Polygenic risk and the development and course of asthma: an analysis of data from a four-decade longitudinal study

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Summary

Background Genome-wide association studies (GWAS) have discovered genetic variants that predispose individuals to asthma. To integrate these new discoveries with emerging models of asthma pathobiology, we aimed to test how genetic discoveries relate to developmental and biological characteristics of asthma.

Methods In this prospective longitudinal study, we investigated a multilocus profile of genetic risk derived from published GWAS of asthma case status. We then tested associations between this genetic risk score and developmental and biological characteristics of asthma in participants enrolled in a population-based long-running birth cohort, the Dunedin Multidisciplinary Health and Development Study (n=1037). We used data on asthma onset, asthma persistence, atopy, airway hyper-responsiveness, incompletely reversible airflow obstruction, and asthma-related school and work absenteeism and hospital admissions obtained during nine prospective assessments spanning the ages of 9 to 38 years. Analyses included cohort members of European descent from whom genetic data had been obtained.

Findings Of the 880 cohort members included in our analysis, those at higher genetic risk developed asthma earlier in life than did those with lower genetic risk (hazard ratio [HR] 1·12, 95% CI 1·01–1·26). Of cohort members with childhood-onset asthma, those with higher genetic risk were more likely to develop life-course-persistent asthma than were those with a lower genetic risk (relative risk [RR] 1·36, 95% CI 1·14–1·63). Participants with asthma at higher genetic risk more often had atopy (RR 1·07, 1·01–1·14), airway hyper-responsiveness (RR 1·16, 1·03–1·32), and incompletely reversible airflow obstruction (RR 1·28, 1·04–1·57) than did those with a lower genetic risk. They were also more likely to miss school or work (incident rate ratio 1·38, 1·02–1·86) and be admitted to hospital (HR 1·38, 1·07–1·79) because of asthma. Genotypic information about asthma risk was independent of and additive to information derived from cohort members' family histories of asthma.

Interpretation Our findings confirm that GWAS discoveries for asthma are associated with a childhood-onset phenotype. Genetic risk assessments might be able to predict which childhood-onset asthma cases remit and which become life-course-persistent, who might develop impaired lung function, and the burden of asthma in terms of missed school and work and hospital admissions, although these predictions are not sufficiently sensitive or specific to support immediate clinical translation.

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Introduction

Asthma is a heterogeneous syndrome with several causes.[1] Research is beginning to uncover variations in the molecular roots and clinical manifestations of asthma.[2] One research stream has discovered molecular genetic markers of asthma risk.[3,4] Another research stream has characterised developmental and biological features of asthma that might represent so-called endotypes—ie, subtypes of disease with distinct pathobiology.[5,6] Bringing these two streams of research together could uncover how recently discovered genetic risks relate to developmental and biological characteristics of asthma.

Our research seeks to address the question: when hypothesis-free methods such as genome-wide association studies (GWAS)[7] make discoveries about heterogeneous syndromes such as asthma, what are these discoveries about? To achieve samples of tens of thousands, the largest asthma GWAS reduce this developmentally and biologically complex syndrome to a single outcome—for example, whether or not a physician has diagnosed asthma. Follow-up research is needed to fully understand discoveries from these studies. One approach is to work from the bottom up by tracing the path from variations in DNA sequences to differences in RNA transcription, subsequent protein production, and onwards up through disease pathogenesis to identify a process or molecule that can be targeted for intervention. A complementary approach is to work from the top down by characterising how genetic discoveries relate to individual differences in developmental and biological phenotypes, and then working backwards to devise interventions that can mitigate genetic risk.[8]

We aimed to take the top-down approach to identify developmental and biological signatures of asthma in

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See Comment page 425

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individuals with high genetic risk. Once identified, these signatures can help to guide bottom-up molecular research. We aimed to construct a multilocus profile of genetic predisposition to asthma—a genetic risk score—from a comprehensive case-control GWAS of asthma[9] and then to genotype this score in an unselected cohort followed up from birth to mid-life[10] with extensive asthma phenotyping across nine assessments spanning the ages of 9–38 years. We then wanted to test how GWAS-discovered genetic risks were related to the development, persistence, and biological characteristics of asthma in this cohort.

Methods

Study design and participants

In this prospective longitudinal study, we used data from members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behaviour in a complete (unselected) birth cohort. Study members (1037; 91% of eligible births; 52% male) were all individuals born between April, 1972, and March, 1973, in Dunedin, New Zealand, who were eligible for the longitudinal study on the basis of residence in the province at age 3 years and who participated in the first follow-up assessment at age 3 years. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island and is mainly white.[11] Assessments were done at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 961 (95%) of the 1007 surviving study members took part. At each assessment wave, study members are brought to the Dunedin research unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the study and informed consent was obtained from all study members.

