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Associations of healthy lifestyle and genetic susceptibility with risks of osteoarthritis: a prospective cohort study

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Abstract

Objectives: To detect the associations of a healthy lifestyle and genetic susceptibility with incident OA in the UK Biobank study.

Methods: We included 314 729 participants from UK Biobank. Five modifiable lifestyle factors including weight management, diet, physical activity, sleep behaviour and sedentary behaviour were included to generate an overall lifestyle score. Genetic susceptibility was calculated by using polygenic risk score (PRS) of OA. Participants diagnosed with OA were identified by using the International Classification of Diseases (ICD)-9 and ICD-10. Covariates included age, sex, education, Townsend deprivation index, glucosamine use, analgesics use and comorbidities. Cox regression analyses were performed to examine the associations of genetic susceptibility and healthy lifestyle with incident OA.

Results: Adopting a more favourable lifestyle can be beneficial in significantly reducing the risk of incident total, knee and hip OA (all $P < 0.01$). PRS was significantly associated with greater risks of total, knee and hip OA. Compared with unfavourable lifestyle, favourable lifestyle was significantly associated with a lower risk of total OA across low [hazard ratio (HR) 0.64; 95% CI 0.58–0.70], intermediate (HR 0.59; 95% CI 0.56–0.63) and high (HR 0.58; 95% CI 0.53–0.64) genetic risk groups. Similar results were observed on knee OA and hip OA. No significant interactions were detected between lifestyle and PRS for total, knee or hip OA.

Conclusion: These data suggest that a healthier lifestyle is consistently associated with a lower risk of OA, regardless of genetic risks. Our findings highlight the importance of adherence to an overall healthy lifestyle in attenuating the risk of OA.

Keywords: osteoarthritis, lifestyle, polygenic risk.

Rheumatology key messages

- Combining moderate and vigorous physical activity with walking behaviour as total physical activity is non-linearly associated with risk of OA.
- Adherence to a healthy lifestyle is associated with lower risk of OA regardless of genetic susceptibility.
- The findings of this study enhance the significance of healthy lifestyle in the protection of OA.

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Introduction

OA is the most common form of arthritis worldwide and affects ~7% of the global population [1]. Previous studies indicated that lifestyle factors including obesity, unhealthy diet, physical inactivity, sleep deprivation and sedentary behaviour were associated with incident OA [2–4]. Obesity has been confirmed as a potential risk factor for OA [5]. Higher intake of junk food and sugar-sweetened beverages may increase OA risk [6]. The risk of OA is higher in people who sleep <7 h and >8 h [7], and significant association of prolonged TV watching time with overall OA and knee OA risks was reported [8]. Nonetheless, previous research focused on single indicators, which may not represent the whole picture of lifestyle factors. Moreover, how much an overall healthy lifestyle can reduce the risk of OA remains unclear.

Meanwhile, genetic susceptibility is also regarded as one of the intrinsic risks of OA [9, 10]. Growing evidence suggests that the genetic underpinnings of OA are polygenic in nature [11]. Genome-wide association studies (GWASs) have been successful in identifying OA-associated genetic variants [9]. Studies have identified over 100 OA-associated genomic loci [9]. Since a single genetic variant may only contribute a small portion to the genetic variability of OA, a polygenic risk score (PRS) that combines multiple risk loci can serve as a valuable tool in identifying individuals with a higher genetic susceptibility to OA [11]. However, whether people with genetic susceptibility to OA could benefit from a healthy lifestyle is still unknown.

Therefore, we conducted a prospective cohort study utilizing data from the UK Biobank to examine the associations between genetic susceptibility, lifestyle factors and risk of OA, and to determine the interactions between genetic susceptibility and lifestyle factors in relation to the risk of OA. This study provides validation evidence for the novel lifestyle score.

Methods

Study populations

The UK Biobank is a population-based cohort of >500 000 participants who attended one of 22 assessment centres across the UK between 2006 and 2010 [12]. Analyses were restricted to individuals with genetic information available. Participants with missing information on covariates, or who had genetic kinship with other participants were excluded from the analysis (Fig. 1). In addition, those with self-reported OA or a diagnosis of OA in hospital inpatient records at baseline were excluded from analysis. Overall, 314 729 participants from UK Biobank were included. The UK Biobank study was approved by the North West Multicentre research ethics committee (REC reference 11/NW/0382) [13] and written informed consent was provided before participation. The current work followed the Declarations of Helsinki.

