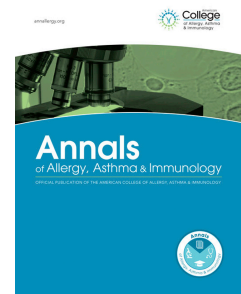


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Serum insulin-like growth factor-1, asthma, and lung function among British adults

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Conflicts of interest: Dr. Celedón has received research materials from Merck and GSK (inhaled steroids), and Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in NIH-funded studies, unrelated to the current work. The other authors report no conflicts of interest.

Abbreviations:

AM: alveolar macrophages

BMI: body mass index

CI: confidence interval

CRP: C-reactive protein

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GH: growth hormone

HbA1c: glycated hemoglobin A1c

ICD code: International Classification of Diseases Clinical Modification code

IGF-1: insulin-like growth factor-1

IGFBP-3: insulin-like growth factor binding protein 3

OR: odds ratio

MS: metabolic syndrome

UK Biobank: United Kingdom Biobank

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Background: Insulin-like growth factor-1 (IGF-1) plays a key role in the pathogenesis of metabolic syndrome (MS), which is in turn associated with asthma. Whether IGF-1 contributes to asthma causation or asthma severity is largely unknown.

Objective : To examine the relation between serum IGF-1 and asthma, asthma outcomes, and lung function in adults.

Methods: Cross-sectional study of 297,590 adults (aged 40-69 years) who participated in the United Kingdom Biobank, had no diagnosis of diabetes, and were not on insulin. Multivariable logistic or linear regression was used to analyze serum IGF-1 and physician-diagnosed asthma, current wheeze, asthma hospitalizations, and lung function measures (FEV₁, FVC and FEV₁/FVC).

Results: Serum IGF-1 levels above the lowest quartile (Q1) were significantly associated with lower odds of asthma (adjusted odds ratio [aOR] for fourth quartile (Q4) vs. Q1=0.88, 95% confidence interval [CI]=0.85-0.91). Among participants with asthma, IGF-1 levels above Q1 were significantly associated with lower odds of current wheeze (aOR for Q4 vs. Q1=0.89, 95% CI=0.83-0.96), but not with asthma hospitalizations. Serum IGF-1 was significantly and positively associated with FEV₁ (b=20.9 mL, 95%CI=19.1-22.7) and FVC (b=25.6 mL, 95%CI=23.4-27.7), regardless of an asthma diagnosis; these associations were significant in men and women, with larger estimated effects in men.

Conclusion: In a large study of British adults, higher serum IGF-1 levels were associated with lower odds of asthma and current wheeze, and higher FEV₁ and FVC. Our findings suggest potential beneficial effects of circulating IGF-1 on asthma and asthma outcomes in adults.

INTRODUCTION

Asthma affects approximately 339 million children and adults worldwide¹. Total yearly asthma costs exceed \$81 billion dollars in the U.S.² and ~72 billion Euros in Europe³. In the United Kingdom (U.K.), 1.1 million children and 4.3 million adults currently receive treatment for asthma, and the disease leads to 93,000 hospitalizations per year and at least £1.1 billion medical care costs annually^{4, 5}. While asthma mortality has been reduced in most age groups, a recent study reported a rise in deaths from asthma among the elderly in England and Wales⁶.

Insulin-like growth factors (IGFs) play an important role in metabolism and growth^{7, 8}. Through bi-directional interactions with the immune system, IGFs can contribute to the pathogenesis of diseases such as cancer, cardiovascular disorders, and inflammatory lung diseases⁹⁻¹². IGF-1 (somatomedin C) is a 70-aminoacid polypeptide with similar sequence and molecular structure to insulin. IGF-1 production primarily occurs in the liver and is induced by growth hormone (GH). IGF-1 can act as a hormone that mediates anabolic and linear growth, thus promoting cell growth and differentiation^{7, 13}. IGF-1 also regulates the metabolism of glucose and lipids⁸.

Although IGF-1 deficiency has been linked to metabolic syndrome (MS), which has in turn been associated with asthma, few human studies have investigated the role of IGF-1 in asthma pathogenesis. IGF-1 may play a role in asthma by modulating airway inflammation, airway hyperresponsiveness, and airway smooth hyperplasia¹⁴. In murine models of asthma, IGF-1 is upregulated in lung tissue, and administration of IGF-1-neutralizing antibodies ameliorates airway resistance and inflammation¹⁵. In an *in vivo* study, IGF-1 promoted airway inflammation by upregulating IGF binding protein 3 (IGFBP-3), which can have profibrotic effects¹⁶. A recent

case-control study reported that serum IGF-1 was higher in subjects with asthma than in control subjects, but those findings must be cautiously interpreted due to small sample size and potential bias by confounding¹⁷. In contrast to those results, serum IGF-1 was positively associated with lung function in two epidemiologic studies in adults^{18, 19}.

Given inconsistent findings for a potential role of IGF-1 in asthma pathogenesis from animal and epidemiologic studies, we examined the relation between peripheral serum IGF-1 and asthma, current wheeze, asthma hospitalizations, and lung function in 297,590 non-diabetic British adults aged 40 to 69 years.

METHODS

Study design and study population

The UK Biobank is a national, prospective, population-based study established to identify determinants of complex diseases and improve the health outcomes of British adults.

Approximately 9.2 million individuals aged 40-69 years who lived within 25 miles of twenty-two assessment centers in England, Wales, and Scotland were invited to enter the cohort, and ~500,000 (5.5%) of those 9.2 million people volunteered to participate in the baseline assessment²⁰. Extensive data, including questionnaires, physical measures, and biological samples were collected at baseline, with longitudinal follow-up for a wide range of health-related outcomes²⁰. The UK Biobank was approved by the UK National Health Service National Research Ethics Service (Ref 11/NW/0382) and informed consent was obtained from all participants. Details of the methods, protocols, and definitions used in the study can be found at the UK Biobank website (<https://www.ukbiobank.ac.uk/>).

