

Association of Body Mass Index and Exhaled Breath Nitric Oxide: A Cross-Sectional Analysis of Shahedieh Cohort Study

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Background: Fractional exhaled nitric oxide is a method of assessing inflammation in the airway and its level may be affected by some factors such as age, gender, and body mass index. This study was performed to assess the relationship between “Body Mass Index” (BMI) and FeNO.

Materials and Methods: This was a cross-sectional study on 879 adult subjects participating in the Shahedieh Cohort Study. BMI and FeNO were measured for each participant. Participants were divided into five BMI groups: underweight, normal, overweight, obese, and morbid obese. FeNO level was compared between groups. The data were analyzed by SPSS (ver. 20) using Kolmogorov-Smirnov, Kruskal-Wallis, Mann-Whitney U tests, Spearman’s correlation, and multivariate logistic regression tests.

Results: The mean FeNO in all participants was 7.87±8.28 ppb. There was a significant positive correlation between age and FeNO. FeNO was declined by increasing BMI, so the highest FeNO was observed in underweight and the lowest FeNO was observed in morbid obese individuals. However, there was not a significant difference in FeNO level between different BMI categories ($P=0.28$). The mean FeNO level was significantly correlated to BMI only in participants younger than 48 years.

Conclusion: The results of this study showed that BMI is probably negatively correlated with FeNO level in middle-aged people younger than 48 years, but not in older people.

Keywords: FeNO; BMI; Obesity; Airway inflammation; Persian Cohort

INTRODUCTION

Obesity and overweight are among the first five causes of mortality in different populations. A significant number of diseases such as diabetes, cancer, cardiovascular diseases, and respiratory diseases are linked to obesity (1). In a national report of recorded mortalities in 2002 in Iran, about 70% of all mortalities have been attributed to chronic diseases which are mostly related to obesity (2, 3). It has also been proposed that some other diseases such as

bronchial hyper-responsiveness and asthma are related to high BMI (4, 5). Some studies have also found a relationship between obesity, lung function, and inflammation (6, 7).

Endogenous nitric oxide (NO) is a free radical and acts as an important mediator in intra and extra-cellular reactions. It is produced by the oxidation of L-arginine and is released in the respiratory tract (8). The health effects of NO in the human body depend on its concentration (9).

Fraction of exhaled nitric oxide (FeNO) is a non-invasive and simple diagnostic method that may be useful as a criterion for airway inflammation (10). Previous studies have found that factors such as age, gender, atopy, smoking, and body weight may affect FeNO (11, 12).

Some possible mechanisms can relate BMI to airway inflammation and FeNO levels. It is known that adipose tissue may produce some inflammatory cytokines such as adiponectin and leptin (13), so a change in adiponectins as anti-inflammatory substances may be associated with airway inflammation, and also NO is considered a central regulator of metabolism and body composition (14, 15).

Due to the increasing prevalence of overweight and obesity all over the world, if there is a relationship between BMI and FeNO level, this should be considered when interpreting FeNO test. There is a controversy in the relationship between BMI and FeNO. Barros et al. showed an inverse relationship between FeNO and BMI in asthmatic patients (16). Maniscalco et al. showed that FeNO decreases in severe obesity and weight loss leads to its increase (7). In a large population-based study, Uppalapati et al. showed a positive correlation between BMI and FeNO in the population under 20 years old (17). Al Khathlan and Salem found a positive correlation between FeNO and different adiposity markers including BMI (18). Another study on children found a positive correlation between obesity and FeNO in asthmatic children (19), but Cibella et al. couldn't find a significant correlation between obesity and BMI in school children (20).

Due to the inconsistent results of the previous studies about the correlation between BMI and FeNO, this study aimed to assess this relationship in an adult suburban population in Shahedieh, Yazd, in the central part of Iran.

