

Brief Communication



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Additive Effect of Obesity and Dyslipidemia on Wheezing in Korean Adults: A Nationwide Representative Survey Study

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ABSTRACT

Besides obesity, there are limited studies regarding the relationship between the individual components of metabolic syndrome and wheezing. It is largely unknown whether the co-existence of other metabolic syndrome components has additive effects on wheezing in the adult population. The association between the individual components of metabolic syndrome and current wheezing was evaluated in adults using data from the Korea National Health and Nutrition Examination Survey from 2008 to 2012. Subjects with metabolic syndrome more frequently had wheezing during the past 12 months (current wheezing) (adjusted odds ratio [aOR] = 1.56; 95% confidence interval [CI] = 1.37–1.77) and wheezing during exercise in the past 12 months (aOR = 1.59; 95% CI = 1.37–1.84). Of the individual metabolic syndrome components, central obesity (aOR = 1.48; 95% CI = 1.31–1.66) and low high-density lipoprotein (HDL) cholesterol (aOR = 1.18; 95% CI = 1.05–1.34) were significantly associated with current wheezing. There were no significant associations between the other components of metabolic syndrome (high triglyceride level, blood pressure, and fasting plasma glucose level) and the presence of current wheezing. In addition, the association was much higher when both central obesity and low HDL cholesterol were present together compared to when either of the conditions was present alone (aOR = 1.67; 95% CI = 1.44–1.94). There is a significant association between metabolic syndrome and current wheezing in Korean adults. Of the components of metabolic syndrome, low HDL cholesterol and central obesity are independently and additively associated with the increased rate of current wheezing.

Keywords: Metabolic syndrome; obesity; body mass index; lipoprotein, HDL; triglycerides; dyslipidemia; asthma; wheezing

INTRODUCTION

Metabolic syndrome is a cluster of metabolic conditions including abdominal obesity, elevated blood pressure (BP), dysregulated glucose level, and dyslipidemia (elevated triglyceride

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level and low high-density lipoproteins [HDL] cholesterol).^{1,3} The prevalence of metabolic syndrome has been increasing worldwide, and this condition is associated with various chronic diseases such as cardiovascular disease and diabetes mellitus (DM).^{1,3} Although the pathogenic mechanism is not clearly understood, obesity, which is a significant component of metabolic syndrome, is considered a possible risk factor for these chronic diseases.^{2,4}

In addition to the relationship between metabolic syndrome and cardiovascular disease/DM, previous studies have shown an association between asthma and metabolic syndrome.^{5,6} Of several components known to comprise metabolic syndrome, obesity is a well-known factor that is associated with wheezing, a major symptom in asthmatic patients.^{7,8} One study conducted on elderly patients over 65 years of age reported that waist circumference and low HDL cholesterol increased the risk of asthma⁹; however, few studies assessed the relationship between metabolic syndrome components other than obesity and wheezing. In addition, it is largely unknown whether the co-existence of other metabolic syndrome components has additive effects on wheezing in the adult population.¹⁰ Consequently, more evidence is needed to demonstrate the relationship between wheezing and the individual components of metabolic syndrome.

Therefore, our study aimed to investigate the relationship between wheezing and the individual components of metabolic syndrome in Korean adults using a nationally representative health survey database.

Materials and METHODS

Study subjects

The Korea National Health and Nutrition Examination Survey (NHANES) is a population-based, cross-sectional survey of health and nutrition conducted by the Korean Ministry of Health and Welfare. Participants were randomly selected through a stratified, multistage, probability sampling method. Here, we analyzed the data from subjects at least 19 years of age who participated in the Korea NHANES 2008–2012 study ($n = 34,670$). We excluded 2,531 subjects with missing values for the following questionnaire questions: “Have you ever been diagnosed with asthma by a physician?” or “Have you had wheezing or whistling sounds while breathing during the past 12 months?”. Thereafter, we further excluded 1,664 subjects with missing values for any component of metabolic syndrome. Finally, 30,475 subjects were included in this study (**Fig. 1**).

