parallel experimental studies targeting shared inflammatory pathways could provide insights into underlying mechanisms. Identifying and validating specific biomarkers common to both conditions could enhance early diagnosis and inform targeted treatments.

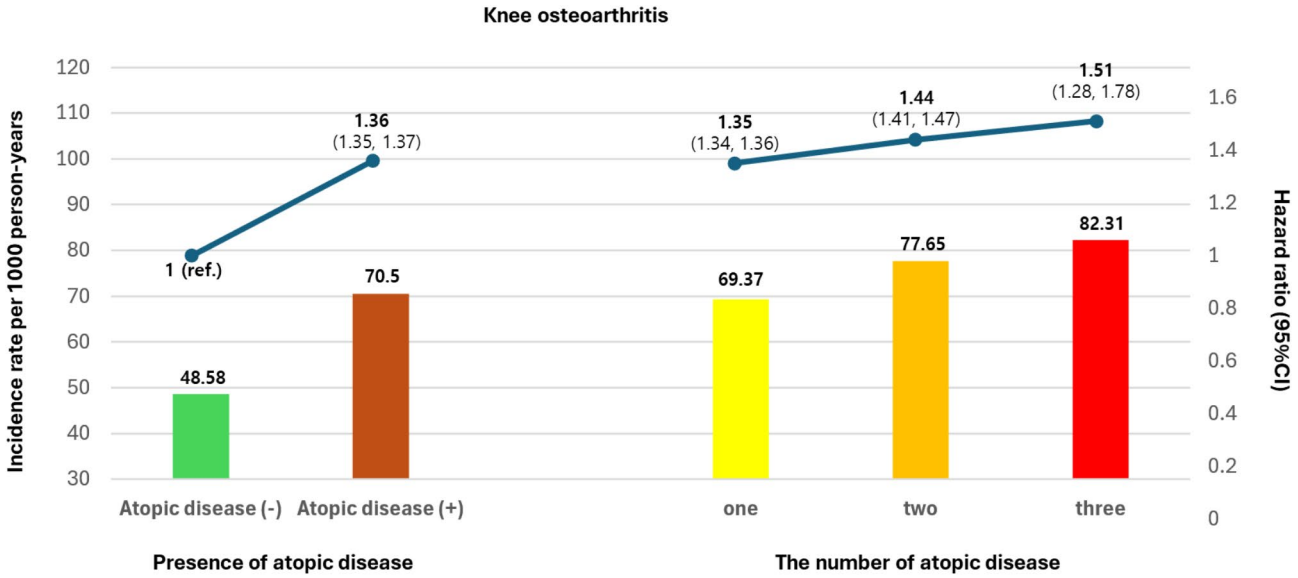

Fig. 2. Incidence rates and hazard ratios for knee osteoarthritis by atopic disease presence. This figure displays the incidence rates (IR) per 1,000 person-years and hazard ratios (HR) for knee osteoarthritis across different groups of atopic disease presence. The bars represent the incidence rates, while the lines represent the hazard ratios with 95% confidence intervals. Data are adjusted for age, sex, income, smoking, drinking, physical activity, diabetes mellitus, dyslipidemia, and hypertension. Atopic diseases include asthma, allergic rhinitis, and atopic dermatitis. CI, confidence interval.

Finally, clinical trials assessing the impact of managing atopic inflammation on knee OA outcomes are essential for translating these findings into practice.

Conclusion

Our nationwide cohort study demonstrates a significant association between atopic diseases and an increased risk of knee OA, with the strongest effect observed in younger individuals. While these findings highlight atopic diseases as a potential risk factor, further research is needed to clarify the underlying mechanisms and the role of atopic-specific inflammation in OA development.

Methods

Study design and population

We conducted a population-based retrospective cohort study using data from the National Health Insurance Services (NHIS) database of Korea, which covers approximately 97% of the Korean population. Demographic, socioeconomic, and clinical data, including sex, age, height, weight, BMI, smoking status, alcohol consumption, exercise habits, income level, blood glucose, cholesterol levels, blood pressure, and eGFR, were obtained from the NHIS database. Height and weight were measured during routine health screenings conducted by trained medical personnel following standardized protocols, and BMI was calculated as weight (kg) divided by height squared (m^2). Our study focused on individuals aged 50 years and above who participated in health screenings during 2009[33].

From an initial population of 4,234,412 individuals, we refined our cohort through a multi-step selection process (Fig. S1). Exclusion criteria included: age below 50 years, pre-existing knee OA or related interventions, insufficient follow-up data, and limited claims (1 or 2 within the year prior to screening) for atopic diseases. The final study cohort consisted of 880,300 individuals.