Assessment of lifestyle factors

All lifestyle information was either self-reported or measured at baseline (2006–2010). In the current study, we considered five OA-specific and modifiable lifestyle factors, including weight management, physical activity, diet, sedentary behaviour and sleep behaviour, to generate a lifestyle score. BMI >30 kg/m^2 was regard as unhealthy weight management [14]. We performed restricted cubic spline (RCS) curves to test whether there was an association of the total physical activity minutes (including walking, moderate activity and vigorous activity) with risks of total, knee and hip OA. Performing >1300 min/week and <2000 min/week was defined as appropriate physical activity (Supplementary Fig. S1A–C, available at *Rheumatology* online). An adequate intake of at least half of the 10 food groups recommended as dietary priorities for cardiometabolic health was defined as a low-risk level for the diet. These food groups include increased consumption of fruits, vegetables, whole grains, fish, dairy and vegetable oils, as well as reduced consumption of refined grains, processed/unprocessed meats and sugar-sweetened beverages [15]. Healthy sleep behaviours were defined as sleep 7–8 h/day according to literature, with early chronotype, never or rarely insomnia symptoms, no snoring and no excessive daytime sleepiness [16]. For each sleep behaviour, low risk was coded as 1 and high risk was coded as 0, respectively. We further summed the five scores to obtain a healthy sleep score ranging from 0 to 5, with higher scores (score of 4 or 5) indicating a healthier sleep pattern [7]. We used television watching, computer use and driving as the total sedentary behaviour, and defined a low risk level as <4 h/day [8]. In addition, to ensure the association between sedentary time and the risk of OA, we additionally drew the RCS curves and found that sitting >4.5 h/day is obviously associated with increased risk of OA (Supplementary Figure S2A-C, available at *Rheumatology* online). Thus, based on the literature evidence and the findings in our study, we defined sitting <4 h/day as the healthier lifestyle status. More details of definition for lifestyle factors were described in Supplementary Table S1, available at *Rheumatology* online.

For each of the five lifestyle factors, a low risk level was assigned one point and otherwise zero point. We first constructed a simple additive lifestyle score as the sum of all five factors, ranging from 0 to 5 and was subsequently categorized into three groups (i.e. 0–1, 2–3 and 4–5). We compared the effects of an additive healthy lifestyle scale and a three-group healthy lifestyle categorization on the risk of total OA, knee OA and hip OA. The categorical scale showed the same direction of effect as additive scale but demonstrated a stronger association with reduced OA risk (Supplementary Table S2, available at *Rheumatology* online). Additionally, regarding construction of the weighted lifestyle score, β coefficients of each lifestyle factor were estimated using a Cox proportional hazards model that included all five lifestyle factors and OA incidence as the outcome. The weighted lifestyle score was constructed as follows: the binary lifestyle variables were multiplied by the β coefficients related to OA incidence, summed up, and then divided by the sum of β coefficients and multiplied by 100 [17]. We then categorized it into three groups (favourable, neutral and unfavourable) based on the distribution of the simple additive lifestyle score.

OA diagnosis

OA was ascertained using hospital inpatient records containing data on admissions and diagnoses obtained from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland and the Patient Episode Database for Wales. Diagnoses were recorded using the International Classification of Diseases (ICD) coding system. Participants with OA were identified by ICD-9 (7151, 7152, 7153, 7158, 7159) and ICD-10 codes (M15–M19, M471, M472, M478,

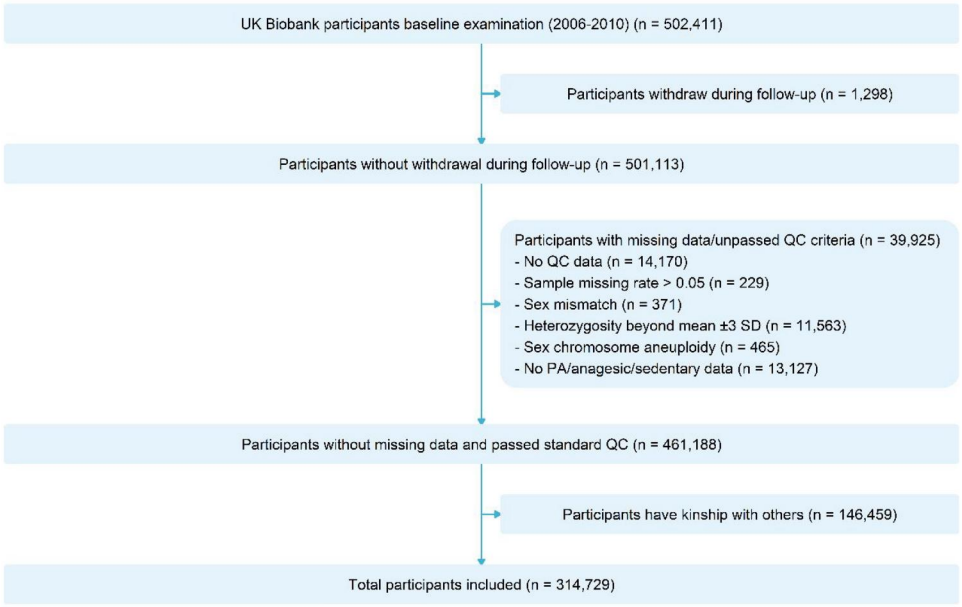

Figure 1. Flow chart of UK Biobank participants screening. QC: quality control; PRS: polygenic risk score; PA: physical activity

M479, M480) [18] (Supplementary Table S3, available at *Rheumatology* online).