The current study was conducted using the UK Biobank Resource under application #43252. The flowchart for selection of participants from the UK Biobank into the current analysis is shown in **Figure 1**. Of 502,506 participants recruited at baseline, 297,590 were not pregnant, had neither a diagnosis of diabetes nor reported use of insulin, and had complete information on asthma status and IGF-1 levels, and were thus included in the current analysis.

Outcomes

Asthma was defined by selection of “asthma” as an answer to the following question: “Has a doctor ever told you that you have had any of the following conditions: blood clot in the leg, blood clot in the lung, emphysema/chronic bronchitis, asthma, hay fever, allergic rhinitis or eczema?” Control subjects were participants who did not select “asthma” as an answer to the question above. Current wheeze was defined as a “Yes” answer to the following question: “In the last year, have you ever had wheeze or whistling in the chest?” In subjects with asthma, a hospitalization for asthma was defined as ever having had a hospitalization with an International Classification of Diseases Clinical Modification (ICD) code of main diagnosis compatible with asthma (ICD-9: 493.x or ICD-10: J45.x and J46.x), excluding hospitalizations with an ICD code for a main diagnosis consistent with chronic obstructive pulmonary disease (COPD, ICD-9: J43, J44, J47 or ICD-10: 490, 491, 492, 494, 496). Data on asthma hospitalizations were available before (range=0 to 27 years, median=6 years) and after (range=1 to 9 years, median=4 years) the participant’s IGF-1 measurement.

Spirometry was performed using a Vitalograph Pneumotrac 6800 spirometer (Vitalograph Ltd., Buckingham, England), following European Respiratory Society/American Thoracic Society criteria for acceptability and reproducibility²¹. Participants were excluded from spirometry testing if they were being treated for tuberculosis, or if they had a chest infection in the last month, history of a detached retina, a heart attack, eye surgery, collapsed lung or a pneumothorax, or surgery in the chest or abdomen in the previous 3 months. Participants with extreme values for FEV₁ or FVC (< 1st or > 99th percentile) were excluded from the analysis of lung function measures.

Peripheral serum insulin-like growth factor-1

The UK Biobank collected blood samples during the baseline assessment visit²². Serum IGF-1 was measured at the UK Biobank central laboratory by a one-step sandwich chemiluminescent immunoassay, on a DiaSorin Liaison XL (Diasorin S.p.A, Borsa Italiana). Internal quality control and external quality assurance schemes were used to verify assay performance. Samples with results exceeding the reportable range of the assay were diluted and re-analyzed (automatic dilution)²³. Serum glycated hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography on a Bio-Rad VARIANT II Turbo hemoglobin testing system. Serum high sensitivity C-reactive protein (CRP) was measured by immuno-turbidimetric method on Beckman Coulter AU5800 analyzer (Beckman Coulter, UK, Ltd).

Statistical analysis

Bivariate analyses were conducted using two-sided Wald chi-square tests or t-tests, as appropriate. Logistic regression was used for the multivariable analyses of serum IGF-1 (as

quartiles) and asthma, current wheeze, and at least one asthma hospitalization (ever). Known or potential confounders of the relation between IGF-1 and asthma were included in the multivariable models. All models were adjusted for age, sex, race/ethnicity (Caucasian vs. other), annual household income ($< \text{£}31,000$ vs. $\geq \text{£}31,000$ per year, near the median household income for the UK in 2019²⁴), body mass index (BMI), smoking status (never, former, or current), pack-years of cigarette smoking, serum levels of HbA1c and CRP, and season and time of the day when the samples were collected (to account for daily and seasonal variation). MS was defined by the presence of at least 3 of the following criteria: fasting glucose level of 110 mg/dL or greater, waist circumference value greater than 102 cm in men or 88 cm in women, triglyceride level of 150 mg/dL or greater, high-density lipoproteins (HDL) level less than 50 mg/dL in men or 40 mg/dL in women, and either systolic blood pressure of 130 mmHg or greater or diastolic blood pressure of 85 or greater²⁵. After the final models were built, we tested for an interaction between IGF-1 and sex, obesity, or MS. Linear regression was used for the multivariable analysis of IGF-1 and lung function measures (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], and FEV₁/FVC), which was first conducted in all subjects, and then separately in subjects with and without asthma. Models for lung function measures were adjusted for an asthma diagnosis (in all participants), age, sex, race/ethnicity, annual household income, BMI, smoking status, pack-years of cigarette smoking, serum levels of HbA1c and CRP, and season and time of the day when the samples were collected. Models for FEV₁ and FVC were additionally adjusted for height and height squared.

Because 142,170 (32%) of the eligible participants were excluded from the analysis due to missing data for covariates (**Figure 1**), a multiple imputation procedure was used to include

those participants in a sensitivity analysis. A fully conditional specification (FCS) method was used to create five imputed datasets, and regression analyses were then repeatedly performed for each of these five datasets. Final results were generated by combining five sets of regression coefficients using Rubin's combining rules²⁶. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and two-sided P-values <0.05 were considered significant.

RESULTS

Table 1 shows the main characteristics of the study participants by asthma status. Of the 297,590 participants, 34,023 (11.4%) reported having physician-diagnosed asthma (hereinafter referred to as "asthma"). Compared to control subjects (n=263,567), participants with asthma were younger and more likely to be female, non-Caucasian, and non-current smokers; and to have higher BMI and higher serum HbA1c and CRP levels, but lower serum IGF-1 and lower lung function measures (FEV₁, FVC and FEV₁/FVC). Participants with asthma were also more likely to have MS. Serum IGF-1 decreased with age in both women and men, regardless of asthma status (**Figure 2**).