See Online for appendix

Procedures

To test whether genetic risk was associated with the timing of onset, course, and persistence of asthma, we analysed longitudinal data on asthma phenotypes derived from standardised interviews of Dunedin Study members. To test whether genetic risk was associated with asthma's biological characteristics, we combined interview data with information derived from assessments of allergy and lung function. We examined three biological characteristics: atopy, which, especially in paediatric populations, is associated with a persistent and severe course of asthma;[12,13] airway hyper-responsiveness, which provides indirect confirmation of active airway inflammation;[14,15] and incompletely reversible airflow obstruction, which identifies harmful changes to the airways resulting from chronic asthma.[16] To accompany these aetiological analyses, we did two additional tests that related to the concerns of patients and clinicians. To test whether genetic risk was associated with disruptions to daily life, we analysed genetic associations with the incidence of days of school and work missed because of asthma, and with asthma-related hospital admissions. To put the magnitude of genetic risk effects in context and to find out whether molecular genetic measurements provided novel information about risk, we compared molecular genetic information with family-history information.[17]

Measures

A challenge for developmental research following up GWAS discoveries is that effect sizes for individual asthma-associated single-nucleotide polymorphisms (SNPs) are small,[9] meaning that longitudinal studies with the data necessary to investigate developmental phenotypes of asthma are underpowered to test individual SNP effects.[18] However, evidence shows that asthma-associated loci make additive contributions to risk, recommending aggregation of risk alleles.[19,20] Summing risk alleles across GWAS-identified SNPs to compute a genetic risk score yields a quantitative index of genetic risk with a normal distribution[21] and a potentially larger effect size.

We derived our genetic risk score from the largest asthma GWAS to date, published in 2010.[9] We selected all SNPs associated with asthma at $p<5\times10^{-8}$. This set of SNPs was then pruned using an R^2 threshold of 0·60 to derive the SNP set for the genetic risk score. This process yielded 17 SNPs located in or near the genes *IL18R1*, *IL13*, *HLA-DQ*, *IL33*, *SMAD3*, *ORMDL3*, *GSDMB*, *GSDMA*, and *IL2RB*.

Genotyping was done in the Dunedin Study cohort with a commercially available array (BeadPlex Array, Illumina, San Diego, CA, USA) using DNA extracted from whole blood (93%) or buccal swabs (7%). Two SNPs near the gene *HLA-DQ* could not be assayed because of the complex repetitive structure of the proximal sequence. Thus, the final genetic risk score included 15 SNPs (appendix).

SNPs were genotyped in 880 (95%) of the 927 cohort members who reported European-descent grandparents. All SNPs met Hardy-Weinberg equilibrium criteria ($p>0·10$ for all tests). For each SNP, the risk allele was defined as the asthma-associated allele in the original GWAS. Of a possible 30 risk alleles, cohort members carried a mean of 13·74 (SD 4·36). Risk allele counts were normally distributed (appendix). For analyses, we standardised the risk allele counts to have a mean of 0 and an SD of 1 (the genetic risk score). Effect sizes presented are for a 1 SD change in genetic risk, which reflects the effect associated with an increase of 4·36 risk alleles. Results of sensitivity analyses that selectively dropped SNPs from the score one by one showed that no single SNP accounted for a disproportionate share of the genetic-risk-score association with asthma (appendix). Cohort members' sex and socioeconomic status were unrelated to their genetic risk (Pearson's r=0·01 for sex and 0·04 for socioeconomic status).

Family histories for asthma—ie, reports of asthma provided by study members and both parents for study members' biological siblings, parents, and grandparents—were available for 99% of the cohort. Family history was summarised as the proportion of family members in the pedigree who had asthma, adjusted for genetic relatedness to the proband (ie, first-degree relatives were counted as 1 and second-degree relatives were counted as 0·5).[22]

Assessments of asthma phenotypes and definitions of biological variables including atopy, airway hyper-responsiveness, and incompletely reversible airflow obstruction have been described in previous publications from this cohort[10,23–33] and are summarised in table 1.

Statistical analysis

We analysed dichotomous outcomes (eg, asthma status) using Poisson regression models to derive relative risks (RRs). We analysed count phenotypes (eg, the number of assessments at which cohort members had current asthma) using negative binomial regression models to account for overdispersion. We report effect sizes from negative binomial models in terms of incident rate ratios (IRRs). We analysed time to asthma onset using Cox regression models to derive hazard ratios (HRs). We analysed longitudinal repeated-measures data on the biological characteristics of asthma with generalised estimating equations to account for the non-independence of repeated observations.[34] These analyses treated each assessment of a biological characteristic as an outcome, allowing us to differentiate cases on the basis of persistence. All analyses were adjusted for sex and used the continuous genetic risk score (standardised to have a mean of 0 and a SD of 1). Effect sizes are reported for a 1 SD increase in genetic risk.

