

Original Article

Glycated Hemoglobin A_{1c}, Lung Function, and Hospitalizations Among Adults with Asthma

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What is already known about this topic? Prediabetes and diabetes have been associated with asthma.

What does this article add to our knowledge? This study shows that an elevated glycated hemoglobin A_{1c} level is associated with asthma-related hospitalizations and lower FEV₁ and forced vital capacity among adults with asthma but no diagnosis of diabetes mellitus.

How does this study impact current management guidelines? Asthmatic patients with an elevated glycated hemoglobin A_{1c} level, even if not diagnosed with diabetes, should be monitored closely because of a potential increased risk of asthma-related hospitalizations.

BACKGROUND: Insulin resistance and metabolic dysfunction have been associated with asthma risk and asthma severity.

OBJECTIVE: To examine the association between glycated hemoglobin A_{1c} (HbA_{1c}), asthma-related hospitalizations, and lung function measures among adults in the United Kingdom.

METHODS: A cross-sectional study was conducted of 47,606 adults aged 40 to 69 years who participated in the UK Biobank and had asthma but no diagnosis of diabetes mellitus. HbA_{1c} level was analyzed as a continuous measure and also categorized as normal (<42 mmol/mol) or as consistent with prediabetes/diabetes (≥42 mmol/mol). An asthma-related hospitalization was defined as ever having had a hospitalization with an *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* code of a main diagnosis compatible with asthma (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 493.x or *International Classification of Diseases, Tenth Revision, Clinical Modification* codes J45.x and

J46.x). Logistic or linear regression was used for the multivariable analysis of asthma hospitalizations and lung function measures (FEV₁, forced vital capacity [FVC], and FEV₁/FVC). All models were adjusted for age, sex, ethnic background, body mass index, average annual household income, current smoking status, pack-years of smoking, fasting time, and C-reactive protein level.

RESULTS: Both HbA_{1c} level (odds ratio, 1.03; 95% CI, 1.01–1.04) and an HbA_{1c} level in the prediabetes/diabetes range (odds ratio, 1.68; 95% CI, 1.18–2.41) were associated with 1 or more asthma hospitalizations. Moreover, both HbA_{1c} level and an HbA_{1c} level in the prediabetes/diabetes range were significantly and inversely associated with FEV₁ and FVC.

CONCLUSIONS: HbA_{1c} is linked to asthma-related hospitalizations and small decrements in FEV₁ and FVC among British adults with asthma but no diagnosis of diabetes mellitus. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■–■)

Key words: Glycated hemoglobin A_{1c} (HbA_{1c}); Asthma hospitalization; Lung function; UK Biobank

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INTRODUCTION

Asthma is a common noncommunicable respiratory disease, currently affecting approximately 235 million people worldwide.¹ In 2016, the prevalence of asthma in the United Kingdom was 9.6%, with the disease leading to nearly 93,000 hospitalizations.² Hospitalizations for asthma, resulting from severe or poorly controlled disease, account for a substantial proportion of direct health care costs from asthma.³

Insulin resistance and metabolic syndrome or its components (eg, high waist circumference and hyperglycemia) have been associated with asthma in children⁴ and adults.⁵ Moreover, metabolic dysfunction and glucose dysregulation have been associated with worse lung function in subjects with and without asthma.^{6–8} Glycated hemoglobin A_{1c} (HbA_{1c}) reflects glucose

Abbreviations used

<i>BMI</i>	Body mass index
<i>COPD</i>	Chronic obstructive pulmonary disease
<i>CRP</i>	C-reactive protein
<i>FVC</i>	Forced vital capacity
<i>HbA_{1c}</i>	Glycated hemoglobin A _{1c}
<i>ICD</i>	International Classification of Diseases
<i>ICD-9-CM</i>	International Classification of Diseases, Ninth Revision, Clinical Modification
<i>ICD-10-CM</i>	International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification
<i>UKB</i>	UK Biobank

control over a 3-month period and is a reasonable indicator of high risk for prediabetes or future diabetes in adults.⁹

Prediabetes or diabetes (defined by doctor-diagnosed diabetes or HbA_{1c} levels) has been associated with asthma exacerbations in some previous studies.¹⁰⁻¹² However, those studies were limited by lack of objective measures of glucose control, potential confounding by treatment, or nongeneralizability to nonobese individuals.¹⁰⁻¹²

We hypothesized that chronic hyperglycemia would lead to worse lung function and hospitalizations among adults with asthma. We examined this hypothesis by testing for association between HbA_{1c} level and lung function measures and hospitalizations for asthma in a cohort of adults with self-reported doctor-diagnosed asthma living in the United Kingdom. Because obesity and sex have been shown to modify the association between HbA_{1c} and lung function or asthma exacerbations,^{13,14} we tested for interactions between HbA_{1c} and these variables.