MATERIALS AND METHODS

Study setting and population

This was a cross-sectional study on 879 adult subjects participating in Shahedieh Cohort Study (SCS) in Yazd. SCS is a part of a national cohort study (PERSIAN Cohort)

on adult middle-aged individuals from 35 to 70 years old (21). The participants of the current study were randomly selected from this population. Those with a history of smoking (cigarette or wind-pipe) or with a diagnosed respiratory disorder were excluded from the study. Demographic data were extracted from the cohort database. This study was a residency thesis in occupational medicine at Shahid Sadoughi University of Medical Sciences. The protocol of the study was approved by the ethics committee of the university (Ethical code: IR.SSU.MEDICINE.REC.1400.214). An informed consent was obtained from all participants of the study during the enrollment phase.

FeNO measurement

FeNO was measured by a portable electrochemistry-based device (NObreath, Bedfont Scientific Ltd., UK). The device concentration range was 5-300ppb with ± 5 ppb accuracy and sensor sensitivity. The measurements were performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (22). After explaining the test procedure to each participant, they were asked to perform a constant expiration in the device for 10 seconds. At least two acceptable maneuvers were recorded for each participant with less than a 4-ppb difference (22). The average of two measurements was reported as the FeNO values for each participant. If there were intervening factors such as heavy exercise, and large meals before the test, it was performed at another time. The tests were performed in the morning in a similar condition for all participants.

BMI

BMI was calculated by dividing weight (in Kg) by the square of height (in m). Participants were divided into five groups according to their BMI: underweight ($BMI < 18.5$), normal ($18.5 \leq BMI \leq 25$), overweight ($25 < BMI \leq 30$), obese ($30 < BMI \leq 40$), and morbid obese ($BMI > 40$) (17).

Statistical analysis

FeNO was compared among different BMI groups. Age and gender as the most important confounders were considered in the analysis. The data were analyzed by

SPSS (ver. 20) using Kolmogorov-Smirnov, Kruskal-Wallis, Mann-Whitney U tests, Spearman's correlation, and multivariate logistic regression test. The level of significance was set at $P < 0.05$.

RESULTS

In total, 879 individuals entered the analysis (56.7% were males and 43.3% were females). The mean age and BMI of the participants were 48.29 ± 8.03 years and 28.25 ± 4.44 kg/m², respectively. Among all participants, 4 individuals (0.5%) were underweight, 201 (22.6%) had normal weight, 406 (46.2%) were overweight, 256 (29.1%) were obese, and 12 (1.4%) suffered from morbid obesity. The mean FeNO in all participants was 7.87 ± 8.28 ppb.

There was a significant correlation between age and FeNO (correlation coefficient=0.11, P value=0.001), so FeNO was significantly increased by increasing age, but this correlation was not observed for BMI (correlation coefficient = -0.04, P value=0.22). FeNO was declined by increasing BMI, so the highest FeNO was observed in underweight and the lowest FeNO was observed in morbid obese individuals. However, there was not a significant difference in FeNO level between different BMI categories ($P=0.28$). Table 1 compares FeNO levels in different BMI categories.

Table 1. FeNO level in different BMI categories

BMI category		FeNO (ppb*)	P value
Underweight	N (%)	4 (0.5)	0.28
	Mean (SD)	13.25 (9.43)	
Normal	N (%)	199 (22.7)	
	Mean (SD)	8.56 (9.86)	
Overweight	N (%)	406 (46.3)	
	Mean (SD)	7.68 (7.62)	
Obese	N (%)	256 (29.2)	
	Mean (SD)	7.68 (8.09)	
Morbid obese	N (%)	12 (1.4)	
	Mean (SD)	4.93 (2.47)	
Total	N (%)	879 (100)	
	Mean (SD)	7.87 (8.28)	

* ppb: part per billion

Pairwise comparison of FeNO levels in different BMI categories did not show a significant difference between groups which is demonstrated in Table 2.