	Number of participants	Assessment method
Developmental phenotypes of asthma		
Asthma onset	305 (35%) of 880 participants	Current asthma status was assessed at ages 9, 11, 13, 15, 18, 21, 26, 32, and 38 years from standardised interviews of study members (or their mothers if the participant was younger than 13 years) done by pulmonary specialists.[10] Current asthma was defined as a diagnosis of asthma in addition to positive symptoms within the past 12 months, including asthma attack, recurrent wheeze (excluding study members reporting only one or two episodes lasting less than 1 h), or medical treatment for asthma.[23–25] Age at asthma onset was defined as the earliest age at which wheezing symptoms or diagnosis by a physician were recorded
Life-course-persistent asthma	96 (11%) of 880 participants	Asthma persistence was defined by the number of assessments (out of nine) at which a cohort member had current asthma. Life-course-persistent asthma was defined as having asthma at two or more assessments up to puberty (age 13 years) and at three or more assessments thereafter (ages 15–38 years)
Biological characteristics of asthma		
Atopy	236 (77%) of 305 participants with asthma	Atopy was assessed once in childhood (at age 13 years) and twice in adulthood (at ages 21 and 32 years) by standardised skin tests[26] for 12 common allergens: house dust mite (*Dermatophagoides pteronyssinus*), grass, cat, dog, horse, kapok, wool, *Aspergillus fumigatus*, *Alternaria*, *Penicillium*, *Cladosporium*, and cockroach (at ages 21 and 32 years only). A weal diameter 2 mm greater than saline control was regarded as positive for epidemiological purposes. Atopy was defined as a positive response to one or more allergens.[27,28] Participants with asthma who tested positive for atopy were classified as having atopic asthma. In addition to allergy testing, total serum IgE, a blood biomarker of atopy, was measured once in childhood (at age 11 years) and twice in adulthood (at ages 21 and 32 years).[29] IgE values were log transformed for analysis
Airway hyper-responsiveness	160 (52%) of 305 participants with asthma	Airway hyper-responsiveness is an indirect measure of airway inflammation. During childhood (ages 9–13 years), and at ages 15 and 21 years, spirometry and methacholine challenge was done using a Godart water spirometer. As described previously,[28,30–32] a concentration of methacholine of 8 mg/mL or less causing a 20% decrease (PC_{20}) in forced expiratory volume in 1 s (FEV_1) was used to identify airway hyper-responsiveness. In cohort members in whom a methacholine challenge was not safe or practical, an increase in FEV_1 of 10% or more after albuterol was regarded as roughly equivalent to a PC_{20} of 8 mg/mL or less. This same method was used to define bronchodilator responsiveness at ages 18, 26, 32, and 38 years. At these ages, spirometry was done with an Ohio computerised spirometer (Ohio Instruments, Cincinnati, OH, USA) at age 18 years, and a Sensormedics body plethysmograph (Sensormedics Corporation, Yorba Linda, CA, USA) at ages 26, 32, and 38 years. Asthma cases who met criteria for airway hyper-responsiveness to methacholine or albuterol were classified as having asthma with airway hyper-responsiveness
Incompletely reversible airflow obstruction	76 (25%) of 305 participants with asthma	Incompletely reversible airflow obstruction was defined at ages 18, 26, 32, and 38 years as a post-bronchodilator ratio of FEV_1 to forced vital capacity (FVC) below the age-specific and sex-specific lower limits of normal.[32] The lower limit of normal was defined from cohort members with no previous history of asthma, no history of smoking, and no reported wheeze within the previous year as follows: the mean FEV_1-to-FVC ratio minus 1·96 SD, delimiting 2·5% of the normal population with the lowest post-bronchodilator FEV_1-to-FVC ratios.[33] Participants with asthma who had incompletely reversible airflow obstruction by the end of follow-up were classified as having asthma with incompletely reversible airflow obstruction. We also analysed post-bronchodilator FEV_1-to-FVC ratio, a continuously distributed biomarker of incompletely reversible airflow obstruction
Asthma-related disruptions to daily life		
Days of school or work missed because of asthma	158 (18%) of 880 participants*	At ages 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, cohort members (or their mothers if aged younger than 13 years) reported the number of days of missed school or work because of asthma
Admission to hospital for asthma or wheezing	72 (8%) of 880 participants	At each assessment, cohort members (or their mothers if aged younger than 13 years) reported whether they had ever been admitted to hospital because of asthma or wheeze[23]

*Resulting in 2398 days off school or work.

Table 1: **Assessments of asthma phenotypes and definitions of biological variables**

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results
Boys and girls in the Dunedin cohort who had higher genetic risk scores had a greater risk of developing asthma over the 38 years of follow-up than did those with lower genetic risk (HR 1·12, 95% CI 1·01–1·26), and developed asthma earlier in life (figure 1). Genetic associations with asthma onset did not differ by sex (p=0·917).

Cohort members at higher genetic risk met criteria for current asthma at more assessments between the ages of 9 and 38 years than did those with lower genetic risk (IRR 1·16, 95% CI 1·03–1·30). Children at higher genetic risk were also more likely to develop life-course-persistent asthma (96 [11%] of 880 participants), defined by onset in childhood (before age 13 years) with recurrent

