Association of genetic risk and lifestyle with incident adult-onset asthma in the UK Biobank cohort

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In this large contemporary population, lifestyle and genetic factors jointly play critical roles in the development of asthma, and poor lifestyle had a greater effect than genetic risk https://bit.ly/3PD7Qhq

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Abstract

Background Both genetic and lifestyle factors contribute to the development of asthma, but whether unfavourable lifestyle is associated with similar increases in risk of developing asthma among individuals with varying genetic risk levels remains unknown.

Methods A healthy lifestyle score was constructed using body mass index, smoking status, physical activities and dietary pattern to further categorise into ideal, intermediate and poor groups. Genetic risk of asthma was also categorised as three groups based on the tertiles of polygenic risk score established using 212 reported and verified single-nucleotide polymorphisms of European ancestry in the UK Biobank study. We examined the risk of incident asthma related with each lifestyle level in each genetic risk group by Cox regression models.

Results Finally, 327 124 participants without baseline asthma were included, and 157 320 (48.1%) were male. During follow-up, 6238 participants (1.9%) developed asthma. Compared to ideal lifestyle in a low genetic risk group, poor lifestyle was associated with a hazard ratio of up to 3.87 (95% CI, 2.98–5.02) for developing asthma in a high genetic risk group. There was interaction between genetic risk and lifestyle, and the population-attributable fraction of lifestyle and genetic risk were 30.2% and 30.0% respectively.

Conclusion In this large contemporary population, lifestyle and genetic factors jointly play critical roles in the development of asthma, and the effect values of lifestyle on incident adult-onset asthma were greater than that of genetic risk. Our findings highlighted the necessity of a comprehensive intervention for the prevention of asthma despite the genetic risk.

Introduction

Asthma, as a chronic airway inflammatory disorder linked to complicated gene–environment interactions, affects >300 million people globally, thus resulting in an immense economic and social burden [1, 2]. Asthma has been demonstrated to have a certain genetic element varying from 35% to 95% heritability [3]. A growing number of genetic variants related to the genetic risk of asthma have been widely identified through genome-wide association studies (GWASs) [4]. In the last 3 years, the number of independent asthma-relevant genetic loci has risen to 128 according to numerous well-established genetic studies [5].

Genetic variations identified so far, however, can only account for a small proportion of asthma incidence, due to the diverse environments of individuals [6]. Several changeable lifestyle risk factors, including smoking status, obesity, physical exercise and dietary patterns, have been linked to the prevalence and incidence of asthma. Body mass index (BMI) has been determined to be an independent risk factor for asthma [7]. In addition, quitting smoking [8] has been demonstrated to reduce the risk of respiratory symptoms of asthma and improve life quality. Similarly, dietary habits and physical exercise have also been linked to incidence and disease control of asthma [9, 10].

In brief, in addition to gene–environment interactions, lifestyle behaviours could also affect the development of asthma. Prior to this study, most scholars concentrated mainly on investigating the influence of a sole lifestyle rather than evaluating the associations between multiple lifestyle behaviours and asthma incidence. Primary aims of the study were to explore whether healthy modifiable lifestyle was linked to similar increased risk of incident adult-onset asthma among participants in low, intermediate or high genetic risk groups in a large cohort, and to explore interactions between lifestyle and heritable factors.

Methods

Study design and population

The UK Biobank study is a large-scale biomedical database and population-based prospective cohort approved by the Northwest Multicenter Research Ethics Committee (Application Number 84979) [11]. Briefly, in 2006–2010, UK Biobank recruited over half a million participants ranging in age from 37 to 73 years from 22 assessment centres across the UK. Data on medical and lifestyle history at baseline has been provided through face-to-face interviews, baseline self-management questionnaires and physical health assessments. In the current study, participants were included in the analysis if they had a white ethnic background (including Irish, British and other white background) and had available genetic and lifestyle data, and had matched sex between genetic and reported sex.

Asthma ascertainment

Diagnosis of adult-onset asthma was mainly confirmed by International Classification Disease codes (J45) with all sources of asthma including self-reported, hospital admission data, primary care and death register. Patients with diagnosed asthma at baseline were excluded from the study. Participants were followed up from the time of recruitment until the time of censor, asthma diagnosis, death or October 2020, whichever came first.

