Highlighting the importance of healthy sleep patterns in the risk of adult asthma under the combined effects of genetic susceptibility: a large-scale prospective cohort study of 455405 participants

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ABSTRACT

Background Individuals with asthma usually have comorbid sleep disturbances; however, whether sleep quality affects asthma risk is still unclear. We aimed to determine whether poor sleep patterns could increase the risk of asthma and whether healthy sleep patterns could mitigate the adverse effect of genetic susceptibility.

Methods A large-scale prospective study was performed in the UK Biobank cohort involving 455405 participants aged 38–73 years. Polygenic risk scores (PRSs) and comprehensive sleep scores, including five sleep traits, were constructed. A multivariable Cox proportional hazards regression model was used to investigate the independent and combined effects of sleep pattern and genetic susceptibility (PRS) on asthma incidence. Subgroup analysis across sex and sensitivity analysis, including a 5-year lag, different covariate adjustments and repeat measurements were performed.

Results A total of 17 836 individuals were diagnosed with asthma during over 10 years of follow-up. Compared with the low-risk group, the HRs and 95% CIs for the highest PRS group and the poor sleep pattern group were 1.47 (95% CI: 1.41 to 1.52) and 1.55 (95% CI: 1.45 to 1.65), respectively. A combination of poor sleep and high genetic susceptibility led to a twofold higher risk compared with the low-risk combination (HR (95% CI): 2.22 (1.97 to 2.49), p<0.001). Further analysis showed that a healthy sleep pattern was associated with a lower risk of asthma in the low, intermediate and high genetic susceptibility groups (HR (95% CI): 0.56 (0.50 to 0.64), 0.59 (0.53 to 0.67) and 0.63 (0.57 to 0.70), respectively). Population-attributable risk analysis indicated that 19% of asthma cases could be prevented when these sleep traits were improved.

Conclusions Individuals with poor sleep patterns and higher genetic susceptibility have an additive higher asthma risk. A healthy sleep pattern reflected a lower risk of asthma in adult populations and could be beneficial to asthma prevention regardless of genetic conditions. Early detection and management of sleep disorders could be beneficial to reduce asthma incidence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individuals with asthma usually have comorbid sleep disturbances, but the relationship between baseline sleep and asthma risk is unclear.
⇒ Several sleep traits, such as insomnia and sleep duration, have been reported to be associated with asthma, but whether a comprehensive sleep pattern plays an important role in asthma risk is largely unknown.
⇒ Asthma is driven by both genetic and non-genetic factors, but the combined effects of healthy sleep patterns and genetic susceptibility on the risk of asthma need to be explored.

WHAT THIS STUDY ADDS

⇒ Unhealthy sleep patterns and sleep traits at baseline were significantly associated with the risk of asthma in adults.
⇒ The combination of poor sleep pattern and high susceptibility could lead to additive asthma risk.
⇒ A healthier sleep pattern could be beneficial in asthma prevention regardless of genetic conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A poor sleep pattern may reflect a higher risk of asthma, which could be a useful biomarker for adults.
⇒ This study highlights the importance of early detection and management of sleep disorders, which could be beneficial in reducing asthma incidence.

INTRODUCTION

Asthma is a chronic respiratory inflammatory disease characterised by variable symptoms and airflow obstruction that affects hundreds of millions of people worldwide and causes a significant global health burden.1–3 This
complex disease may be driven by both genetic and non-genetic factors. Regarding the non-genetic aspect, it is generally recognised that sleep quality is affected by asthma. For example, poor sleep quality and obstructive sleep apnoea were reported more commonly in patients with asthma, especially those with severe asthma. In addition, asthma can also affect sleep duration, sleep quality, napping and daytime sleepiness. However, the association between sleep and asthma may be bidirectional. There could be a possibility that not only can asthma influence sleep quality, but poor sleep itself could also cause or worsen asthma. Regarding the mechanism, previous studies have demonstrated that sleep disorders such as short sleep duration, insomnia, evening chronotype, snoring and excessive daytime sleepiness were all associated with specific inflammatory reactions. Since asthma is also a chronic inflammatory disease, whether poor sleep reflects a higher asthma risk, that is, whether it represents a signal of early progression of asthma, is still unclear. Primary evidence has been revealed from some specific studies. For example, a prospective study showed that insomnia symptoms were associated with an increased risk of incident asthma. A U-shaped association was also observed between sleep duration and asthma in a hospital-based cohort study. In addition, the Mendelian randomisation highlighted that sleep-disordered breathing and poor sleep quality presented a causal association with asthma. Such evidence suggests that sleep may potentially affect the risk of asthma to some extent. A comprehensive evaluation of sleep patterns on asthma risk was required in the current setting. At the genetic level, genome-wide association studies (GWASs) have identified some asthma loci and the investigation of pleiotropy showed large overlaps in genetic variants with autoimmune and inflammatory diseases. Family studies have also demonstrated that genetic factors contribute to asthma risk, with heritability estimates ranging from 25% to 80%. These studies revealed that genetic factors serve as key causes of asthma. Nevertheless, the high variability of heritability estimates reflected the important role of extensive non-genetic exposures in the development of asthma. Further interventions in lifestyle are required to reduce the excess risk. However, whether healthy non-genetic exposure could decrease the risk of asthma and mitigate the adverse effect of genetic risk remains largely unknown. Combined with the potential role of sleep patterns, we hypothesise that healthier sleep could decrease future asthma risk and mitigate the hazards of genetic effects.

