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Sleep patterns, physical activity, genetic susceptibility, and incident rheumatoid arthritis: a prospective cohort study

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Abstract

Background Sleep and physical activity (PA) are thought to be interconnected with the development of rheumatoid arthritis (RA). However, the precise nature and extent of these relationships have yet to be fully quantified. This study aimed to quantify the longitudinal effects of sleep behaviors, PA, and genetic susceptibility on the incidence of RA and to estimate the combined effects and interactions among these exposures.

Methods A total of 363,211 adults were derived from a large European cohort. We incorporated five sleep behaviors (sleep duration, insomnia, snoring, chronotype, and daytime sleepiness) to generate sleep patterns, which were defined based on healthy sleep scores. Multivariate-adjusted Cox proportional hazard models were conducted to assess the individual and combined associations of sleep patterns, PA, and genetic susceptibility with the risk of RA occurrence. Multiplicative and additive interactions were estimated by $P_{interaction}$ and relative excess risk due to interaction (RERI) between each of the two exposures.

Results During a follow-up of 12.5 years, 4262 RA cases were ascertained. A healthy sleep pattern was associated with a decreased risk of RA in a dose-response manner, with an adjusted hazard ratio (HR) of 0.79 (95% confidence interval [CI] = 0.75–0.84), independent of traditional risk factors and genetic predisposition. Under the restricted cubic splines model, a non-linear association was detected for PA and RA risk. Participants in the intermediate quintile 3 showed the lowest risk for developing RA, with a HR 95% CI of 0.84 (0.76–0.92). Moreover, there was an additive interaction effect of intermediate sleep pattern and PA, with a 0.45 (95% CI = 0.02–0.87) RERI of developing RA. Additionally, individuals at high genetic risk had the greatest 10-year absolute risk reduction (10.58 per 1000 person-years) when adopting both favorable behaviors.

Conclusions A healthy sleep pattern and moderate PA were associated with a reduced risk of developing RA, which can offset the deleterious effects of predisposing genetic components. Implementing these modifiable lifestyle factors into public health practices is beneficial for RA prevention.

Keywords Physical activity, Sleep patterns, Cohort study

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Background

Rheumatoid arthritis (RA), a common inflammatory disorder, affects approximately 0.5% to 1.0% general population [1]. Individuals with RA suffer from painful joint damage and limitations in activity and require lifelong pharmacotherapy. The high prevalence and disability of RA have been fueled by global population aging and increasing obesity rates, posing a heavy burden on economic and social development. RA is a complex, heterogeneous disease influenced by both genetic and environmental determinants. Recent evidence highlights the substantial role of modifiable environmental factors such as cigarette smoking, overweight, and vitamin D deficiency in the occurrence of RA [2–4]. Identifying modifiable risk factors and ascertaining the reciprocal relations between them is crucial for reducing the burden of RA.

Sleep disturbances and physical inactivity are two prominent unhealthy lifestyle behaviors intricately linked with inflammatory properties. Sleep and circadian rhythm disturbances can disrupt immune tolerance and enhance inflammatory activities [5–7]. Physical activity (PA) exerts anti-inflammatory properties through releasing various cytokines [8, 9]. However, the association between sleep-related traits, PA, and the onset of RA remains uncertain [10–12]. It is unclear whether PA modulates the association of sleep patterns with RA. Moreover, little is known about whether the genetic susceptibility influences the association between the two lifestyle behaviors and RA incidence.

In current work, using a large-scale population-based cohort, we comprehensively assessed the independent and combined associations of sleep patterns, PA, and genetic risk with incident RA. We also evaluated the benefits of adhering to these two healthy behaviors across different genetic risk categories.

Methods

Study population

The detailed study designs, survey methods, and population characteristics of the UK Biobank have been described previously [13]. Briefly, the UK Biobank is a national, prospective cohort study that enrolled over 500,000 participants aged 38–73 years from 2006 to 2010, across 22 assessment centers in the UK. Participants provided extensive data on sociodemographics, lifestyle, dietary habits, and health status by completing touchscreen questionnaires, oral interviews, and a series of anthropometric and physiological measures during the assessment visit. Blood samples collected were genotyped. The study received approval from the North West Research Ethics Committee (06/MRE08/65), and all participants provided written informed consent.

In this study, we excluded participants who had a diagnosis of RA ($n=3266$) and those with missing values for five sleep behaviors ($n=89{,}431$), PA ($n=29{,}674$), genetic risk score (GRS) ($n=9178$), and other covariate information ($n=7651$) at baseline, leaving a total of 363,211 participants for the primary analysis. The flowchart describing the exclusion criteria was presented in Additional file 1: Fig. S1.

Assessment of sleep behaviors

Information on sleep characteristics was collected via the touchscreen questionnaire at baseline visit between 2006 and 2010. Questions regarding five sleep characteristics were derived from standardized questionnaires [14]. Sleep duration was recorded by asking, "About how many hours sleep do you get in every 24 h? (please include naps)." Chronotype was assessed by asking, "do you consider yourself to be?," with responses options of "definitely a 'morning' type," "a 'morning' more than 'evening' type," "an 'evening' more than 'morning' type," or "definitely an 'evening' type." Insomnia symptoms were assessed based on the question: "do you have trouble falling asleep at night or do you wake up in the middle of the night?," with responses of "never/rarely," "sometimes," or "usually." Snoring information was recorded based on the question, "does your partner or a close relative or friend complain about your snoring?," with responses of "yes" or "no." To assess subjective daytime sleepiness symptoms, participants were asked: "how likely are you to doze off or fall asleep during the daytime when you don't mean to?" with responses of "never" or "rarely," "sometimes," "often," or "always."