Lifestyle factors

Four well-recognised asthma risk factors [7–10] including smoking status, BMI, dietary patterns and physical activity were defined on the basis of national recommendations [12, 13]. BMI was calculated using weight and height at baseline. Poor BMI was classified as $\geqslant 30\ kg{\cdot}m^{-2}$, intermediate as a BMI of 25–29.9 $kg{\cdot}m^{-2}$ and ideal as 18.5–24.9 $kg{\cdot}m^{-2}$. If individuals had never smoked or quitted 12 months before the study, smoking was determined as ideal; if they had ceased within the past 12 months, it was determined as intermediate; or if they currently smoked, it was defined as poor [14]. According to the task-specific metabolic equivalent of task measurements, ideal physical activity was classified as $\geqslant 150\ min{\cdot}week^{-1}$ moderate, $\geqslant 75\ min{\cdot}week^{-1}$ vigorous or $150\ min{\cdot}week^{-1}$ mixed (moderate+vigorous) activities. If individuals had moderate activities 1–149 $min{\cdot}week^{-1}$ or vigorous activities 1–74 $min{\cdot}week^{-1}$ or mixed activities 1–149 $min{\cdot}week^{-1}$, physical activity was determined as intermediate. Physical exercise was categorised as poor if participants did not perform any physical activity (moderate or vigorous) [15]. Healthy diet behaviours were confirmed according to the American Heart Association Guidelines [16]: total weekly fruit intake $\geqslant 3$ servings, total weekly vegetable intake $\geqslant 3$ servings, total weekly fish intake $\geqslant 2$ servings, and weekly red and processed meat intake $\leqslant 1$ serving. Poor diet behaviours were defined as having no healthy diet behaviours, intermediate as 1–2 healthy diet behaviours or ideal as having $\geqslant 3$ healthy diet behaviours [17]. Three categories of healthy lifestyle were then established: ideal was defined as having more than two ideal lifestyle factors, poor as having three or more poor lifestyle factors, or intermediate as all the other combinations.

Polygenic risk score

To investigate whether the relationship between asthma risk and overall healthy lifestyle behaviours varied by heritable risk, a genetic risk score was calculated derived from 212 previously reported risk genetic variations (supplementary e-Table 1) ascertained in previous GWASs of individuals of European ancestry and verified in self-reported doctor-diagnosed asthma from the UK Biobank study [18]. Therefore, the current study was confined to participants of white descent. Quality control of genome-wide genotyping processes and genotyping arrays were performed by the Wellcome Centre for Human Genetics and have

been described elsewhere [19]. The polygenic risk score (PRS) was computed as the aggregate of alleles (0, 1 or 2) of respective risk variants after multiplication with the effect size (β) between the single-nucleotide polymorphism (SNP) and asthma, *i.e.*, PRS $= \left(\sum_{i=1}^{212} \beta_i SNP_i\right) * 212 / \sum_{i=1}^{212} \beta_i$, whose detailed derivation have been described elsewhere [20, 21]. Impact sizes of the correlations between SNP and disease were derived from the outcomes of previous GWASs [18]. The PRS was classified into three genetic hazard categories: low (tertile 1), intermediate (tertile 2) and high (tertile 3) risk [22].

Statistical analysis

All data in the present research was evaluated using SPSS 26.0 software (IBM SPSS, Armonk, NY, USA) or R software version 4.0.2. The relationship of lifestyle and heritable risk groups with incident adult-onset asthma was assessed using multivariable Cox regression models. An interaction term was introduced into the regression models to examine the statistical interaction between lifestyle and genetic factors. Population-attributable fraction (PAF) was computed to assess the fraction of incident asthma cases that would have been prevented if there had not been non-low genetic risk or non-ideal life behaviour groups among all participants [23]. Sensitivity analyses were carried out to assess the impact of different non-crucial covariates (including education, alcohol status and Townsend deprivation index) and mismatched between self-reported and genetic sex on the outcomes. Covariates to be adjusted included sex, age, education, region, alcohol status and Townsend deprivation index (with data about employment, car ownership, social class and housing) in all included models. Models for genetic-related analysis included additional adjustment for number of alleles incorporated in PRS, relatedness and top 20 major constituents of ancestry. Bilateral p-values <0.05 were considered statistically significant.

