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Combined and interactive associations of body mass index and physical activity patterns with osteoarthritis risk: a prospective cohort study in the UK Biobank

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Research Article

Keywords: Osteoarthritis, Body mass index, Physical activity, Interaction, UK Biobank

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11207425/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Obesity and insufficient physical activity are modifiable factors associated with osteoarthritis (OA), but their combined and interactive associations with OA risk remain unclear. We examined the independent, combined, and interactive associations of body mass index (BMI) and physical activity (PA) with OA risk and characterized their dose-response relationships.

Methods

This prospective cohort study included 422,584 participants from the UK Biobank. PA patterns were classified as inactive, weekend warrior, or regularly active, and BMI was categorized as normal and below weight, overweight, or obesity. Cox proportional hazards models were used to assess associations of PA and BMI with OA risk. Additive and multiplicative interactions were evaluated using Aalen additive hazards models and Cox interaction models, respectively. Restricted cubic spline models were used to characterize dose-response relationships.

Results

During follow-up, 62,203 participants developed OA. Compared with participants with normal and below weight, those with overweight and obesity had higher OA risks (HR = 1.34, 95% CI: 1.32–1.37; HR = 2.01, 95% CI: 1.97–2.06, respectively). Inactivity was associated with a modestly higher OA risk than regular activity (HR = 1.04, 95% CI: 1.02–1.06), whereas the weekend warrior pattern was not significantly associated with OA risk. Obesity combined with inactivity showed the highest OA risk and a positive additive interaction, corresponding to 92.16 additional OA cases per 100,000 person-years (95% CI: 29.74–154.58), while no multiplicative interaction was observed. The PA ranges associated with lower OA risk were 150.0–626.1 min/week among participants with normal and below weight, 150.0–374.7 min/week among those with overweight, and 150.0–448.9 min/week among those with obesity.

Conclusions

Higher BMI and inactivity were associated with increased OA risk, with obesity and inactivity showing a positive additive interaction. PA did not fully offset the higher OA risk associated with elevated BMI, although the PA ranges associated with lower OA risk differed across BMI categories.

Introduction

Osteoarthritis (OA) is a common chronic degenerative joint disease characterized by joint pain, stiffness, and progressive functional limitation[1]. The global burden of OA has increased substantially over recent decades, partly due to the rising prevalence of obesity[1, 2]. In 2020, OA affected an estimated 595 million individuals worldwide, representing a 132.2% increase in the number of cases since 1990[2]. Established risk factors for OA include older age, female sex, adiposity, previous joint injury, and physical activity (PA) involving repetitive high joint loading[3, 4]. Among modifiable factors, body weight and PA patterns are particularly relevant for OA because they can be addressed through weight control and changes in PA patterns[5–7].

Obesity, commonly assessed using body mass index (BMI), is among the strongest modifiable risk factors for OA[8, 9], particularly at weight-bearing joints such as the knee. A systematic review and meta-analysis reported that each 5 kg/m² increase in BMI was associated with a 35% higher risk of knee OA[10]. Overweight and obesity may increase OA risk through both greater mechanical loading and systemic pathways involving low-grade inflammation, adipokine imbalance, and metabolic dysfunction [11, 12].

The association between PA and OA risk depends on the amount, intensity, and type of activity performed[13, 14]. Excessive or high-impact PA may impose repeated mechanical loading on weight-bearing joints, thereby increasing cumulative stress and accelerating structural damage[15]. A meta-analysis suggested that PA levels exceeding international recommendations may be associated with a higher risk of knee OA (RR = 1.18, 95% CI : 1.02–1.35)[13]. By contrast, regular moderate PA may help preserve joint health by improving muscle strength and physical function[16, 17]. The biomechanical consequences of PA may also differ according to body composition and joint-loading conditions. In individuals with overweight or obesity, particularly during high-impact or weight-bearing activities, greater joint loading may increase structural stress, although available epidemiological evidence remains inconsistent[14, 15, 18, 19]. Thus, elevated BMI should not preclude PA participation; rather it highlights the need for tailored activity prescriptions that account for BMI-specific loading in order to maximize benefits and minimize joint stress[16, 20].

Relatively few studies have examined the joint or interactive associations of BMI and PA with OA risk, and the available findings have been inconsistent[19, 21, 22]. The Osteoarthritis Initiative reported a male-specific interaction between BMI and PA for knee OA risk[19], whereas the HUNT Study found no significant interaction between BMI and recreational PA for knee OA risk[21]. In addition, it remains unclear whether BMI modifies the association between PA and OA risk, whether their combined and interactive effects differ on additive and multiplicative scales, and whether the dose-response relationships of BMI and PA with OA risk are linear across the observed range[23, 24].

Therefore, using data from the UK Biobank (UKB), we evaluated the independent, combined, and interactive associations of BMI and PA patterns with incident OA, examined whether the combined associations differed by sex, and further characterized the dose-response relationships of continuous BMI and PA with OA risk.

Methods

Study participants

Data from the UK Biobank (UKB), including baseline questionnaire data, anthropometric data, and routinely collected health records, were used in this study[25]. A total of 501,936 participants were initially identified. Participants with prevalent OA at baseline or insufficient information to determine follow-up status were excluded (n = 75,005). Additional exclusions were made for baseline age outside the 40–69 years range, missing PA questionnaire data, or extreme BMI value (< 15 or > 60 kg/m²) (n = 4,347). Consequently, 422,584 participants were included in the final analytic cohort (Fig. 1).