Definition of healthy sleep score and sleep pattern

A healthy sleep score (range 0–5) was constructed based on five identified sleep components: sleep duration, chronotype, insomnia, snoring, and excessive daytime sleepiness. Healthy sleep behavior is defined as sleep 7–8 h per day, early chronotype ("morning" or "morning than evening"), reported never or rarely insomnia symptoms, no snoring, and no frequent daytime sleepiness ("never/rarely" or "sometimes"). For each sleep characteristic, a participant was scored 1 if she or he exhibited low-risk sleep behavior, and 0 otherwise. The sum of all five individual sleep behaviors was regarded as the healthy sleep score. A higher score indicates a healthier sleep pattern. We categorized the healthy sleep score into three categories: healthy sleep pattern (healthy sleep score ≥ 4), intermediate sleep pattern ($2 \leq$ healthy sleep score ≤ 3), and poor sleep pattern (healthy sleep score ≤ 1).

In the sensitivity analysis, we further generated a weighted sleep score based on the five sleep behaviors using the following equation: weighted sleep

score = (β1 × sleep behavior 1 + β2 × sleep behavior 2 + … + β5 × sleep behavior 5) × (5/sum of the β coefficients). The weighted score takes into account the relative risk of each sleep behavior and calculates a weighted average of the five sleep behaviors, resulting in a weighted sleep score ranging from 0 to 5.

Assessment of physical activity

PA information was collected using the well-validated long International Physical Activity Questionnaire (IPAQ), which includes the frequency and duration of three levels of activities: walking, moderate-intensity, and vigorous activity. Participants were asked how many days per week they engaged in each category of activity and the number of minutes they spent each day on these activities. The answer "unable to walk" was coded as 0, and both "unwilling to answer" and "don't know" were set as missing. IPAQ has demonstrated excellent reliability and acceptable validity [15], and its robust validity among older adults in UK has also been verified [16]. Metabolic equivalents (METs) quantify self-reported physical activity, where each MET represents the energy expended sitting quietly for 1 h. The MET value reflects the ratio of energy expended per kilogram of body weight per hour to the energy expended while sitting quietly. The number of MET minutes per day was calculated as follows: the number of minutes per day involved in each activity level was multiplied by the MET score for the corresponding activity level. Weekly MET minutes were then obtained based on the number of MET minutes per day. The METs for walking, moderate, and vigorous activity levels were summed as total METs. According to the IPAQ guidelines, the MET for walking is 3.3, the MET for moderate PA is 4.0, and the MET for vigorous PA is 8.0, and 0 for PA less than 10 min per day in each category [17]. Participants were divided into three groups based on the standard scoring criteria of IPAQ: low (< 600 MET-mins/week), moderate (≥ 600 and < 3000 MET-mins/week), and high (≥ 3000 MET-mins/week) [18, 19]. PA groups can also be grouped according to quintiles of total METs.

Assessment of genetic risks of RA

Detailed information about genotyping process and quality control in the UK Biobank study has been described elsewhere [20]. We obtained the released standard GRS for RA from UK Biobank [21]. GRS algorithms were built from trait-specific meta-analyses using a Bayesian approach, which combined data across multiple ancestries and related traits when appropriate. Unlike general GRS, which were built based on reported top SNPs, per-individual GRS value was calculated as the genome-wide sum of the per-variant posterior effect size multiplied by allele dosage. In this study, GRS was classified as low (lowest quintile), intermediate (2–4 quintiles), and high (highest quintile) genetic risk.

Ascertainment of outcomes

In the UK Biobank, data on incident RA were identified through linkage with NHS hospital inpatient data from hospital event statistics in England, the Scottish Morbidity Records, and the Patient Episode Database for Wales. Diagnostic results were defined using the ICD-10 (International Classification of Diseases, 10th Revision) coding system. Participants with primary or secondary RA coded M05 and M06 were defined as endpoint events. The follow-up time was from recruitment until the data of first diagnosis, loss to follow-up, death or censoring data, whichever occurred first.

Statistical analyses

A multivariate-adjusted Cox proportional hazard model was used to compute hazard ratio (HR) and 95% confidence intervals (CIs) for the associations of sleep patterns and PA with incident RA risk. Models were adjusted for sex (male, female), age at recruitment (continuous, years), ethnicity (White, and other), the Townsend Deprivation Index (continuous), smoking status (current, past, never), alcohol consumption (current, past, never), body mass index (BMI, < 18.5, 18.5–25, 25–30, ≥ 30, kg/m^2), waist hip ratio (WHR, low: < 0.91 for males and < 0.79 for females; medium: 0.91–0.96 for males and 0.79–0.85 for females; high: ≥ 0.96 for males and ≥ 0.85 for females), PA (MET-min/week), history of diabetes (yes, no), history of cancer (yes, no), history of bone fracture (yes, no), vitamin D supplementation (yes, no) and genetic risk score. The proportional hazards assumption model was tested using the Schoenfeld residuals method and no violation was detected. Restricted cubic spline (RCS) regression model was used to analyze the nonlinear relationship between PA and the occurrence of RA. Further stratified analyses were performed to assess the association of sleep patterns with RA incidence across different PA levels or GRS groups as well as the association of PA levels with RA incidence across different sleep patterns or GRS groups. In addition, we evaluated the combined effects of sleep patterns, PA, and GRS on the risk of new-onset RA.