Results

Baseline characteristics of included participants

A total of 502 505 individuals were enrolled at baseline, and after exclusion of participants with missing genetic data (n=15 224), mismatch between genetic and reported sex (n=367), non-white British descent (n=103 192), missing information on lifestyle factors (n=88 906) and prevalent asthma (n=42 831), 327 124 participants were included for final analyses (supplementary e-Figure 1), 6238 (1.91%) of whom developed adult-onset asthma during the median follow-up of 12 years. For lifestyle pattern in participants with incident asthma 22.4% were ideal, 74.9% intermediate and 2.7% poor, compared to 29.4%, 69.1% and 1.6% in participants without asthma. Baseline characteristics of individuals without asthma are compared with those of individuals with incident adult-onset asthma in table 1; supplementary e-Table 2 reveals the characteristics of per stratified outcome. In general, participants with poor lifestyle and high heritable risk had lower levels of mean total household income and education degree and higher BMI.

Association of lifestyle factor with incident asthma

To explore whether unfavourable lifestyle was correlated with increased risk of developing asthma, lifestyle behaviours and asthma risk were examined (table 2). The results suggested that the risk of incident asthma increased monotonically across worsening lifestyle behaviours. In particular, among the four well-established lifestyle factors, BMI was the most powerful hazard factor affecting asthma incidence (HR=1.93, 95% CI 1.81–2.07), followed by smoking (HR=1.32, 95% CI 1.22–1.43), physical activity (HR=1.31, 95% CI 1.23–1.40) and diet (HR=1.25, 95% CI 1.14–1.38). Collectively, individuals with a poor lifestyle were linked to a significantly higher risk of asthma compared to those with an ideal lifestyle (HR=2.33, 95% CI 1.99–2.74).

Association of genetic risk with incident asthma

It is well known that asthma is influenced by genetic susceptibility, and genetic risk of asthma was classified as low to high based on the established PRS. The results consistently demonstrated that participants with intermediate (HR=1.24, 95% CI 1.16–1.34) and high genetic risk (HR=1.59, 95% CI 1.50–1.73) were more likely to develop asthma than those with low genetic risk during follow-up (table 3).

Association and interaction of lifestyle and genetic risk with incident asthma

The study aimed to further investigate correlation of combined lifestyle within heritable risk groups with incident asthma and to explore interaction between lifestyle and heritable factors. Compared to ideal lifestyle in the low heritable risk group, poor lifestyle was connected to a risk ratio of up to 3.87 (95% CI 2.98–5.02) for developing asthma in the high genetic risk group (figure 1). The combined impact of lifestyle and heritable risk was similar to the overall effect while stratified by sex and age (supplementary e-Table 3 and e-Table 4, e-Figure 2 and e-Figure 3). Additionally, we found that asthma risk did not increase monotonically across lifestyle and genetic risk categories, and combined high genetic susceptibility and unfavourable lifestyle exaggerated the detrimental effect, being more than the sum of both factors. Therefore, we speculated that the interaction between genetic susceptibility and lifestyle had

TABLE 1 Baseline characteristics of participants included with incident adult-onset asthma