Measurements

Data on age, sex, body mass index (BMI), waist circumference, and smoking history were obtained from the Korea NHANES database. Waist circumference was measured 3 times, and the mean value was used in the analysis. BP was tested in a seated position and was measured 3 times following at least 5-minute rest between measurements. The lowest measurement was used in the analysis.

Blood samples were obtained after an overnight fast (> 8 hours). Total cholesterol, triglyceride (TG), HDL cholesterol, and fasting plasma glucose (FPG) levels were analyzed via enzymatic methods using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) in a certified central laboratory (Neodin Medical Institute, Seoul, Korea).

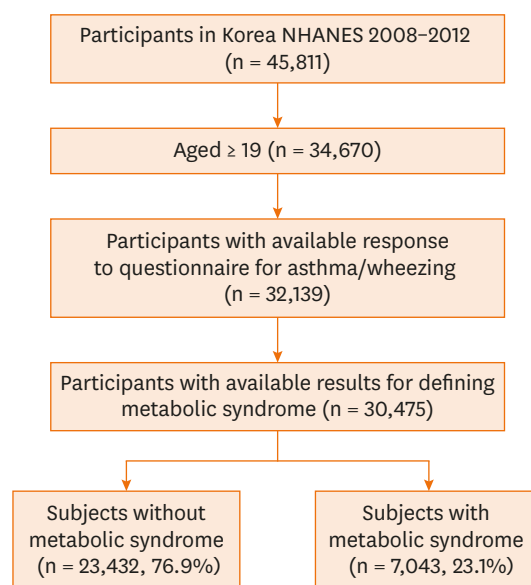


Fig. 1. Flowchart of the enrollment of 30,475 subjects in the analyses. NHANES, National Health and Nutrition Examination Survey

Definitions

BMI was categorized as follows: underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}22.9 \text{ kg/m}^2$), overweight ($23.0\text{--}24.9 \text{ kg/m}^2$), obese ($25.0\text{--}29.9 \text{ kg/m}^2$), and severely obese ($\geq 30 \text{ kg/m}^2$). According to the new criteria of the International Diabetes Federation (IDF) published in 2006,¹¹ patients were defined as having metabolic syndrome when they had central obesity plus 2 or more of the following criteria: 1) raised TG level $\geq 150 \text{ mg/dL}$ or specific treatment for this lipid abnormality; 2) reduced HDL cholesterol: $< 40 \text{ mg/dL}$ in males and $< 50 \text{ mg/dL}$ in females or specific treatment for this lipid abnormality; 3) raised BP: systolic BP $\geq 130 \text{ mmHg}$, diastolic BP $\geq 85 \text{ mmHg}$, or treatment of previously diagnosed hypertension; 4) elevated FPG $\geq 100 \text{ mg/dL}$; and 5) previously diagnosed type 2 DM. Central obesity was defined as a waist circumference of at least 90 cm for Asian men and at least 80 cm for Asian women.

Asthma status was evaluated using the following categories: “lifetime asthma,” “physician-diagnosed asthma,” “current asthma,” “current wheezing,” or “current wheezing during exercise.” Subjects who responded “yes” to “Have you ever had asthma during a lifetime?” “Have you ever been diagnosed with asthma by a physician?” “Are you currently having asthma?” “Have you had wheezing or whistling sounds while breathing during the past 12 months?” “Have you had wheezing or whistling sounds while breathing during or after exercise in the past 12 months?” were defined as having “lifetime asthma,” “physician-diagnosed asthma,” “current asthma,” “current wheezing,” and “current exercise-induced wheezing,” respectively.