The results of the multivariable analysis of serum IGF-1 and asthma are shown in **Figure 3**. In this analysis, participants whose IGF-1 level was above the first (lowest) quartile (Q1) had 7% to 12% significantly lower odds of asthma than those with levels in the first quartile (e.g., adjusted odds ratio [aOR] for the fourth or highest quartile vs. the first quartile=0.88, 95% confidence interval [CI]=0.85-0.91). Because of significant modification of the estimated effect of IGF-1 on asthma by sex (P for interaction=0.01), we repeated the analysis after stratification by sex. In this analysis, women whose IGF-1 level was above the first quartile had 5%-11% lower odds of

asthma than those whose levels were in the first quartile, and men whose IGF-1 level was above the first quartile had 9%-15% lower odds of asthma than those whose levels were in the first quartile. We found no significant modification of the estimated effect of IGF-1 on asthma by obesity (defined as BMI ≥ 30 kg/m², P for interaction P=0.74).

To reduce the impact of potential misclassification of COPD as asthma, we repeated the multivariable analysis of asthma after stratification by smoking status (current smokers vs. never smokers and former smokers with <10 pack-years of cigarette smoking), obtaining similar results (**Table 2**). Similar results were obtained after excluding participants with a self-reported diagnosis of emphysema or chronic bronchitis (**e-Table 1**). In another sensitivity analysis, we repeated the multivariable analysis of serum IGF-1 and asthma after imputing data for missing covariates in all eligible participants (n=439,760). This analysis yielded similar results to those from the analysis that excluded participants with missing covariates (**e-Table 1**).

Table 3 shows the results of the multivariable analysis of serum IGF-1 and current wheeze or at least one asthma-related hospitalization. In this analysis, participants with asthma whose IGF-1 level was above the first quartile had 11%-12% lower odds of current wheeze (aOR for the fourth vs. the first quartile=0.89, 95% confidence interval [CI]=0.83-0.96). This association was significant in both women and men. Serum IGF-1 was not associated with having ever had an asthma hospitalization (in the whole cohort or in each sex). Furthermore, there was no significant association between IGF-1 and subsequent asthma hospitalizations (i.e. those occurring after IGF-1 was measured) or asthma hospitalizations occurring either one year prior to or after the IGF-1 measurement (**e-Table 2**).

To examine whether the estimated effect of the IGF-1 on asthma or asthma outcomes is modified by MS, we conducted a separate analysis that included MS in the multivariate models. This analysis yielded similar results to those from the analysis that did not include MS in the models (**Table 4**). There were no significant interactions between IGF-1 level and MS on asthma ($P=0.24$), current wheeze ($P=0.75$), or asthma-related hospitalizations ($P=0.72$).

Table 5 shows the results of the multivariable analysis of lung function measures in all participants and separately in subjects with and without asthma. Among all participants, each quartile increment in IGF-1 was significantly associated with an increment of 21-26 ml in FEV₁ or FVC, with similar findings in subjects with or without asthma. There was a significant interaction between sex and IGF-1 on lung function measures (P for interaction <0.05 in all instances). In the analysis stratified by sex, each quartile increment in serum IGF-1 was significantly associated with 16-20 mL increased FEV₁ or FVC in women, and 28-34 ml increased FEV₁ or FVC in men. We obtained similar results in a secondary analysis of lung function in which Global Lung Function Initiative (GLI) z-scores were calculated for lung function measures (**e-Table 3**).

DISCUSSION

Among adult non-diabetic participants in the UK Biobank, a higher peripheral serum IGF-1 levels was significantly associated with lower odds of physician-diagnosed asthma and current wheeze, independently of BMI, HbA1c, and other potential confounders. Moreover, serum IGF-1 was significantly and positively associated with FEV₁ and FVC in adults of both sexes, with

larger effect estimates in men. To our knowledge, this is the first large epidemiological study of serum IGF-1, asthma, and asthma outcomes.

Our findings are consistent with some but not all prior studies of IGF-1 and lung function. In a population-based survey of 1,326 German healthy adults aged 20 to 79 years, IGF-1 was positively associated with FEV₁ and FVC¹⁹. A similar association was found in women, but only in those 50 years and older¹⁹. In another study of 843 Welsh men aged 45 to 59 years, the IGF-1 to IGFBP-3 ratio was positively associated with FEV₁/FVC. However, that study did not include women and no information was collected on asthma status¹⁸. Others have reported similar results in other pulmonary diseases, as serum IGF-1 was positively associated with percent-predicted FEV₁ before and after the treatment of children with cystic fibrosis²⁷. Our multivariable analyses reported positive associations between serum IGF-1 and FEV₁ or FVC in both sexes, regardless of a diagnosis of asthma, with larger effect estimates in men. Our sex-specific results may be explained by larger airway diameter and lung volumes in men than in women, as well as differences in the levels of sex steroid hormones²⁸.

In contrast to our finding of an inverse association between IGF-1 level and asthma or wheezing, a case-control study of 50 subjects reported a positive association between serum IGF-1 and asthma, and a negative correlation between IGF-1 and FEV₁/FVC and asthma control¹⁷. However, that study was limited by small sample size and under-representation of males (3/27 cases and 4/23 controls), having IGF-1 levels well below the expected normal range, and lack of analyses unadjusted for potential confounders.