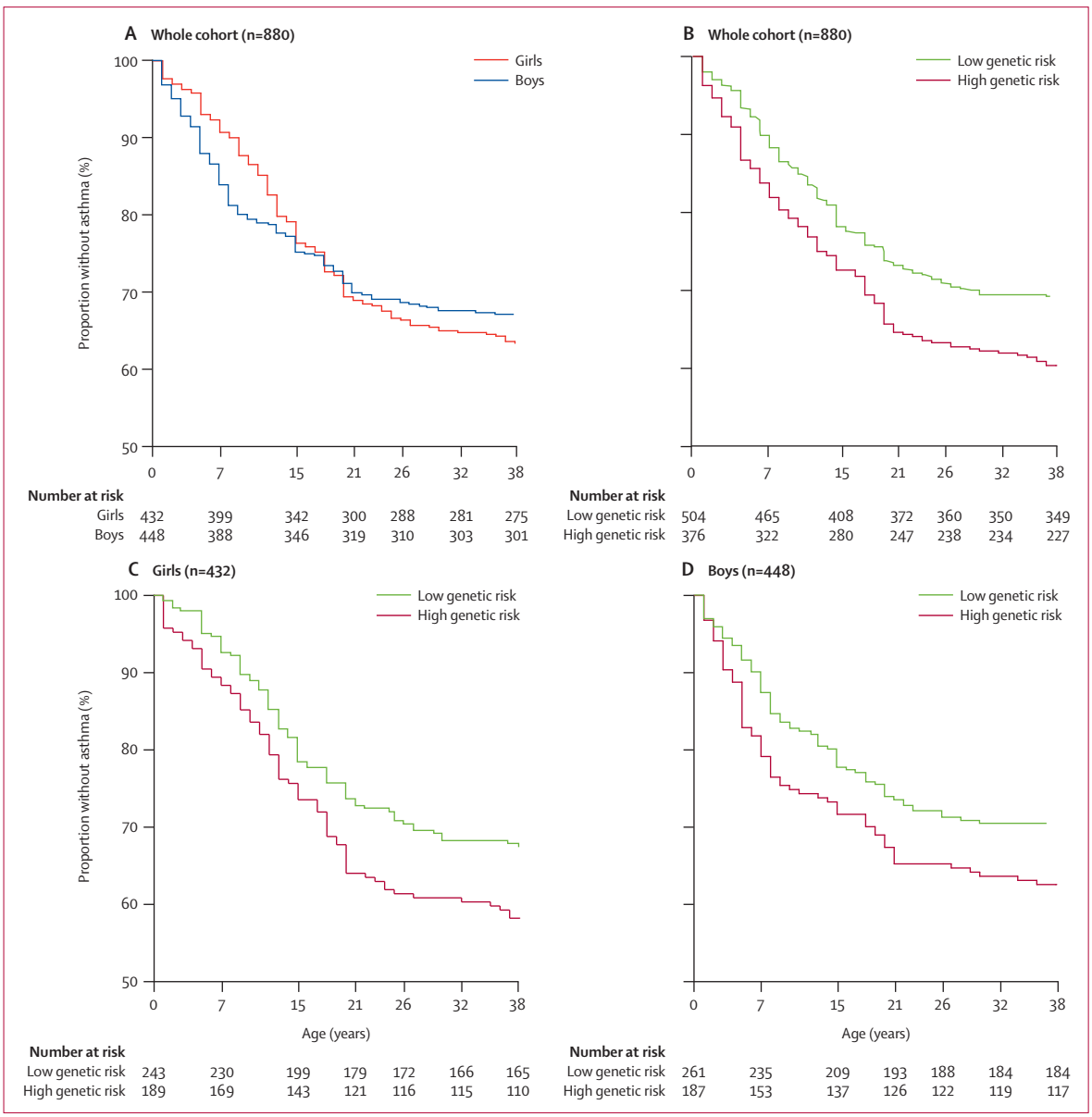

Figure 1: **Kaplan-Meier plots for development of asthma over time, by sex and genetic risk score**
Kaplan-Meier plots show asthma onset in the whole Dunedin cohort according to sex (A) and high or low genetic risk score (B), and in girls only (C) and boys only (D) according to high or low genetic risk score. For illustrative purposes, high genetic risk was defined as a genetic risk score above the cohort median. Numbers at risk are reported at ages 0, 7, 15, 21, 26, 32, and 38 years.

symptoms up to age 38 years (RR 1·36, 95% CI 1·14–1·63; figure 2A). The shift in the genetic risk distribution that underlies this effect is presented in the appendix. Specifically, in the subset of cohort members with asthma onset in childhood (187 [21%] of 880 participants), those at higher genetic risk developed asthma earlier in life than did those with lower genetic risk (HR 1·17, 95% CI 1·01–1·34) and were more likely to develop life-course-persistent asthma (RR 1·20, 1·05–1·38; figure 2B). Our receiver operating characteristic curve analysis showed that the genetic risk score slightly improves individual-level predictions of which participants with childhood-onset asthma developed life-course-persistent asthma (appendix). We did sensitivity analyses that restricted the life-course-persistent subgroup to the 93 participants with asthma onset before the age of 9 years to test if results changed after exclusion of the three participants in the life-course-persistent group who developed asthma around the time of puberty. We noted that the results were unchanged (effect sizes for genetic associations with life-course-persistent asthma were RR 1·37 [95% CI 1·14–1·65] in the whole cohort and RR 1·20 [1·05–1·39] in participants who developed asthma in childhood).

The results of our analyses in the 305 (35%) participants who developed asthma during follow-up showed that those at higher genetic risk were at increased risk of atopy compared with those with asthma and a lower genetic risk (RR 1·07, 95% CI 1·01–1·14) across assessments at age 13, 21, and 32 years. Participants with asthma at higher genetic risk also had raised serum IgE concentrations (r=0·13; p=0·02) across assessments at age 11, 21, and 32 years.

