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Association between triglyceride-glucose index and fractional exhaled nitric oxide in adults with asthma from NHANES 2007–2012

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Abstract

Background Several studies have shown a potential relationship between triglyceride-glucose index (TGI) and asthma. However, limited research has been conducted on the relationship between TGI and fractional exhaled nitric oxide (FeNO).

Methods A total of 1,910 asthmatic individuals from the National Health and Nutrition Examination Survey (NHANES) database were included in this study. Linear regression analyses were used to investigate the relationship between TGI and FeNO in patients with asthma. Subsequently, a trend test was applied to verify whether there was a linear relationship between the TGI and FeNO. Finally, a subgroup analysis was performed to confirm the relationship among the different subgroup populations.

Results Multivariable linear regression analyses showed that TGI was linearly related to FeNO in the asthmatic population. The trend test additionally validated the positive linear relationship between TGI and FeNO. The result of XGBoost revealed the five most influential factors on FeNO in a ranking of contrasted importance: eosinophil (EOS), body mass index (BMI), poverty-to-income ratio (PIR), TGI, and white blood cell count (WBC).

Conclusions This investigation revealed a positive linear relationship between TGI and FeNO in patients with asthma. This finding suggests a potential relationship between TGI and airway inflammation in patients with asthma, thereby facilitating the prompt identification of irregularities and providing a basis for clinical decision making. This study provides a novel perspective on asthma management.

Keywords Asthma, Triglyceride-glucose index (TGI), Fractional exhaled nitric oxide (FeNO), XGBoost

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Introduction

Asthma is a prevalent health problem worldwide that affects individuals of all ages and has become the second most common cause of mortality in chronic airway disorders [1]. It is characterized by chronic inflammation with distinct symptoms, including shortness of breath, cough, chest distress, and/or wheezing. Global population surveys report that the current prevalence of asthma is approximately 11.5% [2]. Asthma caused 0.461 million deaths in 2019, resulting in an age-standardized mortality rate of 5.8 per 100,000 individuals. Despite a 51.3% decline in asthma incidence and death rates between 1990 and 2019, the total number of asthma cases continues to increase owing to population expansion [3, 4]. It is a highly prevalent chronic non-contagious disease associated with substantial morbidity, mortality, and loss of productivity [5].

Nitric oxide (NO) is widely acknowledged as a cellular messenger with a short half-life that contributes to several biological processes, including inflammation, immunity, cell survival, and apoptosis [6, 7]. NO plays a pathophysiological role in the complex environments of airways and lungs and induces airway hyperresponsiveness (AHR) by inflammatory mediation [8]. Under physiological conditions, NO weakly relaxes smooth muscles and protects against AHR [8]. During respiration, NO generates from the airway lining. IL-13 increases NO synthase levels in bronchial epithelial cells, a process associated with inflammation [9]. Accordingly, exhaled NO can be considered an indirect marker of elevated airway inflammation, indicative of exacerbation risk. Nowadays, fractional exhaled nitric oxide (FeNO) testing is a rising, convenient, available, and non-intrusive method. This useful tool evaluates asthmatic patients by objectively measuring cytokines, chemokines, and alarm signaling of ongoing type 2 airway inflammation, which are targets of standard anti-inflammatory therapies, such as omalizumab, dupilumab, and tezepelumab [10–12].

Inflammation and metabolism are extensively studied areas in lung disease research. Metabolic syndrome (MetS), characterized by insulin resistance (IR) and several comorbidities, has been linked to an increased incidence, prevalence, and severity of asthma [13]. Moreover, Peters et al. found that IR was associated with decreased lung function in patients with asthma [14]. TGI, an effective measure of evaluating IR [15], is associated with an increased risk of pulmonary disorders and has gradually become a biomarker for impaired lung function [16]. Zhou et al. discovered that asthmatic patients with critical illness who had a TGI greater than 4.8 had a higher likelihood of death, indicating that measuring the TGI could aid in assessing the risk and predicting the prognosis of extremely ill asthmatic patients [17].

Research on the relationship between TGI and FeNO remains scarce. Therefore, this study aimed to evaluate the relation between TGI and FeNO in asthmatic populations using NHANES data.

Materials and methods

Data source and study population

Every two years, the CDC conducts the NHANES to collect data on the nutritional and health conditions of the American population. Using a complicated and stratified approach, the NHANES carefully selects an accurately representative sample of non-institutionalized citizens. This study utilized data from 2007 to 2012, including three NHANES cycles. The following individuals were excluded: (1) those without asthma (2), those aged < 18 years (3), those with missing FeNO data, and (4) those with missing TGI data. Finally, the study included 1,910 people with asthma. The screening flowchart is shown in Fig. 1.