Despite the dearth of epidemiological and clinical studies of IGF-1 and asthma, there is substantial preclinical evidence of a potential role of IGF-1 in asthma pathobiology. In an ovo-albumin (OVA)-induced murine model of asthma, IGF-1 was upregulated in the airways, and administration of IGF-1 neutralizing antibodies improved airway resistance, airway inflammation, and airway wall thickening. An increase in IGFBP-3, an inhibitor of cell growth and promoter of apoptosis, was also observed after OVA challenge¹⁵. *In vivo*, IGFBP-3 has been shown to be induced by IGF-1, and IGFBP-3 level has been found to increase in airway epithelial cells of patients with asthma as compared to individuals without asthma¹⁶. In another murine model of asthma, IGF-1 in the lungs was upregulated by interleukin (IL)-33, and such elevated IGF-1 was predominantly derived from alveolar macrophages. Moreover, IGF-1 prevented the phagocytosis of apoptotic cells by alveolar epithelial cells and increased the release of inflammatory contents of apoptotic cells, leading to increased airway inflammation^{29, 30}. Thus, findings from preclinical experimental studies suggest that increased IGF-1 or IGF-1 receptor signaling increase asthma risk, while results from the current study and other epidemiologic studies suggest that IGF1 is associated with lower risk for asthma.

The apparent paradoxical findings for IGF-1 and asthma could be partly explained by the fact that preclinical models have measured IGF-1 in the lung, while epidemiologic studies have assessed peripheral (circulating) serum IGF-1 levels, which could plausibly have different effects on immune responses and airway inflammation. Moreover, a bidirectional feedback between IGF-1 and T helper (Th) 2 cytokines may contribute to the conflicting findings of experimental and epidemiologic studies. An *in vitro* study reported that IL-17F induces expression of IGF-1 in bronchial epithelial cells, while both IL-4 and IL-13 enhanced IL-17F-induced IGF-1 expression,

suggesting that an IL-17F/IGF-1 axis may contribute to pulmonary allergic responses³¹. On the other hand, a negative feedback between proinflammatory cytokines and IGF-1 has been suggested¹². Tumor necrosis factor (TNF)- α and IL-1 β can decrease IGF-1 sensitivity by enhancing IGFBP production and impeding IGF-1 binding to its receptor IGF-1R through an insulin receptor substrate (IRS) – Akt pathway. In contrast, IGF-1 can suppress proinflammatory cytokine signaling by increasing IL-10 secretion or directly via c-Jun N terminal kinase (JNK) and NF- κ B pathways¹².

Proinflammatory cytokines implicated in IGF-1 resistance may further explain potential beneficial effects of IGF-1 on respiratory health from epidemiologic studies, which were not considered in preclinical IGF-1 models. Lower IGF-1 levels have been associated with characteristics of MS, including higher waist-to-hip ratio, triglycerides levels, and systolic and diastolic blood pressure, as well as impaired insulin sensitivity in non-diabetic individuals³². MS was associated with a 34% increase in asthma in a study of 4,060 elderly Koreans (≥ 65 years), and this association was substantially mediated by insulin resistance and systemic inflammation³³. In a study of adolescents with and without asthma, we previously reported that insulin resistance is negatively associated with FEV₁ and FVC, and that MS is associated with lower FEV₁/FVC³⁴. The absence of effect modification of MS in our analysis also highlights the importance of metabolic signaling pathways in lung health independent of MS or overt diabetes. Collectively, these findings support further investigation of how the endocrine system modulates key immune responses in asthma.

Our study has several limitations. First, we cannot examine temporal relationships in this cross-sectional study. Second, IGFBP-3 can modulate IGF-1 bioavailability or function, and it was not measured in the UK Biobank. Circulating IGF-1 is bound to one of seven IGF binding proteins, of which IGFBP-3 is the most abundant⁷, and the IGF-1/IGFBP-3 ratio may represent a better index for metabolic risk³⁵. Third, the fasting time of UK Biobank participants varied (median =3 hours). Therefore, MS assessment was not ideal in our study, as fasting glucose levels should be measured after at least 8 hours of fasting. However, we excluded subjects with diabetes or taking insulin, and adjusted for HbA1c in our models to account for undiagnosed diabetes. Fourth, a “healthy volunteer” selection bias has been suggested for the UK Biobank, and thus our findings may not be generalizable to the British population at large. Compared with the general population, UK Biobank participants were less likely to be obese or to smoke, and had fewer self-reported health conditions³⁶. Lastly, we lack data on several potential confounders, including allergic sensitization, environmental exposure to endocrine disruptors, physical activity, and use of medications such as metformin or corticosteroids. However, we excluded participants who were diagnosed with diabetes or who used insulin, and thus the number of participants on metformin (if any) would be small. Moreover, we obtained similar results in a sensitivity analysis excluding participants who reported current use of asthma medications (data not shown).

In summary, higher serum IGF-1 levels are associated with lower odds of physician-diagnosed asthma and current wheeze in middle-aged and older British adults in the UK Biobank. In this population, higher IGF-1 levels are also associated with higher FEV₁ and FVC, with a slightly larger estimated effects in men. Given opposite results in prior preclinical studies, our findings warrant further assessment in longitudinal studies including young and old adults.

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FIGURE LEGENDS

Figure 1- Flowchart for selection of the UK Biobank participants included in the current analysis

Figure 2- Serum levels of IGF-1 in women and men, by age group and asthma status

Figure 3- Multivariable analysis of IGF-1 and asthma in all participants, and separately in women and men.

Footnote:

Q=quartile. All models adjusted for sex (in all participants), age, ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, and C-reactive protein.