Statistical analysis

Data are presented as weighted mean \pm standard deviation or weighted percentage (standard error). To evaluate the association between the presence of metabolic syndrome and asthma status/wheezing in the previous year, we employed a multivariable logistic regression model in which age, sex, and smoking status were included. We further evaluated the association between the individual components of metabolic syndrome and the presence of wheezing in the previous year using multivariable logistic regression. Consequently, the components

of metabolic syndrome age, sex, and smoking history were inserted in model 1. In model 2, all components of metabolic syndrome, age, sex, and smoking history were inserted. All data were analyzed using Statistical Package for the Social Sciences (SPSS) 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the study subjects are summarized in **Table 1**. Subjects with metabolic syndrome were older (mean 53.7 vs. 42.4 years, $P < 0.001$) than those without. Females (57.5% vs. 48.2%, $P < 0.001$) and never-smokers (56.7% vs. 52.0%, $P < 0.001$) were more frequent in subjects with metabolic syndrome compared to those without. Those with metabolic syndrome were more likely to be obese or severely obese (75.3% vs. 21.0%, $P < 0.001$). Compared to subjects without subjects with metabolic syndrome had greater waist circumference (91.9 vs. 78.3 cm, $P < 0.001$) and higher blood pressure (systolic BP: 128.0 vs. 114.8 mmHg, $P < 0.001$; diastolic BP: 81.6 vs. 75.3 mmHg, $P < 0.001$) than those without.

Table 1. Clinical and demographic characteristics of the patients

Characteristics	All participants (n = 30,475*)	Non-metabolic syndrome (n = 23,432*)	Metabolic syndrome (n = 7,043*)	P value*
Age (yr)	44.7 ± 0.17	42.4 ± 0.17	53.7 ± 0.26	< 0.001
19–29	19.9 (0.4)	23.6 (0.5)	5.0 (0.5)	
30–39	21.4 (0.4)	23.4 (0.5)	13.5 (0.6)	
40–49	22.2 (0.4)	22.5 (0.4)	21.1 (0.7)	
50–59	17.8 (0.3)	16.2 (0.3)	24.0 (0.7)	
60–69	10.5 (0.2)	8.1 (0.2)	20.0 (0.5)	
≥ 70	8.2 (0.2)	6.1 (0.2)	16.4 (0.5)	
Sex				< 0.001
Male	50.0 (0.3)	51.8 (0.4)	42.5 (0.7)	
Female	50.0 (0.3)	48.2 (0.4)	57.5 (0.7)	
Smoking status				< 0.001
Current smoker	27.1 (0.3)	28.0 (0.4)	23.5 (0.7)	
Ex-smoker	19.8 (0.3)	19.8 (0.3)	19.6 (0.6)	
Never-smoker	53.0 (0.3)	52.0 (0.4)	56.7 (0.8)	
BMI (kg/m ²)		22.8 ± 0.02	27.1 ± 0.05	< 0.001
Underweight (< 18.5)	4.7 (0.2)	5.9 (0.2)	0 (0)	
Normal (18.5–22.9)	39.9 (0.4)	48.5 (0.4)	5.6 (0.3)	
Overweight (23.0–24.9)	23.3 (0.3)	24.4 (0.3)	18.9 (0.6)	
Obesity (25.0–29.9)	27.6 (0.3)	19.3 (0.3)	60.7 (0.8)	
Severe obesity (≥ 30)	4.3 (0.2)	1.7 (0.1)	14.6 (0.6)	
Comorbidities				
Hypertension	16.8 (0.3)	10.7 (0.3)	41.2 (0.8)	< 0.001
Diabetes	6.2 (0.2)	3.7 (0.1)	16.1 (0.5)	< 0.001
Physical measurement				
Waist (cm)	81.0 ± 0.10	78.3 ± 0.09	91.9 ± 0.11	< 0.001
Systolic BP (mmHg)	117.5 ± 0.17	114.8 ± 0.17	128.0 ± 0.28	< 0.001
Diastolic BP (mmHg)	76.5 ± 0.01	75.3 ± 0.13	81.6 ± 0.18	< 0.001
Laboratory findings				
Total cholesterol (mg/dL)	187.2 ± 0.30	184.3 ± 0.32	198.6 ± 0.58	< 0.001
Triglyceride (mg/dL)	134.4 ± 0.91	117.7 ± 0.81	201.0 ± 2.50	< 0.001
HDL cholesterol (mg/dL)	48.8 ± 0.10	50.4 ± 0.11	42.6 ± 0.14	< 0.001
Fasting glucose (mg/dL)	96.7 ± 0.16	93.6 ± 0.15	109.2 ± 0.42	< 0.001
Hemoglobin A1C (mg/dL)	5.86 ± 0.01	5.69 ± 0.01	6.40 ± 0.29	< 0.001