Measurement of TGI and FeNO

TGI = Ln (fasting triglyceride [mg/dL] × fasting glucose [mg/dL]/2). Triglycerides and fasting glucose were quantified using enzymatic assays on a Roche Modular P and Roche/Hitachi Cobas C 501 chemical analyzer employing a hexokinase-mediated reaction, respectively. Aerocrine, a company based in Stockholm, Sweden, created a portable NIOXMINO device that utilizes an electrochemical sensor to quantify the FeNO level. We computed the average value after each participant completed two repeated FeNO tests. The average of two reproducible FeNO measurements was used for the analysis.

Covariables

The investigation incorporated covariables to reduce the potential influence of confounding factors. Confounders in the analysis were age, sex, race, PIR, education, marriage, BMI, smoking, alcohol intake, hypertension, diabetes, cardiovascular disease (CVD), and other chronic airway disease (CAD), glucocorticoids (GCS) usage (whether used within 1 month), inhaled corticosteroids (ICS) (whether used within 2 days), and lipid-lowering medications (whether within a month), serum cholesterol, WBC, NEU, EOS.

Statistical analysis

First, FeNO was classified into three tertiles. The weighted chi-square test was used to determine the P-value for categorical variables. For continuous variables, the Kruskal–Wallis rank-sum test was applied to calculate the P-value. We calculated the median and IQR for non-normally distributed continuous variables and the mean and standard error (SE) for