Variables	Total	Incident asthma	No asthma	p-value
Participants n	327 124	6238	320 886	
Age years, mean±SD	56.60±8.03	57.75±7.90	56.58±8.03	<0.001
Age category years, n (%)				<0.001
<50	75 084 (23.0)	1189 (19.1)	73 895 (23.0)	
50–59	109 138 (33.4)	1892 (30.3)	107 246 (33.4)	
⩾60	142 902 (43.7)	3157 (50.6)	139 745 (43.5)	
Sex, n (%)				<0.001
Female	169 804 (51.9)	3523 (56.5)	166 281 (51.8)	
Male	157 320 (48.1)	2715 (43.5)	154 605 (48.2)	
Alcohol status, n (%)				<0.001
Never	9543 (2.9)	201 (3.2)	9342 (2.9)	
Previous	10 439 (3.2)	305 (4.9)	10 134 (3.2)	
Current	306 982 (93.8)	5728 (91.8)	301 254 (93.9)	
Unknown	160 (0.0)	4 (0.1)	156 (0.0)	
Mean total household income before tax (EUR), n (%)				<0.001
<18 000	59 375 (18.2)	1569 (25.2)	57 806 (18.0)	
18 000 to 30 999	72 976 (22.3)	1461 (23.4)	71 515 (22.3)	
31 000 to 51 999	78 106 (23.9)	1271 (20.4)	76 835 (23.9)	
52 000 to 100 000	63 323 (19.4)	862 (13.8)	62 461 (19.5)	
>100 000	17 316 (5.3)	215 (3.4)	17 101 (5.3)	
Unknown	36 028 (11.0)	860 (13.8)	35 168 (11.0)	
Education, n (%)				<0.001
College or university degree	112 606 (34.4)	1702 (27.3)	110 904 (34.6)	
Professional qualifications	37 937 (11.6)	761 (12.2)	37 176 (11.6)	
A Levels/AS levels or equivalent	38 542 (11.8)	619 (9.9)	37 923 (11.8)	
O Levels/GCSEs or equivalent	87 599 (26.8)	1717 (27.5)	85 882 (26.8)	
None of the above	50 440 (15.4)	1439 (23.1)	49 001 (15.3)	
BMI kg·m^{-2}, mean±SD	27.19±4.59	28.51±5.20	27.16±4.58	<0.001
BMI category, n (%)				<0.001
Ideal	112 288 (34.3)	1616 (25.9)	110 672 (34.5)	
Intermediate	141 139 (43.1)	2574 (41.3)	138 565 (43.2)	
Poor	73 697 (22.5)	2048 (32.8)	71 649 (22.3)	
Smoking, n (%)				<0.001
Ideal	176 857 (54.1)	3033 (48.6)	173 824 (54.2)	
Intermediate	116 741 (35.7)	2437 (39.1)	114 304 (35.6)	
Poor	33 526 (10.2)	768 (12.3)	32 758 (10.2)	
Physical activity, n (%)				<0.001
Ideal	263 807 (80.6)	4797 (76.9)	259 010 (80.7)	
Intermediate	19 314 (5.9)	373 (6.0)	18 941 (5.9)	
Poor	44 003 (13.5)	1068 (17.1)	42 935 (13.4)	
Diet, n (%)				0.017
Ideal	89 129 (27.2)	1612 (25.8)	87 517 (27.3)	
Intermediate	210 896 (64.5)	4071 (65.3)	206 825 (64.5)	
Poor	27 099 (8.3)	555 (8.9)	26 544 (8.3)	
Healthy lifestyle, n (%)				<0.001
Ideal (⩾3 ideal factors)	95 586 (29.2)	1396 (22.4)	94 190 (29.4)	
Intermediate (all other combinations)	226 357 (69.2)	4671 (74.9)	221 686 (69.1)	
Poor (⩾3 poor factors)	5181 (1.6)	171 (2.7)	5010 (1.6)	

BMI: body mass index.

an effect on asthma incidence (supplementary e-Tables 5–7). When categorised by heritable risk, the hazard of poor lifestyle factors was slightly lower in the high heritable risk population (HR=1.98, 95% CI 1.54–2.55) compared to low heritable risk population (HR=3.59, 95% CI 2.69–4.79) (supplementary e-Table 6). Likewise, the possibility of developing asthma was also lower in the poor lifestyle group (HR=1.08, 95% CI 0.76–1.54) compared to the ideal lifestyle group (HR=1.92, 95% CI 1.68–2.20) among participants with high genetic risk (supplementary e-Table 7). Therefore, the interaction between lifestyle and heritable susceptibility was further analysed, and indicated that individuals with poor lifestyle and high

