



The Role of Metabolic Syndrome Components in Sensorineural Hearing Loss in Adolescents: A Case-Control Study

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Abstract

Introduction Metabolic syndrome (MetS) and its associated components were reported as a possible cause of inner ear dysfunction. However, research about the influence of cardiovascular risk factors on hearing thresholds are conducted mainly in adult patients.

Objective The aim of the present study was to investigate auditory function in adolescents with MetS compared with healthy controls.

Methods One hundred adolescents with metabolic syndrome and 200 sex- and age-matched controls were recruited from a university pediatric endocrine clinic from May 2018 to July 2020. Hearing loss was defined as hearing level ≥ 15 dB at speech frequency (SFHL) or high frequency (HFHL) in one or both ears. A multivariable conditional logistic regression analysis examined the correlation between MetS components and several important demographic characteristics, and hearing loss.

Results A total of 165 (55.0%) boys and 135 (45.0%) girls participated in this study. The rates of SFHL and HFHL in adolescents with MetS were 32.0% and 51.0%, respectively. Those values for controls were 5.0% and 15.5%, respectively. The regression analysis showed high triglycerides as a significant predictor for SFHL (odds ratio 10.87; 95% confidence interval: 1.98, 59.74). Neither predictor of interest was significant for HFHL.

Conclusion Hypertriglyceridemia may be an important factor in the pathogenesis of SFHL. However, the strength of the association was not significant with a wide confidence interval. Also, we were unable to find an association between predictors and HFHL with the current sample size. Larger and prospective studies are recommended.

Keywords

- ▶ sensorineural hearing loss
- ▶ metabolic syndrome
- ▶ triglycerides
- ▶ adolescent

Introduction

Despite many advances in medicine, several children have one or more cardiovascular risk factors and metabolic syndrome (MetS). The International Diabetes Federation (IDF)

defined MetS as abdominal obesity plus any two of the other four factors: triglycerides (TGs) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in males and < 50 mg/dL in females, systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg, and fasting plasma

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glucose (FPG) ≥ 100 mg/dL or known type 2 diabetes mellitus.¹ A systematic review showed the global prevalence rates of MetS to be 3.3% (range 0–19.2%) among children and adolescents in 2013.² Previous studies indicated that MetS is a common metabolic disorder among Iranian children.^{3,4} A systematic review revealed prevalence rates of MetS between 1 and 22% in Iran.⁵ In a recent community-based study, Ahmadi et al.⁴ reported the prevalence of the metabolic syndrome to be 7.6% in adolescents aged 10 to 18 years old. The most prevalent metabolic syndrome components were low HDL-C (56.2%) and abdominal obesity (27.8%).

Metabolic syndrome or its related components can cause many comorbidities, including inner ear dysfunction. The mechanism underlying the correlation between MetS and hearing loss has not yet been determined, but peripheral blood vessel disorder has been suggested.⁶ It is believed that insulin resistance is the main cause of MetS, and it can induce lipid accumulation. When adipocytes become larger, they release fatty acids and adipokines that can lead to the lipotoxicity of blood vessels, ultimately leading to cochlear microangiopathy and decreased blood supply.⁷ Cochlear ischemia has been found to cause damage to stria vascularis injury, resulting in dysfunction of the ion transport system and hearing loss.⁸

There are many studies on damage caused by type 1 diabetes mellitus (T1DM) in the cochlear and retrocochlear tracts of the auditory pathway.^{9,10} In a recent meta-analysis, Teng et al.¹¹ revealed that patients with T1DM had a significantly higher prevalence of hearing loss than controls (odds ratio 49.08). Although hearing loss was mild and subclinical, the hearing threshold had markedly increased trend at high frequency. Histologically, atrophy or thickening of the stria vascularis and loss of outer hair cells of the cochlea were reported due to diabetes.^{12,13} Several reports suggest that microangiopathy in vascular membranes of stria vascularis, basilar membrane, and endolymphatic sac is the most common feature in the cochlea of diabetic patients.^{14,15} It is known that dyslipidemia, including low levels of HDL-C, high levels of low-density lipoprotein cholesterol (LDL-C), and high levels of TGs, is associated with hearing loss.^{16–18} Several studies showed the effects of hypertension on the peripheral (e.g., deterioration of hearing thresholds at 8 kHz and a higher frequency of abnormal otoacoustic emissions) and central auditory pathways (decreased sound localization ability and spatial hearing resolution).^{19,20} It is worth mentioning that adolescents are becoming more prone to developing sensorineural hearing loss (SNHL) during early adulthood due to increased use of personal music devices that are used at dangerously high volumes.²¹