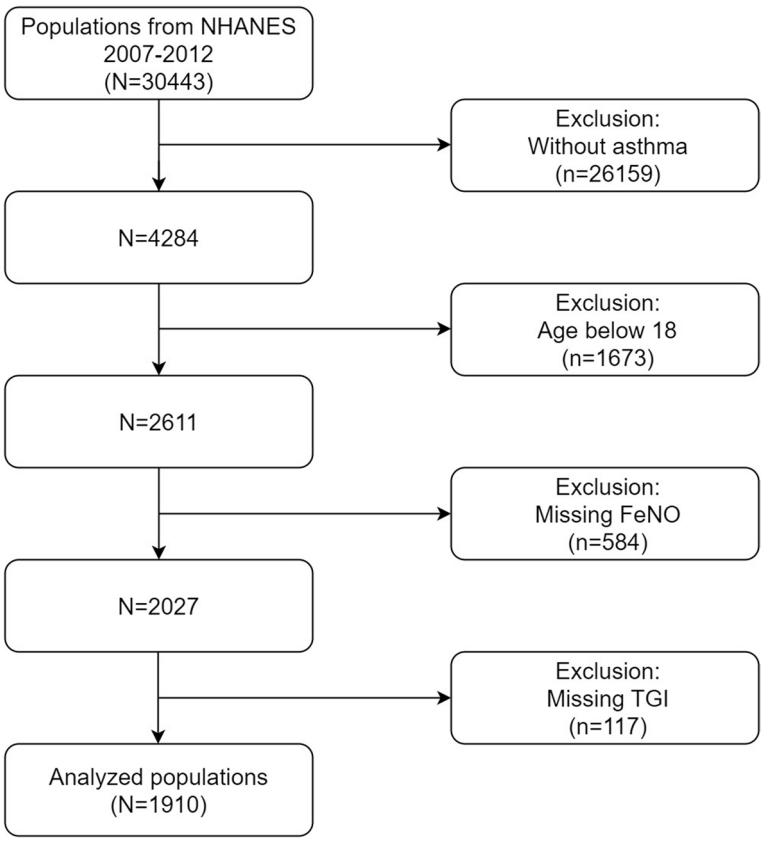

Fig. 1 Flow chart for choosing populations for study

normally distributed variables. Categorical variables were described using proportions. Moreover, in the asthmatic population, three linear regression models were used to ascertain the relationship between TGI and FeNO. Model X controlled for no covariables; Model Y controlled for sex, age, race, education, marriage, PIR, and BMI; Model Z controlled for sex, age, race, education, marriage, PIR, BMI, smoking, alcohol, hypertension, diabetes, CVD, history of other CAD, GCS use, ICS use, lipid-lowering drug use, cholesterol, WBC, NEU, and EOS. The multicollinearity of the variables was evaluated using variance inflation factor (VIF) values. A VIF greater than 10 indicates the presence of multicollinearity. Covariables were selected in the multivariable regression model to meet the following requirement: if adjusted in the model, the covariable would change the effect estimate by at least 10%. Trend tests were used to investigate whether the association between TGI and FeNO was linear. Subgroup analyses and interaction tests were performed to analyze the relationship between TGI and FeNO in various groups. Finally, the XGBoost model was applied to analyze the influence of various variables on FeNO. Multiple imputations (MICE package) were applied to address variables with missing values, and the overall percentage of missing values for each covariable was < 10%. The specific numbers of missing variables were as follows: other CAD ($n=149$), marriage ($n=145$), smoking ($n=144$), PIR ($n=137$), alcohol intake ($n=62$), BMI ($n=14$), NEU ($n=8$), EOS ($n=8$), WBC ($n=6$), and education ($n=1$). All missing covariables were randomly absent. Sample weights were implemented to accommodate the intricate sample design of the NHANES. The R program (version 4.3.1) was used to perform statistical analyses. Statistical significance was defined as a *P*-value of less than 0.05.

Results

Baseline characteristic

The study population had a mean age of 42.27 years, and most participants were white people (Table 1). This study found significant variations in the distribution of sex, race, education, PIR, smoking status, CVD, other CAD, ICS usage within 2 days, WBC, BNEU, and BEOS. However, the different FeNO tertile groups did not show any statistically significant variations in age, marital status, BMI, alcohol intake, hypertension, diabetes, GCS usage within a month, lipid-lowering drug within a month, cholesterol, or TGI.

Table 1 Baseline characteristics of investigation's population

	T1 (3.5–10)	T2 (10.5–19.5)	T3 (20-183.5)	*P* value
Gender (%)				0.0008
Female	65.28	56.82	51.30	
Male	34.72	43.18	48.70	
Age (years)	39.00 (27.00 ,53.00)	41.00 (28.00 ,55.00)	42.00 (28.00 ,57.00)	0.1052
Race (%)				0.0106
Other Race population	12.70	17.25	18.26	
White population	71.78	70.32	71.34	
Black population	15.52	12.43	10.40	
Education (%)				< 0.0001
Less than high school	24.00	14.48	11.59	
High school	24.40	21.99	20.23	
More than high school	51.60	63.53	68.18	
Marriage (%)				0.1449
Married	44.08	49.07	49.84	
Single	44.98	40.9	43.32	
Living with a partner	10.94	10.04	6.84	
PIR	2.03 (0.98 ,4.05)	3.08 (1.41 ,5.00)	3.54 (1.58 ,5.00)	< 0.0001
BMI (kg/m2)	29.41 ± 0.39	30.52 ± 0.47	29.44 ± 0.43	0.0803
Smoked at least 100 cigarettes in life (%)				< 0.0001
Yes	66.09	42.32	39.24	
No	33.91	57.68	60.76	
Alcohol intake (gm)	14.69 ± 1.69	11.28 ± 1.64	12.35 ± 1.39	0.3387
Hypertension (%)				0.8794
Yes	31.31	31.88	30.16	
No	68.69	68.12	69.84	
Diabetes (%)				0.2229
Yes	11.19	10.10	8.04	
No	88.81	89.90	91.96	
CVD (%)				0.0019
Yes	12.37	8.72	4.96	
No	87.63	91.28	95.04	
Other CAD (%)				0.0001
Yes	25.45	19.07	14.06	
No	74.55	80.93	85.94	
GCS within a month (%)				0.0656
Yes	14.61	14.68	20.52	
No	85.39	85.32	79.48	
ICS within 2 days (%)				0.0137
Yes	22.77	15.74	23.43	
No	77.23	84.26	76.57	
Lipid-lowering drug (%)				0.5448
Yes	16.16	13.68	14.44	
No	83.84	86.32	85.56	
WBC (1000 cells/uL)	7.75 ± 0.11	7.23 ± 0.10	7.02 ± 0.10	< 0.0001
NEU (1000 cells/uL)	4.65 ± 0.09	4.34 ± 0.09	4.11 ± 0.07	< 0.0001
EOS (1000 cells/uL)	0.20 (0.10 ,0.30)	0.20 (0.10 ,0.20)	0.20 (0.10 ,0.40)	< 0.0001
Cholesterol (mmol/L)	4.93 ± 0.05	5.03 ± 0.06	5.01 ± 0.05	0.3934
TGI	8.56 ± 0.04	8.63 ± 0.04	8.69 ± 0.04	0.0720

We applied the median and IQR for non-normally distributed continuous variables and the mean and SE for normally distributed continuous variables. Proportions were utilized for describing categorical variables. T1-T3 were FeNO's three tertile groups

Relationship between TGI and FENO

Multivariable linear regression analyses (models Y and Z) showed a positive relationship between TGI and FeNO in patients with asthma (Table 2). In Model Z, after controlling for all confounders, FeNO exhibited an increase of 2.32 ppb for each additional unit of TGI. The trend tests proved a linear relationship between the TGI and FeNO in models Y and Z.