[Figure 1 near here]

Outcome ascertainment and follow-up

The occurrence of OA was ascertained using UKB first occurrence data and linked health records, and defined according to ICD-10 codes M15–M19, including polyarthrosis, hip OA, knee OA, hand/wrist OA, and other arthrosis. Follow-up began on the date of baseline assessment and continued until the first diagnosis of incident OA, death, or the end of available linked hospital records, whichever occurred first. Follow-up was censored at the latest available hospital record date for England (31 March 2023), Scotland (31 August 2022), and Wales (31 May 2022). During follow-up, 62,203 participants developed incident OA, and 360,381 remained free of OA.

Assessment of PA and BMI

PA and BMI were assessed at baseline. PA was measured using the touchscreen questionnaire administered at UKB assessment centres. Participants reported the number of days per week and the usual duration per day of walking, moderate-intensity PA, and vigorous-intensity PA lasting at least 10 minutes. These items corresponded to the short form of the International Physical Activity Questionnaire (IPAQ)[26]. BMI was calculated as weight in kilograms divided by height in metres squared, based on measurements obtained during the initial assessment centre visit, and was expressed as kg/m².

Definition of PA patterns and BMI categories

Total PA was calculated from reported walking, moderate-intensity PA, and vigorous-intensity PA. Vigorous-intensity activity was converted to moderate intensity equivalent minutes using a 2:1 weighting[27, 28]. Participants were classified as inactive (IN; < 150 min/week), weekend warrior (WW; ≥ 150 min/week accumulated on 1–2 days/week), or regularly active (RA; ≥ 150 min/week accumulated across ≥ 2 days/week) [29].

BMI was categorized according to World Health Organization classification cut points as underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥ 30 kg/m²)[30]. Because of the small number of underweight participants, the underweight and normal weight categories were combined into a single category (BMI < 25 kg/m²) as the normal and below group.

Assessment of interaction effects

Absolute-scale additive interaction

Additive interaction between PA patterns and BMI categories was evaluated using the Aalen additive hazards model[31]. Time since baseline was used as the underlying time scale in Cox proportional hazards regression models, and baseline age was included as a covariate.

To quantify the absolute excess risk, the Aalen additive hazards model was applied. The hazard rate was modeled as the sum of an unspecified baseline hazard function and the additive effects of PA patterns, BMI categories, and their interaction term.

The Aalen additive hazards model was specified as follows:

$$\lambda(t|X)=\lambda_0(t)+\beta_1(t)\,PA+\beta_2(t)\,BMI+\beta_3(t)\,(PA\times BMI)$$

where $\lambda(t|X)$ represents the OA risk hazard at follow-up time t, $\lambda_0(t)$ denotes the unspecified baseline hazard, and $\beta_3(t)$ represents the additive interaction effects between PA and BMI. The estimated coefficients and their corresponding confidence intervals (obtained from variance estimates) were multiplied by 100,000 and interpreted as the absolute increase in additional OA cases per 100,000 person-years.

Additionally, to evaluate additive interaction using relative effect estimates, standard measures were calculated based on hazard ratios (HRs) derived from the Cox proportional hazards models:

$$RERI = HR_{11} - HR_{10} - HR_{01} + 1$$

$$AP = RERI / HR_{11}$$

$$SI = (HR_{11}-1) / [(HR_{10}-1) + (HR_{01}-1)]$$

Additive interaction measures (RERI, AP, and SI) and their 95% CIs were estimated using a parametric bootstrap approach based on the multivariate normal distribution of regression coefficients[32]. Additive interaction was considered present when the 95% CIs excluded 0 for RERI and AP and excluded 1 for SI: positive RERI and AP values together with SI > 1 were interpreted as synergistic interaction, whereas negative RERI and AP values together with SI < 1 were interpreted as antagonistic interaction[33].

Multiplicative interaction

Multiplicative interaction was assessed by including a product term for PA and BMI in the model. For additive interaction, a joint indicator of PA patterns and BMI categories was constructed, with the joint category of normal and below and regular activity serving as the reference group [34, 35].

Multiplicative interaction was defined as follows:

$$INTM = HR_{11}/(HR_{10} \times HR_{01})$$

The 95% confidence intervals (95% CIs) for multiplicative interaction were derived using the delta method[36].

Statistical analysis

All analyses were performed using R software (version 4.1.1). Baseline characteristics were summarized as mean ± standard deviation (SD), median with interquartile range (IQR), or number (percentage), as appropriate, and compared using the Student's t-test or chi-square test. Cox proportional hazards models were used to evaluate the combined effects of PA patterns and BMI categories with OA risk. Multiplicative and additive interactions between PA patterns and BMI categories were assessed using Cox proportional hazards models and Aalen additive hazards models, respectively. Sex-stratified analyses were further performed to assess potential effect modification by sex. In addition, dose-response relationships were explored using restricted cubic spline models. Missing covariate data were imputed using multiple imputation, and sensitivity analyses excluded participants who developed OA within the first 2 years of follow-up. These approaches were applied to minimize potential bias arising from missing data, residual confounding, and reverse causation. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Baseline characteristics

Among the 422,584 participants, the median follow-up duration was 13.79 years (Interquartile range(IQR), 12.85–14.51 years), corresponding to 5,297,150 person-years of follow-up. During follow-up, 62,203 participants developed incident OA. Compared with participants who did not develop OA, individuals with OA were older (58.74 ± 7.25 years vs. 55.29 ± 8.15 years, $P < 0.001$), and had a higher mean BMI (28.50 ± 5.12 kg/m² vs. 26.93 ± 4.52 kg/m², $P < 0.001$). Women accounted for a larger proportion of participants with OA group than of those without OA (57.67% vs. 52.48%, $P < 0.001$). In the OA group, 42.31% of participants were overweight and 32.28% were obese, compared with 42.73% and 20.76% in the non-OA group, respectively ($P < 0.001$). IN was more common among participants with OA than among those without OA (27.54% vs 25.26%), whereas RA was less common (71.49% vs 73.63%, $P < 0.001$). In addition, the distributions of education level, ethnicity, household income, smoking status, drinking status, cancer history, diabetes, and cardiovascular disease differed significantly between the OA and non-OA groups ($P < 0.001$). Baseline characteristics according to OA status are summarized in Table 1.