To the best of our knowledge, there is more literature about the influence of cardiovascular risk factors on hearing thresholds in adult patients, while the literature concerning the effects of these risk factors on the inner ear functions in children with MetS is scarce. Kilic et al.²² examined the effects of MetS on hearing in childhood. There was no significant difference in terms of mean hearing levels and results of transient evoked otoacoustic emission (TEOAE) between obese and healthy children. However, the authors

reported significantly higher hearing thresholds at low frequencies in MetS children compared with the controls.

Thus, the present case-control study aimed to investigate the evaluation of auditory function in pediatric patients diagnosed with MetS compared with age- and gender-matched controls. The primary outcome was to determine the possible predictors of sensorineural hearing loss (speech frequency and high frequency) in adolescents.

Method

This cross-sectional observational study was conducted in accordance with the Strengthening the Reporting of the Observational studies in Epidemiology (STROBE) guidelines.²³ This study was carried out after obtaining approval by the ethical committee of Guilan University of Medical Sciences (GUMS), Iran (IR.GUMS.REC.1397.006) and complied with the rules delineated in the Helsinki Declaration. Written informed consent was obtained from all patients and their parents after a full discussion about the aims of the study. We recruited adolescents with MetS from the pediatric endocrine clinic of 17-Shahrivar Hospital, Guilan University of Medical Sciences, Iran from May 2018 to July 2020. The inclusion criteria of the study were adolescents aged 12 to 18 years with a diagnosis of metabolic syndrome (at least 1 year) as defined by the International Diabetes Federation (IDF). Metabolic syndrome is diagnosed with abdominal obesity (an essential component) plus any 2 of the other 4 factors: TG ≥ 150 mg/dL, HDL-C < 40 mg/dL in males and < 50 mg/dL in females, systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg, and FPG ≥ 100 mg/dL or known type 2 diabetes mellitus. Abdominal obesity is considered as elevated waist circumference (WC), based on age- and gender-specific percentile curves ($\geq 90^{\text{th}}$ percentile).^{1,24} To determine obesity in children and adolescents, the body mass index (BMI) is determined, applying age- and gender-specific BMI-centiles.²⁵ The Center for Disease Control and Prevention (CDC)'s gender-specific growth tables²⁶ were used to determine the BMI percentile for age. For categorical analysis, the CDC's established pediatric BMI categories were used: obese ($\geq 95^{\text{th}}$ percentile), overweight (85th to $< 95^{\text{th}}$ percentile), and normal weight (5th to $< 85^{\text{th}}$ percentile). The exclusion criteria of the study included hearing loss due to an identified etiology, such as otitis media with effusion, chronic otitis media, and congenital sensorineural hearing loss, and noise-induced hearing loss. We evaluated the medical history of participants using parental recall and medical records. We considered high-frequency notched audiometric configurations suggestive of noise-induced hearing loss using the Niskar criteria.²⁷

For each case, two controls were simultaneously selected from schools in the urban areas of Rasht. Children without IDF criteria of MetS served as controls and were individually matched to cases by age (± 2 years) and gender. To minimize selection bias, the control subjects were selected using random number generation. Control selection was based on the same inclusion/exclusion criteria as used for case selection.