Lung function analyses showed that participants with asthma at higher genetic risk were at increased risk of airway hyper-responsiveness to methacholine or albuterol relative to those with a lower genetic risk (RR 1·16, 95% CI 1·03–1·32) across nine assessments between the ages of 9 and 38 years. These analyses also showed that participants with asthma at higher genetic risk had poorer lung function, as measured by a post-albuterol ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC), than did those at lower genetic risk (r=0·13, p=0·03) and were more likely to develop incompletely reversible airflow obstruction, as defined by post-bronchodilator FEV_1-to-FVC ratios of more than 2 SD below the mean of participants who never developed asthma, than were those at lower genetic risk (RR 1·28, 95% CI 1·04–1·57) across assessments at ages 18, 26, 32, and 38 years. Genetic associations with lifetime risk for atopy, airway hyper-responsiveness, and incompletely reversible airflow obstruction in participants with asthma are shown in the appendix.

Because smoking affects the lung function characteristics that we analysed,[35] we did sensitivity analyses testing genetic associations with lung function phenotypes of asthma in non-smokers (figure 3). By age 38 years, 214 (70%) of the 305 cohort members with asthma had smoked at some point during follow-up (in the full cohort, 627 [71%] of 880 had smoked). We previously constructed developmental phenotypes of smoking behaviour in the Dunedin cohort that identified when cohort members began smoking.[36] We selectively excluded data from participants with asthma that were obtained after those individuals had begun smoking—eg, for a child who developed asthma at age 11 years and who took up

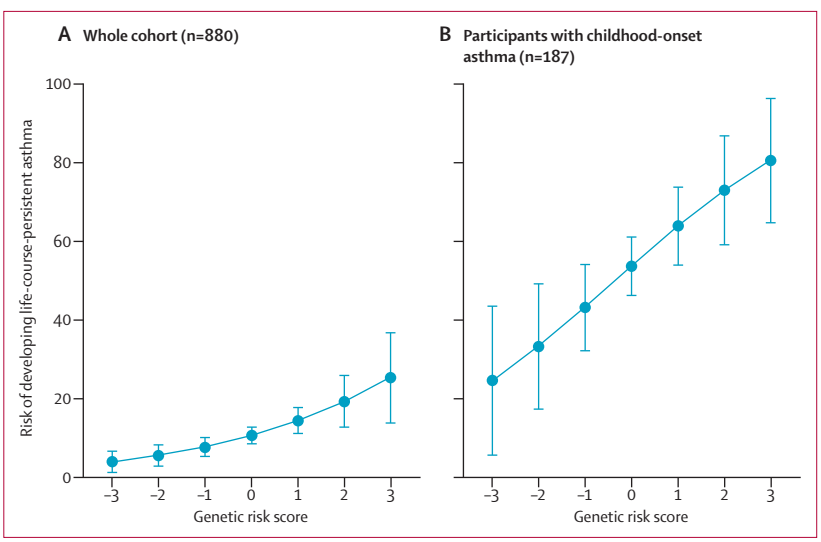

Figure 2: **Risk of developing life-course-persistent asthma according to genetic risk score**
(A) Whole cohort (relative risk [RR] 1·36, 95% CI 1·14–1·63). (B) Subset of cohort members with asthma onset by age 13 years (RR 1·20, 1·05–1·38). Error bars show 95% CIs for point estimates. The genetic risk score is the count of risk alleles standardised to have a mean of 0 and an SD of 1.

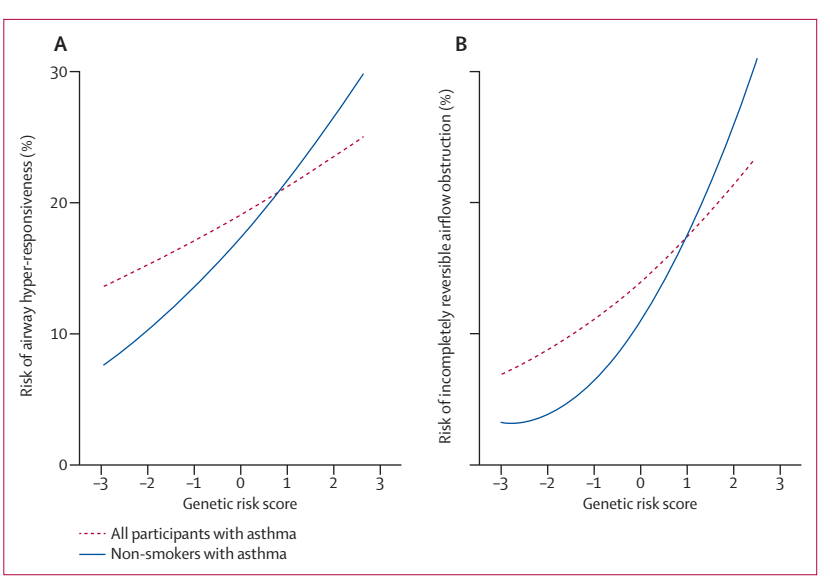

Figure 3: **Lung function in non-smokers with asthma according to genetic risk score**
(A) Predicted probability of airway hyper-responsiveness in 188 non-smokers with asthma and all 305 participants with asthma. (B) Predicted probability of incompletely reversible airflow obstruction in 105 non-smokers with asthma and all 305 participants with asthma. Probabilities were estimated from models including all participants with asthma and models including only non-smoking participants with asthma. The genetic risk score is the count of risk alleles standardised to have a mean of 0 and an SD of 1.