Table 1
Baseline characteristics by OA status

Variable	Overall	No OA	OA	t/χ^2	*P*
	N = 422584 (%)	N = 360381 (%)	N = 62203 (%)		
age	55.80 ± 8.11	55.29 ± 8.15	58.74 ± 7.25	-107.39	< 0.001
gender				574.90	< 0.001
Female	224982 (53.24)	189110 (52.48)	35872 (57.67)		
Male	197602 (46.76)	171271 (47.52)	26331 (42.33)		
education				2041.47	< 0.001
Low	137326 (32.50)	112977 (31.35)	24349 (39.14)		
Medium	139934 (33.11)	119102 (33.05)	20832 (33.49)		
High	145324 (34.39)	128302 (35.60)	17022 (27.37)		
ethnicity				274.25	< 0.001
White	398853 (94.38)	339265 (94.14)	59588 (95.80)		
Others	23731 (5.62)	21116 (5.86)	2615 (4.20)		
household income				2857.87	< 0.001
Low	196272 (46.45)	161741 (44.88)	34531 (55.51)		
Medium	112124 (26.53)	96633 (26.81)	15491 (24.90)		
High	114188 (27.02)	102007 (28.31)	12181 (19.58)		
smoking				746.24	< 0.001
Current	45413 (10.75)	39082 (10.84)	6331 (10.18)		
Never	234725 (55.55)	202788 (56.27)	31937 (51.34)		
Previous	142446 (33.71)	118511 (32.88)	23935 (38.48)		
drinking				72.17	< 0.001
Current	390415 (92.39)	333399 (92.51)	57016 (91.66)		
Never	18015 (4.26)	15242 (4.23)	2773 (4.46)		
Previous	14154 (3.35)	11740 (3.26)	2414 (3.88)		
cancer				13.99	< 0.001
No	392665 (92.92)	334645 (92.86)	58020 (93.28)		
Yes	29919 (7.08)	25736 (7.14)	4183 (6.72)		
diabetes				340.52	< 0.001
No	402070 (95.15)	343800 (95.40)	58270 (93.68)		
Yes	20514 (4.85)	16581 (4.60)	3933 (6.32)		
cardiovascular disease				1851.02	< 0.001
No	315908 (74.76)	273712 (75.95)	42196 (67.84)		
Yes	106676 (25.24)	86669 (24.05)	20007 (32.16)		
				151.91	< 0.001
IN	108148 (25.59)	91015 (25.26)	17133 (27.54)		
WW	4616 (1.09)	4013 (1.11)	603 (0.97)		
RA	309820 (73.32)	265353 (73.63)	44467 (71.49)		

Variable	Overall	No OA	OA	t/χ^2	*P*
	N = 422584 (%)	N = 360381 (%)	N = 62203 (%)		
BMI	27.16 ± 4.65	26.93 ± 4.52	28.50 ± 5.12	-72.07	< 0.001
BMI categories				5012.91	< 0.001
Normal and below	147382 (34.88)	131575 (36.51)	15807 (25.41)		
Overweight	180321 (42.67)	154004 (42.73)	26317 (42.31)		
Obese	94881 (22.45)	74802 (20.76)	20079 (32.28)		

[Table 1 near here]

Associations of PA patterns and BMI categories with risk of OA

Table 2 shows the independent associations of PA patterns and BMI categories with OA risk. Compared with RA, IN was associated with a modestly higher OA hazard in the fully adjusted model (HR = 1.04, 95% CI :1.02–1.06; *P* < 0.001), whereas WW was not associated with OA risk (HR = 1.01, 95% CI : 0.93–1.09; *P* = 0.863). Compared with BMI < 25 kg/m², overweight and obesity were associated with higher OA hazards (HR = 1.34, 95% CI : 1.32–1.37, and HR = 2.01, 95% CI : 1.97–2.06, respectively; both *P* < 0.001). These associations were broadly consistent across progressively adjusted models.

Table 2
Independent associations of PA patterns and BMI categories with OA risk

Factor	Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	P value	HR (95% CI)	*P*	HR (95% CI)	*P*
PA						
RA	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
IN	1.05 (1.04–1.07)	< 0.001	1.04 (1.02–1.06)	< 0.001	1.04 (1.02–1.06)	< 0.001
WW	1.00 (0.92–1.08)	0.970	1.01 (0.93–1.09)	0.886	1.01 (0.93–1.09)	0.863
	Model 4[d]		Model 5[e]		Model 6[f]	
BMI						
Normal and below	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Overweight	1.38 (1.35–1.41)	< 0.001	1.36 (1.33–1.39)	< 0.001	1.34 (1.32–1.37)	< 0.001
Obese	2.13 (2.09–2.18)	< 0.001	2.07 (2.03–2.12)	< 0.001	2.01 (1.97–2.06)	< 0.001
P for trend < 0.01						
CI, confidence interval; HR, hazard ratio.						
a Cox proportional hazards regression for PA patterns adjusted for age, gender, and BMI categories.						
b Cox proportional hazards regression for PA patterns adjusted for model 1 plus education, ethnicity, and household income.						
c Cox proportional hazards regression for PA patterns adjusted for model 2 plus smoking, drinking, cancer, diabetes, and cardiovascular disease.						
d Cox proportional hazards regression for BMI categories adjusted for age, gender, and PA patterns.						
e Cox proportional hazards regression for BMI categories adjusted for model 4 plus education, ethnicity, and household income.						
f Cox proportional hazards regression for BMI categories adjusted for model 5 plus smoking, drinking, cancer, diabetes, and cardiovascular disease.						