TABLE 2 Lifestyle factors and the risk of incident adult-onset asthma

Variables	HR (95% CI) from model[#]	p-value	HR (95% CI) from model[¶]	p-value
BMI				
Ideal	Ref.		Ref.	
Intermediate	1.30 (1.22–1.39)	<0.001	1.30 (1.22–1.38)	<0.001
Poor	1.98 (1.86–2.12)	<0.001	1.93 (1.81–2.07)	<0.001
p_{trend}	<0.001		<0.001	
Smoking				
Ideal	Ref.		Ref.	
Intermediate	1.20 (1.13–1.26)	<0.001	1.18 (1.12–1.25)	<0.001
Poor	1.41 (1.30–1.52)	<0.001	1.32 (1.22–1.43)	<0.001
p_{trend}	<0.001		<0.001	
Physical activity				
Ideal	Ref.		Ref.	
Intermediate	1.09 (0.98–1.21)	0.112	1.09 (0.98–1.21)	0.101
Poor	1.34 (1.26–1.43)	<0.001	1.31 (1.23–1.40)	<0.001
p_{trend}	<0.001		<0.001	
Diet				
Ideal	Ref.		Ref.	
Intermediate	1.13 (1.07–1.20)	<0.001	1.13 (1.07–1.20)	<0.001
Poor	1.28 (1.16–1.42)	<0.001	1.25 (1.14–1.38)	<0.001
p_{trend}	<0.001		<0.001	
Healthy lifestyle				
Ideal	Ref.		Ref.	
Intermediate	1.48 (1.39–1.57)	<0.001	1.45 (1.37–1.54)	<0.001
Poor	2.53 (2.16–2.97)	<0.001	2.33 (1.99–2.74)	<0.001
p_{trend}	<0.001		<0.001	

HR: hazard ratio; BMI: body mass index. [#]: adjusted by sex and age; [¶]: adjusted by sex and age, and further adjusted by education, Townsend Index, alcohol status and region.

inherited risk had the strongest coeffect on incident asthma (coeffect=2.46) (table 4). This demonstrated that the effect of genetic risk might be overshadowed by a strong association between lifestyle and incident asthma.

PAFs and sensitivity analysis

In order to further investigate the specific degree of effect of lifestyle and heritable factors on asthma, the PAF of genetic hazard and lifestyle behaviours was then evaluated individually. During follow-up, 30.2% (95% CI 25.9–34.2%) of incident asthma cases might have been prevented if all participants had persisted with ideal life behaviours. On the other hand, 30.0% (95% CI 26.0–33.8%) of subsequent incident cases would have been reduced if all participants had low heritable susceptibility (supplementary e-Table 8). The PAFs of four lifestyle behaviours at distinct genetic susceptibility levels were also assessed, and the

TABLE 3 Risk of incident adult-onset asthma according to genetic risk group

Genetic risk	Total[#]	Incident asthma[¶]	No asthma[+]	HR (95% CI) from Model 1[§]	p-value	HR (95% CI) from Model 2[f]	p-value
Low	109 031	1617	107 414	Ref		Ref	
Intermediate	109 030	2021	107 009	1.25 (1.17–1.33)	<0.001	1.24 (1.16–1.34)	<0.001
High	109 063	2600	106 463	1.61 (1.51–1.71)	<0.001	1.59 (1.50–1.73)	<0.001
p_{trend}					<0.001		<0.001

HR: hazard ratio. [#]: n=327 124; [¶]: n=6238; [+]: n=320 886; [§]: adjusted by age, sex, education, Townsend Index, alcohol status and region; [f]: adjusted by age, sex, education, Townsend Index, alcohol status and region, and further adjusted by relatedness, number of alleles included in the polygenic risk score and first 20 principal components of ancestry.

	Total no. of participants	No. of asthma cases/person-years	IR (per 1000 person-years)	HR (95% CI)
Low genetic risk				
Ideal lifestyle	31 850	321/377 616	0.85	Ref.
Intermediate lifestyle	75 556	1240/892 401	1.39	1.67 (1.48–1.89)
Poor lifestyle	1625	56/19 164	2.92	3.53 (2.66–4.69)
Intermediate genetic risk				
Ideal lifestyle	31 952	461/377 720	1.22	1.43 (1.24–1.65)
Intermediate lifestyle	75 340	1514/888 012	1.7	2.05 (1.82–2.31)
Poor lifestyle	1738	46/20 588	2.23	2.72 (1.99–3.70)
High genetic risk				
Ideal lifestyle	31 784	614/374 321	1.64	1.92 (1.67–2.19)
Intermediate lifestyle	75 461	1917/886 487	2.16	2.59 (2.30–2.92)
Poor lifestyle	1818	69/21 373	3.23	3.87 (2.98–5.02)