Polygenic risk score

Genetic susceptibility was calculated by using the PRS of OA. The PRS was constructed for individuals by using a polygenic score model constructed via Bayesian regression framework with continuous shrinkage prior on SNP effect sizes, as implemented in the PRS-CS software [19]. We included all SNPs reported by the GWAS meta-analysis summary statistics for OA [9]. For the external linkage disequilibrium reference panel, the UK Biobank Linkage Disequilibrium reference panel was used to calculate the PRSs. After calculating the PRS for individuals, we further classified the PRS as low, intermediate and high genetic risk groups based on the first quintile, the second to the fourth quintile and the fifth quintile of the PRSs across population.

Covariates

Covariates were obtained via questionnaires including age, sex, Townsend deprivation index, education level, glucosamine use, analgesics use and joint injury history. Baseline prevalence of comorbidities including coronary artery disease, chronic obstructive pulmonary disease, RA, gout, depression and type 2 diabetes were also regarded as covariate through the self-reported illnesses, history as well as ICD-9 and ICD-10 code. The first 10 principal components of ancestry were regarded as covariates when we were investigating the association between PRS and risk of OA. (Supplementary Table S1, available at *Rheumatology* online).

Statistical analysis

Baseline characteristics were described across different levels of lifestyle score, and differences among groups were tested by analysis of variance for continuous variables and χ^2 test for categorical variables. We used Cox proportional hazard regression models to estimate the hazard ratios (HR) and 95% CI of outcomes associated with PRS and lifestyle score. Person-years were calculated from baseline until the date of death or diagnosis for OA, or end of follow-up (31 December 2021), whichever occurred first. We further conducted multiplicative interaction analyses by PRS to investigate associations of the lifestyle score (neutral lifestyle, favourable lifestyle) with incident OA among adults in different genetic risk subgroups (intermediate PRS, high PRS).

To avoid spurious findings and test the robustness of the results, we conducted several sensitivity analyses. First, we created a weighted score for each healthy lifestyle factor to accommodate the varying strengths of associations between different lifestyle factors and outcomes. Second, we additionally constructed a lifestyle score excluding weight management, since weight management might be the consequence of unhealthy dietary habits and inadequate physical activities. Third, we excluded participants who were diagnosed with OA within the initial 2 years of follow-up to mitigate the effects of potential reverse causality. Fourth, among individuals who did not develop OA, we excluded those who had deceased before the end of follow-up to eliminate the effect of competing event affecting the probability of incident OA. Fifth, we conducted a competing risk model considering death as competing event to provide more accurate estimations. Sixth, to explore early-onset OA, we analysed a subset of younger individuals under 55 years of age. Seventh, we examined the association between a healthy lifestyle scale previously developed for dementia and the risk of OA. Finally, we imputed missing values for covariates and re-evaluated their associations with OA risk. Since each comparison was considered individually, multiple hypothesis testing correction was not applied to the results. All analyses were conducted using R software (version 4.2.1).

Results

Baseline characteristics of participants

Baseline characteristics of participants are shown in Table 1. Overall, 35.66% of participants had an unfavourable

Table 1. Baseline characteristic of participants in different level of healthy lifestyle

Mean (S.D.)/*n* (%)	Healthy lifestyle			*P*-value
	Unfavourable (*n* = 111 992)	Neutral (*n* = 176 919)	Favourable (*n* = 25 818)	
Age, years	56.75 (7.91)	56.39 (8.12)	55.78 (8.12)	$\mathbf{6.0 \times 10^{-72}}$
Female	60 454 (54.0)	77930 (44.0)	8072 (31.3)	$\mathbf{<2.2 \times 10^{-308}}$
Deprivation index	–0.84 (3.38)	–1.21 (3.27)	–1.27 (3.22)	$\mathbf{1.4 \times 10^{-179}}$
Education	35 354 (31.6)	75 248 (42.5)	14 218 (55.1)	$\mathbf{<2.2 \times 10^{-308}}$
Comorbidities	28 717 (25.6	26 924 (15.2)	2634 (10.2)	$\mathbf{<2.2 \times 10^{-308}}$
CAD	7972 (7.1)	7440 (4.2)	692 (2.7)	$\mathbf{<2.2 \times 10^{-308}}$
COPD	1205 (1.1)	918 (0.5)	69 (0.3)	$\mathbf{8.1 \times 10^{-84}}$
RA	1507 (1.3)	1786 (1.0)	203 (0.8)	$\mathbf{6.7 \times 10^{-22}}$
Gout	2412 (2.2)	1915 (1.1)	138 (0.5)	$\mathbf{4.5 \times 10^{-157}}$
Depression	8536 (7.6)	9477 (5.4)	1060 (4.1)	$\mathbf{6.1 \times 10^{-176}}$
T2DM	13742 (12.3)	9142 (5.2)	718 (2.8)	$\mathbf{<2.2 \times 10^{-308}}$
Glucosamine use	20 318 (18.1)	35 067 (19.8)	5559 (21.5)	$\mathbf{5.6 \times 10^{-46}}$
Analgesic use	51 543 (46.0)	64 978 (36.7)	7793 (30.2)	$\mathbf{<2.2 \times 10^{-308}}$
Joint injury history	1424 (1.3)	2268 (1.3)	349 (1.4)	5.8×10^{-01}
Healthy weight management	56 226 (50.2)	159 040 (89.9)	25 481 (98.7)	$\mathbf{<2.2 \times 10^{-308}}$
Healthy diet	5422 (4.8)	45 885 (25.9)	18 004 (69.7)	$\mathbf{<2.2 \times 10^{-308}}$
Healthy physical activity	8185 (7.3)	53 332 (30.1)	17 119 (66.3)	$\mathbf{<2.2 \times 10^{-308}}$
Healthy sleep behaviour	9375 (8.4)	85 853 (48.5)	22 663 (87.8)	$\mathbf{<2.2 \times 10^{-308}}$
Non-sedentary	6459 (5.8)	79 812 (45.1)	22 850 (88.5)	$\mathbf{<2.2 \times 10^{-308}}$
Total OA	27 742 (24.8)	31 415 (17.8)	3678 (14.2)	$\mathbf{<2.2 \times 10^{-308}}$
Knee OA	11 529 (10.3)	10 989 (6.2)	1177 (4.6)	$\mathbf{<2.2 \times 10^{-308}}$
Hip OA	6208 (5.5)	7875 (4.5)	1007 (3.9)	$\mathbf{2.5 \times 10^{-50}}$