[Table 2 near here]

Combined effects of PA patterns and BMI categories with OA risk

RA participants with normal and below were used as the reference group, No increase in OA risk was observed across WW participants with normal and below and IN participants with normal and below (HR_{modal3} = 1.10, 95% CI : 0.94–1.30, P = 0.230; HR_{modal3} = 1.03, 95% CI : 1.00–1.07, P = 0.075, respectively). In the overweight category, OA risk was elevated across all PA patterns (HR_{modal3} = 1.35, 95% CI : 1.32–1.38, P < 0.01 for RA participants; HR_{modal3} = 1.35, 95% CI : 1.19–1.53, P < 0.01 for WW participants; HR_{modal3} = 1.37, 95% CI : 1.33–1.42 for IN participants, respectively). In participants with obesity, the risk of OA further increased (HR_{modal3} = 1.99, 95% CI : 1.94–2.04, P < 0.01 for RA participants; HR_{modal3} = 1.97, 95% CI : 1.72–2.27, P < 0.01 for WW participants; HR_{modal3} = 2.12, 95% CI : 2.06–2.19, P < 0.01 for IN participants).

[Table 3 near here]

Table 3
Combined effects of PA patterns and BMI categories with OA risk

PA patterns	BMI categories	Case/Total	Person-years	Incidence (/1,000 PY)	Model 1		Model 2		Model 3	
					HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
RA	Normal and below	12187/114356	1477951.3	8.25	–		–		–	
WW	Normal and below	148/1460	19173.9	7.72	1.08 (0.92–1.27)	0.351	1.11 (0.94–1.30)	0.213	1.10 (0.94–1.30)	0.230
IN	Normal and below	3472/31566	405446.3	8.56	1.05 (1.02–1.10)	0.006	1.04 (1.00–1.08)	0.055	1.03 (1.00–1.07)	0.075
RA	Overweight	19432/133562	1677474.6	11.58	1.39 (1.36–1.42)	< 0.001	1.36 (1.33–1.40)	< 0.001	1.35 (1.32–1.38)	< 0.001
WW	Overweight	252/2041	26387.2	9.55	1.35 (1.19–1.53)	< 0.001	1.36 (1.20–1.54)	< 0.001	1.35 (1.19–1.53)	< 0.001
IN	Overweight	6633/44718	560952.4	11.82	1.43 (1.39–1.47)	< 0.001	1.39 (1.35–1.44)	< 0.001	1.37 (1.33–1.42)	< 0.001
RA	Obese	12848/61902	740374.9	17.35	2.12 (2.07–2.17)	< 0.001	2.04 (1.99–2.10)	< 0.001	1.99 (1.94–2.04)	< 0.001
WW	Obese	203/1115	13691.7	14.83	2.07 (1.80–2.38)	< 0.001	2.02 (1.76–2.33)	< 0.001	1.97 (1.72–2.27)	< 0.001
IN	Obese	7028/31864	375697.4	18.71	2.29 (2.22–2.35)	< 0.001	2.19 (2.12–2.25)	< 0.001	2.12 (2.06–2.19)	< 0.001

Sex-stratified analyses of the combined associations between PA patterns and BMI categories with OA risk were presented in Fig. 2, and the analysis results for men were consistent with the overall results. However, among women, compared with the participants in reference group, all other participants who engaged in different types of PA patterns and in different BMI categories showed a higher risk of OA. IN participants with obesity showed a stronger association of women (HR = 2.18, 95% CI : 2.10–2.27) than that of men on OA risk (HR = 2.01, 95% CI : 1.91–2.11, $P_{interaction}$ = 0.006). In addition, in the normal and below category, the WW pattern showed a non-significant trend in men, whereas it acted as a significant risk factor in women (male: HR = 0.86, 95% CI : 0.63–1.16; female: HR = 1.25, 95% CI : 1.03–1.51; $P_{interaction}$ = 0.046).

[Figure 2 near here]

Interaction of PA patterns and BMI categories with OA risk analyses

Table 4 summarizes multiplicative and additive interaction between PA patterns and BMI categories on OA risk. No statistically significant multiplicative interaction was observed between PA patterns and BMI categories (all P > 0.05). In contrast, a significant positive additive interaction was identified between IN and obesity, the additional cases attributable to interaction were 92.160 per 100,000 person–years (95% CI : 29.74–154.58), and Cox proportional hazards model measures were also consistent with positive additive interaction (RERI = 0.095, 95% CI : 0.029–0.163, AP = 0.045, 95% CI : 0.014–0.076, and SI = 1.094, 95% CI : 1.027–1.170). A RERI > 0 indicated that the combined effect of obesity

and IN on OA risk exceeded the sum of their independent effects. The HRs for obesity and IN were 2.01(95% CI : 1.97–2.06) and 1.04(95% CI : 1.02–1.06), respectively. Compared with RA participants with normal and below, the combined exposure to IN and obesity was associated with a 2.14-fold higher risk of OA. The AP quantified the proportion of excess risk attributable to the interaction between the two exposures, indicating that 4.5% of the excess risk was attributable to the interaction between IN and obesity, while SI > 1 further indicated a synergistic interaction.