Hence, we prospectively investigated the associations between a combination of sleep traits (healthy sleep scores) and the risk of asthma in a large Biobank cohort. We also explored the combined effects of sleep patterns and genetic susceptibility on the risk of asthma. Finally, we investigated whether adherence to a healthy sleep pattern could mitigate the hazards of genetic susceptibility to asthma.

METHODS

Study population

The UK Biobank is a national large prospective cohort including more than 500 000 adults aged 38–73 years at recruitment. Participants were enrolled between 2006 and 2010 from 22 assessment centres in the general population across the UK. The cohort includes extensive phenotypic and genotypic details about its participants, including data from questionnaires, physical measures, biological samples and genome-wide genotyping. In this study, we constrained the participants to unrelated Caucasian British individuals to minimise the influence of diverse population structures as in previous studies. As shown in figure 1A, participants who withdrew from the study (n=68), were lost to follow-up (n=1298), had no genotype data (n=15138), had a self-reported sex that did not match genetic information (n=372), had sex chromosome aneuploidy (n=469), had >10 putative third-degree relatives in the kinship table (n=196), had excessive heterozygosity (top 1%) (n=4844), had missing sleep variables (n=3082) and had missing basic covariates (including age, sex, body mass index, smoking status, drinking status, Townsend Deprivation Index (TDI) and qualification) (n=4839) were excluded. The UK Biobank study has approval from the North West Multi-Center Research Ethics Committee (http://www.ukbiobank.ac.uk/ethics/). More details about this cohort have been introduced elsewhere and are also described on the official website (www.ukbiobank.ac.uk).

Definition of sleep patterns

The sleep traits of UK Biobank participants were self-reported and recorded by the touch screen questionnaire from 2006 to 2010. Five sleep factors, including chronotype, sleep duration, insomnia, snoring and excessive daytime sleepiness, were defined by a specific question for each. The details about the five questions for the corresponding sleep traits are shown in the online supplement text and have also been reported elsewhere. To define healthy sleep behaviour, we used the criteria of Fan et al and Zhou et al for the same five sleep traits. Each sleep trait was dichotomised into a binary variable where a score of ‘1’ represented a healthy sleep behaviour while ‘0’ indicated an unhealthy sleep behaviour. Besides, some systematic reviews showed that the evening chronotype was usually viewed as a potential risk factor while the early chronotype was protective for health-related outcomes (more healthy). Additionally, healthy sleep duration was defined as 7–9 hours/day according to the National Sleep Foundation’s recommendations. Therefore, the five healthy sleep behaviours were defined as (1) early chronotype, (2) 7–9 hours sleep duration per day, (3) never or rare insomnia, (4) no snoring and (5) no frequent daytime sleepiness. Comprehensive sleep scores ranging from 0 to 5 were constructed by summing the five scores, with higher scores representing healthier sleep patterns. Then, we defined the overall sleep patterns as...

'healthy sleep' (sleep score=5, n=73223), 'intermediate sleep' (sleep score=3 or 4, n=284267) and 'poor sleep' (sleep score ≤2, n=97915) according to the distribution. In addition, a total of 45217 participants in this study underwent repeat assessment of sleep traits by imaging visit starting from 2014 ('2014+', https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=1160). We defined sleep patterns according to the same standard for this subset in subsequent analysis.