Data are presented as percent (standard error) or mean ± standard deviation.

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

*Unweighted number.

HDL cholesterol (42.6 vs. 50.4 mg/dL, $P < 0.001$) was higher in subjects without metabolic syndrome whereas laboratory findings such as total cholesterol (198.6 vs. 184.3 mg/dL, $P < 0.001$), TG (201.0 vs. 117.7 mg/dL, $P < 0.001$), fasting glucose (109.2 vs. 93.6 mg/dL, $P < 0.001$), and hemoglobin A1c (6.40 vs. 5.69 mg/dL, $P < 0.001$) were higher in subjects with metabolic syndrome than in those without metabolic syndrome.

Association between current wheezing and metabolic syndrome

As shown in **Table 2**, subjects with metabolic syndrome were more likely to have lifetime asthma (adjusted odds ratio [aOR] = 1.30; 95% confidence interval [95% CI] = 1.12–1.51), physician-diagnosed asthma (aOR = 1.26; 95% CI = 1.07–1.49), or current asthma (aOR = 1.29; 95% CI = 1.04–1.58) compared to those without. In addition, subjects with metabolic syndrome more frequently had wheezing in the previous year (aOR = 1.56; 95% CI = 1.37–1.77) and wheezing during exercise in the previous year (aOR = 1.59; 95% CI = 1.37–1.84).

Table 3 summarizes the OR of the individual components of metabolic syndrome for the presence of current wheezing. In both models 1 and 2, central obesity (aOR = 1.51; 95% CI = 1.35–1.69 in model 1 and aOR = 1.48; 95% CI = 1.31–1.66 in model 2) and low HDL cholesterol (aOR = 1.24; 95% CI = 1.11–1.40 in model 1 and aOR = 1.18; 95% CI = 1.05–1.34 in model 2)

Table 2. The odds ratio of the presence of metabolic syndrome for asthma status and wheezing

Variables	Crude model		Adjusted model*	
	Non-metabolic syndrome	Metabolic syndrome	Non-metabolic syndrome	Metabolic syndrome
Lifetime asthma	Reference	1.62 (1.40–1.87)	Reference	1.30 (1.12–1.51)
Physician-diagnosed asthma	Reference	1.53 (1.30–1.80)	Reference	1.26 (1.07–1.49)
Current asthma	Reference	1.95 (1.59–2.39)	Reference	1.29 (1.04–1.58)
Current wheezing	Reference	1.73 (1.54–1.96)	Reference	1.56 (1.37–1.77)
Current exercise-induced wheezing	Reference	1.58 (1.38–1.82)	Reference	1.59 (1.37–1.84)

Data are presented as an adjusted odds ratio (95% confidence interval).

*Adjusted for age, sex, and smoking status.