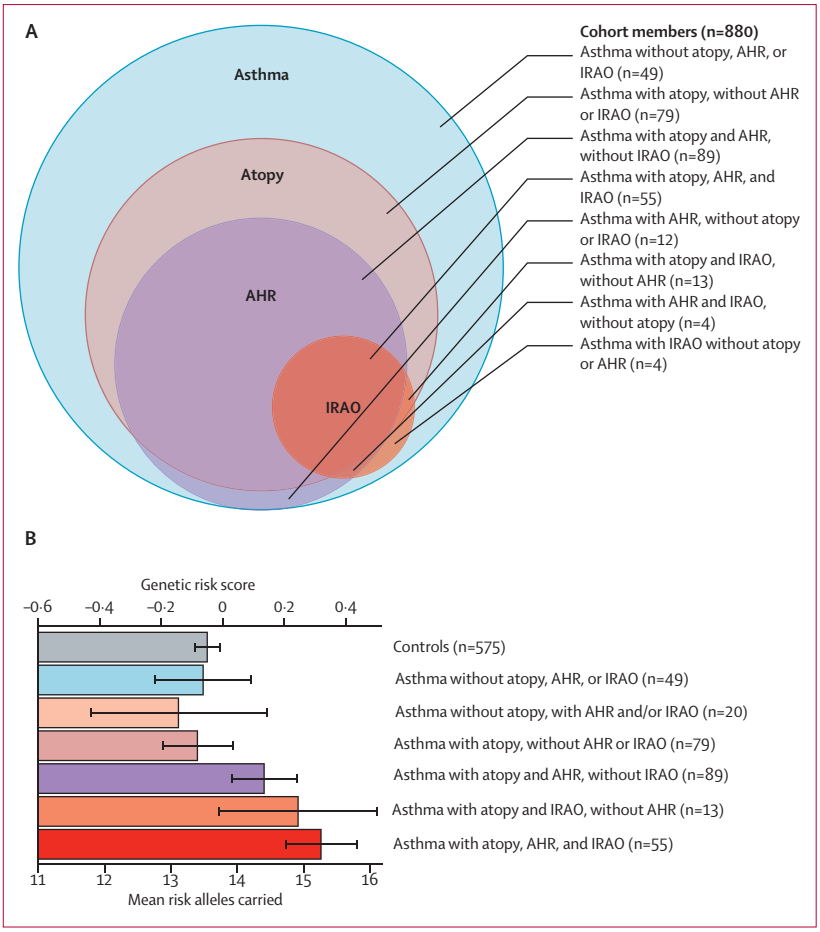

Figure 4: **Atopy, airway hyper-responsiveness, and incompletely reversible airflow obstruction in participants with asthma**

(A) Overlap between different biological characteristics of asthma. (B) Mean genetic risk within subgroups of participants with asthma. Participants with asthma who did not have atopy but who did have airway hyper-responsiveness or incompletely reversible airflow obstruction are grouped together because of the small number of cases in each group. Error bars show SE for subgroup means. The genetic risk score is the count of risk alleles standardised to have a mean of 0 and a SD of 1. AHR=airway hyper-responsiveness. IRAO=incompletely reversible airflow obstruction.

smoking at age 18 years, observations at ages 11, 13, and 15 years were included in the analysis of airway hyper-responsiveness, whereas all observations from age 18 years onwards were excluded. Participants who developed asthma after starting smoking were excluded from the analysis entirely. Excluding smokers increased the magnitudes of associations between genetic risk and airway hyper-responsiveness (RR 1·38, 95% CI 1·16–1·64) and incompletely reversible airflow obstruction (RR 1·63, 1·10–2·41).

Our results showed substantial overlap between atopy, airway hyper-responsiveness, and incompletely reversible airflow obstruction in participants with asthma. For example, 55 (72%) of 76 cohort members with asthma and incompletely reversible airflow obstruction also had atopy and airway hyper-responsiveness during follow-up (figure 4A). Individuals with asthma who did not develop atopy had genetic risk scores similar to those without asthma. Of participants with asthma who developed atopy, those who also developed airway hyper-responsiveness and incompletely reversible airflow obstruction had higher genetic risk scores than did those who had asthma and atopy only, and had the highest genetic risk scores of all participants (figure 4B).

Over three decades of follow-up, cohort members at higher genetic risk missed more days of school or work because of asthma than did those at lower genetic risk (IRR 1·38, 95% CI 1·02–1·86) and were more likely to be admitted to hospital for breathing problems (HR 1·38, 1·07–1·79).