METHODS

Study population

The UK Biobank (UKB) is a large prospective population-based study of adults aged 40 to 69 years in the United Kingdom.¹⁵ The UKB recruited about 500,000 participants who lived within 40 km of any of the 22 assessment centers in England, Scotland, and Wales between 2006 and 2010.¹⁶ Figure 1 shows the flowchart for selection of participants in this analysis. A total of 47,606 adults met the following criteria and were included in the present analysis: (1) self-reported doctor-diagnosed asthma, (2) no doctor-diagnosed chronic obstructive pulmonary disease (COPD), (3) no doctor-diagnosed diabetes mellitus, and (4) complete data on HbA_{1c} and body mass index (BMI).

The UKB was approved by the UK National Health Service National Research Ethics Service (ref. no. 11/NW/0382). Informed consent was obtained from all participants. The present study was conducted using the UKB Resource under application number 43252. Details of the methods, protocols, and definitions used in the UKB can be found at <https://www.ukbiobank.ac.uk/>.

Study procedures

Blood samples were received by the UKB laboratory store after collection at the assessment centers. HbA_{1c} levels were measured in these samples using high-performance liquid chromatography on a Bio-Rad VARIANT II Turbo hemoglobin testing system (Bio-Rad Laboratories, Irvine, Calif). Spirometry was performed using a Vitalograph Pneumotrac 6800 spirometer (Vitalograph Ltd, Buckingham, England), following the European Respiratory Society/American Thoracic Society criteria for acceptability and

reproducibility.¹⁷ Participants were excluded from spirometry testing if they were pregnant (in their first or third trimester) or were being treated for tuberculosis, or if they had a chest infection in the last month (ie, influenza, bronchitis, severe cold, or pneumonia), history of a detached retina, a heart attack, eye surgery, surgery in the chest or abdomen in the previous 3 months, or history of a collapsed lung. Only spirometry testing that met the European Respiratory Society/American Thoracic Society reproducibility guidelines was included in the analysis of lung function measures.

A hospitalization for asthma was defined as ever having had a hospitalization with an *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9-CM/ICD-10-CM) code of main diagnosis compatible with asthma (ICD-9-CM code 493.x or ICD-10-CM codes J45.x and J46.x), excluding hospitalizations with an ICD code for a main diagnosis consistent with COPD (ICD-9-CM codes J43, J44, and J47 or ICD-10-CM codes 490, 491, 492, 494, and 496). Data on asthma hospitalizations were available before (range, 0-27 years; median, 7 years) and after (range, 0-11 years; median, 5 years) the participant's HbA_{1c} level measurement.

Statistical analysis

For data analysis, HbA_{1c} level was considered as both a continuous variable and a categorical variable (defined as normal [<42 mmol/mol, corresponding to an HbA_{1c} level of $<6\%$] vs consistent with prediabetes/diabetes [≥ 42 mmol/mol, corresponding to an HbA_{1c} level of $\geq 6\%$]) on the basis of UK guidelines.¹⁸ For the analysis of asthma hospitalizations, cases were subjects with asthma and 1 or more asthma-related hospitalizations (ever), and control subjects were those with asthma but no asthma-related hospitalizations (ever). For the analysis of lung function, z scores were first calculated for lung function measures on the basis of recommendations from the Global Lung Function Initiative 2012¹⁹ and then derived as inverted z scores.²⁰ We converted all inverted z scores to standard z scores by multiplying by -1 .