Table 3. Odds ratio of the individual components of the metabolic syndrome for current wheezing: associations between the individual components of metabolic syndrome and current wheezing

Variables	Model 1*	Model 2†
Age, increasing by 10 years	1.19 (1.15–1.24)	1.15 (1.10–1.20)
Sex		
Male	Reference	Reference
Females	1.60 (1.35–1.91)	1.47 (1.23–1.76)
Smoking status		
Never smoker	Reference	Reference
Current smoker	3.14 (2.64–3.75)	3.17 (2.66–3.80)
Ex-smoker	1.44 (1.14–1.82)	1.47 (1.16–1.87)
Central obesity‡	1.51 (1.35–1.69)	1.48 (1.31–1.66)
Dyslipidemia (TG)§	1.08 (0.96–1.23)	0.94 (0.82–1.07)
Dyslipidemia (HDL)¶	1.24 (1.11–1.40)	1.18 (1.05–1.34)
High BP¶¶	1.13 (0.99–1.28)	1.05 (0.92–1.20)
High FPG**	1.09 (0.96–1.24)	1.00 (0.88–1.14)

Data are presented as an adjusted odds ratio (95% confidence interval).

TG, triglyceride; HDL, high-density lipoprotein; BP, blood pressure; FPG, fasting plasma glucose.

*Model 1: the individual components of metabolic syndrome age, sex, or smoking status were included. †Model 2: all components of metabolic syndrome age, sex, and smoking status were included. ‡Central obesity is defined as waist circumference ≥ 90 cm for males and ≥ 80 cm for females. §Dyslipidemia was defined as TG level ≥ 150 mg/dL. The subjects who are taking lipid-lowering agents were excluded. ¶Dyslipidemia was defined as HDL cholesterol < 40 mg/dL in males and < 50 mg/dL in females. The subjects who are taking lipid-lowering agents were not included. ¶¶High BP was defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension. **High FPG ≥ 100 mg/dL or previously diagnosed type 2 diabetes mellitus.

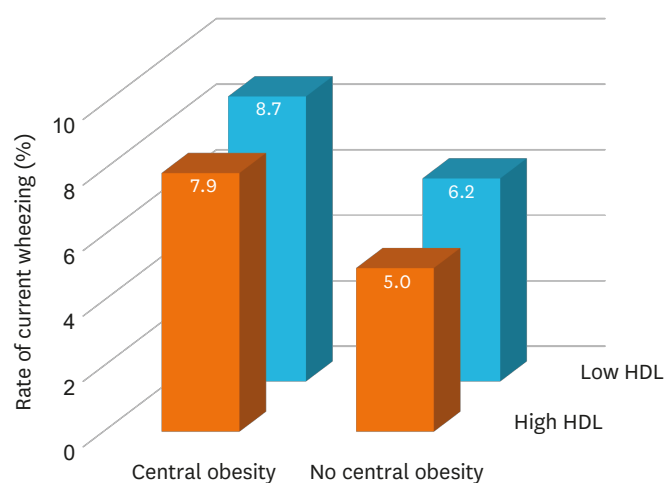


Fig. 2. The rate of current wheezing according to the presence of central obesity and HDL cholesterol level. HDL, high-density lipoprotein.

were significantly associated with the presence of current wheezing. However, there were no significant associations between other components of metabolic syndrome (high TG, BP, and FPG level) and the presence of wheezing in either model 1 or 2.

The additive effect of central obesity and low HDL cholesterol level for the presence of wheezing

The rate of current wheezing according to the presence of central obesity and the HDL cholesterol level (high or low) is shown in **Fig. 2**. The rate of current wheezing in the central obesity group/low HDL cholesterol group was highest at 8.7%, followed by 7.9% in the central obesity/high HDL cholesterol group. Current wheezing was at 6.2% in the non-central obesity/low HDL cholesterol group and lowest at 5.0% in the non-central obesity/high HDL cholesterol group.

There was a dose-dependent association between low HDL cholesterol level and central obesity and the presence of wheezing. The adjusted OR for wheezing was highest when both central obesity and low HDL cholesterol were present (aOR = 1.67; 95% CI = 1.44–1.94), which was followed by when only central obesity was present (aOR = 1.45; 95% CI = 1.27–1.74) or low HDL cholesterol (aOR = 1.19; 95% CI = 1.03–1.39) were present.