Genotype and family history provided similar amounts of information about asthma risk; effect sizes were similar for the genetic risk score and the family history score in models predicting developmental phenotypes of asthma, airway hyper-responsiveness, and asthma-related disruptions to daily life (table 2). Family history was not associated with risks of participants with asthma manifesting atopy or incompletely reversible airflow obstruction.

Genotype-based and family-history-based measures provided different information about asthma risk. Cohort members' genetic risk scores were unrelated to their family history scores (r=0·05; appendix). Adding statistical adjustments for family history to regression models testing genetic associations with asthma phenotypes and complications did not change the effect size or statistical significance estimated for the genetic risk score. The one exception was that after adjustment for family history, the genetic association with incidence of days of school or work missed because of asthma was no longer statistically significant (IRR 1·32, 95% CI 0·98–1·79; p=0·07).

Discussion

Results from our population-level analyses advance asthma genetics beyond the original GWAS discoveries in three ways. First, we show that genetic risks predict which individuals with childhood-onset asthma remit and which develop life-course-persistent asthma, although these predictions are not sufficiently sensitive or specific to support immediate translation into clinical practice. Second, we elucidate a biological profile of asthma that arises from these genetic risks: atopic asthma characterised by airway hyper-responsiveness and leading to incompletely reversible airflow obstruction. Third, we describe the real-life effects of GWAS discoveries by quantifying genetic associations with missed school and work, and hospital admissions.

Cohort members at higher genetic risk developed asthma earlier in life, supporting GWAS reports of early-onset asthma as the developmental phenotype most strongly associated with discovered genetic risks (panel).[9,37–39] We refined this developmental phenotype by showing that discovered genetic risks were specifically associated with a life-course-persistent developmental

phenotype of asthma: of participants with childhood-onset asthma, those with a higher genetic risk were more likely to have persistent asthma up to age 38 years. Higher genetic risk asthma cases were also more likely to be atopic, supporting preliminary GWAS evidence that at least some asthma-associated loci are specific to atopic asthma.[40] We also show that in participants with asthma who also developed atopy, higher genetic risk predisposes these individuals to airway hyper-responsiveness and the development of incompletely reversible airflow obstruction. Collectively, these findings describe a biological profile of asthma associated with GWAS discoveries. Research is now needed to trace molecular pathways from these variants to atopy, airway hyper-responsiveness, and incompletely reversible airflow obstruction in asthma.

Genetic associations with developmental and biological characteristics of asthma translated to an increased burden of asthma-related disruptions to daily life. Participants with asthma at higher genetic risk missed more days of school and work over three decades of follow-up and were more likely to be admitted to hospital for asthma than were those with a lower genetic risk. Magnitudes of genetic effects were small, with each SD increase in genetic risk score predicting an increase in risk for these disruptions to daily life by about a third. Nevertheless, results suggest that full mitigation of genetic risk could reduce the burden asthma imposes on patients, with potential benefits accruing to society through reductions in school and work absenteeism, and in health-care costs.

Finally, we tested whether recent GWAS discoveries captured information that might otherwise be obtained through a family history.[41,42] GWAS discoveries for asthma provided novel information about inherited risk that was not captured by family history of asthma; the genetic risk score made independent, additive contributions to prediction models over and above family history. Both genotype-based and family-based risk measures predicted asthma onset and persistence, but genotype was a more consistent predictor of the biological characteristics of asthma. Surprisingly, genotypic risk was only weakly related to family history of asthma, with some cohort members with a negative family history carrying a high genetic risk for asthma. This lack of concordance between genotypic and family-based risk assessments is not unique to asthma. We previously noted this finding in patients with obesity and smoking problems,[36,43] and others have reported similar results for some patients with cancers.[41] In studies of diabetes and cancer, taking family history into account did not change effect sizes estimated for GWAS-discovered genetic risks,[44,45] suggesting low correlation between genotypic and family-history risk measures. In turn, this lack of correlation suggests that family history captures more than the additive contributions of common variants. Replication is needed of the non-association between

	Statistic	Genetic risk score	Family history score
Developmental phenotypes of asthma (n=880)			
Time to asthma onset	HR	1·12 (1·01 to 1·26)	1·21 (1·10 to 1·34)
Asthma persistence	IRR	1·16 (1·03 to 1·30)	1·24 (1·13 to 1·37)
Life-course-persistent asthma	RR	1·36 (1·14 to 1·63)	1·33 (1·19 to 1·48)
Life-course-persistent asthma in participants with asthma onset by age 13 years (n=162)	RR	1·20 (1·05 to 1·38)	1·09 (1·00 to 1·18)
Biological characteristics of asthma (n=305)*			
Atopy			
Positive skin test (at ages 13, 21, and 32 years)	RR	1·07 (1·01 to 1·13)	1·03 (0·98 to 1·08)
Serum IgE (at ages 11, 21, and 32 years)	*r*	0·13 (0·02 to 0·25)	0·10 (0·00 to 0·19)
Airway hyper-responsiveness			
Case status (at ages 9, 11, 13, 15, 18, 21, 26, 32, and 38 years)	RR	1·16 (1·03 to 1·32)	1·12 (1·05 to 1·21)
Incompletely reversible airflow obstruction			
Case status (at ages 18, 26, 32, and 38 years)	RR	1·28 (1·04 to 1·57)	1·05 (0·90 to 1·22)
Post-albuterol FEV_1-to-FVC ratio (at ages 18, 26, 32, and 38 years)	*r*	−0·13 (−0·24 to −0·02)	−0·07 (−0·16 to 0·02)
Disruptions to daily life (n=305)*			
Days off school or work because of asthma	IRR	1·38 (1.02-1.86)	1·28 (1·02 to 1·61)
Admitted to hospital for asthma	HR	1·38 (1·07 to 1·79)	1·21 (1·05 to 1·38)