χ^2 and t tests were used for bivariate analyses of binary and continuous variables, respectively. Logistic or linear regression was used for the multivariable analysis of asthma hospitalizations and lung function measures. The analysis of asthma hospitalizations was adjusted for age, sex, ethnicity (non-Caucasian [including black or black British, mixed ethnic background, Asian or Asian British, Chinese, and other ethnic groups] or Caucasian [including white, British, Irish, and any other white background]), BMI (normal weight vs overweight vs obese), total annual household income ($<£18,000$; $£18,000-£100,000$; or $>£100,000$), smoking status (never/former vs current smoker), pack-years of smoking, fasting time, and C-reactive protein (CRP) level (a marker of systemic inflammation). Models for lung function measures (as z scores) were adjusted for BMI, total annual household income, smoking status, pack-years of smoking, fasting time, CRP level, and asthma-related hospitalizations (as an indicator of asthma severity or control). Because obesity and/or sex may modify the effect of hyperglycemia on asthma,¹³ we tested for an interaction between HbA_{1c} and weight status (as BMI or categories of weight status [normal weight, overweight, and obesity]) or sex on either asthma hospitalizations or lung function measures in the multivariable models. R program version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

RESULTS

Table I presents the main characteristics of the 47,606 participants, including 45,984 subjects who had asthma but were



To reduce potential misclassification of COPD as asthma, we conducted a sensitivity analysis restricted to 30,044 subjects who were never smokers or former smokers who smoked 10 pack-years or less, obtaining similar results for HbA_{1c} level but weaker and less significant results for an HbA_{1c} level in the

Table IV presents the results of the multivariable analysis of HbA_{1c} level or an HbA_{1c} level in the prediabetes/diabetes range and lung function measures (as *z* scores). In this analysis, HbA_{1c} level was significantly and negatively associated with FEV₁ and FVC, but not with FEV₁/FVC. For example, each mmol/mol increment in HbA_{1c} level was significantly associated with a decrement of 0.015 in FEV₁ *z* score. Similarly, an HbA_{1c} level in the prediabetes/diabetes range was significantly associated with decrements in FEV₁ and FVC. There was no significant effect of an interaction between sex or weight status (as BMI or categories of weight status [normal weight, overweight, and obesity]) and HbA_{1c} level or an HbA_{1c} level in the prediabetes/diabetes range on any lung function measure ($P \geq .10$ in all instances). Moreover, a sensitivity analysis restricted to never smokers and former smokers with 10 pack-years or less of smoking yielded very similar results for HbA_{1c} level, which remained significantly and inversely associated with FEV₁ and FVC, but not with FEV₁/FVC. In this subgroup analysis, an HbA_{1c} level in the prediabetes/diabetes range remained significantly associated with lower FEV₁ and FVC, although the magnitude of the effect estimates was attenuated (**Table V**).

TABLE I. Characteristics of study participants (N = 47,606)*

Characteristic	No asthma-related hospitalization (N = 45,985 [96.6%])	≥1 asthma-related hospitalizations (N = 1,621 [3.4%])
Age (y)	55.4 ± 8.3	55.6 ± 8.5
Sex: male	19,063 (41.7)	522 (32.4)†
Ethnic background‡, n (%)		
Non-Caucasian	2,162 (4.7)	116 (7.2)†
Caucasian	43,667 (95.3)	1,499 (92.8)
BMI (kg/m ²)	27.8 ± 5.1	28.9 ± 5.8†
Normal weight (BMI < 25)	14,411 (31.3)	401 (24.7)†
Overweight (25 ≤ BMI < 30)	19,179 (41.7)	662 (40.8)
Obese (BMI ≥ 30)	12,395 (27.0)	558 (34.4)
Total annual household income (£)		
<18,000	8,641 (21.8)	400 (29.3)†
18,000-100,000	28,637 (72.2)	929 (68.1)
>100,000	2,373 (6.0)	35 (2.6)
Smoking status		
Never/former smoker	41,716 (91.1)	1,447 (89.8)
Current smoker	4,092 (8.9)	164 (10.2)
Pack-years of smoking	22.1 ± 18.2	21.7 ± 17.9
Fasting time (h)	3.8 ± 2.5	3.9 ± 2.6§
<4	25,528 (55.5)	843 (52.0)†
≥4	20,454 (44.5)	778 (48.0)
HbA _{1c} (mmol/mol)	35.3 ± 4.6	35.9 ± 4.5†
Normal (<42)	43,786 (95.2)	1,500 (92.5)†
Prediabetes/diabetes range (≥42)	2,199 (4.8)	121 (7.5)
CRP (mg/L)	2.9 ± 4.7	3.7 ± 5.7†
FEV ₁ z score	-0.84 ± 1.17	-1.26 ± 1.24†
FVC z score	-0.38 ± 1.07	-0.65 ± 1.10†
FEV ₁ /FVC z score	-0.86 ± 1.02	-1.15 ± 1.15†