Table 1. Characteristics of study participants, by asthma status

Characteristics	Asthma (n=34,023)	Controls (n=263,567)
Age at recruitment	55.0 ± 8.2 [*]	55.9 ± 8.1
Female sex	19394 (57.0) [*]	141031 (53.5)
Ethnicity		
Caucasian	32517 (95.6) [*]	252582 (95.8)
Other	1512 (4.4)	11019 (4.2)
Annual household income < £30,000	16083 (47.3)	124012 (47.1)
BMI (kg/m ²)	27.8 ± 5.1 [*]	27.1 ± 4.5
Obesity (BMI > 30 kg/m ²)	9094 (26.9) [*]	57050 (21.8)
Smoking		
Never	21981 (64.6) [*]	170159 (64.6)
Former	8983 (26.4)	67130 (25.5)
Current	3059 (9.0)	26278 (10.0)
Pack-years of cigarette smoking	8.1 ± 15.6	7.9 ± 15.1
IGF-1 (nmol/L)	21.4 ± 5.8 [*]	21.6 ± 5.6
HbA1c (mmol/mol)	35.3 ± 4.6 [*]	35.1 ± 4.6
CRP (mg/L)	3.0 ± 4.9 [*]	2.5 ± 4.1
Metabolic syndrome [†]	8496 (29.2) [*]	59055 (26.3)
FEV ₁ (ml) [†]	2677 ± 725 [*]	2913 ± 724
FVC (ml) [†]	3682 ± 929 [*]	3837 ± 919
FEV ₁ /FVC (%) [†]	72.5 ± 7.6 [*]	76.1 ± 5.9
Wheeze in the last year	21991 (65.5)	-
Asthma-related hospitalization, ever	1086 (3.4)	-

Abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor 1; HbA1c, glycated hemoglobin A1c; CRP, C-reactive protein; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity

Results are shown as mean ± standard deviation (SD) for continuous variables, and as N (%) for binary variables. [†]Numbers (%) may vary due to missingness.

^{*} P <0.05 for comparison of participants with current asthma vs. controls, within each study cohort.

Table 2. Multivariable analysis of IGF-1 and asthma by smoking status

IGF-1 quartile (nmol/L)	Current smokers (n=29,337)	Never smoker and former smokers with < 10 pack-year cigarette smoking (n=214,907)
	Odds Ratio (95% Confidence Interval)	
Q1 (< 17.8)	1.0	1.0
Q2 (17.8- < 21.5)	0.86 (0.78-0.95)*	0.95 (0.91-0.98)*
Q3 (21.5- < 25.0)	0.80 (0.72-0.89)*	0.92 (0.88-0.95)*
Q4 ($\geq$ 25.0)	0.77 (0.69-0.86)* [†]	0.89 (0.85-0.92)* [†]

Abbreviation: IGF-1, insulin-growth like factor 1

All models adjusted for age, sex, ethnicity, annual household income, body mass index, pack-years of cigarette smoking (in current smokers), the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, and C-reactive protein.

*P < 0.01, [†]P for trend < 0.05

Table 3. Multivariable analysis of quartiles of serum IGF-1 level and asthma outcomes in participants with asthma (n=34,023)

	All participants	Women	Men
IGF-1 quartile (Q), nmol/L	Odds Ratio (95% Confidence Interval)		
Wheeze in the last year	n=21,991	n=12,477	n=9,514
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.88 (0.83-0.95) [†]	0.90 (0.82-0.97) [*]	0.87 (0.78-0.97) [*]
Q3 (21.2- < 24.8)	0.88 (0.83-0.95) [†]	0.89 (0.82-0.98) [*]	0.87 (0.78-0.97) [*]
Q4 (≥ 24.8)	0.89 (0.83-0.96) ^{†‡}	0.92 (0.84-1.00)	0.87 (0.78-0.97) ^{*‡}
At least one asthma-related hospitalization	n=1,086	n=713	n=373
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.98 (0.82-1.16)	0.95 (0.77-1.17)	1.04 (0.75-1.44)
Q3 (21.2- < 24.8)	1.18 (0.99-1.40)	1.17 (0.95-1.44)	1.23 (0.90-1.68)
Q4 (≥ 24.8)	0.97 (0.81-1.17)	0.87 (0.69-1.10)	1.17 (0.85-1.62)

Abbreviation: IGF-1, insulin-like growth factor 1

All models adjusted for sex (in all participants), age, ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, and C-reactive protein.

*P <0.5, [†]P <0.01, [‡]P for trend <0.05

Table 4. Multivariable analysis of IGF-1 and asthma and asthma outcomes adjusting for metabolic syndrome

IGF-1 quartile (nmol/L)	All participants (n=253,718)	Women (n=135, 541)	Men (n=118, 177)
	Odds Ratio (95% Confidence Interval)		
Asthma	n=29,146	n=16,463	n=12,683
Q1 (< 17.8)	1.0	1.0	1.0
Q2 (17.8- < 21.5)	0.94 (0.91-0.97) [†]	0.95 (0.91-0.99) [*]	0.92 (0.87-0.97) [†]
Q3 (21.5- < 25.0)	0.90 (0.87-0.93) [†]	0.92 (0.88-0.97) [†]	0.87 (0.82-0.92) [†]
Q4 (≥ 25.0)	0.88 (0.85-0.91) ^{†‡}	0.89 (0.85-0.94) ^{†‡}	0.85 (0.81-0.90) ^{†‡}
Participants with asthma			
Wheeze in the last year	n=18,824	n=10,587	n=8,237
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.87 (0.81-0.94) [†]	0.87 (0.80-0.96) [†]	0.87 (0.77-0.97) [*]
Q3 (21.2- < 24.8)	0.89 (0.82-0.95) [†]	0.90 (0.82-0.99) [*]	0.86 (0.77-0.97) [*]
Q4 (≥ 24.8)	0.87 (0.81-0.94) ^{†‡}	0.91 (0.83-1.01)	0.83 (0.74-0.93) ^{†‡}
At least one asthma-related hospitalization	n=896	n=590	n=306
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.99 (0.82-1.20)	0.94 (0.75-1.19)	1.12 (0.78-1.60)
Q3 (21.2- < 24.8)	1.21 (0.99-1.46)	1.14 (0.91-1.44)	1.37 (0.96-1.92)
Q4 (≥ 24.8)	1.01 (0.83-1.24)	0.91 (0.71-1.17)	1.23 (0.86-1.76)

Abbreviation: IGF-1, insulin-like growth factor 1

All models adjusted for age, sex (in all participants), ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, C-reactive protein, and metabolic syndrome. Analyses stratified by sex, given evidence of effect modification (P for interaction=0.01).