DISCUSSION

We investigated the relationship between the individual components of metabolic syndrome and current wheezing. In this study, we identified 2 major findings. One is that current wheezing was observed much more frequently in subjects with metabolic syndrome in comparison to those without. The other is that, of the components of metabolic syndrome, central obesity and low HDL cholesterol were significantly associated with the presence of current wheezing. Moreover, the co-existence of central obesity and low HDL cholesterol has additive effects on wheezing in adults.

Many previous studies have indicated the relationship between metabolic syndrome and asthma or asthma symptoms, and have shown that metabolic syndrome is associated with

asthma,⁵ as well as lung function impairment¹² or asthma-like symptoms such as wheezing, resting dyspnea, or exercise-induced dyspnea.^{13,14} For example, Lee *et al.*¹³ showed that abdominal obesity, a major component of metabolic syndrome, is significantly associated with wheezing. However, the study population was localized to certain cities, and the age range was limited. Our study overcomes these limitations by analyzing a nationwide representative sample. The high correlation between central obesity and BMI is in line with previous findings that increased BMI is associated with increased risk of incident asthma.¹⁵⁻¹⁸ However, since data are limited regarding the role of central obesity and wheezing in different BMI categories (*e.g.*, central obesity can also be present in normal or underweight population), future studies are needed for this issue.

Metabolic syndrome consists of various metabolic components, such as central adiposity, high BP, abnormal level of cholesterol, and uncontrolled state of the blood sugar level. Previous studies have dealt with the relationship between the individual components of metabolic syndrome and wheezing. One cross-sectional study in the US assessed the relationship between 3 cholesterol states (total cholesterol, HDL cholesterol, and non-HDL cholesterol) and wheezing.¹⁴ In that study, serum total cholesterol and non-HDL cholesterol levels were related to wheezing in the US population. Another large-cohort Spanish study assessed whether the components of metabolic syndrome are associated with wheezing and showed that high serum TG and low serum HDL cholesterol levels were associated with wheezing.¹⁰ In our study, low HDL cholesterol level was related with current wheezing in adults. Along with previous findings, our study supports the previous hypothesis suggesting a significant link between cholesterol, inflammation, and asthma.¹⁹ Interestingly, the type of cholesterol associated with current wheezing differed by country, and the reasons may be differences in racial and genetic factors, eating habits, and socioeconomic factors. Additional studies are needed to clarify the reasons for this phenomenon. In addition, we need to reveal whether this difference can be associated with different presentation and prognosis of asthma.

Our study is noteworthy in that we provide data showing the additive effect of central obesity and low HDL cholesterol on asthma. As previous studies separately evaluated the relationship between the individual components of metabolic syndrome and wheezing, the additive effects of the components of metabolic syndrome on asthma have not been identified. Our study results provide an important clinical implication that control of both lipid profiles and obesity may be more effective for prevention and treatment of asthma with the obesity phenotype.²⁰

The use of a large, nationwide sample of Korean adults across all age groups is one of the major advantages of our study. However, this advantage also becomes a limitation in that our study results may not be generalizable to subjects in other countries or ethnic groups. Secondly, our study is cross-sectional. Due to the study design, we could not clarify a causal relationship between the individual components of metabolic syndrome and current wheezing. Well-designed prospective studies are needed to clarify the causal relationship. Thirdly, our analysis focusing on wheezing episodes may overestimate the association between metabolic syndrome and asthma, since wheezing can be present in conditions other than asthma, such as obesity and vocal cord palsy.⁹ However, given that asthma is underdiagnosed in Korea, the analysis focusing on wheezing episodes would be more sensitive to defining symptomatic subjects with asthma compared to other methods.

In conclusion, we show the association between the individual components of metabolic syndrome and wheezing in a nationwide population cohort. Low HDL cholesterol level

and central obesity had a meaningful effect on current wheezing, while other components of metabolic syndrome did not show a significant relationship. In addition, we found the association of wheezing to be much stronger when central obesity and low HDL cholesterol are present together.

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