Table 4
Additive and multiplicative interactions between PA patterns and BMI categories in relation to OA risk

Interactioneffects	**Aalen'sadditivehazardsmodel**			**Coxproportionalhazardsmodel**				
	AdditionalOAcasesper100000PY	**95%CI**	***P***	**RERI (95%CI)**	**AP (95%CI)**	**SI (95%CI)**	**MultiplicativeHR (95%CI)**	***P***
IN & Overweight	-11.182	(-57.78, 35.41)	0.638	-0.008 (-0.061, 0.047)	-0.006 (-0.045, 0.034)	0.98 (0.853, 1.141)	0.985 (0.94, 1.033)	0.538
IN & Obese	92.160	(29.74, 154.58)	0.004	0.095 (0.029, 0.163)	0.045 (0.014, 0.076)	1.094 (1.027, 1.17)	1.03 (0.982, 1.081)	0.220
WW & Overweight	-123.474	(-290.48, 43.53)	0.147	-0.105 (-0.345, 0.129)	-0.078 (-0.28, 0.089)	0.765 (0.4, 1.45)	0.905 (0.738, 1.11)	0.339
WW & Obese	-191.315	(-433.71, 51.08)	0.122	-0.118 (-0.454, 0.194)	-0.06 (-0.257, 0.088)	0.892 (0.629, 1.191)	0.901 (0.728, 1.115)	0.339
CI, confidence interval; HR, hazard ratio; OA, osteoarthritis;								
PA, physical activity; IN, inactive; WW, weekend warrior;								
RA, regularly active; RERI, relative excess risk due to interaction;								
AP, attributable proportion due to interaction; SI, synergy index.								
The reference group was participants with regularly activity and normal or below BMI.								
Additive interaction was considered present when the 95% CI excluded 0 for RERI and AP and excluded 1 for SI.								

[Table 4 near here]

Dose–Response Associations of BMI and PA patterns with OA risk

BMI was nonlinearly and positively associated with OA risk, and no significant interaction between BMI and PA patterns was detected ($P_{overall}$ < 0.001, $P_{nonlinearity}$ <0.001, and $P_{interaction}$ = 0.656) (Fig. 3A). For three PA patterns, BMI all showed a J-shaped association with OA risk across. Using BMI = 25 kg/m² as the reference value, the estimated hazard of OA was lower at BMI values below 25 kg/m². For BMI ≥ 25 kg/m², OA risk increased progressively with increasing BMI across all PA patterns, while no significant differences were observed between PA patterns (For WW vs RA, HRs = 0.970, *P* = 0.538; for WW vs IN, HR = 0.950, *P* = 0.303) .

PA was nonlinearly associated with OA risk, and no significant interaction between PA and BMI categories was detected ($P_{overall}$ < 0.001, $P_{nonlinearity}$ < 0.001, and $P_{interaction}$ = 0.084) (Fig. 3B). Across all BMI categories, PA showed an approximately U-shaped association with OA risk. Using PA = 150 min/week as the reference value, OA risk initially decreased with increasing PA levels and subsequently increased at higher PA levels. Across the three BMI categories, PA < 150 min/week was associated with an increased risk of OA. Among participants with normal weight or below, PA levels between 150.0 and 626.1 min/week were associated with HRs below 1.0, with the lowest estimated hazard observed at 300.7 min/week (HR = 0.97, 95% CI : 0.96–0.98). Similarly, among participants with overweight and obesity, PA ranges of 150.0–374.7 min/week and 150.0–448.9 min/week were associated with HRs below 1.0, with the lowest estimated hazards observed at 244.3 min/week (HR = 0.98, 95% CI : 0.97–0.99) and 272.5 min/week (HR = 0.97, 95% CI : 0.96–0.98), respectively. Beyond these ranges, the estimated OA hazards gradually increased with increasing PA levels.

Sensitivity analyses using a 2-year lag model yielded consistent results, with no material changes observed in the dose-response associations for either BMI or PA with OA risk (Supplementary Fig. 1).

[Figure 3 near here]

Discussion

In this large prospective cohort study, overweight and obesity were associated with 34% and 101% higher risks of OA, respectively, compared with a BMI below 25 kg/m². Among the PA patterns, IN was associated with a modestly increased OA risk. The highest combined effect estimate occurred among participants with both obesity and IN, and this association was stronger in women than in men. We found no evidence of interaction on the multiplicative scale; however, obesity and IN showed a positive interaction on the additive scale, indicating that the excess absolute risk associated with their joint presence exceeded the sum of the excess risks associated with each factor separately. Dose-response analyses further suggested a J-shaped association between BMI and OA risk and an approximately U-shaped association between PA and OA risk.

The combined effects analysis showed that OA risk increased progressively across BMI categories within each PA pattern. Among overweight individuals, the WW and IN patterns showed approximately 35% and 37% higher OA hazards, respectively, with the corresponding increases reaching approximately 97% and 112% among individuals with obesity. These findings indicate that PA pattern may further stratify risk within BMI categories, but it does not fully offset the excess OA risk associated with elevated BMI. This finding is consistent with the HUNT Study, which also identified BMI as the predominant determinant of OA risk across activity levels[21]. In sex-stratified analyses, the combined effect of obesity and IN was stronger in women than in men, contrasting with the findings of Soutakbar et al., who reported that the adverse association of high PA combined with higher BMI with OA risk was mainly observed in men[19]. Differences in PA assessment and OA definitions may partly explain this discrepancy, while Sex-specific biomechanical and anatomical factors, together with potential effects of estrogen depletion after menopause, may partly contribute to this difference, although the role of estrogen in OA remains incompletely established[37, 38].