Data are shown as mean (S.D.) for continuous variables or *n* (%) for categorical variables. *P*-values were calculated with one-way ANOVA test and χ^2 test for continuous and categorical variables, respectively. Bold type denotes statistically significant. CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes.

lifestyle, 56.17% had a neutral lifestyle and 8.17% had a favourable lifestyle. 20.06% of participants had a low PRS, 60.04% had an intermediate PRS and 19.90% had a high PRS. Individuals with an unfavourable lifestyle were more likely to be women, be less educated, use more analgesics and to have a higher prevalence of comorbidities. Regarding OA incidence, there were 27 742, 31 415 and 3678 cases in the unfavourable, neutral and favourable lifestyle groups for total OA, accounting for 24.8%, 17.8% and 14.2%, respectively. Similarly, 10.3%, 6.2% and 4.6% of participants suffer from knee OA, while 5.5%, 4.5% and 3.9% participants suffer from hip OA in the unfavourable, neutral and favourable groups, respectively.

Association between lifestyle score and incident OA

For total OA, compared with unfavourable lifestyles, healthy lifestyles were significantly associated with reduced risk of OA incidence. However, compared with unhealthy diet, healthy diet has no significant association with risk of total OA. Similar results were observed for knee OA and hip OA (Supplementary Table S4, available at *Rheumatology* online). Cumulative hazard analyses with risk tables indicate that shorter times to event for total OA, knee OA and hip OA were observed in the group adhering to an unfavourable lifestyle compared with those with a favourable lifestyle (Supplementary Figs S3–S5, available at *Rheumatology* online). Adhering to a more favourable lifestyle can be beneficial in significantly reducing the risk of total, knee and hip OA. The HR of total, knee and hip OA for individuals in the favourable lifestyle group were 0.65 (95% CI 0.62–0.67), 0.53 (95% CI 0.49–0.57) and 0.77 (95% CI 0.71–0.83), respectively (Supplementary Table S5, available at *Rheumatology* online).

Association between polygenic risk score and incident OA

We further detected the association between PRS and risk of incident OA. We first regarded the genetic risk score as a continuous variable and examined the trend of the risk of OA for increasing PRS with RCS curves based on Cox proportional hazard model. The curves showed that higher PRS was significantly associated with high risk of total, knee and hip OA (Fig. 2A–C). Furthermore, high genetic risk for OA was significantly associated with increased risks of incident total OA (HR 1.46; 95% CI 1.42–1.50), knee OA (HR 1.88; 95% CI 1.79–1.97) and hip OA (HR 2.14; 95% CI 2.01–2.07) (Table 2).

Interaction analysis of healthy lifestyle and polygenic risk score with risk of OA

Table 3 shows the interactions between PRS and healthy lifestyle score on the risk of OA. In the low genetic risk group, favourable lifestyle was significantly associated with a lower risk of total OA (HR 0.70; 95% CI 0.64–0.77), compared with unfavourable lifestyle. In intermediate genetic risk group and high genetic risk group, the results were largely similar (HR 0.63; 95% CI 0.60–0.67 and HR 0.66; 95% CI 0.61–0.77, respectively). Compared with unfavourable lifestyle, favourable lifestyle was significantly associated with lower risk of knee OA across low, intermediate and high genetic risk groups (HR 0.53; 95% CI 0.44–0.63, HR 0.54, 95% CI 0.49–0.59 and HR 0.55; 95% CI 0.48–0.63, respectively). For hip OA, adherence to favourable lifestyle was also significantly associated with lower risk of OA incidence across low, intermediate and high genetic risk groups (HR 0.74; 95% CI 0.59–0.91, HR 0.77, 95% CI 0.70–0.85 and HR 0.79; 95% CI 0.69–0.91, respectively). No statistically significant