All participants underwent a complete clinical interview, comprehensive ear exam, audiometry, and blood tests for the MetS components. Audiometric tests included pure-tone audiometry (PTA), speech audiometry (by GN Otometrics Astera, Madsen, Denmark), and tympanometry (Zodiac 901 Middle Ear Analyzer, Madsen, Denmark). The hearing levels at 0.5, 1, 2, and 4 kHz were averaged to describe the speech frequency hearing loss (SFHL), and hearing levels at 3, 4, and 8 kHz were averaged to describe the high frequency hearing loss (HFHL).²⁸ Normal hearing was defined as hearing levels < 15 dB (dB) at SFHL or HFHL in both ears. Children with hearing level \geq 15 dB for at least 1 threshold and < 20 dB PTA were considered in the minimal loss category, and those with hearing level 20 to 40 dB were considered in the mild loss category.²⁹

We collected data about several important factors such as smoking, passive smoking, otitis, and use of personal musical players (how many hours a day do you listen to music through the personal musical players?). Waist circumference, weight, and height of the participants were determined. Blood workup was done by measuring FPG, TG, cholesterol, HDL-C, LDL-C, and glycosylated hemoglobin (HbA1c).

Statistical Analysis

The sample size for the study was estimated assuming a mean hearing threshold of 3.1 dB (4.6) in the control group and 5.1 dB (6.10) in the children with obesity.³⁰ With an α of 0.05, a sample of 83 cases and 166 controls would provide 80% power for a difference of 1.9 between the 2 groups. This does not take into account matching, which would have reduced the required sample size to achieve the same power. The Pass 11 statistical software, version 11.0.8 (NCSS, LLC, Kaysville, Utah, USA) was used for these calculations.

The Shapiro-Wilk test was used as normality test. Continuous variables are expressed as the mean (standard deviation [SD]). Categorical data are expressed as frequencies and percentage. The normality of distribution of data was examined by the Kolmogorov-Smirnov test. The equality of variances in the two groups was analyzed by the Levene test. The means were compared using analysis of variance, and the percentages were compared using the chi-squared test. Appropriate effect sizes were calculated for all eligible comparisons. For continuous variables (e.g., hearing threshold), the effect size was computed using the Cohen's *d*. For dichotomous variables, the odds ratio (OR) was calculated. To determine the possible predictor factors of hearing loss in children, the odds ratio (OR) and 95% confidence interval (CI) were calculated using univariable and multivariable conditional logistic regression analyses to take into account the design match. In this study, independent variables which included in the conditional logistic model, were components of MetS and several important variables such as smoking, passive smoking, otitis, hands free usage (above 4 hours per day), and body mass index (BMI). All statistical tests were two-sided, and a *p*-value < 0.05 was set as the level of statistical significance. Statistical analyses were conducted

using the Stata 14.0 software (StataCorp LP, College Station, TX, USA).

Results

One hundred children with MetS participated in the present study. The mean duration of MetS was 1.5 (0.3) years. Of the 100 participants, 45 were female. We included 200 healthy controls at a 1:2 ratio. The mean (standard deviation) age of subjects in the case and the control groups was 13.4 (1.8) and 13.3 (1.8) years, respectively. In the case group, overweight or obesity was found in 82 children (82.0%), while the prevalence of overweight/obesity was observed in only 5 (2.5%) participants in the control group. ► **Table 1** shows the demographic characteristics of participants in detail. Abnormal metabolic syndrome components were found in more than three-quarters of cases. The most frequent risk factors in the case group were abdominal obesity and diabetes mellitus. However, the most frequent risk factors in the

Table 1 Demographic characteristics of participants

Variables (%)	Children with MetS (n = 100)	Children without MetS (n = 200)	P-value
Sex (male, %)	55.0	55.0	1.00
Passive smoker (%)	36.0	62.0	< 0.001
History of otitis (%)	23.0	12.0	0.01
Hands-free usage (%)*			< 0.001
Low	63.0	39.0	
Medium	22.0	58.5	
High	15.0	2.5	
Body mass index (%)			< 0.001
Lean	0.0	2.5	
Normal	7.0	70.0	
Overweight	20.0	24.0	
Obese	73.0	3.5	
SFHL (%)**			< 0.001
Normal	68.0	95.0	
Minimal	27.0	4.0	
\geq Mild	5.0	1.0	
HFHL (%)***			< 0.001
Normal	49.0	84.5	
Minimal	44.0	14.5	
\geq Mild	7.0	1.0	

Abbreviations: HFHL, high-frequency hearing loss; MetS, metabolic syndrome; SFHL, short-frequency hearing loss.