*P <0.05, [†]P <0.01, [‡]P for trend <0.05

Table 5 – Multivariable analysis of IGF-1 and lung function measures

	All participants (n=212,462)	Women (n=113,769)	Men (n=98,693)
IGF-1 per quartile increment	β (95% Confidence Interval)		
All Participants			
FEV ₁ (ml)	20.9 (19.1, 22.7)*	15.9 (13.8, 17.9)*	28.4 (25.3, 31.5)*
FVC (ml)	25.6 (23.4, 27.7)*	19.5 (17.0, 22.0)*	34.0 (30.4, 37.6)*
FEV ₁ /FVC (%)	0.01 (-0.02, 0.03)	0.001 (-0.03, 0.03)	0.02 (-0.02, 0.06)
Participants without asthma			
	n=188,123	n=100,031	n=88,092
FEV ₁ (ml)	20.8 (18.9, 22.7)*	15.9 (13.7, 18.1)*	27.8 (24.6, 31.0)*
FVC (ml)	25.5 (23.2, 27.7)*	19.8 (17.1, 22.4)*	33.2 (29.4, 37.0)*
FEV ₁ /FVC (%)	0.003 (-0.02, 0.03)	-0.01 (-0.03, 0.02)	0.02 (-0.02, 0.05)
Participants with asthma			
	n=24,339	n=13,738	n=10,601
FEV ₁ (ml)	21.37 (15.5, 27.2)*	15.4 (9.0, 21.8)*	33.0 (22.5, 43.6)*
FVC (ml)	26.3 (19.8, 32.7)*	17.6 (10.3, 24.9)*	40.2 (28.9, 51.6)*
FEV ₁ /FVC (%)	0.03 (-0.05, 0.12)	0.04 (-0.06, 0.14)	0.07 (-0.07, 0.21)

Abbreviation: IGF-1, insulin-like growth factor 1; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

All models adjusted for asthma status (in all participants), age, sex (in all participants), ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season and the time of the day when the examination was performed, and serum level of glycated hemoglobin A1c, and C-reactive protein. Models for FEV₁ and FVC were additionally adjusted for height and height squared.