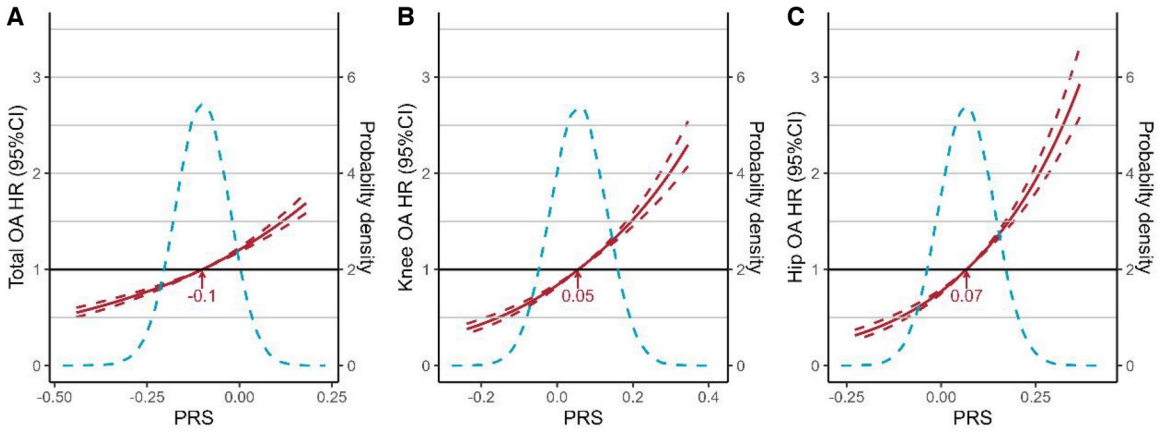

Figure 2. Multivariable adjusted hazard ratios for risk of total, knee and hip OA according to PRS on a continuous scale. Solid red lines are multivariable adjusted hazard ratios, with dashed red lines showing 95% CIs derived from restricted cubic spline regressions with three knots. Reference lines for no association are indicated by the solid bold black lines at a hazard ratio of 1.0. Dashed blue curves show the probability density with different PRS. Arrows indicate the PRS with the transformation of low hazard ratios to high hazard ratio for total (**A**), knee (**B**) and hip OA (**C**). Analyses were adjusted for age, sex, Townsend deprivation index, education level, glucosamine use, analgesics use, joint injury history and comorbidity at baseline. PRS: polygenic risk score

Table 2. Association between polygenic risk score and incident OA

PRS	Total OA No. cases/ person-years	HR (95% CI)	*P*-value	Knee OA No. case/ person-years	HR (95% CI)	*P*-value	Hip OA No. cases/ person-years	HR (95% CI)	*P*-value
Low	15 497/ 1 012 330	Reference		5497/ 1 082 654	Reference		3349/ 1 103 468	Reference	
Intermediate	16 023/ 1 010 977	**1.21 (1.18, 1.24)**	$\mathbf{8.3\times10^{-52}}$	5946/ 1 080 303	**1.38 (1.32, 1.44)**	$\mathbf{1.1\times10^{-47}}$	3997/ 1 100 448	**1.49 (1.41, 1.57)**	$\mathbf{2.0\times10^{-45}}$
High	16 801/ 1 008 345	**1.46 (1.42, 1.50)**	$\mathbf{1.9\times10^{-148}}$	6283/ 1 079 836	**1.88 (1.79, 1.97)**	$\mathbf{1.0\times10^{-143}}$	4572/ 1 098 268	**2.14 (2.01, 2.27)**	$\mathbf{3.4\times10^{-135}}$
P for trend			$\mathbf{2.3\times10^{-151}}$			$\mathbf{2.7\times10^{-152}}$			$\mathbf{6.8\times10^{-146}}$

Cox proportional hazard regression model adjusted for age, sex, education, Townsend deprivation index, CAD, COPD, RA, gout, depression, T2DM, glucosamine use, analgesic use and joint injury history. Bold type denotes statistically significant. HR: hazard ratio; PRS: polygenetic risk score; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes.

interactions were detected between lifestyle and PRS on total OA, knee OA or hip OA.

Accumulative analysis of lifestyle pattern and PRS with risk of OA

Compared with having an unfavourable lifestyle and high genetic risk, adherence to healthier lifestyle score and having lower genetic risk had the lowest risk of total OA, knee OA and hip OA (Supplementary Figs S6–S8, available at *Rheumatology* online). Compared with having unfavourable lifestyle and high genetic risk, the HRs of adherence to healthier lifestyle score and having lower genetic risk are 0.48 (95% CI 0.44–0.52), 0.28 (95% CI 0.24–0.33) and 0.34 (95% CI 0.28–0.42) for total OA, knee OA and hip OA, respectively.

Sensitivity analysis

We conducted several sensitivity analyses to examine the robustness of these associations. Adherence to a weighted healthy lifestyle or a healthy lifestyle without healthy weight management were significantly associated with reduced risk of total OA in different PRS group (Supplementary Table S6, available at *Rheumatology* online). After excluding participants with occurrence of OA within 2 years, adherence to a favourable lifestyle was consistently associated with reduced risk of total, knee and hip OA (Supplementary Table S7, available at *Rheumatology* online). A competing risk analysis showed that these association remained consistent after ruling out the effect of competing events, including death and total joint replacement (Supplementary Table S8, available at *Rheumatology* online). Adherence to weighted neutral and favourable lifestyle was consistently and significantly associated with lower risks of OA incidence, regardless of genetic risks (Supplementary Table S9, available at *Rheumatology* online). Individuals under 55 years old showed higher genetic susceptibility, particularly for hip OA and total OA, and were more substantially impacted by lifestyle factors (Supplementary Tables S10 and S11, available at *Rheumatology* online). Healthy lifestyle score constructed by dementia lifestyle factors was not associated with incident OA (Supplementary Table S12, available at *Rheumatology* online). After imputing missing values of covariates, adherence to neutral and favourable lifestyles was also associated with lower risks of OA incidence (Supplementary Table S13, available at *Rheumatology* online).