Effect sizes are presented for a 1 SD increase in genetic risk and a 1 SD increase in family history. Analyses of biological characteristics of asthma used generalised estimating equations to account for the non-independence of repeated observations of individuals. All models were adjusted for sex. HR=hazard ratio (Cox regression model). IRR=incident rate ratio (negative binomial regression model). RR=relative risk (Poisson regression model). *r*=standardised coefficient (interpreted as Pearson's *r* from a linear regression model). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Analyses included only the 305 cohort members who developed asthma during follow-up.

Table 2: **Effect sizes for genetic risk score and family history score**

Panel: Research in context

Systematic review

We searched databases, including PubMed and the National Human Genome Research Institute GWAS Catalog, to identify the largest and most comprehensive genome-wide association studies (GWAS) of asthma using the search terms "asthma" and "genome-wide association study". We did not apply any publication date restrictions and did the last search on Sept 1, 2012. We identified a GWAS done by the European GABRIEL Consortium,[9] from which we selected single nucleotide polymorphisms (SNPs) that were genome-wide significant ($p<5\times10^{-8}$) and that were at least partially independent of one another ($R^2<0·6$) to construct a genetic risk score.

Interpretation

Our results, when added to those of the original GWAS,[9] show that genetic risks predict which childhood-onset asthma cases remit and which become life-course-persistent cases, describe a biological profile of the asthma that arises from these genetic risks, and show the real-life effects of GWAS discoveries by quantifying genetic associations with missed school and work, and hospital admissions. Because the effect sizes we noted were small, the predictions offered by genetic risk scores might be weak. More research is needed to clarify the clinical significance of the small increments in risk that can be predicted using SNPs.

genetic risk and family history, using whole-genome scores.[46] If replicated, future genetic discovery research in asthma could focus on genetic features of family history not detectable in GWAS, including rare variants, interactions among genes (epistasis) and, because family histories capture shared environments as well as genes, interactions between genes and environmental factors.[8,47–49] Our findings also suggest that GWAS discoveries might help to identify which childhood-onset asthma cases are most likely to become life-course-persistent cases, even after accounting for differences in family histories of asthma. Because the effect sizes we recorded were small, the predictions offered by genetic risk scores might be weak. More work is needed to clarify the clinical significance of the small increments in risk that can be predicted using SNPs.[50]

We acknowledge several limitations. First, our analyses were based on cohort members of European descent and for whom follow-up has extended only to age 38 years, limiting the extent to which we can generalise the results. Replication of findings in non-white cohorts and extension of findings beyond mid-life are crucial. Nevertheless, this birth cohort is one of the longest running with detailed clinical and objective measurements pertinent to asthma, and the cohort is representative of the population studied; it originated as an unselected birth cohort and has been followed up with a 95% retention. Second, because our study did not include medical records, some cases of asthma and hospital admission might have been missed or misclassified, leading to underestimation of genetic effects. Third, our genetic risk score included only SNPs meeting genome-wide significance criteria in GWAS,[9] and omitted two of these because of technical limitations of the genotyping array. The genotyped SNPs represent only a subset of asthma-causing variants, many of which remain undiscovered.[51] Further, because the relative effect sizes of these SNPs on the developmental and biological characteristics of asthma that we analysed remain unknown, we did not weight the SNPs in our score. Whole-genome genetic risk score approaches that include hundreds or thousands of variants that meet more liberal significance criteria and that apply empirically defined weighting schemes might yield more comprehensive measures of genetic risk.[52] Such whole-genome scores are a work in progress in the case of asthma; effect sizes reported in a recent whole-genome score study of asthma[19] were similar to those in our study. Finally, because our genetic risk score approach studied the aggregate effect of several asthma-associated SNPs, we cannot address the question of molecular mechanism. Larger samples and meta-analyses are needed to assess the specific contributions of individual risk variants to developmental and biological characteristics of asthma. The contribution of our study is to guide such investigations by pointing to target phenotypes: early-onset, life-course-persistent asthma, and atopic asthma characterised by airway hyper-responsiveness and incompletely reversible airflow obstruction.

Contributors

DWB, AC, MRS, and RJH did the scientific literature search; DWB, MRS, TEM, RP, and AC designed the study; TEM, MRS, RJH, RP, and AC obtained the data; DWB, HLH, RH, TEM, KS, BW, and AC analysed the data; DWB, TEM, MRS, RJH, and AC interpreted the data; DWB, TEM, and AC drafted the manuscript; and DWB, TEM, AC, MRS, RJH, RP, KS, BW, RH, and HLH provided critical revision.

Conflicts of interest

We declare that we have no conflicts of interest.

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