*Values are presented as n (%) or mean ± SD. Values may vary because of missingness.

†*P* < .01.

‡Non-Caucasian ethnic background includes black or black British, mixed ethnic background, Asian or Asian British, Chinese, and other ethnic groups. Caucasian ethnic background includes white, British, Irish, and any other white background.

§*P* < .05.

DISCUSSION

HbA_{1c} level, a surrogate marker of blood glucose levels over the previous 2 to 3 months, has been integrated into the standard diagnosis criteria for diabetes mellitus since 2009.²¹ Among 47,606 British adults with asthma, we found that both the HbA_{1c} level and the prediabetes/diabetes level (range defined on the basis of an elevated HbA_{1c} level) were significantly associated with asthma-related hospitalizations and decreased FEV₁ and FVC.

Diabetes mellitus has been previously linked to asthma exacerbations among adults in the United States and the United Kingdom. In a cross-sectional analysis of data from 709 participants in the US-based Severe Asthma Research Program 3 cohort, subjects with exacerbation-prone asthma were more likely to self-report a diagnosis of diabetes mellitus than those without exacerbation-prone asthma (*P* = .005). However, this finding was nonstatistically significant after adjustment for covariates in a multivariable analysis.¹² In contrast, a historical study of 130,547 patients (aged 12-80 years) in 2 databases from the United Kingdom showed that a diagnosis of diabetes type 1 or type 2 was significantly associated with 1.53 times increased odds of asthma-related hospitalizations within the next year, even

after accounting for overweight or obesity, smoking status, and other potential confounders.¹⁰ Using HbA_{1c} levels instead of a historical or self-reported diagnosis of diabetes, a claims-based study of 5722 obese adults in the United States found that participants with an HbA_{1c} level in the prediabetic (defined as 5.7% HbA_{1c} ≤ HbA_{1c} ≤ 6.4%) or diabetic (defined as HbA_{1c} ≥ 6.5%) range had 1.27 to 1.33 times significantly higher odds of severe asthma exacerbations (including hospitalizations, emergency department visits, and use of systemic corticosteroids for asthma) than those with a normal HbA_{1c} level.¹¹ However, that study did not account for BMI and only partially adjusted for cigarette smoking. Moreover, 1 study of 297 adults (≥18 years old) with coexistent severe asthma and diabetes showed that the severity of asthma was negatively associated with diabetes control (odds ratio, 1.55; 95% CI, 1.32-2.21).²²

Our study differs from previous reports with regard to study design,^{10-12,22} adjustment for confounders including cigarette smoking and BMI, inclusion of participants with asthma who had normal weight or were overweight,¹¹ use of a biomarker for the diagnosis of diabetes (HbA_{1c}), availability of data on asthma hospitalizations up to 13 years after the HbA_{1c} level measurement, and exclusion of participants with doctor-diagnosed

TABLE II. Analysis of the relation between HbA_{1c} level or prediabetes/diabetes status and asthma-related hospitalizations among all participants (N = 47,606) in the UKB

Exposure	Odds ratio (95% CI)	
	Unadjusted analysis	Adjusted analysis*
HbA _{1c} level (per each mmol/mol increment)	1.02 (1.02-1.03) [†]	1.03 (1.01-1.04) [†]
Normal HbA _{1c} level (<42 mmol/mol) (N = 45,286)	1.0	1.0
Prediabetes/diabetes range (≥42 mmol/mol) (N = 2,320)	1.61 (1.33-1.94) [†]	1.68 (1.18-2.41) [†]

*Models adjusting for age, sex, ethnicity, BMI, total annual household income, smoking status, pack-years of smoking, fasting time, and CRP level.