Discussion

In the current prospective cohort study with >12 years of follow-up, those adhering to a healthy lifestyle had a nearly

Table 3. Association of healthy lifestyle with OA by different genetic risk

OA phenotypes	PRS	Healthy lifestyle score	HR (95%CI)	*P*-value	*P* for trend	*P* for interaction
Total OA	Low	Unfavourable	1 (Reference)			
		Neutral	**0.79 (0.75, 0.82)**	$\mathbf{7.6\times10^{-24}}$		
		Favourable	**0.70 (0.64, 0.77)**	$\mathbf{1.6\times10^{-13}}$	$\mathbf{1.5\times10^{-26}}$	
	Intermediate	Unfavourable	1 (Reference)			
		Neutral	**0.77 (0.75, 0.79)**	$\mathbf{1.9\times10^{-96}}$		8.7×10^{-01}‡
		Favourable	**0.63 (0.60, 0.67)**	$\mathbf{2.7\times10^{-69}}$	$\mathbf{8.3\times10^{-126}}$	1.1×10^{-01}#
	High	Unfavourable	1 (Reference)			
		Neutral	**0.78 (0.75, 0.81)**	$\mathbf{2.6\times10^{-36}}$		7.0×10^{-01}§
		Favourable	**0.66 (0.61, 0.71)**	$\mathbf{4.3\times10^{-24}}$	$\mathbf{2.5\times10^{-45}}$	4.7×10^{-01}¶
Knee OA	Low	Unfavourable	1 (Reference)			
		Neutral	**0.66 (0.61, 0.72)**	$\mathbf{5.1\times10^{-22}}$		
		Favourable	**0.53 (0.44, 0.63)**	$\mathbf{2.1\times10^{-12}}$	$\mathbf{1.5\times10^{-25}}$	
	Intermediate	Unfavourable	1 (Reference)			
		Neutral	**0.67 (0.65, 0.70)**	$\mathbf{2.3\times10^{-82}}$		4.4×10^{-01}‡
		Favourable	**0.54 (0.49, 0.59)**	$\mathbf{2.9\times10^{-42}}$	$\mathbf{6.6\times10^{-96}}$	5.8×10^{-01}#
	High	Unfavourable	1 (Reference)			
		Neutral	**0.68 (0.64, 0.72)**	$\mathbf{8.3\times10^{-37}}$		4.0×10^{-01}§
		Favourable	**0.55 (0.48, 0.63)**	$\mathbf{3.5\times10^{-18}}$	$\mathbf{1.7\times10^{-42}}$	5.2×10^{-01}¶
Hip OA	Low	Unfavourable	1 (Reference)			
		Neutral	**0.88 (0.79, 0.98)**	$\mathbf{1.7\times10^{-02}}$		
		Favourable	**0.74 (0.59, 0.91)**	$\mathbf{5.4\times10^{-03}}$	$\mathbf{1.3\times10^{-03}}$	
	Intermediate	Unfavourable	1 (Reference)			
		Neutral	**0.86 (0.81, 0.90)**	$\mathbf{1.3\times10^{-09}}$		5.9×10^{-01}‡
		Favourable	**0.77 (0.70, 0.85)**	$\mathbf{2.1\times10^{-07}}$	$\mathbf{4.5\times10^{-12}}$	7.7×10^{-01}#
	High	Unfavourable	1 (Reference)			
		Neutral	**0.84 (0.78, 0.91)**	$\mathbf{3.4\times10^{-06}}$		7.5×10^{-01}§
		Favourable	**0.79 (0.69, 0.91)**	$\mathbf{9.6\times10^{-04}}$	$\mathbf{1.6\times10^{-06}}$	3.9×10^{-01}¶

Logistic regression adjusted for age, sex, education, deprivation index, CAD, COPD, RA, gout, depression, T2DM, glucosamine use, analgesic use and joint injury history. Bold type denotes statistically significant.

‡ Interaction of neutral Healthy lifestyle score in intermediate PRS and neutral Healthy lifestyle score in low PRS.

Interaction of Favorable Healthy lifestyle score in intermediate PRS and Favorable Healthy lifestyle score in low PRS.

§ Interaction of neutral Healthy lifestyle score in high PRS and neutral Healthy lifestyle score in low PRS.

¶ Interaction of Favorable Healthy lifestyle score in high PRS and Favorable Healthy lifestyle score in low PRS.

50% reduction in the risk of OA. Moreover, adherence to healthier lifestyle score and having lower genetic risk had the lowest risk of total OA, knee OA and hip OA. We did not observe statistically significant interactions between lifestyle factors and genetic susceptibility on the risks of OA incidence. These findings suggest that maintaining a healthy lifestyle could substantially decrease the risk of developing OA.