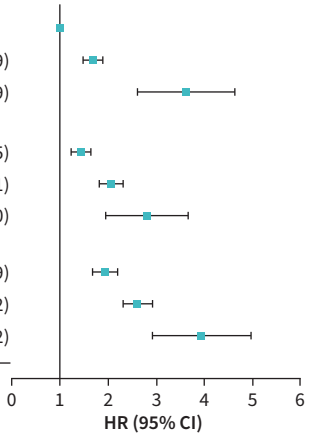

FIGURE 1 Risk of incident adult-onset asthma in different genetic and lifestyle risk groups. Adjusted by age, sex, education, Townsend Index, alcohol status, region, relatedness, number of alleles included in the polygenic risk score and first 20 principal components of ancestry. Hazard ratios (HR) are provided with 95% confidence intervals. The vertical line indicates the reference value of 1. IR: incidence rate.

findings indicated that ideal lifestyle was more protective in the high heritable risk population (supplementary e-Table 9). Sensitivity analysis of non-critical missing variables and mispairing between reported and genetic sex presented a similar effect on asthma cases (supplementary e-Table 10), indicating that the detrimental effect on asthma caused by poor lifestyle was very robust.

Discussion

In this large population-based prospective cohort, we observed that high genetic susceptibility and unfavourable lifestyle were related to a greater risk of incident adult-onset asthma. Additionally, we examined the joint impact of genetic susceptibility and overall lifestyle behaviours and discovered that high heritable susceptibility and poor lifestyle had the greatest detrimental effect in asthma risk. Last but not least, we demonstrated that the effect size of lifestyle factors on risk of adult-onset asthma was greater than that of genetic risk.

The current study indicates that poor lifestyle is critical in developing asthma. The aforementioned studies [7–10] examined the effect of various lifestyle factors on asthma risk. However, genetic risk factors and health behaviours have typically been assessed individually rather than cooperatively to construct asthma risk evaluation and stratification. Our findings not only revealed the cooperative effects of four lifestyle behaviours on asthma risk within >10 years of follow-up, but also validated the varying degree of influence of four major lifestyles on asthma in participants from the same cohort.

Moreover, we identified BMI as the most potent hazard for incidence of asthma, followed by smoking, physical activity and dietary patterns. Various mechanisms have been postulated to explicate why lifestyle

TABLE 4 Interaction effect between genetic risk and healthy lifestyle

	Coeffect[#]	p-value
Intermediate genetic risk × intermediate lifestyle	1.31	<0.001
High genetic risk × intermediate lifestyle	1.65	<0.001
Intermediate genetic risk × poor lifestyle	1.72	<0.001
High genetic risk × poor lifestyle	2.46	<0.001

[#]: adjusted by sex, age, education, Townsend Index, alcohol status, region, relatedness, number of alleles included in the polygenic risk score and first 20 principal components of ancestry.

behaviours are correlated with incident asthma. Obesity was not only linked to asthma incidence through altering immune inflammatory responses in diverse ways [24], but was also associated with a decrease in response to asthmatic medications, especially inhaled corticosteroids [25]. Smoking has been confirmed to be a risk factor for asthma from this large prospective cohort, which was consistent with most other cross-sectional studies [26, 27]. Cigarette smoking could induce goblet cell hyperplasia, impair mucociliary clearance and alter airway inflammatory cell phenotypes [28]. Adherence to weekly moderate physical exercise, as a well-known beneficial factor, could lower an individual's BMI by decreasing fat mass and increasing muscle mass, thereby resulting in a reduction of airway responsiveness, reduced risk of asthma exacerbations and improved pulmonary function [29, 30]. Meanwhile, physical exercise modulated pulmonary allergic inflammation by increasing anti-inflammatory cytokines and decreasing proinflammatory mediators, thus playing a protective role in asthma [31, 32]. Moreover, different dietary patterns have been reported to affect asthma incidence, possibly through production of unique intestinal microbiota [33] or through food ingredients characterised by antioxidant, anti-allergic and anti-inflammatory properties [34]. For example, consumption of a high fat diet and small amounts of fruit and vegetables was associated with worse asthma outcomes, while a high intake of fish, fruit and vegetables decreased asthma risk [35].