*Low: < 2 hours/day; Medium: 2–3 hours/day; High: \geq 4 hours/day.

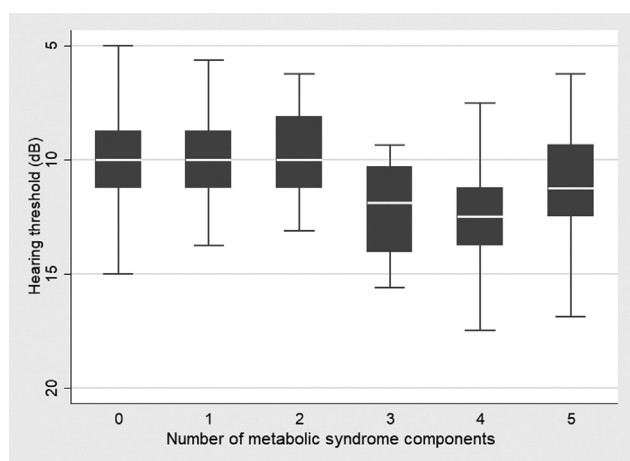
**Speech-frequency hearing loss.

***High-frequency hearing loss.

Table 2 Relative frequency of metabolic syndrome components in the children with or without metabolic syndrome

Variables	Children with MetS (n = 100)	Children without MetS (n = 200)	P-value
Diabetes mellitus (%)	86	8.0	< 0.01
Hypertension (%)	71	11.5	< 0.01
High TG (%)	84	5.5	< 0.01
Low HDL-C (%)	72	19.0	< 0.01
High WC (%)	100	17.5	< 0.01

Abbreviations: HDL-C, high-density lipoprotein cholesterol; METS, metabolic syndrome; TG, triglycerides; WC, waist circumference.

**Fig. 1** Mean (standard deviation) of hearing threshold according to the number of metabolic syndrome components.

controls were low HDL-C (19.0%) and WC > 90th percentile (17.5%). The statistical results of the MetS components in the case and control groups were shown in **Table 2**.

In the children with MetS, the mean SFHL and HFHL were 12.4 (3.6) and 12.1 (4.1) dB hearing level, respectively. In the healthy controls, these values were 10.3 (2.5) and 10.1 (3.9) dB hearing level, respectively. There were significant differences in the mean SFHL and HFHL between the case and control groups (both *p*-values < 0.001). As shown in **Table 1**, the minimal/mild hearing loss at SFHL was present in 32.0% of children with MetS and 5.0% of control participants, and it was associated with an 8.94-fold increase in the odds of SNHL (95% CI: 4.17, 19.16; *p* < 0.001). Minimal/mild HFHL in children with and without MetS was found in 51.0% and 15.5%, respectively (OR 5.28; 95% CI: 2.97, 9.40; *p* < 0.001).

The frequency of 3, 4, and 5 cardiovascular risk factors in the MetS group was 4.0%, 79.0%, and 17.0%, respectively, whereas 57.0% of participants in the control group had no risk factor. The frequency of 1 and 2 risk factors was 34.5% and 8.5%, respectively. The mean hearing threshold for participants without any MetS components was 10.4 (2.5) dB hearing level. However, the corresponding value for participants with all 5 components was 11.1 (4.4) dB hearing level (**Fig. 1**). There was a significant linear trend of hearing threshold with an increase in the number of MetS components ($F [1,296] = 28.63$; *p* < 0.001).