Lifestyle risk factors for OA have been widely studied. A higher BMI was found to be positively associated with increased risk of knee OA, hip OA and hand OA [20–22]. Besides, diet-induced weight loss alone or combined with exercise was shown to improve the physical function and relieve pain in knee OA participants with overweight or obesity [23]. However, most of the studies did not consider cumulative risk over time. The current study added evidence of the association between weight management and cumulative risks OA. For dietary intake, several studies have demonstrated that increased consumption of fruits, vegetables, whole grains, fish, dairy and vegetable oils are inversely associated with risk of OA [24]. Nonetheless, our study was the first to combine the dietary component as an overall score, while we did not find a significant association with OA. This could be attributed to unmeasurable confounding factors that might influence the potential benefit of healthy diet on OA patients.

Appropriate walking has been proved to be protective against an increase in MRI-detected osteophytes in OA patients [25]. Appropriate moderate or vigorous physical activity has been proved to be associated with reduced risk of OA and attenuated pain in OA patients [26]. Our study was the first to combine them, and employed RCS curves to test whether there was any nonlinear association of total physical activity with OA, and found that an appropriate amount of total physical activity could be beneficial to reducing the risk of OA. A study has illustrated the increasing risk of OA with excessive sleep or sleep deprivation [27]. However, a recent study examining the causal effect of sleep disturbances on risk of OA has shown that only short sleep duration and insomnia could have a causal effect on the increased risk of OA, but not long sleep duration [28]. Given these controversial results, our study included sleep duration, insomnia, snoring, chronotype and daytime sleepiness to generate healthy sleep scores, which are significantly associated with reduced risk of OA.

A longitudinal study suggested that extensive sitting time might not be associated with incident radiographic knee OA [29]. However, a Mendelian randomization study indicated that spending too much time watching TV might be causally associated with the risk of overall OA as well as knee OA [8]. Nonetheless, spending time watching TV is not an accurate proxy for sedentary time. Therefore, our study using RCS curve to test whether there is a non-linear association of sedentary behaviour, including watching TV, using a computer and driving, with risk of OA, and found that for those who spend <4.5 h per day sitting, the risk of OA rose rapidly with the increasing time, while for those who spend >4.5 h per

day, the risk of OA also rose with the increasing time, but less rapidly. In addition, our study conducted an analysis classifying the healthy status of sitting duration based on the cut-off threshold of 4 h per day and found that spending >4 h per day sitting was significantly associated with the risk of OA.

A previous study investigated the interaction between physical activity and genetic susceptibility with risk of OA and found that moderate adherence to patterns of 'strenuous sports' and 'walking for pleasure' might be associated with reduced risk of OA, and the association was consistent across different genetic susceptibility [30]. Distinct from this study, our study took a different approach by adopting three intensity levels of physical activity and consolidating them into a continuous measure of exercise intensity. This alternative methodology was employed to examine the impact of exercise on the risk of developing OA, as exercise has been found to exert a substantial influence on OA risk.

A similar lifestyle scale developed for dementia incorporated smoking, alcohol consumption, physical activity and diet [17]. However, smoking and alcohol consumption are not commonly recognized as significant risk factors for OA. Therefore, this study investigated the association of these lifestyle factors with the risk of OA over time, presenting a novel lifestyle scale and providing validation evidence for the risk of OA. The findings of this study indicate that promoting a healthy lifestyle might be an effective strategy to attenuate the risk of OA, regardless of the genetic risk level. This study was conducted in a large-scale population, and consistent evidence from literature supports the reliability of lifestyle scale for future use. However, the lifestyle scale should be used cautiously, as the effect size of lifestyle factors on OA risk may vary across ethnic groups. Alternatively, researchers should consider developing a new healthy lifestyle scale tailored to their specific population.

This study introduces a novel lifestyle scale that integrates multiple well-evidenced lifestyle factors. We ensured content validity by using threshold determined by RCS curves to confirm that the scale items comprehensively captured the construct of a healthy lifestyle. Additionally, we evaluated criterion validity by examining the association between each lifestyle factor, the overall lifestyle scale and OA incidence. The results demonstrated strong and consistent relationships. Our study analysed the joint association of genetic and lifestyle factors to gain a comprehensive understanding of the risk of OA. Moreover, our study performed a series of sensitivity analyses. Nevertheless, we acknowledge several potential limitations. First, adherence to a healthy lifestyle may change over the follow-up period, but this information was not available in our study, preventing us from examining how lifestyle changes might influence the association estimates. Evidence from a clinical trial indicate that transitioning to a healthier lifestyle can provide considerable benefits for patients with OA [31]. Second, although important known covariates were used for adjustment in the models, we cannot rule out the possibility of residual confounding. Last, although this study included a multi-ethnic population, the predominance of European ancestry (96.2%) limits the generalizability of the findings to other ethnic groups. Future studies should aim to include more diverse populations.