*P <0.01

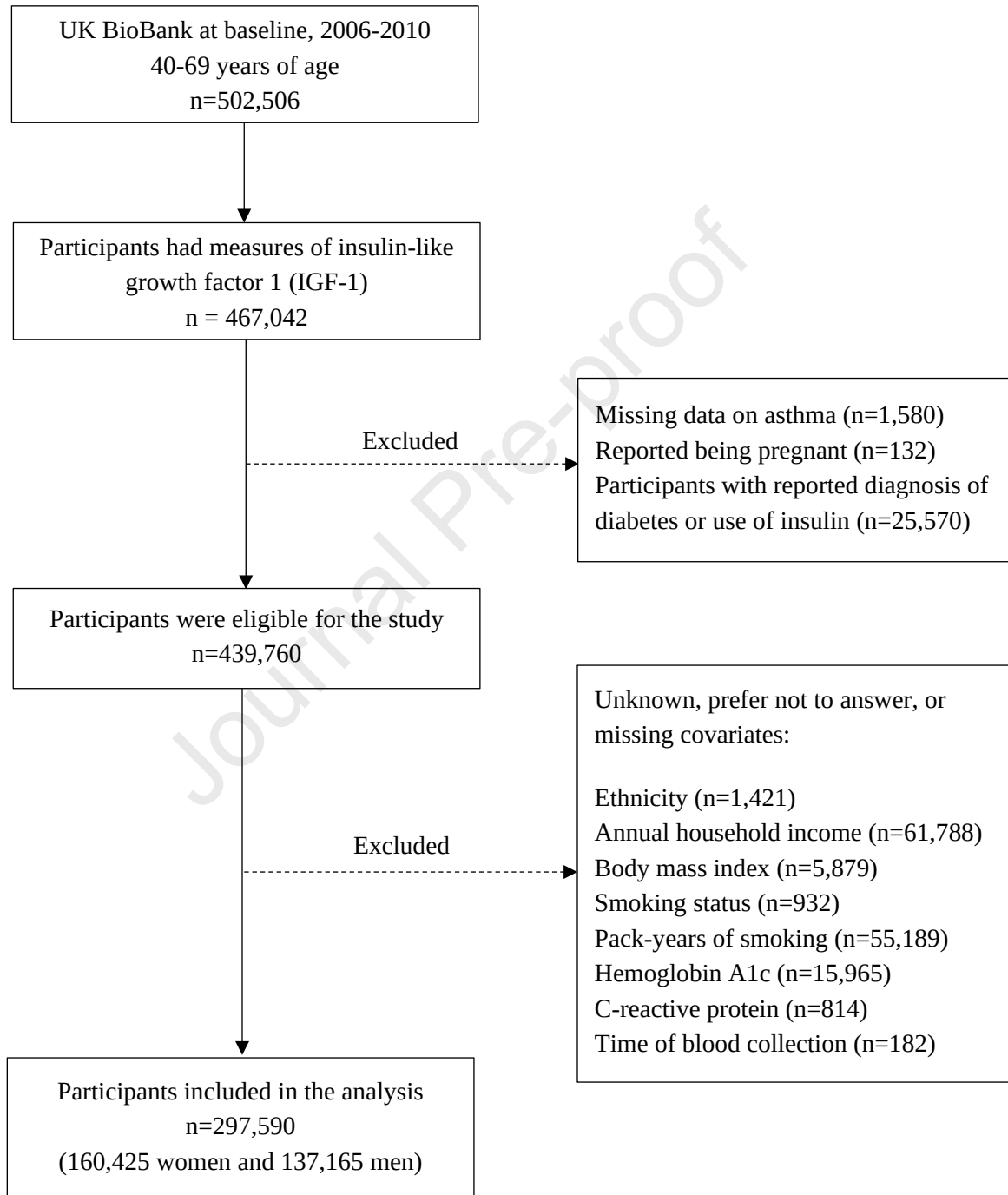
Figure 1

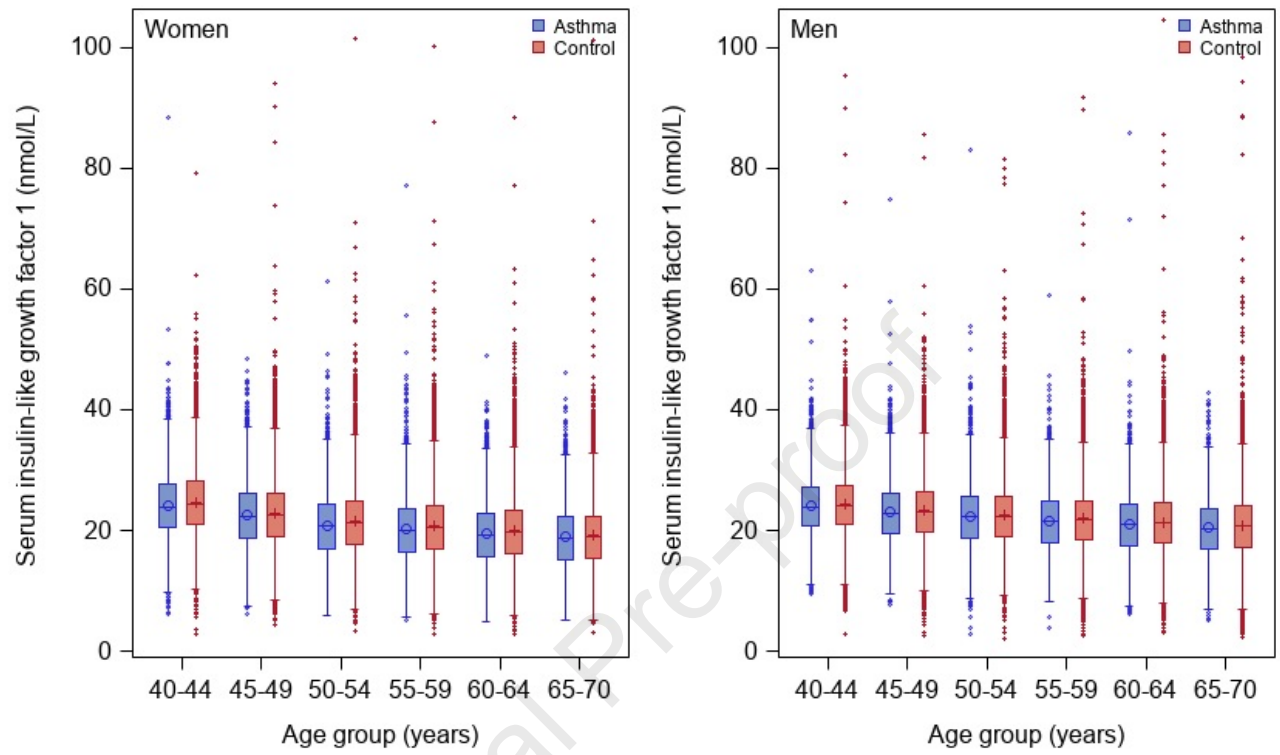
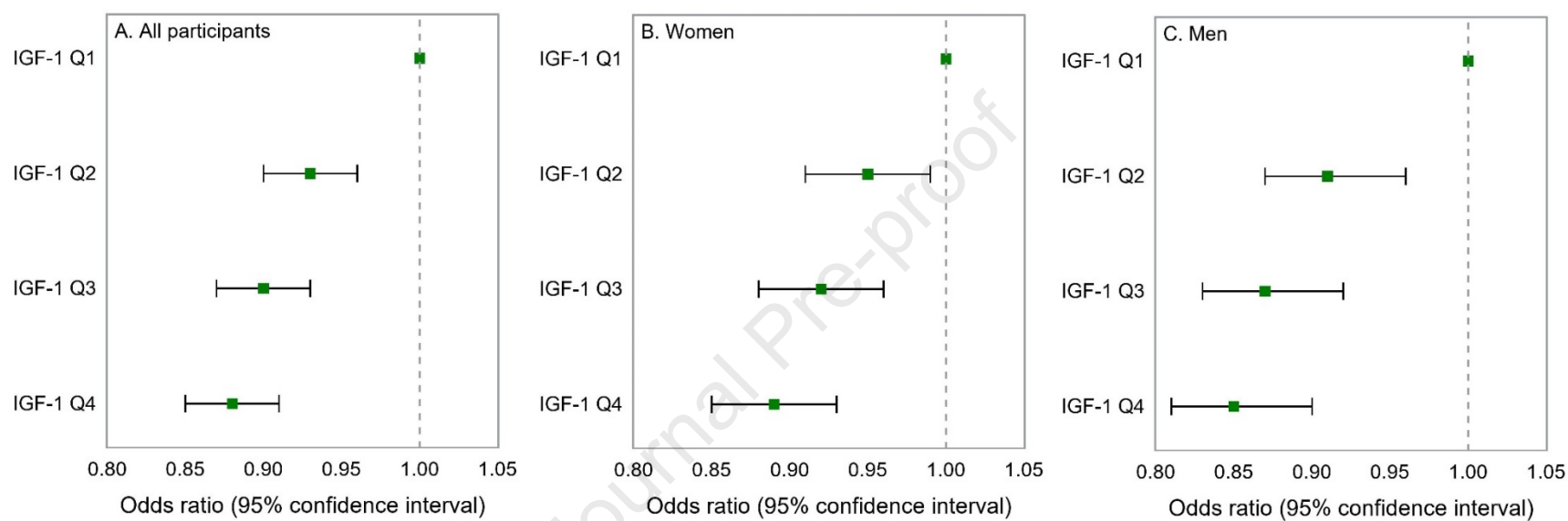
Figure 2