To investigate the potential impact of the relationship between sleep patterns, PA, and GRS on RA, we used multiplicative and additive interaction to evaluate the interaction between each of the two exposures in the Cox proportional hazard models. In terms of multiplicative interaction, we derived the HR 95% CI and $P_{interaction}$ by using a likelihood ratio test to compare Cox models with and without a product term (exposure 1 × exposure 2), while the additive interaction can be calculated by relative excess risk due to interaction (RERI) and attributable

proportion due to interaction (AP). The 95% CI for both the RERI and the AP was calculated by drawing 5000 bootstrap from the estimation dataset [22, 23]. If the 95% CI of RERI and AP contains 0, there is no additive interaction.

In order to test the reliability and robustness of the primary associations, we performed a series of sensitivity analyses: (1) participants who were diagnosed with RA within the first 1, 2, and 3 years of follow-up were excluded respectively; (2) participants with shift work; (3) participants who were non-White; (4) the missing values of covariates were filled by multiple inference through chained equations (the R package of "mice" had less than 3% missing values for all covariates) [24]; (5) in the analysis of the relationship between PA and RA, air pollution data (NO_2, NO_X, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$) related to PA were additionally adjusted; (6) re-calculating the relationship between weighted sleep score and risk of RA. We also conducted a stratified subgroup analysis to evaluate the modification effect of covariates on the association of sleep pattern with RA risk.

All statistical analyses were performed using R software (version 4.2.2). A two-sided test $p < 0.05$ was defined as statistically significant.

Results

Baseline characteristics

Of the 363,211 eligible participants, 4.20%, 57.80%, and 38.00% were categorized into the poor, intermediate, and healthy sleep pattern, respectively. Except for GRS, all baseline characteristics differed significantly across sleep pattern categories. Detailed baseline characteristics of all participants were provided in Additional file 1: Table S1.

Independent association of sleep behaviors, PA with incident RA

During a median follow-up of 12.5 years (interquartile range [IQR]: 11.7–13.2 years; 4,367,592 total person-years), 4262 cases of incident RA were documented. Table 1 displays the associations of sleep behaviors and PA with incident RA. A healthy sleep pattern was associated with a decreased risk of RA in a dose–response manner, with a HR of 0.72 (95% CI = 0.68–0.76) in model 1 ($P_{trend} < 0.001$). After fully adjustment in model 2, although the estimate was slightly attenuated, an inverse association of the healthy sleep pattern with RA risk was observed (HR = 0.79, 95% CI = 0.75–0.84). Compared with individuals in the poor sleep pattern, those with a favorable sleep pattern had a decreased risk for RA after fully adjustment (HR = 0.76, 95% CI = 0.67–0.86 for intermediate group; HR = 0.61, 95% CI = 0.53–0.69 for the healthy group, respectively). A similar pattern of association was found with the healthy sleep score and incident RA (Fig. 1A). The fully adjusted HR of participants with a sleep score of 5 compared to those with a sleep score of 0–1 (Fig. 1B) was 0.55 (95% CI = 0.46–0.66).

For each binary sleep component, adequate sleep duration, no frequent insomnia, and no frequent daytime sleepiness were each independently associated with a 23%, 25%, and 24% lower risk of developing RA, respectively. Under the restricted cubic splines model, a non-linear association was detected between PA and RA risk ($P_{non\text{-}linear} < 0.001$) (Additional file 1: Fig. S2). Participants with moderate PA levels had a lower risk of RA incidence after full adjustment than those with low PA levels (HR = 0.85, 95% CI = 0.79–0.92). When PA was categorized into five categories, participants in the intermediate (quintile 3) group showed the lowest risk for developing RA (HR = 0.84, 95% CI = 0.76–0.92) (Fig. 1C, D).

In stratified analysis of PA and GRS, a healthy sleep pattern was significantly associated with reduced RA risk compared to a poor sleep pattern (Fig. 2A, B, Additional file 1: Table S2-S3). Compared with participants with low PA, those with moderate PA were significantly associated with a lower RA risk in both poor and intermediate sleep patterns (Fig. 2C, Additional file 1: Table S4). Furthermore, the inverse association between moderate PA and RA risk was only observed in the intermediate GRS group, compared to those with low PA (Fig. 2D, Additional file 1: Table S5).