It is well known that the development of asthma is closely correlated to genetic susceptibility, and numerous studies have identified some gene loci that are strongly associated with prevalence and incidence of asthma [36]. Commonly reported asthma-associated genetic variants may affect a wide range of different pathways in immune system cascade response [5]. PRS has been increasingly used to measure the genetic risk of specific diseases [37]. We validated that the established PRS is an effective predictor for asthma based on 212 SNPs. The rs2230624 variant on chromosome 1p36.22 had the greatest effect on asthma risk among all 212 genetic risk variants and could cause replacement of a site in TNFRSF8 by detrimental Cys273Tyr. The coding site for CD30 was found on TNFRSF8, and CD30 levels have been reported to be correlated with asthma severity [38]. Tyr273, a missense allele of rs2230624, decreased levels of cellular and soluble CD30 [39], and then CD30 promoted the production of proinflammatory cytokines by $CD4^+$ T-cells in the context of asthma-associated immune responses such as the T-helper cell 2 (Th2) response [40]. The rs4526212 (6q23.3) encoding AHI1 suppressed expression of proinflammatory molecules and participated in JAK-STAT signalling and downstream effects on Th1/2 cells [41, 42]. However, there are still a large number of loci and their functions to be explored, which could help us better understand the true relationship between genetics and asthma.

Whether the influence of lifestyle on incident asthma is related to genetics remains unclear. The favourable correlation of lifestyle factors with asthma was clearly found in all heritable categories, and the joint influence of four lifestyle factors critically reduced asthma risk in each genetic category. We further discovered that the impact of lifestyle on asthma incidence increased progressively with increase in genetic susceptibility. In contrast, the influence of genetic factors decreased gradually when stratified by lifestyle. The asthma risk due to poor lifestyle was high even in the low genetic risk group, while the role of genetic factors was largely overshadowed in participants with poor lifestyle, and this provided strong evidence that the effect of lifestyle was greater than that of heritable factors. Thus, a substantial proportion of subsequent asthma events can be prevented through lifestyle alteration regardless of an individual's genetic risk, which is consistent with prior findings on advantageous impacts of favourable behaviours on asthma [43–45]. In our study, we determined that favourable lifestyle was critical in reducing asthma risk, particularly in participants with high heritable susceptibility.

To the best of our knowledge, no previous study has evaluated the relationship between a combination of lifestyle behaviour and heritable risk factors and asthma risk. We initially reported the significant effects of lifestyle–gene interaction, which revealed that the interactive influence of high genetic risk and poor lifestyle was greater than cumulative effects of the two factors alone, thus synergistically increasing asthma risk. Considering these results, it can be supposed that a healthly lifestyle modifies the impact of genetic susceptibility on asthma. Moreover, the observed interactions are significant due to emphasising the advantages of insisting on a healthy lifestyle for individuals with high genetic risk level in asthma prevention. Therefore, people with high heritable risk should pay more attention to maintaining a healthy lifestyle.

Strengths and limitations

This study firstly assesses the correlations and interaction of joint genetic risk and changeable healthy lifestyle for asthma with adjustment for diverse demographic confounders. The principal advantage of the research was the prospective design based on a large-scale population. It suggested that a combined assessment of asthma risk for participants was important, thus recommending establishing a comprehensive ideal lifestyle for asthma prevention, especially in those with high heritable risk.

However, there are also some limitations of the present study that should not be ignored. First, only participants of European ancestry were recruited, which diminishes the universality of findings compared to other racial populations. In addition, self-reported lifestyle factors were assessed at baseline, while alterations in lifestyle behaviours over time were not fully considered. Moreover, SNPs included in the analysis were partially based on UK Biobank data, which resulted in a lack of statistical independence. Furthermore, the sample in this study was restricted to participants aged 37–73 years with self-reported doctor-diagnosed asthma, which could mean there was study population selection bias, thus restricting the interpretation of the results to childhood and adolescent-onset asthma [46]. Finally, this study did not involve other behavioural and environmental factors that might play a role in developing asthma. Regardless of adjustment for major and potential confounders, residual confounding from unknown or unmeasured factors is inevitable, which could lead to some uneliminated bias such as health bias [47].

Conclusion

The current study demonstrates that lifestyle behaviour and genetic risk play significant roles in developing adult-onset asthma. The ideal lifestyle was related to a lower asthma risk in individuals with distinct heritable susceptibility. There is an interaction effect between healthy lifestyle and genetic susceptibility factors. Our observations emphasise the necessity of a comprehensive intervention for asthma prevention regardless of the genetic susceptibility status.

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Data sharing statement: Individual-level participant data are available from UK Biobank (https://www.ukbiobank.ac.uk/enable-yourresearch/apply-for-access).

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