**Definition of the asthma polygenic risk score**

Genotyping, imputation and quality control were already performed by the UK Biobank. In this research, the single nucleotide polymorphisms (SNPs) that are significantly associated with asthma were ascertained from the latest GWASs of 23948 asthma cases and 118538 controls (p<5×10⁻8, r²<0.001) in non-UK Biobank participants. A total of 18 independent loci reached genome-wide significance in this multiancestry meta-analysis. In the UK Biobank data set, 17 of the 18 SNPs were included in our analyses, and 1 was excluded because it was triallelic (rs11071558). Each SNP was coded as 0, 1 or 2 according to the number of risk alleles. We constructed a weighted polygenic risk score (PRS) for each participant by adding the number of risk alleles and multiplying the corresponding effect size of each SNP with the formula: 

$$PRS = \beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_n \times SNP_n.$$ 

The effect size was obtained from the above GWAS, and details about these SNPs are reported in the initial publication. We divided these individuals into three groups according to tertiles: 'high genetic risk' (tertile 3), 'intermediate genetic risk' (tertile 2) and 'low genetic risk' (tertile 1).

**Definition of asthma outcomes**

Follow-up of the UK Biobank participants for health-related outcomes is conducted through linkages to routinely available national data sets including the hospital admission data and death registry records. The outcome was defined according to the International Classification of Diseases edition 10 (ICD-10) code, which was acquired from the above resources. All diagnoses and the diagnosis dates were pooled together, including the main cause of death, secondary cause of death, ICD-10 diagnosis, main ICD-10 diagnosis and secondary ICD-10 diagnosis columns in the UK Biobank data set. Participants with the ICD-10 code ‘J45’ were defined as asthma cases, and the outcome date was defined as the first time of asthma record. Complete follow-up was available from 13 March 2006 to 31 March 2017. Follow-up time was calculated from the baseline date to the date of asthma diagnosis, death or censoring (31 March 2017), whichever occurred first. Asthma cases diagnosed in the first year after being recruited (n=16816) were also excluded to avoid potential reverse association due to delayed diagnosis and register (figure 1A). A total of 455405 participants were used in our analysis.
Definition of covariates

The covariates used in this study were selected from some conventional covariates or potential confounders that may affect both sleep and asthma as shown in the directed acyclic graph (figure 1B). The basic covariates included age, sex, obesity, smoking status, alcohol consumption, TDI, education level, genetic ethnicity, assessment centre and top five genetic principal components for population stratification. These covariates were conventionally used in some previous studies with the UK Biobank data set in the analysis of sleep and health-related outcomes. The TDI is an area-based proxy measure for socioeconomic status provided by the UK Biobank, which has been introduced in a previous study and on the UK Biobank website (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=189). Since both sleep and asthma are related to the respiratory system and air pollution has been reported to be associated with sleep and asthma, air pollution variables (nitrogen oxide, nitrogen dioxide, particulate matter ≤ 2.5 μm (PM$_{2.5}$), PM$_{2.5-10}$ and PM$_{10}$) were also included in the covariates as potential confounders. In addition, we also included some chronic diseases, such as hypertension, diabetes, depression and gastro-oesophageal reflux, as potential confounders, which have also been reported to be associated with both sleep and asthma in previous research.

Statistical analysis

The baseline characteristics between asthma and no asthma individuals were compared by t-tests (continuous variables) and χ$^2$ tests (categorical variables). The cumulative incidence curve was drawn according to the PRS and sleep pattern subgroups and compared by the log-rank test. A Cox proportional hazards model was used to assess the HR and 95% CI of exposures in asthma risk. The proportional hazards assumptions were evaluated by an uncrossed cumulative incidence curve and Schoenfeld residuals. The multivariable Cox model was built to assess the effect of sleep patterns through the full model adjusted for all defined covariates (figure 1B). The independent effects of sleep and PRS were assessed in the same multivariable model to adjust for each other. The joint effect of sleep plus PRS was evaluated by combining two variables into a comprehensive variable as reported by Fan et al. As shown in figure 1C, the PRS was divided into three groups. Then, in each PRS group, the sleep pattern was also divided into three groups according to the above standard. Therefore, a nine-group comprehensive variable was formed, and lowest PRS plus a healthy sleep pattern was viewed as the reference group. In addition, the association between sleep patterns and asthma under different genetic risks was assessed in three PRS groups (figure 1D). The interactions between sleep and PRS were tested by adding an interaction term in the multivariable model. The linear trend test was performed by treating the corresponding exposures as a continuous variable. To estimate the reduction in the proportion of asthma if all participants had a low-risk trait, we calculated the population attributable risk per cent (PAR%) assuming a causal relationship between a specific risk factor and asthma to evaluate the potential benefits of improving this factor.