An important feature of this study was the assessment of interaction on both multiplicative and additive scales. No significant multiplicative interaction was observed, indicating no evidence of effect modification between BMI and PA patterns on the relative risk scale. This finding was consistent with the HUNT Study but contrasted with the findings reported by Soutakbar et al., who observed a significant interaction between BMI and PA on OA risk primarily in men. Notably, both studies focused on multiplicative interaction, whereas our analysis additionally identified interaction on the additive scale[19, 21]. Because additive interaction more directly reflected excess case burden and potential impact of preventive interventions, our finding of a significant positive additive interaction between obesity and IN may have important public health implications. Specifically, the additive interaction between IN and obesity corresponded to 92.16 excess OA cases per 100,000 person–years compared with the number expected under additivity, highlighting individuals with both obesity and inactivity as a potential priority population for OA prevention. When obesity coexists with inactivity, increased mechanical loading and reduced muscular support may create a “high-load and low-protection” biomechanical state[15, 17]. Obesity-related metabolic inflammation may further promote cartilage degradation, thereby increasing OA risk through converging mechanical and metabolic pathways[39–42].

Dose-response analyses identified BMI = 25 kg/m² as a clinically meaningful reference point in the BMI–OA association. Relative to this value, lower BMI levels were associated with lower estimated OA hazards, whereas BMI above 25 kg/m² was associated with progressively increased OA hazards. Notably, this threshold coincides with the WHO recommended cutoff between normal weight and overweight, highlighting its clinical and public health significance. The consistency of this pattern across PA groups suggests that PA pattern alone may be insufficient to counteract the adverse association of excess body weight with OA, highlighting the importance of maintaining BMI below 25 kg/m² regardless of PA pattern.

Dose–response analyses identified a U-shaped association between PA and OA risk. Across the PA ranges associated with lower estimated hazards (150.0–626.1, 150.0–374.7, and 150.0–448.9 min/week for participants with normal and below, overweight, and obesity, respectively), the association with lower estimated hazard strengthened up to the optimal points (300.7, 244.3, and 272.5 min/week, respectively) and gradually attenuated thereafter. Beyond these ranges, higher PA levels were associated with increased estimated hazards of OA, and OA hazard increased progressively with further increases in PA. Moderate PA may serve as beneficial mechanical stimulation, promoting physiological adaptations to exercise that enhance function and muscle strength.[16, 17]. At higher PA levels, these benefits may plateau while repetitive loading continues to accumulate, eventually exceeding the adaptive capacity of joint tissues and increasing OA risk[43].

Several limitations warrant consideration. First, PA was self-reported at baseline and may be affected by recall error, misclassification, and changes in activity over time. Second, incident OA was identified from linked health records and may preferentially capture clinically recognized disease while underascertaining milder or subclinical OA. Third, the primary outcome combined multiple OA phenotypes (ICD-10 M15–M19), and the associations of BMI and PA may differ across anatomical sites. Fourth, underweight and normal-weight participants were combined because of the small number of underweight participants, which may have obscured risk heterogeneity at the lower end of the BMI distribution. Fifth, despite multivariable adjustment and the 2-year lag analysis, residual confounding and reverse causation cannot be excluded. Finally, UK

Biobank participants are not fully representative of the general population, which may limit generalizability. As an observational study, the present findings do not establish causality.

Conclusions

Higher BMI showed a substantially stronger association with incident OA than PA pattern in this cohort. Inactivity was associated with a modestly higher OA risk, whereas the weekend warrior pattern was not independently associated with OA overall. Obesity combined with inactivity was associated with the highest OA risk and showed positive additive, but not multiplicative, interaction. Dose-response analyses suggested nonlinear associations for both BMI and PA. Dose–response analyses indicated that PA could not fully offset the increased OA risk associated with BMI ≥ 25 kg/m². Nevertheless, different PA levels may be appropriate across BMI categories to help reduce OA risk.

Abbreviations

Full term	Abbreviation
Osteoarthritis	OA
Physical activity	PA
Body mass index	BMI
UK Biobank	UKB
Inactive	IN
Weekend Warrior	WW
Regularly active	RA
Hazard ratio	HR
Confidence interval	CI
Relative excess risk due to interaction	RERI
Attributable proportion due to interaction	AP
Synergy index	SI
Standard deviation	SD
Interquartile range	IQR
Person-years	PY
Restricted cubic spline	RCS
Risk ratio	RR
World Health Organization	WHO
International Physical Activity Questionnaire	IPAQ

Declarations

Ethics approval and consent to participate

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee, and all participants provided written informed consent. The present study used de-identified UK Biobank data and was conducted in accordance with the UK Biobank's ethical framework.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available from the UK Biobank to bona fide researchers upon approved application through the UK Biobank access process.

Competing interests

The authors declare that they have no competing interests.

Funding

No specific funding was received for this study from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors attest to the accuracy and integrity of the work and approved the final version of the manuscript. LZ, FW, and YZ contributed to the conceptualization and study design. FW contributed to data resources. WN, ZZ, LX, SX, and TT contributed to data curation. TZ performed the formal analysis and visualization. TZ, LZ, and YZ contributed to the interpretation of the results. LZ supervised and coordinated the study. TZ drafted the original manuscript. LZ, FW, and YZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors gratefully acknowledge the participants and staff of the UK Biobank for their important contributions to this research.

Authors' information

Not applicable.

Clinical trial number

Clinical trial number: not applicable.

Consent to participate

All participants provided written informed consent before participation in the UK Biobank.