Figure 3

e-Table 1. Sensitivity analysis on IGF-1 and asthma

	All participants	Women	Men
IGF-1 quartile (nmol/L)	Odds Ratio (95% Confidence Interval)		
Excluding participants with a diagnosis of emphysema or chronic bronchitis	n=293,114	n=158,226	n=134,888
Q1 (< 17.6)	1.0	1.0	1.0
Q2 (17.6- < 21.3)	0.93 (0.90-0.97) [†]	0.95 (0.91-0.99) [*]	0.92 (0.87-0.96) [†]
Q3 (21.3- < 24.9)	0.90 (0.87-0.93) [†]	0.91 (0.87-0.95) [†]	0.87 (0.83-0.92) [†]
Q4 (≥ 24.9)	0.87 (0.84-0.90) ^{†‡}	0.87 (0.85-0.93) ^{†‡}	0.85 (0.81-0.90) ^{†‡}
Multiple imputation	n=439,760	n=242,249	n=197,511
Q1 (< 17.6)	1.0	1.0	1.0
Q2 (17.6- < 21.3)	0.92 (0.90-0.95) [†]	0.92 (0.89-0.96) [†]	0.92 (0.88-0.96) [†]
Q3 (21.3- < 24.9)	0.89 (0.87-0.92) [†]	0.91 (0.88-0.94) [†]	0.88 (0.84-0.92) [†]
Q4 (≥ 24.9)	0.88 (0.85-0.90) ^{†‡}	0.89 (0.86-0.92) ^{†‡}	0.86 (0.83-0.90) ^{†‡}

All models adjusted for age, sex (in all participants), ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, and C-reactive protein.

*P < 0.05, [†]P < 0.05, [‡]P for trend < 0.05

e-Table 2. Multivariable analysis of IGF-1 and asthma hospitalization in participants with asthma (n=34,023)

	All participants	Women	Men
IGF-1 quartile (nmol/L)	Odds Ratio (95% Confidence Interval)		
≥1 asthma hospitalization after IGF-1 measure	n=440	n=286	n=154
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.88 (0.68-1.15)	0.87 (0.63-1.20)	0.92 (0.57-1.48)
Q3 (21.2- < 24.8)	1.04 (0.80-1.35)	0.98 (0.71-1.35)	1.16 (0.74-1.82)
Q4 (≥ 24.8)	0.82 (0.61-1.09)	0.82 (0.58-1.18)	0.84 (0.51-1.37)
≥1 asthma hospitalization 1 year prior to or after IGF-1 measure	n=147	n=95	n=154
Q1 (< 17.4)	1.0	1.0	1.0
Q2 (17.4- < 21.2)	0.99 (0.62-1.59)	0.97 (0.56-1.71)	1.03 (0.42-2.50)
Q3 (21.2- < 24.8)	1.32 (0.84-2.07)	1.14 (0.65-2.00)	1.67 (0.75-3.76)
Q4 (≥ 24.8)	1.02 (0.62-1.68)	0.96 (0.52-1.78)	1.17 (0.49-2.80)

All models adjusted for age, sex (in all participants), ethnicity, annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season of the examination, the time of the day when the examination was performed, serum level of glycated hemoglobin A1c, and C-reactive protein.

*P <0.5, †P <0.01, ‡P for trend <0.05

e-Table 3 – Multivariable analysis of IGF-1 and lung function measures (as z-scores)

	All participants (n=212,462)	Women (n=113,769)	Men (n=98,693)
IGF-1 quartile	β (95% Confidence Interval)		
All Participants			
FEV ₁ z-score	0.020 (0.016, 0.024)*	0.021 (0.015, 0.026)*	0.027 (0.021, 0.034)*
FVC z-score	0.020 (0.017, 0.024)*	0.022 (0.017, 0.027)*	0.028 (0.022, 0.034)*
FEV ₁ /FVC z-score	0.002 (-0.001, 0.006)	-0.002 (-0.006, 0.002)	0.001 (-0.004, 0.006)
Participants without asthma			
	n=188,123	n=100,031	n=88,092
FEV ₁ z-score	0.020 (0.016, 0.024)*	0.020 (0.014, 0.026)*	0.025 (0.018, 0.031)*
FVC z-score	0.020 (0.016, 0.024)*	0.022 (0.016, 0.027)*	0.026 (0.020, 0.032)*
FEV ₁ /FVC z-score	0.003 (-0.004, 0.006)	-0.004 (-0.006, 0.002)	-0.001 (-0.006, 0.004)
Participants with asthma			
	n=24,339	n=13,738	n=10,601
FEV ₁ z-score	0.023 (0.010, 0.036)*	0.025 (0.008, 0.042)*	0.049 (0.028, 0.070)*
FVC z-score	0.027 (0.015, 0.038)*	0.025 (0.010, 0.040)*	0.046 (0.028, 0.064)*
FEV ₁ /FVC z-score	0.001 (-0.010, 0.012)	0.003 (-0.010, 0.017)	0.017 (-0.001, 0.036)

Abbreviation: IGF-1, insulin-growth like factor 1. FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

All models adjusted for asthma status (in all participants), annual household income, body mass index, smoking status, pack-years of cigarette smoking, the season and the time of the day when the examination was performed, and serum level of glycated hemoglobin A1c, and C-reactive protein.

*P <0.01