Joint effect and interaction of sleep patterns, PA and genetic risk with incident RA

Participants were classified into six groups based on combinations of sleep patterns and PA. Individuals with a healthy sleep pattern and moderate PA had the lowest risk of incident RA, with an adjusted HR of 0.49 (95% CI = 0.41–0.59), compared to those with a poor sleep pattern and low/high PA (Additional file 1: Table S6). For the group with an intermediate sleep pattern and low/high PA, the RERI was 0.45 (95% CI = 0.02–0.87), which suggested that 45% relative excess risk might be attributed to additive interaction, accounting for 22% (1%–39%) of the risk (Additional file 1: Table S7). Furthermore, the combined effects of each exposure and GRS were shown in Additional file 1: Table S8-S9. Additionally, there were no statistically additive and/or multiplicative interactions between sleep pattern/PA and genetic susceptibility to RA, indicating that the associations of sleep pattern/PA and genetic factor with RA risk were independent of each other (Additional file 1: Table S10).

Benefits of adherence to healthy sleep pattern and moderate PA with RA prevention

The benefits in reducing relative risk of RA development from healthy behaviors stratified by genetic risk were

Table 1 Associations of sleep patterns and physical activity with incident RA

Exposure	No. of incident cases/total participants	Model 1		Model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sleep patterns					
Poor (0–1)	274/15285	1.00		1.00	
Intermediate (2–3)	2688/209849	0.67 (0.59–0.75)	< 0.001	0.76 (0.67–0.86)	< 0.001
Healthy (4–5)	1300/138077	0.49 (0.43–0.56)	< 0.001	0.61 (0.53–0.69)	< 0.001
P trend	4262/363211	0.72 (0.68–0.76)	< 0.001	0.79 (0.75–0.84)	< 0.001
Individual sleep component					
Sleep 7–8 h/day	2579/249986	0.71 (0.67–0.75)	< 0.001	0.77 (0.72–0.82)	< 0.001
Morning chronotype	2706/229409	0.93 (0.88–0.99)	0.030	0.99 (0.93–1.05)	0.653
Never/rarely insomnia	716/90300	0.72 (0.67–0.78)	< 0.001	0.75 (0.69–0.81)	< 0.001
No snoring	2653/229028	0.88 (0.82–0.93)	< 0.001	0.96 (0.90–1.02)	0.201
No frequent daytime sleepiness	4098/353894	0.67 (0.57–0.78)	< 0.001	0.76 (0.65–0.89)	< 0.001
Physical activity (MET–min/week)					
Low (MET: ≤ 600)	934/69036	1.00		1.00	
Moderate (MET: 600–3000)	1998/185597	0.78 (0.72–0.84)	< 0.001	0.85 (0.79–0.92)	< 0.001
High (MET: > 3000)	1330/108578	0.88 (0.81–0.96)	0.003	0.98 (0.90–1.06)	0.597
Physical activity (MET-min/week)					
Quartile 1	973/72783	1.00		1.00	
Quartile 2	822/72511	0.83 (0.76–0.91)	< 0.001	0.89 (0.81–0.98)	0.014
Quartile 3	756/72681	0.76 (0.69–0.84)	< 0.001	0.84 (0.76–0.92)	< 0.001
Quartile 4	787/72624	0.79 (0.72–0.86)	< 0.001	0.88 (0.80–0.97)	0.010
Quartile 5	924/72612	0.93 (0.85–1.02)	0.111	1.02 (0.94–1.12)	0.607
Genetic risk score					
Low	568/72866	1.00		1.00	
Moderate	2408/218252	1.42 (1.29–1.55)	< 0.001	1.42 (1.30–1.56)	< 0.001
High	1286/72093	2.30 (2.08–2.53)	< 0.001	2.30 (2.09–2.54)	< 0.001
P trend	4262/363211	1.54 (1.47–1.62)	< 0.001	1.54 (1.47–1.62)	< 0.001

Model 1: adjusted for age at recruitment and sex

Model 2: Model 1 additionally adjusted for ethnicity, Townsend deprivation index, body mass index, waist hip ratio, alcohol consumption, smoking status, physical activity (only in the sleep patterns analysis), sleep patterns (only in the physical activity analysis), history of diabetes, history of cancer, history of bone fracture, vitamin D supplementation and genetic risk score

Abbreviations: *No* number, *RA* rheumatoid arthritis, *HR* hazard ratio, *95% CI*, 95% confidence interval, *MET* metabolic equivalent

shown in Fig. 3. Participants with both favorable behaviors at low GRS level exhibited the lowest standardized 10-year absolute risk. For the group of a healthy sleep pattern and moderate PA, the standardized 10-year absolute reduction across different GRS groups were 9.49 (95% CI = 2.98–14.84), 10.44 (95% CI = 6.91–13.90), and 10.58 (95% CI = 4.05–16.69) per 1000 person-years, compared with group of both unhealthy behaviors, respectively.

Sensitivity analyses and subgroup analyses

The association of sleep patterns and PA with the risk of RA were robust in all sensitivity analyses, when we excluded those possible subclinical RA participants (Additional file 1: Table S11-13), as well as those with shift work (Additional file 1: Table S14) or were non-White decent (Additional file 1: Table S15), filled in missing covariate values (Additional file 1: Table S16), further adjusted for air pollution (NO_2, NO_X, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$) (Additional file 1: Table S17), and replaced the sleep pattern as weighted sleep score (Additional file 1: Table S18). Moreover, stratified analyses revealed a consistent association between a healthier sleep pattern and a lower risk of RA across various subgroups (Additional file 1: Table S19). The protective effect of a healthy sleep pattern against RA risk was more pronounced among those less than 60 years ($P_{interaction} = 0.002$).