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Figures

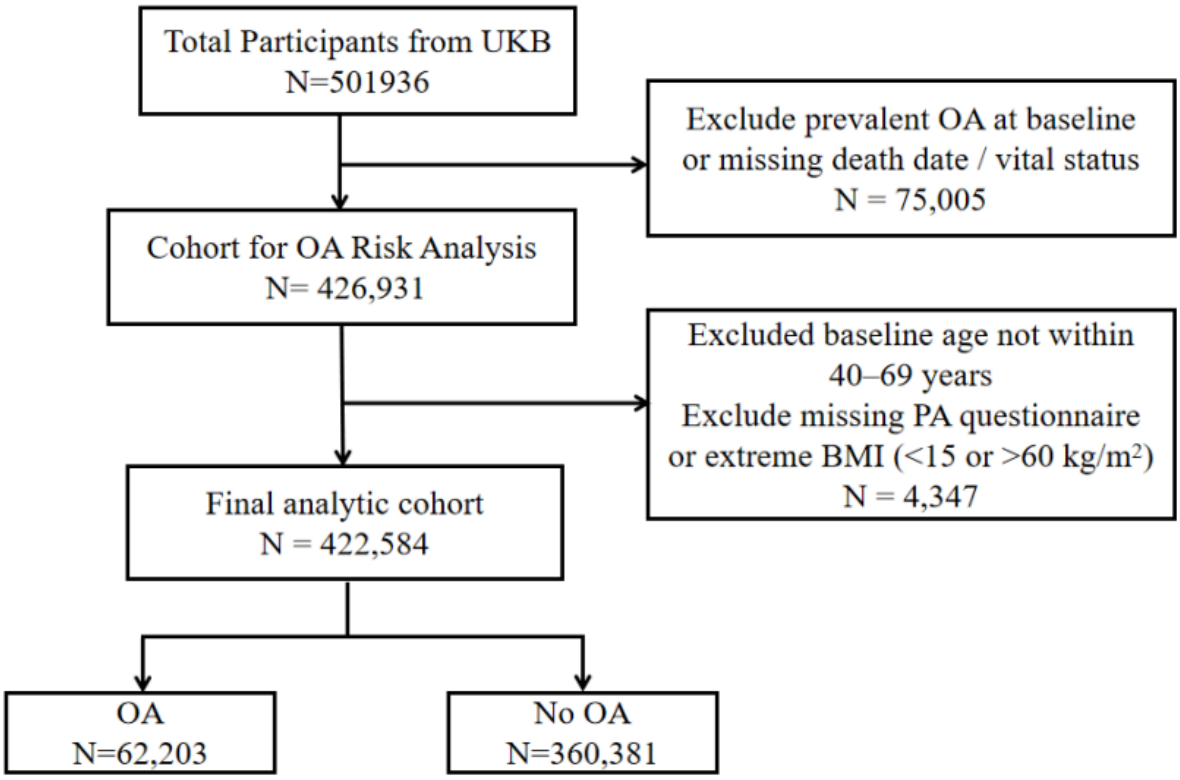


Figure 1

Flowchart of participant selection for the UK Biobank analytic cohort.

The flowchart summarizes participant inclusion and exclusion criteria and the derivation of the final analytic cohort.

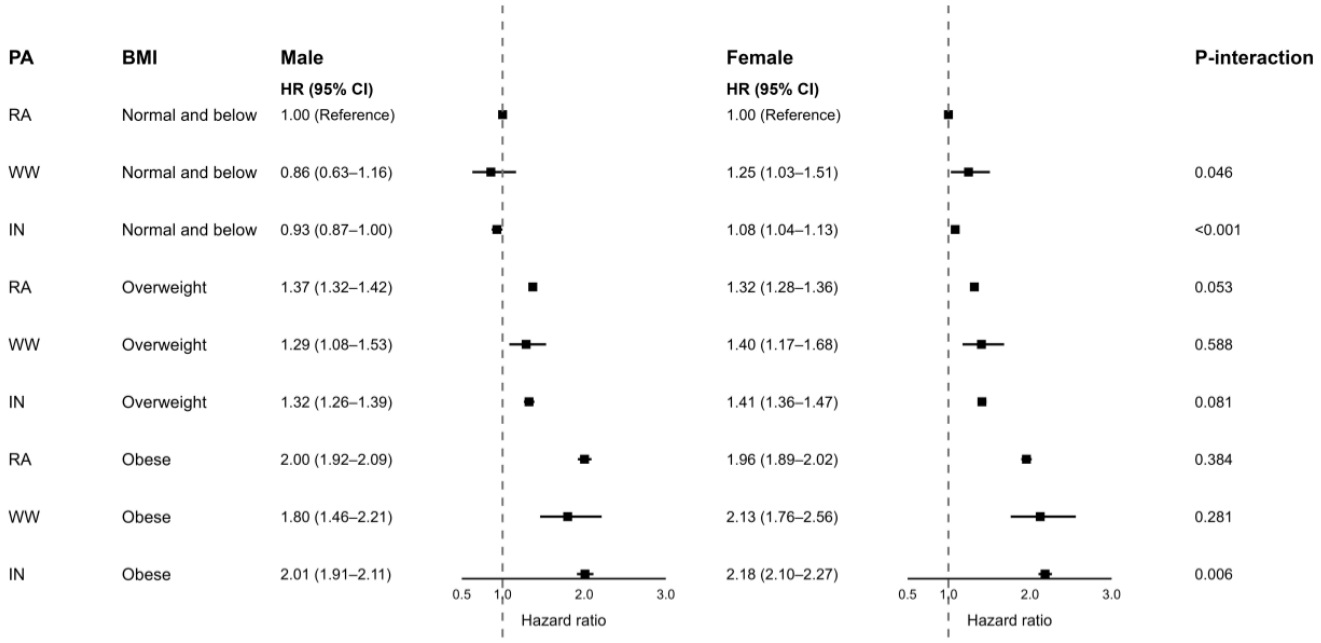


Figure 2

Combined associations of PA patterns and BMI categories with OA risk, stratified by sex.