Table 2. Pairwise comparison of FeNO level between different BMI groups

BMI groups	Mean difference	Standard deviation	P value	
Underweight	Normal	4.66	4.18	0.27
	Overweight	5.57	4.16	0.18
	Obese	5.57	4.18	0.17
	Morbid obese	8.31	4.78	0.08
Normal	Overweight	0.90	0.72	0.21
	Obese	0.91	0.71	0.25
	Morbid obese	3.64	2.45	0.14
Overweight	Obese	0.002	0.65	0.99
	Morbid obese	2.74	2.43	0.26
Obese	Morbid obese	2.74	2.45	0.26

Comparing normal weight participants with overweight and obese ones together, the difference in mean FeNO measurements was not significantly different between the two groups as well (8.58 ± 9.87 vs. 7.63 ± 7.75 , $P=0.21$)

The participants were divided into two groups according to their age, using an age median: 48 years and lower, and higher than 48 years. The mean FeNO level was significantly and negatively correlated to BMI in the younger age group ($\text{age} \leq 48$ yr., correlation coefficient = -0.098, P value=0.026), but in the older age group there was not a significant correlation between FeNO level and BMI ($\text{age} > 48$ yr., correlation coefficient=-0.003, P value=0.95). Figure 1 shows the mean FeNO levels in different BMI categories among all participants and in two age groups.

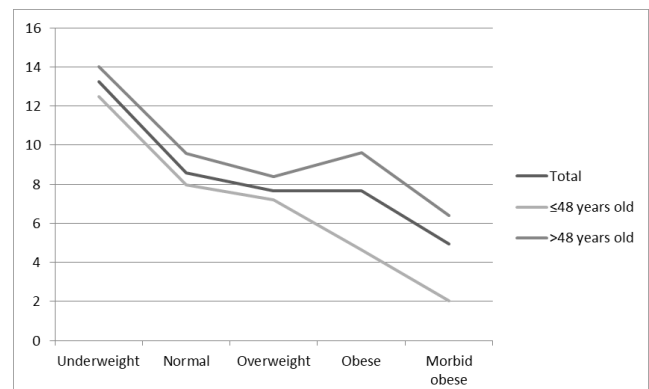


Figure 1. Comparison of mean FeNO (ppb) in different BMI groups considering age

Among all participants, 498 (56.6%) individuals were males and 381 (43.4%) were females. There was a significant difference between the two genders regarding age, BMI, and FeNO (Table 3).

Table 3. Comparison of age, BMI, and FeNO level between two genders

	Gender	Number	Mean	SD	P value
BMI (Kg/m ²)	Male	498	27.19	3.86	< 0.001
	Female	381	29.63	4.78	
Age (yr.)	Male	498	49.37	8.56	< 0.001
	Female	381	46.87	7.04	
FeNO level (ppb*)	Male	498	8.48	9.08	0.009
	Female	381	7.05	7.01	

* ppb: part per billion

Due to the difference between the two genders, the correlation between BMI and age and FeNO level was calculated in each gender separately (Table 4), and the effect of age and gender was adjusted in a multivariate logistic regression model (Table 5).

Table 4. Correlation between FeNO level, BMI, and age in two genders

Gender			BMI	Age
Male	FeNO level	Correlation coefficient	0.001	0.11
		P value	0.98	0.02
Female	FeNO level	Correlation coefficient	-0.049	0.09
		P value	0.34	0.07

Table 5. Multivariate logistic regression of the correlation between FeNO and BMI, adjusting for age and gender

Variable*	Unstandardized coefficients		Standardized coefficients	t	P value	95% Confidence interval for β	
	β	Standard error	β			Lower	Upper
Constant	5.749	2.453		2.344	0.019	0.935	10.564
BMI	-0.061	0.065	-0.033	-0.927	0.354	-0.189	0.068
Age	0.109	0.035	0.106	3.096	0.002	0.040	0.178
Gender	-0.999	0.593	-0.060	-1.685	0.092	-2.162	0.165

* Dependent variable: Mean FeNO

DISCUSSION

In this study, we explored the association between BMI and FeNO level (as a marker of respiratory inflammation) in a middle-aged suburban population in Yazd, a central

province in Iran. We found decreased FeNO levels by increasing BMI, however, the difference was not statistically significant. After categorizing the participants into two age groups, in the younger age group (≤ 48 years), there was a significant negative correlation between BMI and FeNO level. Age and gender were significantly correlated with FeNO level so the FeNO level was higher in males and older participants.