Discussion

To our knowledge, this is the first prospective study to evaluate the independent and joint effects of sleep patterns, PA, and genetic risk on the incidence of RA. We discovered that a healthy sleep pattern significantly reduces the risk of RA in a dose-response manner,

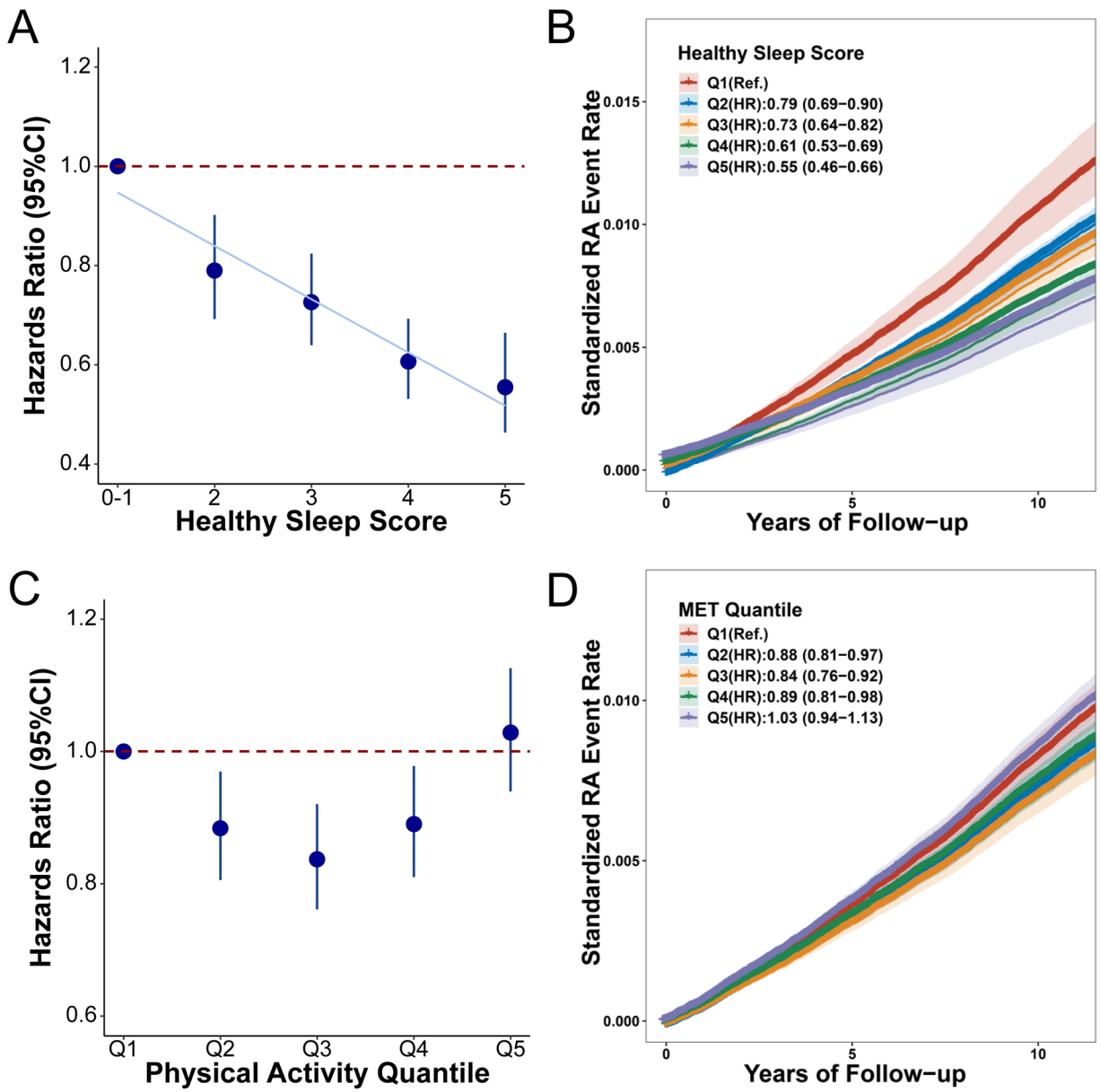


Fig. 1 The associations of healthy sleep score and PA with incident RA in UK Biobank. **A** The association of healthy sleep score with incident RA. **B** Standardized cumulative RA rates in different healthy sleep score groups. **C** The association of PA with incident RA. **D** Standardized cumulative RA rates in different PA groups. Healthy sleep score was divided into five groups: Q1, 0–1; Q2, 2; Q3, 3; Q4, 4; Q5, 5. PA was categorized into quintiles: Q1, quintile1; Q2, quintile1; Q2, quintile2; Q3, quintile3; Q4, quintile4; Q5, quintile5. HRs and 95% CIs were estimated with adjustment for age, sex, ethnicity, Townsend deprivation index, body mass index, waist hip ratio, alcohol consumption, smoking status, history of diabetes, history of cancer, history of bone fracture, vitamin D supplementation and genetic risk score. Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; RA, rheumatoid arthritis; PA, physical activity

independent of traditional risk factors and genetic predisposition. We also observed a non-linear relationship between PA and RA risk, with moderate PA showing a protective effect against RA development. Moreover, we noted a synergistic interaction between sleep patterns and PA in reducing RA risk, although no significant interaction was found between these lifestyle behaviors and genetic risk. In addition, individuals at high genetic risk achieved the greatest 10-year absolute risk reduction when adopting both favorable behaviors. These findings suggest that individuals can mitigate RA risk by maintaining moderate PA and a healthy sleep pattern, especially those genetically predisposed to the disease.