HRs were estimated using Cox proportional hazards models and are presented separately for males and females.

Within each sex, RA participants with normal weight or below were used as the reference group. Models were adjusted for age, education, ethnicity, household income, smoking, drinking, cancer, diabetes, and cardiovascular disease. P for interaction tests whether the association of each combined exposure group with OA risk, relative to the reference group, differs by sex. A significant P-interaction indicates significant heterogeneity between sexes.

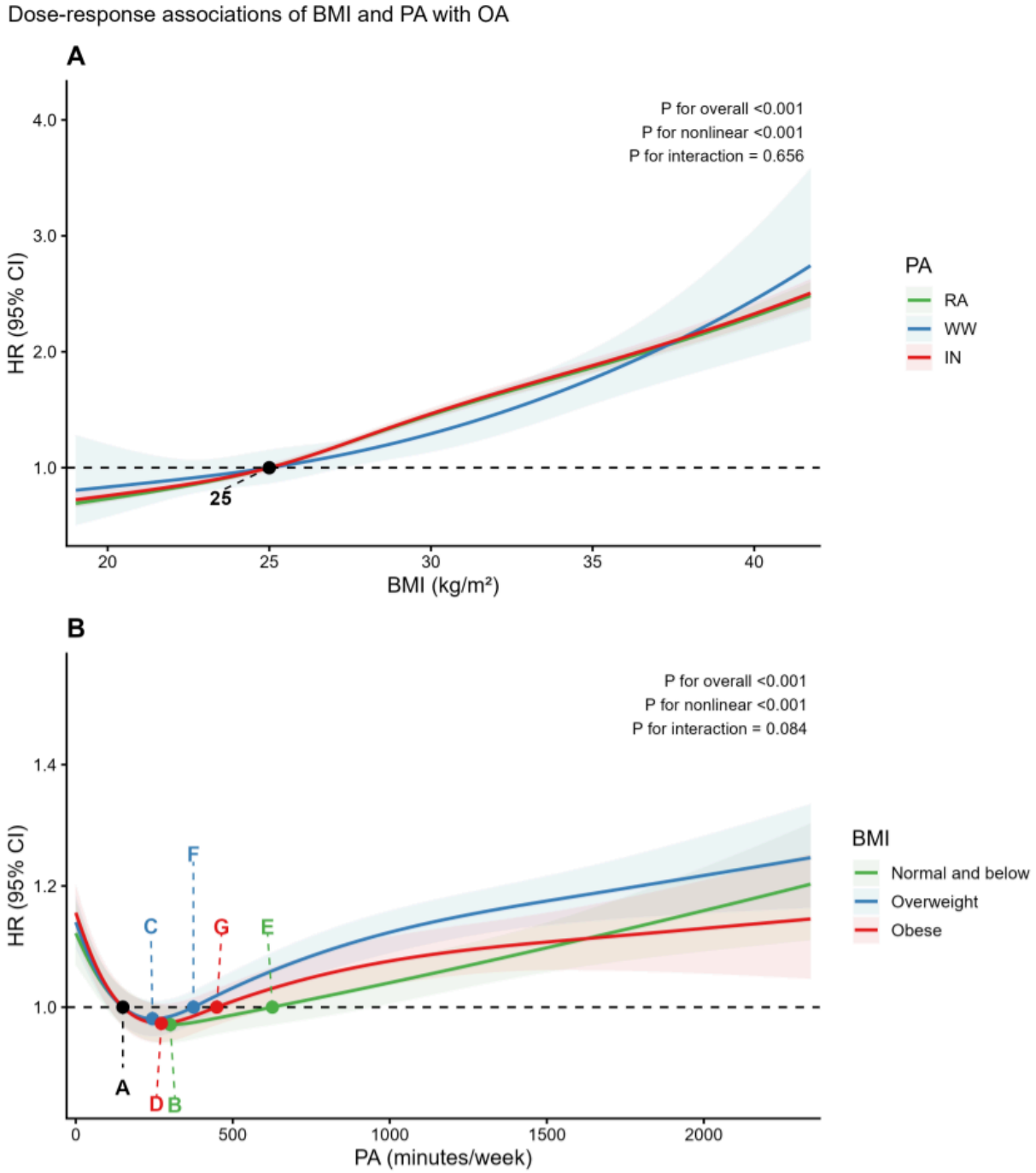


Figure 3

Dose-response associations of BMI and physical activity with OA risk

A. Dose-response association between BMI and OA risk stratified by PA pattern. The marked values indicate BMI levels of 25.0 and 37.3 kg/m².

B. Dose-response association between weekly PA duration and OA risk stratified by BMI category. Point A indicates the lower HR = 1.0 intersection at 150 min/week. Points B–D indicate the PA levels associated with the lowest OA risk (B = 300.7 min/week for normal or below-normal BMI, C = 244.3 min/week for overweight, and D = 272.5 min/week for obesity). Points E–G indicate the upper HR = 1.0 intersections (E = 626.1 min/week, F = 374.7 min/week, and G = 448.9 min/week, respectively). Shaded areas represent 95% confidence intervals, and dashed horizontal lines indicate HR = 1.

Supplementary Files

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