We followed up each participant starting one year after their health screening date in 2009 until they received a knee OA diagnosis, died, or until December 31, 2020, whichever came first.

Data sources and ethical considerations

This study utilized the National Health Insurance Services (NHIS) database of Korea, a comprehensive resource covering approximately 97% of the Korean population. Established by the Korean government, the NHIS database provides extensive healthcare service claims and screening data. The reliability of NHIS cohorts has been validated in previous studies, ensuring a robust foundation for our research[34,35].

We conducted the study in accordance with the Declaration of Helsinki, and the Institutional Review Board (IRB) of the Catholic University of Korea approved it (protocol number VC24ZISI0188). Given the retrospective nature of the study and the use of de-identified data, the IRB of the Catholic University of Korea waived the requirement for individual informed consent. This approach ensured ethical rigor while facilitating access to a large-scale, representative dataset for population-based analysis.

By Age Group, Sex, Obesity, Diabetes Mellitus, Dyslipidemia, and Hypertension							
Subgroup	**Atopic disease**	**N**	**Event**	**Duration**	**IR per 1,000**	**Model 3**	***p* for interaction**
Age, 50–59	No	442,864	153,008	3696040.73	41.40	1 (ref.)	< 0.0001
	Yes	76,183	35,965	575189.45	62.53	1.40 (1.38, 1.41)	
Age, 60–69	No	212,481	93,683	1565008.84	59.86	1 (ref.)	
	Yes	43,635	23,718	289314.11	81.98	1.32 (1.31, 1.34)	
Age, 70–79	No	73,800	31,710	480265.01	66.03	1 (ref.)	
	Yes	18,232	8879	107967.64	82.24	1.30 (1.27, 1.33)	
Age, 80 and above	No	10,756	3232	55983.96	57.73	1 (ref.)	
	Yes	2349	800	11430.64	69.99	1.35 (1.25, 1.46)	
Sex, male	No	448,364	133,193	3710690.04	35.89	1 (ref.)	< 0.0001
	Yes	75,372	29,903	565043.40	52.92	1.41 (1.39, 1.42)	
Sex, female	No	291,537	148,440	2086608.50	71.14	1 (ref.)	
	Yes	65,027	39,459	418858.43	94.21	1.33 (1.31, 1.34)	
Obesity (-)	No	496,351	176,378	3946472.67	44.69	1 (ref.)	< 0.0001
	Yes	92,305	43,360	657771.78	65.92	1.39 (1.37, 1.40)	
Obesity (+)	No	243,550	105,255	1850825.87	56.87	1 (ref.)	
	Yes	48,094	26,002	326130.05	79.73	1.31 (1.29, 1.33)	
Diabetes mellitus (−)	No	633,138	243,595	4984785.28	48.87	1 (ref.)	0.2154
	Yes	119,271	59,417	841508.95	70.61	1.36 (1.35, 1.37)	
Diabetes mellitus (+)	No	106,763	38,038	812513.27	46.82	1 (ref.)	
	Yes	21,128	9945	142392.89	69.84	1.38 (1.35, 1.41)	
Dyslipidemia (−)	No	563,026	208,179	4444982.85	46.83	1 (ref.)	0.035
	Yes	100,639	48,513	712897.59	68.05	1.37 (1.36, 1.38)	
Dyslipidemia (+)	No	176,875	73,454	1352315.69	54.32	1 (ref.)	
	Yes	39,760	20,849	271004.24	76.93	1.34 (1.32, 1.36)	
Hypertension (−)	No	448,774	167,100	3591246.20	46.53	1 (ref.)	0.0173
	Yes	80,290	39,196	577131.74	67.92	1.37 (1.36, 1.39)	
Hypertension (+)	No	291,127	114,533	2206052.35	51.92	1 (ref.)	
	Yes	60,109	30,166	406770.09	74.16	1.35 (1.33, 1.36)	

Table 3. Subgroup analysis of incidence rates and hazard ratios for knee osteoarthritis by presence of atopic diseases. Model 3 : adjusted for age, sex, income, smoking, drinking, physical activity, diabetes mellitus, dyslipidemia, and hypertension. IR, incidence rate.

Definition of atopic diseases

We defined atopic diseases in this study as asthma, atopic dermatitis, and allergic rhinitis, using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes: asthma (J45-46), atopic dermatitis (L20), and allergic rhinitis (J301-304)[33]. We classified participants as having an atopic disease if they had at least one confirmed diagnosis of any component of the atopic triad. To ensure diagnostic accuracy, we required a minimum of three documented clinical visits per year for each condition. This threshold has been previously applied in NHIS-based studies to identify clinically significant atopic disease cases[36,37]. Individuals without any atopic triad diagnosis were categorized as nonatopic.