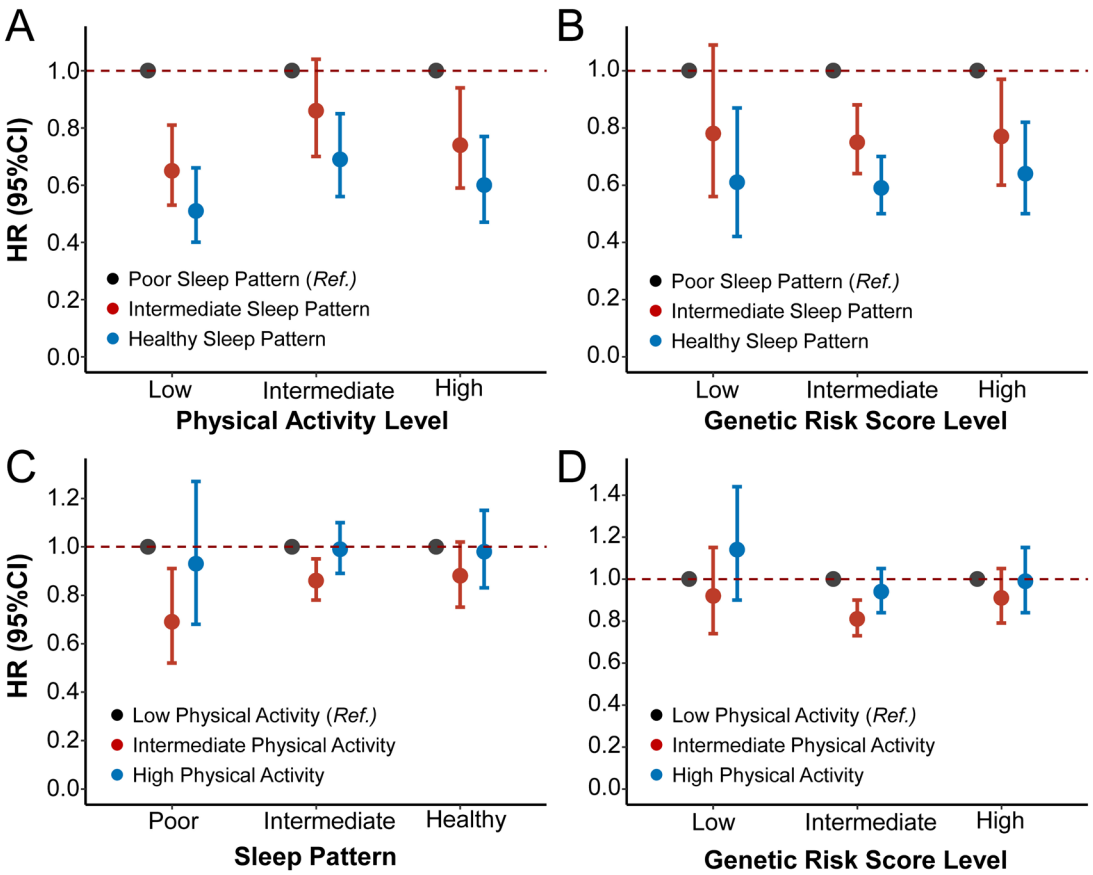
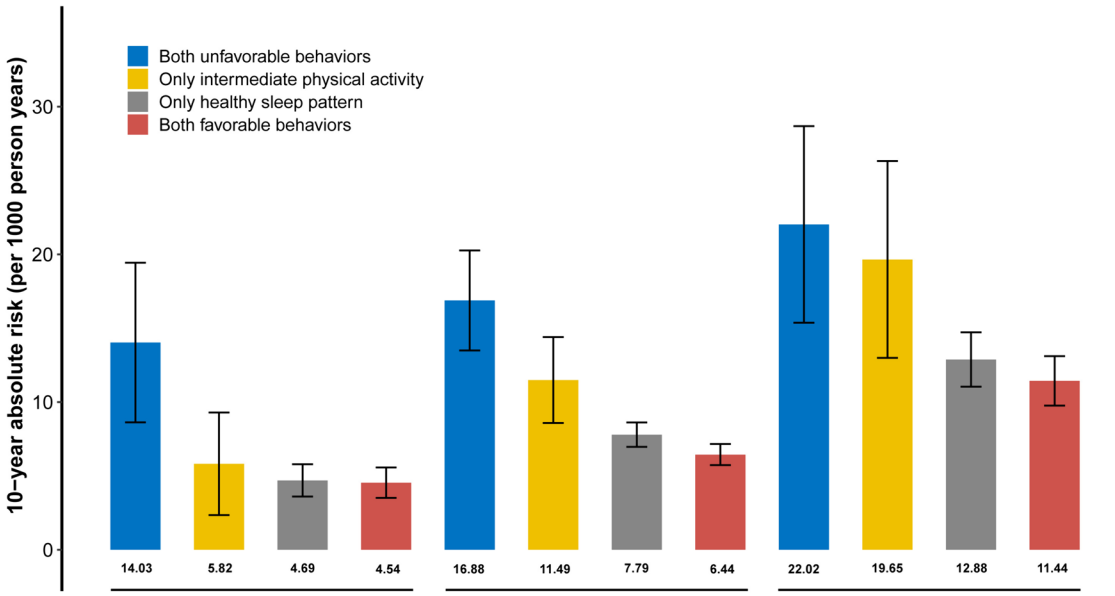