[†]P < .01.**TABLE III.** Analysis of the relation between HbA_{1c} level or prediabetes/diabetes status and asthma-related hospitalizations among all participants (N = 46,802) who had at least 1 hospitalization after the HbA_{1c} level measurement

Exposure	Odds ratio (95% CI)	
	Unadjusted analysis	Adjusted analysis*
HbA _{1c} level (per each mmol/mol increment)	1.03 (1.02-1.04) [†]	1.03 (1.00-1.05) [‡]
Normal HbA _{1c} level (<42 mmol/mol) (N = 44,537)	1.0	1.0
Prediabetes/diabetes range (≥42 mmol/mol) (N = 2,265)	1.75 (1.36-2.26) [†]	1.58 (0.95-2.64)

*Models adjusting for age, sex, ethnicity, BMI, total annual household income, smoking status, pack-years of smoking, fasting time, and CRP level.

[†]P < .01.[‡]P < .05.**TABLE IV.** Analysis of the relation between HbA_{1c} level or prediabetes/diabetes status and lung function measures (as z scores) among 47,606 participants in the UKB*

Exposure	β coefficient (95% CI)		
	FEV ₁	FVC	FEV ₁ /FVC
HbA _{1c} level (per each mmol/mol increment) (N = 47,606)	-0.015 (-0.021 to -0.010) [†]	-0.015 (-0.020 to -0.010) [†]	-0.003 (-0.008 to 0.002)
Prediabetes/diabetes range (≥42 mmol/mol) (N = 2,320)	-0.210 (-0.328 to -0.093) [†]	-0.227 (-0.331 to -0.124) [†]	-0.044 (-0.143 to 0.056)

*Models adjusting for BMI, average total household income, smoking status, pack-years of smoking, fasting time, CRP level, and having ever been hospitalized for asthma.

[†]P < .01.**TABLE V.** Analysis of the relation between HbA_{1c} level or prediabetes/diabetes status and lung function measures (as z scores) among 30,044 never smokers and former smokers who smoked ≤10 pack-years*

Exposure	β coefficient (95% CI)		
	FEV ₁	FVC	FEV ₁ /FVC
HbA _{1c} level (per each mmol/mol increment) (N = 30,044)	-0.013 (-0.017 to -0.009) [†]	-0.015 (-0.019 to -0.012) [†]	0.001 (-0.003 to 0.004)
Prediabetes/diabetes range (≥42 mmol/mol) (N = 1,281)	-0.102 (-0.202 to -0.001) [‡]	-0.156 (-0.246 to -0.066) [†]	0.064 (-0.019 to 0.148)

*Models adjusting for BMI, smoking status, average total household income, fasting time, CRP level, and having ever been hospitalized for asthma.

[†]P < .01.[‡]P < .05.

diabetes mellitus to minimize confounding of the analysis of HbA_{1c} level by diabetes *per se* and/or increased access to health care.^{10,12,22} Moreover, we used an HbA_{1c} level of 42 mmol/mol (corresponding to 6.0%) as the cutoff for the diagnosis of prediabetes/diabetes, which is lower than that used in the previous study of obese adults in the United States.¹¹

Findings from previous studies suggest that there may be a bidirectional association between HbA_{1c} level and asthma hospitalizations.^{11,23} Despite reduced statistical power, findings from a sensitivity analysis, including only 817 cases with 1 or more asthma hospitalizations after their HbA_{1c} level was checked, suggest that an elevated HbA_{1c} level may indeed lead to an increased risk of subsequent asthma exacerbations. HbA_{1c} (a surrogate of chronic hyperglycemia) can indicate insulin

resistance, which has been linked to reduced lung function. *In vivo* and *in vitro* experiments suggest that hyperinsulinemia can induce hypercontractility of tracheal smooth muscle by inducing airway smooth muscle proliferation and collagen release²⁴ and by modifying the expression of extracellular matrix protein (eg, laminin²⁵). Moreover, insulin resistance may induce systemic inflammation, leading to severe asthma exacerbations.²⁶