In the sensitivity analysis, we only used the basic covariates to show whether the results suffered from overadjustment. Another sensitivity analysis was performed by a 5-year lag analysis (excluding individuals with less than 5 years of follow-up) to avoid reverse causality and to test whether the discovered relationships changed over time. We also performed a sensitivity analysis in participants with repeated measurements of sleep behaviours (the second round measurements) to avoid changes during the follow-up period and exposure misclassification. Finally, we performed a subgroup analysis by sex to examine potential sex differences and tested the significant difference by adding an interaction term of sex×sleep in the full model of the main analysis.

All analyses were performed using the R software (V.3.6.3). The statistical tests were two-sided and the statistical significance threshold was p<0.05.

Patient and public involvement

Patients and/or the public did not take part in the development, conduct, reporting or dissemination of this study.

RESULTS

The baseline characteristics are shown in table 1. Of 455405 participants, 17836 were diagnosed with asthma during a median follow-up period of 8.10 years. The mean age of all participants was 56.5±8.07 years. Compared with non-cases, asthma cases were more likely to have lower education levels, unhealthy sleep traits and patterns, obesity, higher PRS, more smoking, more alcohol consumption, hypertension, diabetes, depression, gastro-oesophageal reflux and more air pollution exposure. The cumulative incidence curve shows that the curves of genetic risk and sleep pattern groups displayed the expected risk gradients and were significantly different (log-rank test p<0.001) (figure 2A).