Fig. 2 Risk of incident RA according to sleep patterns, PA and genetic risk category. **A**, **B** Risk of incident RA according to sleep patterns within each PA and genetic risk category. **C**, **D** Risk of incident RA according to PA within each sleep pattern category and genetic risk category. HRs and 95% CIs were estimated with adjustment for age, sex, ethnicity, Townsend deprivation index, body mass index, waist hip ratio, alcohol consumption, smoking status, history of diabetes, history of cancer, history of bone fracture, vitamin D supplementation, sleep pattern, PA and genetic risk score. Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; RA, rheumatoid arthritis; PA, physical activity; Ref, reference

Recent evidence has demonstrated that adherence to a healthy sleep pattern and moderate PA can prevent several diseases, including dementia, cancer, and cardiovascular diseases [25–28]. However, relatively few epidemiological studies have focused on the impact of these modifiable lifestyle behaviors on RA risk. A recent meta-analysis of four observational studies in women indicated that PA was correlated with a decreased risk of RA, although a Mendelian randomization (MR) analysis suggested that genetically predicted PA did not prevent RA [11]. We identified a non-linear relationship between PA and RA, suggesting that promoting moderate PA might be beneficial for RA prevention. This aligns with findings from a previous cohort study which linked ideal PA levels to a reduced incidence of coronary heart disease [8]. We found that adequate sleep duration (7–8 h/day), no frequent insomnia, and no frequent daytime sleepiness were independently associated with a lower risk of developing RA. Apart from their independent effects, different sleep components also had a combined impact on RA risk. Consistent with our findings, a case–control study involving 4176 individuals demonstrated that shift work was associated with a higher risk of RA [10]. Another MR analysis confirmed the adverse causal effect of sleep disturbance on RA risk [12]. Our study built a comprehensive sleep score and categorized it into three sleep patterns, observing a dose–response relationship between sleep patterns and the onset of RA, independent of traditional risk factors and genetic predisposition.

Several potential mechanisms have been proposed to explain the associations of sleep and PA with RA risk. As is known, sleep and immunity are closely linked [29]. Sleep disturbances can indirectly mediate RA pathogenesis by disrupting inflammation homeostasis and triggering the release of pro-inflammation cytokines such as IL-6 and TNF-α [30, 31]. Furthermore, sleep deprivation disturbs the activity of CD4 regulatory T cells (Tregs) rhythm [32]. In experimentally



Person years	18281	17941	161088	177012	57477	52521	484531	527732	19129	16962	159559	170210
No. of case	27	11	80	85	98	61	382	344	43	34	210	199
Adjusted HR (95% CI)	Ref	0.43 (0.21-0.87)	0.44 (0.28-0.69)	0.44 (0.28-0.70)	Ref	0.70 (0.50-0.96)	0.55 (0.44-0.69)	0.47 (0.37-0.59)	Ref	0.92 (0.59-1.44)	0.64 (0.46-0.90)	0.59 (0.42-0.82)
10-year absolute risk Reduction (per 1000 person years)	Ref	8.21 (0.77-14.87)	9.34 (2.78-14.88)	9.49 (2.98-14.84)	Ref	5.39 (0.83-9.89)	9.09 (5.64-12.48)	10.44 (6.91-13.90)	Ref	2.37 (-7.54-12.05)	9.14 (2.16-15.56)	10.58 (4.05-16.69)

Fig. 3 Absolute risk and risk reduction of incident RA according to sleep patterns and PA within each genetic risk category. Genetic risk was categorized into low (lowest quintile), intermediate (2–4 quintiles), and high (highest quintile). The 10-year absolute risks were standardized for age and sex in the UK Biobank. The HRs were estimated using Cox proportional hazards regression with adjustment for age, sex, ethnicity, Townsend deprivation index, body mass index, waist hip ratio, alcohol consumption, smoking status, history of diabetes, history of cancer, history of bone fracture, vitamin D supplementation and genetic risk score. The 10-year absolute risk reduction and 95% CI were generated by drawing 1000 bootstrap samples from the estimation dataset. Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; RA, rheumatoid arthritis; PA, physical activity; Ref, reference

sleep-deprived mice, sleep loss was found to activate Th17 differentiation, pathogenicity, and myeloid cells activation [33]. The imbalance of Treg/Th17 plays an important role in the occurrence of RA [34, 35]. Appropriate PA can inhibit inflammatory responses and stimulate glucose metabolism [36, 37]. Cambré et al. demonstrated that mechanical loading can impact site-specific localization of inflammation and tissue damage in arthritis [38]. Regular exercise therapy reduces the level of chronic inflammation markers and alleviates pain in RA patients [39]. An important finding from our study was the additive interactive joint association of an intermediate sleep pattern and unfavorable PA with RA risk, suggesting that sleep and PA are co-dependent. Based on these results, we speculated that PA might modify the impact of sleep behavior on RA. In agreement with this, Liang et al. reported that both sleep duration and PA had additive and multiplicative interactions on the risk of mortality [40].