Subgroup analysis

Subgroup analysis was performed to determine the relationship between the TGI and FeNO in various subgroup populations. Supplementary Table 1 presents the results grouped by sex, age, race, BMI, CVD, hypertension, diabetes, other CAD, usage of GCS within a month, ICS within 2 days, and lipid-lowering drug within a month. Subgroup analysis findings demonstrated that a statistically significant positive relationship between TGI and FeNO existed among female and white individuals over 40 years with a BMI≥30 and without CVD, diabetes, or other CAD, and without using lipid-lowering medications, GCS, or ICS. Additionally, we observed the absence of interaction effects in each subgroup analysis.

XGBoost model

The XGBoost model was applied to analyze the importance of the variables in FeNO. According to the XGBoost model, FeNO was mainly affected by five variables listed in the following decreasing order of significance: EOS, BMI, PIR, TGI, and WBC (Fig. 2).

Discussion

This is the first cross-sectional study to quantitatively assess the relationship between TGI and FeNO in asthmatic patients. Multivariable regression analyses revealed a positive linear relationship between TGI and FeNO, which was revalidated using the trend test. We then performed subgroup analyses to find a positive linear association between TGI and FeNO among female and white individuals over 40 years of age with a BMI exceeding 30 and no CVD, diabetes, other CAD, lipid-lowering drugs, GCS, or ICS. The XGBoost results showed the five most

Table 2 Association between TGI and FeNO in asthmatic populations

	Model X β (95% CI) *P* value	Model Y β (95% CI) *P* value	Model Z β (95% CI) *P* value
TGI	0.94 (-0.47, 2.35) 0.1969	1.59 (0.12, 3.06) 0.0406	2.32 (0.80, 3.83) 0.0060
TGI tertiles groups			
T1 (6.73–8.26)	Reference	Reference	Reference
T2 (8.27–8.88)	2.78 (-0.36, 5.92) 0.0897	3.26 (-0.09, 6.62) 0.0646	2.87 (0.12, 5.61) 0.0516
T3 (8.89–13.09)	2.43 (-0.51, 5.38) 0.1123	3.66 (0.42, 6.90) 0.0328	4.89 (2.06, 7.72) 0.0024
P for trend	0.1048	0.0303	0.0021

Model X controlled for none. Model Y controlled for gender, age, race, education, marriage, PIR, and BMI. Model Z = Model Y + controlled for smoking, alcohol, hypertension, diabetes, CVD, other CAD history, GCS use, ICS use, lipid-lowering drug use, cholesterol, WBC, NEU, and EOS. T1-T3 were TGI's three tertile groups

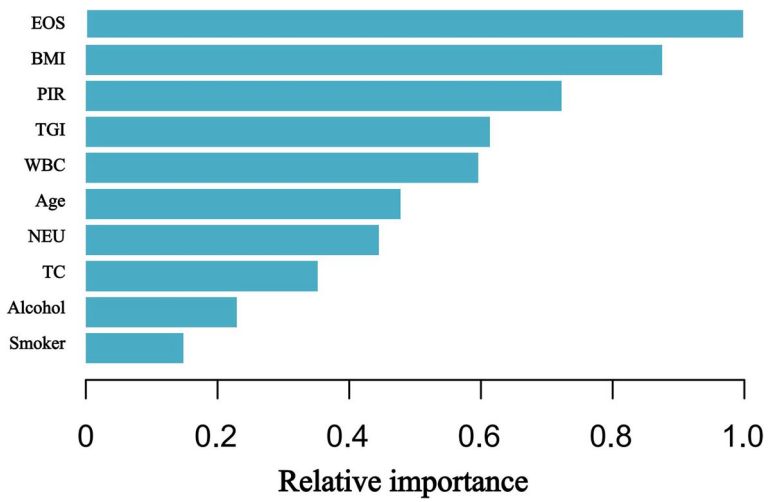

Fig. 2 The XGBoost model provided the relative importance of each variable on FeNO

influential factors on FeNO, in the following ranking of contrasted importance: EOS, BMI, PIR, TGI, and WBC.