Diabetes and HbA_{1c} level have been shown to be negatively associated with lung function measures in some studies with a smaller sample size.^{7,8,27,28} In a multivariable analysis of 15,792 US adults in the Atherosclerosis Risk in Communities Study, FEV₁% predicted and FVC% predicted were 3.6% and 2.4% significantly lower in adults with diabetes than in those without diabetes, after adjusting for BMI, waist circumference, smoking,

and other covariates. In contrast to the Atherosclerosis Risk in Communities Study, a US nationwide survey study demonstrated that there was a significant nonlinear inverse association between an elevated HbA_{1c} percentage and FEV₁, FVC, and FEV₁/FVC ratio, after adjusting for BMI and waist-to-hip ratio in 4257 adults without a clinical diagnosis of diabetes.²⁸ Neither of these 2 studies considered potential effects of respiratory comorbidities, such as asthma, on glucose metabolism. Furthermore, another study analyzing the data from 2945 nonsmoking African Americans revealed that both women (n = 357) and men (n = 124) with diabetes had lower FEV₁ and FVC than those with normal glucose tolerance (1445 women and 654 men), but there was no significant difference in FEV₁ or FVC between women (n = 236) or men (n = 129) with impaired glucose tolerance and those with normal glucose tolerance.⁸ In a cross-sectional study of 3161 Japanese adults, each 1% increment in HbA_{1c} level was significantly associated with decrements of 128 mL (95% CI, 94-163) in FVC and 73 mL (95% CI, 44-101) in FEV₁ in 2175 men. There was no significant association between HbA_{1c} level and lung function among 986 women, which could be due to smaller sample size, as no evidence of a significant interaction between sex and HbA_{1c} level was demonstrated.⁷ In contrast to the present analysis, the Japanese adults did not exclude diabetic participants, and thus confounding by diabetes is possible because they cannot determine the effect of HbA_{1c} level on lung function among participants without a diagnosis of diabetes mellitus.

We found a significant but weak inverse association between HbA_{1c} level or an HbA_{1c} level in the prediabetes/diabetes range and FEV₁ and FVC, but such associations were weak. Although this suggests nonclinically significant effects of HbA_{1c} level on lung function in subjects with asthma but no diagnosis of diabetes mellitus, we cannot estimate the cumulative effects of a persistently elevated HbA_{1c} level on lung function in this cross-sectional analysis.

We recognize additional study limitations. First, we lack data on potential confounders or modifiers of the relation between HbA_{1c} level and asthma hospitalizations or lung function, such as medication use for asthma²³ and lipid dysregulation.²⁹ Second, misclassification of COPD as asthma is possible in any study of asthma in adults. However, we obtained very similar results for HbA_{1c} level and asthma hospitalizations or lung function measures after excluding current and former smokers who smoked more than 10 pack-years from the analysis. In this sensitivity analysis, the strength of the observed association between an HbA_{1c} level in the prediabetes/diabetes range and asthma hospitalizations or lung function measures was attenuated, which could be explained by smaller sample size and/or possibly reduced effects of prediabetes/diabetes in nonsmokers. Third, our findings are not generalizable to adults without asthma and adults younger than 40 years, children, and adolescents.

CONCLUSIONS

Our results suggest that an elevated HbA_{1c} level is linked to increased risk of asthma hospitalizations in British adults with asthma but no physician-diagnosed diabetes mellitus.

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TABLE E1. Analysis of the relation between HbA_{1c} level or an HbA_{1c} level in the prediabetes/diabetes range and asthma-related hospitalizations among 30,044 subjects who were never smokers or former smokers who smoked ≤ 10 pack-years*

Exposure	Odds ratio (95% CI)	
	Unadjusted analysis	Adjusted analysis [†]
HbA _{1c} level (per each mmol/mol increment)	1.03 (1.02-1.04) [‡]	1.02 (1.00-1.03) [‡]
Normal HbA _{1c} level (<42 mmol/mol) (N = 28,763)	1.0	1.0
Prediabetes/diabetes range (≥ 42 mmol/mol) (N = 1,281)	1.63 (1.27-2.10) [‡]	1.20 (0.88-1.63)

*Models adjusting for age, sex, ethnicity, BMI, smoking status, total annual household income, fasting time, and CRP level.

[†] $P < .01$.[‡] $P < .05$.