Healthy lifestyle behaviors have been inversely related with several unhealthy immune-related diseases [41–43]. Our study further demonstrated that a healthy sleep pattern and moderate PA were associated with a lower risk of RA across different genetic risk categories, with individuals at high genetic risk level obtaining the greatest benefit from simultaneously adopting these two favorable behaviors. Therefore, it is noteworthy that promotions targeting both PA and sleep abnormalities could be an effective strategy against RA, particularly for genetically susceptible individuals.

The current work has some limitations. Firstly, the observational study design inherently limits a definitive causal interpretation of our findings due to the confounding factors and reverse causation. The main results remained robust even after omitting participants with possible subclinical RA, suggesting that reverse causality might not seriously affect the associations observed in the current study. Even though we carefully adjusted

for multiple potential confounders and performed subgroup analysis, the possibility of unobserved and residual confounding cannot be fully eliminated. Further intervention studies should be undertaken to validate our findings. Secondly, since the sleep characteristics and PA were measured through subjective questionnaires, recall bias and potential misclassifications cannot be inevitably avoided. In a UK Biobank subsample with first repeated measurement of both exposures between 2012 and 2013, we found 71.59% (10,576/14,772) and 58.20% (10,347/17,779) of the participants maintained their sleep patterns and physical activity, respectively. The stable levels of sleep and PA in both baseline and follow-up survey have been validated in existing studies [44, 45]. From a public health standpoint, the utilization of self-report data significantly enhances the interpretability and practical applicability of epidemiological findings, making them not only more informative but also more accessible to the general public. Thirdly, given that the UK Biobank did not provide information on rheumatoid factor and/or anticitrullinated peptide during diagnosis, we only assessed the overall RA risk. Finally, the majority of participants were British ancestry, which might limit the generalizability of our results to other ethnic populations.

Conclusions

A healthy sleep pattern and moderate PA were associated with a reduced risk of developing RA, which can offset the deleterious effects of predisposing genetic components. Implementing these modifiable lifestyle factors into public health practices is beneficial for RA prevention.

Abbreviations

AP	Attributable proportion due to interaction
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
IPAQ	International Physical Activity Questionnaire
GRS	Genetic risk score
MET	Metabolic equivalent
MR	Mendelian randomization
PA	Physical activity
RA	Rheumatoid arthritis
RCS	Restricted cubic spline
RERI	Relative excess risk of the interaction
WHR	Waist hip ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03615-5.

Additional file 1. Figure S1. The flowchart of this study. Figure S2. Nonlinear relationships between physical activity and RA risk. Table S1. Baseline characteristics of the participants according to the sleep patterns (N= 363,211). Table S2. Risk of incident RA according to sleep patterns within each physical activity category. Table S3. Risk of incident RA according to sleep patterns within each genetic risk category. Table S4. Risk of incident RA according to physical activity within each sleep patterns category. Table S5. Risk of incident RA according to physical activity within each genetic risk category. Table S6. Joint associations of sleep patterns and physical activity with incident RA. Table S7. Interactions between sleep patterns and physical activity on the risk of incident RA. Table S8. Joint associations of sleep patterns and genetic risk score with incident RA. Table S9. Joint associations of physical activity and genetic risk score with incident RA. Table S10. Interactions between sleep patterns, physical activity and genetic risk score on the risk of incident RA. Table S11. Associations between sleep patterns and physical activity with incident RA after excluding incident cases occurred in the first 1 year of follow-up (N=362,980). Table S12. Associations between sleep patterns and physical activity with incident RA after excluding incident cases occurred in the first 2 years of follow-up (N=362,600). Table S13. Associations between sleep patterns and physical activity with incident RA after excluding incident cases occurred in the first 3 years of follow-up (N=362,361). Table S14. Associations between sleep patterns and physical activity with incident RA after excluding shift work participants (N=328,473). Table S15. Associations between sleep patterns and physical activity with incident RA after excluding non-white participants (N=345,828). Table S16. Associations between sleep patterns and physical activity with incident RA after filling in missing values (N=370,862). Table S17. Associations between physical activity and incident RA after further adjusting for air pollution (N=333,134). Table S18. Association between a weighted healthy sleep score and incident RA. Table S19. Association of sleep patterns with incident RA across different subgroups.

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Authors' contributions

JN and QZ contributed equally to this work and are joint first authors. HP and JN designed the study. SM, TT, and TZ conducted the statistical analysis. HP critically revised of the manuscript for important intellectual content. HP and JN conducted the study supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The data of current study can be requested from the UK Biobank (https://www.ukbiobank.ac.uk/). This work was conducted under UK Biobank application number 80827.

Declarations

Ethics approval and consent to participate

The UK Biobank study received approval from the National Information Governance Board for Health and Social Care and the National Health Service Northwest Multi-Centre Research Ethics Committee (Ref: 11/NW/0382).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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