NO is a short-lived signaling molecule with a straightforward structure that varies in function according to its manufacturing site, concentration, and interactions with other molecules and proteins. NO functions as a bronchodilator and an inhibitor of inflammatory cell signaling proteins. Conversely, NO plays a pathological role by acting as a pro-inflammatory mediator. When a large amount of NO is present in the oxidative environment of the asthmatic airway, it damages and swells the airway, creating toxic reactive nitrogen species (RNS) and breaking down proteins. This makes the airways more sensitive, a characteristic of asthma [8, 9]. Furthermore, NO concentrations in exhaled air in asthmatic individuals are three times higher than those in normal individuals [8]. Over time, FeNO has become an important tool for increasing the probability of asthma diagnosis. Recently, researchers have discovered that FeNO serves as a valuable indicator for identifying type-2 asthma, determining the risk of exacerbation, and predicting the effectiveness of ICS and biologics [11, 18, 19]. The American Thoracic Society suggests that individuals with asthma undergo FeNO testing along with regular treatment, and FeNO-guided management can evidently reduce the number of asthma flare-ups [20]. Price et al. found that FeNO levels above 50 ppb can indicate eosinophilic airway inflammation and the likelihood that corticosteroids will work [21]. Bacharier et al. found that FeNO is a clinically useful biomarker of asthma exacerbations and dupilumab responses in children with uncontrolled moderate-to-severe asthma [22]. In addition, FeNO serves as a practical and nonintrusive method for monitoring the frequency of asthma attacks and is one of the primary methods of contemporary asthma management [23].

Abnormalities in glucose metabolism such as IR and diabetes are associated with increased contractility and proliferation of airway smooth muscles, identified risk factors for asthma exacerbation [24]. TGI, a recently developed marker for assessing IR, offers a more feasible alternative to previous methods, such as the homeostasis model assessment of IR. Studies have demonstrated a strong relationship between elevated TGI levels and an increased risk of vascular diseases [25–27]. Wu et al. found that higher TGI levels were directly associated with respiratory symptoms, self-reported chronic bronchitis, and restrictive spirometry patterns, suggesting the effectiveness of TGI as an indicator in pulmonary health assessment [16, 28]. Another study found a positive linear relationship between TGI and EOS in an American asthmatic population [29]. Furthermore, elevated TGI levels may be valuable predictive markers of all-cause mortality in critically ill patients with asthma or COPD. Comprehensive studies have also supported the relatively independent role of TGI, regardless of traditional predictors, in identifying patients with asthma who require intensive treatment [17, 30]. Preliminary detection of TGI can prompt patients to seek more standardized diagnoses and treatments at higher-level hospitals. Thus, the TGI has implications for further FeNO detection.

Few studies have examined the TGI and FeNO. This is the first investigation to establish a link of TGI and FeNO in patients with asthma. The relationship between TGI and FeNO levels across different groups was analyzed using subgroup analyses, accounting for confounders. We employed the XGBoost model to evaluate the importance of distinct variables associated with FeNO. Compared with other models, XGBoost handles large datasets, accommodates nonlinear relationships more efficiently, and provides more accurate predictions. However, this study had some limitations. First, the cross-sectional design of the investigation resulted in an inability to determine a cause-and-effect relationship. Second, this study did not include data on the severity of asthma or sputum eosinophil counts because of database limitations. Furthermore, the survey did not clearly identify the acute attack or remission period of asthma when the individuals participated. This study identified individuals with asthma using a questionnaire instead of a bronchial provocation or relaxation test.

Conclusion

This investigation revealed a positive linear relationship between TGI and FeNO in patients with asthma. This finding suggests a potential relationship between TGI and airway inflammation in patients with asthma, thereby facilitating the prompt identification of irregularities and providing a basis for clinical decision making. This study provides a novel perspective on asthma management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02323-6.

Supplementary Material 1.

Acknowledgements

The National Center for Health Statistics (NCHS) authorized the NHANES database. The participants provided informed consent before implementing the data collection protocols and comprehensive health assessments. This study used the NHANES data and received approval from the NAHNES Institutional Review Board/NCHS Research Ethics Review Board (Protocol #2006-07, Protocol #2011-17).

Authors' contributions
Conceptualization: YP, LZW, JW, SYY, JX Data collection: YP, LZW Statistical analysis: YP, JW, JX Original draft: YP, LZW, SYY, JX Review & editing: JW, MG, SMZ Project administration: SMZ.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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