Figure 2B shows the independent risk of PRS and sleep patterns. Compared with the low-risk group, the highest PRS and poor sleep pattern groups presented a 1.47 and 1.55-fold risk for asthma, respectively. The HRs and 95% CIs were 1.47 (1.41 to 1.52) and 1.55 (1.45 to 1.65), respectively. These associations remained significant in the trend test (p<0.001) when considered as a continuous variable. The effects of PRS and sleep patterns exhibited a dose-response relationship with asthma risk. The sleep pattern had no evident interactions with PRS (p for interaction=0.07). These results were replicated in the sensitivity analysis (online supplemental figures S1–S3). From the subgroup analysis, the effect of the sleep pattern was slightly larger in females (HR=1.38 in men, HR=1.50 in...
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Overall</th>
<th>No asthma</th>
<th>Asthma</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>455405</td>
<td>437569</td>
<td>17836</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.54 (8.07)</td>
<td>56.50 (8.07)</td>
<td>57.41 (7.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>246076 (54.03)</td>
<td>235508 (53.82)</td>
<td>10568 (59.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genetic ethnic, Caucasian ancestry (%)</td>
<td>385706 (84.70)</td>
<td>370634 (84.70)</td>
<td>15072 (84.50)</td>
<td>0.474</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>32605 (7.16)</td>
<td>31030 (7.09)</td>
<td>1575 (8.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8856 (1.94)</td>
<td>8381 (1.92)</td>
<td>475 (2.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>3642 (0.80)</td>
<td>3421 (0.78)</td>
<td>221 (1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux (%)</td>
<td>10663 (2.34)</td>
<td>10035 (2.29)</td>
<td>628 (3.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Townsend Deprivation Index</td>
<td>-1.37 (3.05)</td>
<td>-1.38 (3.05)</td>
<td>-1.12 (3.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education level (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>College or higher</td>
<td>149167 (33.07)</td>
<td>144141 (33.25)</td>
<td>5026 (28.56)</td>
<td></td>
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<tr>
<td>Lower than college</td>
<td>226147 (50.14)</td>
<td>217366 (50.15)</td>
<td>8781 (49.90)</td>
<td></td>
</tr>
<tr>
<td>None of the above</td>
<td>75746 (16.79)</td>
<td>71955 (16.60)</td>
<td>3791 (21.54)</td>
<td></td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never</td>
<td>249839 (54.86)</td>
<td>240538 (54.97)</td>
<td>9301 (52.15)</td>
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<tr>
<td>Previous</td>
<td>158036 (34.70)</td>
<td>151339 (34.59)</td>
<td>6697 (37.55)</td>
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<tr>
<td>Current</td>
<td>47530 (10.44)</td>
<td>45692 (10.44)</td>
<td>1838 (10.31)</td>
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<tr>
<td>Alcohol consumption (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Daily or almost daily</td>
<td>94141 (20.67)</td>
<td>90717 (20.73)</td>
<td>3424 (19.20)</td>
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<td>Three or four times a week</td>
<td>106785 (23.45)</td>
<td>103003 (23.54)</td>
<td>3782 (21.20)</td>
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<td>One or two times a week</td>
<td>118294 (25.98)</td>
<td>113935 (26.04)</td>
<td>4359 (24.44)</td>
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<td>One to three times a month</td>
<td>50583 (11.11)</td>
<td>48488 (11.08)</td>
<td>2095 (11.75)</td>
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<tr>
<td>Special occasions only</td>
<td>51022 (11.20)</td>
<td>48598 (11.11)</td>
<td>2424 (13.59)</td>
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<tr>
<td>Never</td>
<td>34580 (7.59)</td>
<td>32828 (7.50)</td>
<td>1752 (9.82)</td>
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<td>Body mass index groups (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<td>Normal</td>
<td>152429 (33.47)</td>
<td>147707 (33.76)</td>
<td>4722 (26.47)</td>
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<td>Overweight</td>
<td>194583 (42.73)</td>
<td>187294 (42.80)</td>
<td>7289 (40.87)</td>
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<tr>
<td>Obesity</td>
<td>108393 (23.80)</td>
<td>102568 (23.44)</td>
<td>5825 (32.66)</td>
<td></td>
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<tr>
<td>Air pollution</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NO</td>
<td>43.86 (15.42)</td>
<td>43.84 (15.41)</td>
<td>44.36 (15.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NO₂</td>
<td>26.56 (7.55)</td>
<td>26.55 (7.55)</td>
<td>26.69 (7.59)</td>
<td>0.02</td>
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<tr>
<td>PM₂.₅</td>
<td>9.98 (1.06)</td>
<td>9.97 (1.05)</td>
<td>10.03 (1.07)</td>
<td>&lt;0.001</td>
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<tr>
<td>PM₂.₅−₁₀</td>
<td>6.42 (0.90)</td>
<td>6.42 (0.90)</td>
<td>6.43 (0.91)</td>
<td>0.375</td>
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<td>PM₁₀</td>
<td>16.21 (1.90)</td>
<td>16.21 (1.90)</td>
<td>16.24 (1.88)</td>
<td>0.033</td>
</tr>
<tr>
<td>Sleep traits</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sleep 7–9 hours/day (%)</td>
<td>334944 (73.55)</td>
<td>322806 (73.77)</td>
<td>12138 (68.05)</td>
<td>&lt;0.001</td>
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<td>Early chronotype (%)</td>
<td>255160 (56.03)</td>
<td>245252 (56.05)</td>
<td>9908 (55.55)</td>
<td>0.191</td>
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<tr>
<td>Never/rarely insomnia (%)</td>
<td>328835 (72.21)</td>
<td>317283 (72.51)</td>
<td>11552 (64.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No self-reported snoring (%)</td>
<td>266478 (58.51)</td>
<td>256582 (58.64)</td>
<td>9896 (55.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No frequent daytime sleepiness (%)</td>
<td>347711 (76.35)</td>
<td>334818 (76.52)</td>
<td>12893 (72.29)</td>
<td>&lt;0.001</td>
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<tr>
<td>Sleep pattern (%)</td>
<td></td>
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<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Healthy sleep</td>
<td>73223 (16.08)</td>
<td>70950 (16.21)</td>
<td>2273 (12.74)</td>
<td></td>
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<tr>
<td>Intermediate sleep</td>
<td>284267 (62.42)</td>
<td>273679 (62.55)</td>
<td>10588 (59.36)</td>
<td></td>
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<tr>
<td>Poor sleep</td>
<td>97915 (21.50)</td>
<td>92940 (21.24)</td>
<td>4975 (27.89)</td>
<td></td>
</tr>
<tr>
<td>Polygenic scores (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>153006 (33.60)</td>
<td>148023 (33.83)</td>
<td>4983 (27.94)</td>
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Table 1  Continued

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Overall</th>
<th>No asthma</th>
<th>Asthma</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Intermediate</td>
<td>151970 (33.37)</td>
<td>146222 (33.42)</td>
<td>5748 (32.23)</td>
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<tr>
<td>High</td>
<td>150429 (33.03)</td>
<td>143324 (32.75)</td>
<td>7105 (39.84)</td>
<td></td>
</tr>
</tbody>
</table>

The continuous variables were described with the mean (SD) and compared by t-test. The categorical variables were described with n (%) and compared by the χ² test.