In conclusion, these data suggest that healthier lifestyle is consistently associated with lower risk of OA, regardless of genetic risks. Further research in diverse populations is needed to establish predictive validity, assess generalizability and develop targeted strategies for reducing the burden of this condition.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The UK Biobank data is available from the UK Biobank on request (www.ukbiobank.ac.uk/).

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References

1. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. Lancet 2020;396:1711–2.
2. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2018;14:674–81.
3. Kanavaki AM, Rushton A, Hale E *et al.* Physical activity, sedentary behaviour and well-being: experiences of people with knee and hip osteoarthritis. Psychol Health 2024;39:1023–41.
4. Salwen JK, Smith MT, Finan PH. Mid-treatment sleep duration predicts clinically significant knee osteoarthritis pain reduction at 6 months: effects from a Behavioral Sleep Medicine Clinical Trial. Sleep 2017;40:2.
5. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. Maturitas 2016;89:22–8.
6. Grout L, Mizdrak A, Nghiem N *et al.* Potential effect of real-world junk food and sugar-sweetened beverage taxes on population health, health system costs and greenhouse gas emissions in New Zealand: a modelling study. BMJ Nutr Prev Health 2022;5:19–35.
7. Cho Y, Jung B, Lee YJ *et al.* Association between sleep duration and osteoarthritis and their prevalence in Koreans: a cross-sectional study. PLoS One 2020;15:e0230481.
8. Cao Z, Li Q, Li Y, Wu J. Causal association of leisure sedentary behavior with arthritis: a Mendelian randomization analysis. Semin Arthritis Rheum 2023;59:152171.
9. Boer CG, Hatzikotoulas K, Southam L *et al.*; Regeneron Genetics Center. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. Cell 2021;184:4784–818.e17.

10. Aubourg G, Rice SJ, Bruce-Wootton P, Loughlin J. Genetics of osteoarthritis. Osteoarthritis Cartilage 2022;30:636–49.
11. Sedaghati-Khayat B, Boer CG, Runhaar J *et al.* Risk assessment for hip and knee osteoarthritis using polygenic risk scores. Arthritis Rheumatol 2022;74:1488–96.
12. Sudlow C, Gallacher J, Allen N *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
13. Ahmed NN, Sherman SJ, Vanwyck D. Frailty in Parkinson's disease and its clinical implications. Parkinsonism Relat Disord 2008;14:334–7.
14. Lee R, Kean WF. Obesity and knee osteoarthritis. Inflammopharmacology 2012;20:53–8.
15. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank Study. JAMA Cardiol 2018; 3:693–702.
16. Fan M, Sun D, Zhou T *et al.* Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. Eur Heart J 2020;41:1182–9.
17. Lourida I, Hannon E, Littlejohns TJ *et al.* Association of lifestyle and genetic risk with incidence of dementia. JAMA 2019; 322:430–7.
18. Casalone E, Tachmazidou I, Zengini E *et al.*; arcOGEN Consortium. A novel variant in GLIS3 is associated with osteoarthritis. Ann Rheum Dis 2018;77:620–3.
19. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 2019;10:1776.
20. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open 2015;5:e007568.
21. Jiang L, Rong J, Wang Y *et al.* The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2011;78:150–5.
22. Yusuf E, Nelissen RG, Ioan-Facsinay A *et al.* Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761–5.
23. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A. Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2019;48:765–77.
24. Xu C, Marchand NE, Driban JB *et al.* Dietary Patterns and Progression of Knee Osteoarthritis: data from the Osteoarthritis Initiative. Am J Clin Nutr 2020;111:667–76.
25. Zhu Z, Aitken D, Cicuttini F, Jones G, Ding C. Ambulatory activity interacts with common risk factors for osteoarthritis to modify increases in MRI-detected osteophytes. Osteoarthritis Cartilage 2019;27:650–8.
26. Master H, Thoma LM, Dunlop DD *et al.* Joint association of moderate-to-vigorous intensity physical activity and sedentary behavior with incident functional limitation: data from the osteoarthritis initiative. J Rheumatol 2021;48:1458–64.
27. Park HM, Kwon YJ, Kim HS, Lee YJ. Relationship between sleep duration and osteoarthritis in middle-aged and older women: a nationwide population-based study. J Clin Med 2019;8:3.
28. Ni J, Zhou W, Cen H *et al.* Evidence for causal effects of sleep disturbances on risk for osteoarthritis: a univariable and multivariable Mendelian randomization study. Osteoarthritis Cartilage 2022;30:443–50.
29. Chang AH, Lee JJ, Chmiel JS *et al.* Association of long-term strenuous physical activity and extensive sitting with incident radiographic knee osteoarthritis. JAMA Netw Open 2020;3:e204049.
30. Zhu J, Chen W, Hu Y *et al.* Physical activity patterns, genetic susceptibility, and risk of hip/knee osteoarthritis: a prospective cohort study based on the UK Biobank. Osteoarthritis Cartilage 2022;30:1079–90.
31. Walrabenstein W, Wagenaar CA, van de Put M *et al.* A multidisciplinary lifestyle program for metabolic syndrome-associated osteoarthritis: the "Plants for Joints" randomized controlled trial. Osteoarthritis Cartilage 2023;31:1491–500.

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