Some mechanisms have been proposed to link FeNO and obesity. Changes in adiponectins (anti-inflammatory substances) and central regulation of metabolism and body composition are among the proposed mechanisms (14, 15).

NO is a free radical with some biological activities such as regulatory actions on physiology and cell function (15). Some activities of NO include angiogenesis and regulation of blood flow, cellular respiration, and metabolism (23, 24). NO is considered an inflammatory marker of airways and its production and release may be associated with different factors such as respiratory diseases, smoking, occupational exposures, and BMI (18, 19, 25, 26). Animal models of obesity have shown a lower bioavailability of NO (27). It has also been shown that NO bioavailability is decreased in obese individuals (28), which is probably induced by its decreased production or increased degradation that may affect FeNO level.

FeNO measurement is used to determine inflammation in the airways and it may show the severity of inflammation as well (29), but it should be interpreted cautiously due to some confounding factors, which may affect its level. Due to the relationship between metabolism and FeNO, BMI may affect its level and influence the correct diagnosis of diseases.

Previous studies across various age groups and populations have shown inconsistent results regarding the relationship between BMI and FeNO levels, ranging from positive correlation to no correlation, and even negative correlation. Some studies have shown a negative relationship between BMI and FeNO level (7, 30-32), which was consistent with the results of the current study in people younger than 48 years old. Other studies, in

contrast with the results of the current study, have observed a significant positive relationship between BMI and FeNO level (18, 33). Some other studies, consistent with the results of the current study, especially in older individuals, couldn't find a significant relationship between BMI and FeNO levels (20, 31, 34). Many of these studies have been conducted on people with some inflammatory diseases such as asthma, atopy, and some other allergies and significant relationships have been observed mostly in these studies.

Czubaj-Kowal et al. and Ai et al. found a positive and significant correlation between BMI and FeNO levels in children (35, 36), which was consistent with the results of the current study in the younger age group. Although our population was quite different from that in this study, we observed a decline in FeNO levels as BMI increased; however, this difference was not statistically significant. In contrast, Yao et al. found a significant negative relationship between BMI and FeNO levels in atopic children (32).

Discrepancies between studies may be due to variability in race, ethnicity, age, sample size, occupational and environmental exposures, and different health status of the participants. Yao et al. in their first study found a negative independent association between BMI and FeNO level in children (11), but in their recent study, they found this negative association only in atopic children (32). In this study, we tried to exclude people with known respiratory diseases, but some biases such as recall bias or inattention to mild diseases may have affected this exclusion criterion.

Cibella et al. (20) found that severely obese individuals have lower FeNO levels than normal-weight subjects, which was consistent with the results of the current study in the younger group (<48 years old). Studies that have shown a positive relationship between BMI and FeNO (i.e., increase in FeNO level in overweight and obese individuals) have proposed some mechanisms for this relationship such as a change in adiponectins and metabolism in people with high BMI, and those studies with the negative relationship between BMI and FeNO level have proposed some other mechanisms such as

decreased production of NO in airways, and/or reduced airway diffusing capacity in obese individuals (10). This study supported the negative relationship between FeNO level and BMI in individuals younger than 48 years old, but this correlation was not seen in individuals older than 48 years old. It should be considered that the populations in the studies were very different regarding their age and probably their occupational and environmental exposures. In the current study, the participants were middle-aged and were selected from a suburban region with some specific environmental and occupational exposures that may have affected the FeNO level, especially among the younger age group who were mostly in their working age.

This study had the advantage of selecting a large population sample of middle-aged individuals, but there were some limitations: It was a cross-sectional study with its limitations; the sample size in some BMI categories (underweight and morbidly obese) was too small; There were some other confounding factors which may affect the results, such as occupational and environmental exposures.

CONCLUSION

The results of this study showed that BMI is probably negatively correlated with FeNO level in middle-aged people younger than 48 years, but not in older people. Due to the limitations of the study, the results should be cautiously interpreted.

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