NO, nitrogen oxide; NO₂, nitrogen dioxide; PM, particulate matter.

Figure 2  The cumulative incidence curve and multivariable-adjusted HRs (95% CIs) for asthma risk by polygenic risk score (PRS) and sleep patterns. (A) The cumulative incidence curve was drawn by PRS and sleep pattern groups. The unit of follow-up time was months, and the start point was defined as the 12th month (1 year after recruitment). (B) The multivariable models were adjusted with each other for PRS and sleep patterns and additionally adjusted for age, sex, smoking status, alcohol consumption, Townsend Deprivation Index, education, genetic ethnicity, assessment centre, top five genetic principal components, nitrogen oxide, nitrogen dioxide, PM₁₀, PM₁₀−₂.₅, PM₂.₅−₁₀, PM₁₀−₂.₅, hypertension, diabetes, depression and gastro-oesophageal reflux. PM, particulate matter.
women, p for interaction=0.01) (online supplemental figure S4 and S5).

When considering the genetic risk and sleep patterns together (figure 3), individuals with both poor sleep and high genetic risk had a 122% increased risk compared with those with healthy sleep and low genetic risk (HR: 2.22, 95% CI: 1.97 to 2.49, p<0.001). Healthy sleep patterns in the high genetic risk group presented a slightly lower risk than poor sleep patterns in the low genetic risk group (HR=1.64 vs HR=1.68), suggesting that a healthy sleep pattern could offset high genetic risk. Sensitivity analysis and subgroup analysis also showed similar associations (online supplemental figures S6–S10).

Figure 4 shows the relationship between sleep patterns and asthma in different genetic risk groups. A healthy sleep pattern decreased the risk of asthma by 44% (HR: 0.56, 95% CI: 0.50 to 0.64), 41% (HR: 0.59, 95% CI: 0.53 to 0.67) and 37% (HR: 0.63, 95% CI: 0.57 to 0.70) in the low, intermediate and high genetic risk groups, respectively. These results showed that a healthy sleep pattern could significantly decrease asthma risk in any genetic subgroup. In the sensitivity analysis, the relationships were largely similar to the above results after 5-year lag analysis, basic covariate adjustment and repeated measurements (online supplemental figures S11–S13). We also found consistent results in men and women (online supplemental figures S14 and S15).

The effects of each healthy factor after collapsing into binary categories of low risk versus high risk (reference group) are shown in figure 5. Individuals with low genetic risk had a 25% lower risk than other participants (HR: 0.76, 95% CI: 0.74 to 0.79, p<0.001). Except for genetic risk, all five sleep factors (sleep 7–9 hours/day, early chronotype, never/rare insomnia, no self-reported snoring and no frequent daytime sleepiness) were independently associated with 20%, 8%, 25%, 9% and 15% lower risks for asthma, respectively. In addition, an individual with all healthy sleep factors (sleep score=5 vs others) would have a 22% lower risk than other individuals (HR: 0.78, 95% CI: 0.74 to 0.83, p<0.001). PAR% indicated that low genetic risk and combined healthy sleep patterns would theoretically reduce 17.26% and 19.03% of asthma cases in the population, respectively. These results were largely similar in sensitivity analyses (online supplemental figures S16–S20).

**DISCUSSION**

In this study, our evidence shows that both sleep and genetic factors play an important role in asthma risk. A combination of poor sleep with high genetic susceptibility would lead to a more than twofold risk compared with a low-risk combination. Further analysis showed that a healthy sleep pattern could reduce the risk of asthma in individuals with high genetic susceptibility by 37%, suggesting that a healthy sleep pattern would benefit the control of asthma incidence regardless of genetic conditions. Finally, it has been estimated that 19% of asthma cases in the population could be prevented when the five sleep traits (chronotype, sleep duration, insomnia,
snoring and excessive daytime sleepiness) were improved under a causal assumption.