Primary outcome

The primary endpoint was the new onset of knee OA. We identified knee OA using ICD-10 codes specific to knee OA (M17) or general OA (M15 for polyarthrosis, M19 for other forms of arthrosis), along with a procedure code for knee X-ray within the same medical claim. This methodology is consistent with validated approaches from previous research[38]. The follow-up period commenced one year after the initial health screening and continued until knee OA diagnosis, death, or December 31, 2020, whichever occurred first.

Assessment of health behaviors and comorbidities

We assessed lifestyle factors and the presence of comorbid conditions through a comprehensive review of patient-reported outcomes and clinical data. Lifestyle behaviors were self-reported via standardized questionnaires. Socioeconomic status was determined through income tiers, with the lowest tier representing the bottom 25% of the population by income. Smoking habits were categorized into three distinct groups: non-smokers, former smokers, and active smokers. Alcohol consumption was classified based on daily intake: non-drinkers, moderate consumption (less than 30 g per day), and significant consumption (30 g or more per day). Physical activity levels were delineated based on type and frequency: non-exercisers, moderate exercisers (over 30 min of moderate activity at least once a week), and regular exercisers (over 30 min of moderate activity at least five times a week or over 20 min of vigorous activity at least three times a week).

Comorbid health conditions such as hypertension, diabetes mellitus, and dyslipidemia were identified using a combination of ICD-10-CM diagnostic codes, prescribed medication records, and biometric measures from health examinations. The criteria for these conditions were consistent with previously established and validated protocols[39]. In our health screenings, fasting blood tests were conducted to measure serum glucose and lipid levels, following at least eight hours of fasting, to ensure the accuracy of these diagnostic markers. Further information on the operational definitions used comorbid conditions can be found in the supplementary material of this study, delineated in table S1.

Statistical evaluation methods

Our data analysis commenced with the delineation of baseline characteristics, where we reported continuous variables as mean values with their corresponding standard deviations and categorized variables in frequencies and proportions. Comparative analysis of continuous data was executed via the application of the t test or non-parametric alternatives when appropriate. Chi-square testing facilitated the comparison of categorized variables.

We determined the incidence rates of knee OA by tallying new cases and dividing by the accumulated person-years, expressing the result as the number of events per 1,000 person-years. The risk estimation for the occurrence of knee OA was performed using the Cox proportional hazards regression model, yielding hazard ratios and 95% confidence intervals[40]. Our model adjustments progressed sequentially: the primary model accounted for age and gender, the secondary model additionally considered lifestyle factors and comorbidities, and the tertiary model incorporated further adjustments for chronic inflammatory conditions.

The strength of association was quantified using Cohen's d, calculated from the natural logarithm of the hazard ratio and standardized[41]. We conducted a retrospective power calculation to validate the robustness of our findings. Subgroup analyses were stratified based on demographics, lifestyle factors, and comorbidity status, with the Bonferroni method employed to adjust for multiple testing.

The Kaplan-Meier estimator was used to plot survival curves, with the log-rank test comparing the curves. The Cox model also supported the survival analysis, and interactions were tested to identify significant differences between subgroups. We established significance for all tests at a p-value of less than 0.05 and conducted two-tailed analyses.

All statistical computations were performed with SAS (version 9.4, SAS Institute, Inc, Cary, NC, 2013) and R program (version 3.2.4, R Core Team, Vienna, Austria, 2017), ensuring rigorous data handling and analysis integrity.

Data availability

The datasets used and/or analyzed during the current study were provided by the Korean National Health Insurance Service (NHIS) and are part of a customized, de-identified database to ensure privacy. Due to NHIS data access restrictions, the raw data cannot be shared. Further information on accessing NHIS data is available at https://nhiss.nhis.or.kr. The datasets used in this study are available from the corresponding author on reasonable request, subject to NHIS approval and data access policies.

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Author contributions

DP, HSK and KH conceived the presented idea. KH collected the study data and did the statistical analyses. DP wrote the initial draft of the paper. All authors reviewed the manuscript. HSK, YHC, and KH supervised the manuscript. All authors approved the paper. The authors thank the participants of the Korean National Health Insurance Service-Health Screening program.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical statement
Approval of the research protocol: This study was approved the IRB of the Catholic University of Korea (VC24ZISI0188).

Informed consent
N/A (the need for informed consent was waived by the IRB of the Catholic University of Korea due to the retrospective nature of the study and the anonymized nature of the data).

Additional information
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