In previous research, sleep was recognised to be affected by asthma. However, the relationship between sleep and asthma may be bidirectional. There is a possibility that not only can asthma affect sleep quality, but poor sleep quality could also affect asthma risk. A large number of studies have already focused on sleep traits in the risk of asthma. A cross-sectional survey of US adults showed that ≤5 hours or ≥9 hours of sleep per night were significantly associated with reduced lung function and ≤5 hours of sleep per night was reported to be associated with current asthma. A strong association between short or long sleep duration and asthma was also observed in 18–64 years old women. Another study demonstrated that persistent short sleep duration was associated with an increased risk of new-onset asthma in young adults. Apart from sleep duration, the relationships of other sleep traits with asthma were also explored. Mendelian randomisation studies highlighted that genetic liability for insomnia might be causally associated with asthma, but not vice versa. Population-based studies also supported that baseline insomnia could increase asthma risk. In addition, late chronotype and night shift work were also potential risk factors for asthma.

Driven by substantial evidence on sleep and asthma risk, this study synthesised five sleep characteristics into different sleep patterns in a large prospective cohort to further explore the relationship between sleep patterns and asthma. In our research, all of the five sleep traits (chronotype, sleep duration, insomnia, snoring and excessive daytime sleepiness) were strongly associated with asthma. A poor sleep pattern independently increased asthma risk by 55%, similar to the risk of genetic susceptibility. These associations remained significant when a 5-year lag analysis and repeated measurement analysis were used, suggesting that they were less likely to be prone to reverse association and would not alter over time. Combined with previous research showing that sleep quality could be affected by asthma, the relationship between sleep and asthma may be bidirectional.

Mechanistically, several possible pathways could explain the role of sleep in the development of asthma. First, the negative impact of sleep disorders on asthma, which is generally considered a chronic inflammatory disease, might be mediated by sleep-induced chronic inflammation. In addition, chronotype, snoring and sleepiness were all shown to be associated with specific inflammatory reactions. In theory, the immune response to inflammation could generate proinflammatory cytokines that result in cellular infiltration and airway inflammation, further increasing the risk of asthma. Studies have found activation of mononuclear cell nuclear factor (NF)-κB, higher...
levels of high-sensitivity C-reactive protein (hs-CRP) and increased nocturnal interleukin-6 excretion in individuals with insomnia or sleep loss.\textsuperscript{53-55} Activated NF-κB can act on asthma through inflammatory protein regulation, and increased hs-CRP is also related to airflow obstruction and airway inflammation.\textsuperscript{56-58} Furthermore, sleep disorders are also accompanied by chronic activation of the stress response, increased activity in the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, disordered microbiome-based brain-gut axis and triggered aberrations of RNA modifications, which all play key roles in the development of asthma.\textsuperscript{7,8,59} Overall, the role of all five sleep traits in the risk of asthma could be partly explained by the mechanism of inflammatory response. As a result, a healthier sleep pattern derived from the five specific sleep traits that presented a lower asthma risk may reflect a lower inflammation level.

Our research also showed the potential benefits of a healthy sleep pattern. Although low genetic susceptibility could also theoretically decrease the incidence similarly, it is unmodifiable. As a modifiable risk factor, a healthy sleep pattern could decrease the excess risk for individuals with high genetic susceptibility. Considering that poor sleep combined with high genetic susceptibility yielded a greater than two-fold asthma risk, sleep patterns could be recommended as an effective lifestyle intervention to prevent future asthma, especially for individuals with high-risk genetics. On the other hand, we found a small difference in the effect of sleep on adult asthma between men and women, which suggested that targeted interventions could be created across genders. Adjustment using only basic covariates showed that the benefit of a healthy sleep pattern would not disappear, which indicates the robustness of this finding under different confounders. The analysis with repeated measurements for a subset of participants also strengthened our evidence by minimising the influence of the change during the follow-up period and exposure misclassification.

Our study has several advantages. We constructed a comprehensive sleep score and defined the different

<table>
<thead>
<tr>
<th>Healthy factors</th>
<th>HR(95%CI)</th>
<th>P Value</th>
<th>% of participants at risk</th>
<th>PAR%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic trait</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low genetic risk</td>
<td>0.76(0.74 to 0.79)</td>
<td>&lt;0.001</td>
<td>66.40</td>
<td>17.26</td>
</tr>
<tr>
<td><strong>Sleep traits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep 7–9 h/day</td>
<td>0.80(0.76 to 0.83)</td>
<td>&lt;0.001</td>
<td>26.45</td>
<td>6.35</td>
</tr>
<tr>
<td>Early chronotype</td>
<td>0.92(0.89 to 0.96)</td>
<td>&lt;0.001</td>
<td>43.97</td>
<td>3.45</td>
</tr>
<tr>
<td>Never/rarely insomnia</td>
<td>0.75(0.72 to 0.79)</td>
<td>&lt;0.001</td>
<td>27.79</td>
<td>8.30</td>
</tr>
<tr>
<td>No self-reported snoring</td>
<td>0.91(0.87 to 0.95)</td>
<td>&lt;0.001</td>
<td>41.49</td>
<td>3.88</td>
</tr>
<tr>
<td>No frequent daytime sleepiness</td>
<td>0.85(0.81 to 0.89)</td>
<td>&lt;0.001</td>
<td>23.65</td>
<td>3.96</td>
</tr>
<tr>
<td><strong>All healthy sleep factors</strong></td>
<td>0.78(0.74 to 0.83)</td>
<td>&lt;0.001</td>
<td>83.92</td>
<td>19.03</td>
</tr>
</tbody>
</table>

Figure 5  Multivariable-adjusted HRs (95% CIs) and PAR% for asthma risk by low-risk factors. Low-risk factors: for the genetic trait, the low genetic risk was compared with intermediate and high genetic risk according to polygenic score groups; for sleep traits, each low-risk trait was defined according to a sleep score of 1 as described in the methods section; all healthy sleep patterns was a sleep score=5 compared with others. The multivariable models were adjusted for age, sex, smoking status, alcohol consumption, Townsend Deprivation Index, education, genetic ethnicity, assessment centre, top five genetic principal components, nitrogen oxide, nitrogen dioxide, PM\textsubscript{2.5}, PM\textsubscript{2.5–10}, PM\textsubscript{10}, hypertension, diabetes, depression and gastro-oesophageal reflux. PAR, population attributable risk; PM, particulate matter.
sleep patterns as exposure to asthma for the first time in a large 10-year follow-up cohort. Importantly, we also assessed the impact of sleep quality in terms of genetic predisposition on incident asthma risk. Furthermore, sensitivity and subgroup analyses enhanced the robustness and practicality of our evidence. The use of repeated measurements of sleep behaviours as a sensitivity analysis also strengthened our evidence compared with similar research. Some limitations should also be noted. First, the UK Biobank only provided information on adults aged 38–73; therefore, the effect on children and younger adults is still unclear. Second, the repeated records for sleep were only available for a small subset of participants, and the effects of dynamic sleep patterns can only be assessed after collecting larger samples. Third, the relationship between sleep and asthma cannot be interpreted as causality since residual confounders were unclear. The residual confounders may include but are not limited to chronic diseases, early exposures in childhood and unknown factors that could not be fully assessed in the current data set. Adjustment for baseline hypertension, diabetes, depression, gastro-oesophageal reflux, etc., and the robust results from the sensitivity analysis may mitigate the influence of confounding to some extent. More potential confounders should be considered in future studies. Fourth, the self-reported sleep traits may lead to bias due to measurement error; however, such a situation usually causes results to be skewed towards 0 rather than significant associations. Fifth, our results are limited to individuals of European ancestry, and generalisation to other populations should be done with caution. In addition, the UK Biobank is not representative of the sampling population, which may suffer a ‘healthy volunteer’ selection bias. Nonetheless, previous researchers have explained that valid assessment of exposure-disease relationships may be widely generalisable and does not require participants to be representative of the population at large.50

Conclusions

This large prospective study indicates that individuals with poor sleep patterns and higher genetic susceptibility have an additive higher asthma risk. A healthy sleep pattern was beneficial in asthma prevention regardless of the genetic conditions. Early detection and management of sleep disorders could be beneficial to reduce asthma incidence.

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Contributors
BX and FX have the conception. FX acquired the data set. BX did the statistical analyses and drafted the initial manuscript. QW and FX obtained the funding. BX guides the work in the revision. All authors participated in the interpretation of the results, edited and reviewed the manuscript. QW is responsible for the overall content as guarantor.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
The ethics approval for the use of UK Biobank individual data has been acquired by the UK Biobank team and consent to participate. UK Biobank received approval from the UK Biobank Research Ethics Committee (REC reference 11/NW/0382).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available in a public, open access repository. Data are available in a public, open access repository (https://www.ukbiobank.ac.uk/). Our research used the UK Biobank resource with application ID: 51470. Researchers only have access to the UK Biobank dataset by submitting application to the UK Biobank official website.

Supplemental material
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