Using conditional logistic regression analyses showed that the odds of smoking, BMI, and all five components of MetS in subjects with speech frequency hearing loss (\geq minimal loss) were significantly higher than in controls (**Table 3**). We also found that the odds of all five components of MetS in subjects with high frequency hearing loss (\geq minimal loss) were significantly higher than in controls (**Table 3**). Variables with a *p*-value < 0.05 in the univariable analysis were included in the multivariable conditional

Table 3 Unadjusted odds ratios for hearing loss (\geq minimal loss) according to some selected risk factors*

	Speech-frequency hearing loss			High-frequency hearing loss		
	OR	95% CI	P value	OR	95% CI	P value
Smoking	0.08	0.01, 0.63	0.02	0.44	0.17, 1.16	0.10
Passive smoker	0.48	0.20, 1.14	0.10	0.56	0.27, 1.12	0.10
History of otitis	1.85	0.72, 4.77	0.20	1.27	0.54, 2.97	0.58
High hands-free usage	6.61	0.72, 60.86	0.10	2.38	0.65, 8.74	0.19
High WC	10.08	3.88, 26.19	< 0.001	4.02	2.23, 7.26	< 0.001
BMI (\geq overweight)	11.33	3.93, 32.69	< 0.001	3.50	1.91, 6.43	< 0.001
Diabetes mellitus	5.54	2.35, 13.05	< 0.001	3.84	2.03, 7.28	< 0.001
Hypertension	5.91	2.37, 14.75	< 0.001	3.22	1.71, 6.06	< 0.001
High TG	12.37	4.33, 35.40	< 0.001	4.07	2.20, 7.51	< 0.001
Low HDL-C	5.47	2.32, 12.90	< 0.001	2.77	1.50, 5.11	0.001
Metabolic syndrome	9.65	4.02, 23.18	< 0.001	4.64	2.59, 8.32	< 0.001

*Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; High hands-free usage: \geq 4 hours/day; OR, odds ratio; TG, triglyceride WC, waist circumference.

Table 4 Multivariable logistic regression analysis for hearing loss according to selected cardiovascular risk factors*

	Speech-frequency hearing loss			High-frequency hearing loss		
	Adjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Diabetes	0.25	0.03, 1.96	0.19	1.72	0.69, 4.30	0.25
Hypertension	2.43	0.52, 11.23	0.26	1.46	0.60, 3.54	0.41
Low HDL-C	1.48	0.33, 6.61	0.61	1.14	0.46, 2.81	0.78
High TG	10.87	1.98, 59.74	0.006	2.32	0.97, 5.52	0.06
BMI (\geq overweight)	3.60	0.56, 23.10	0.18	1.01	0.31, 3.23	0.99

*Abbreviations: BMI: body mass index \geq 85th percentile; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; OR, odds ratio; TG, triglyceride.

logistic regression analysis. In the beginning of the analysis, we examined a strong correlation between two or more independent variables. To determine this, multicollinearity was evaluated by having variance inflation factors (VIFs) and tolerance. Among the variables selected from the univariable analysis, high TG and high WC were highly correlated. When the second variable was regressed upon the first variable, a VIF $<$ 2.5 was obtained. After removing the high WC variable, the multivariable analysis revealed that the rate of high TG in the participants with SFHL was significantly higher when compared with the controls (**►Table 4**). Children with high TG were \sim 10 times more likely to have SFHL than those without. However, our original model of multivariable logistic regression failed to show any significant predictors for HFHL.

Discussion

This study indicated that the frequency of SNHL (minimal/mild) was higher in children with MetS than in controls (51.0% versus 15.5%). Furthermore, our findings showed that there was a linear trend of increased hearing threshold as the components of MetS increased. According to findings of the multivariable logistic regression, a significant predictor of hearing loss in SFHL was high TG. Interestingly, there was a strong correlation among two components of large WC (a proxy of central adiposity) and high TG. According to a consensus statement from the IDF, central obesity may be a more important risk factor than BMI for defining MetS.³¹

The present case-control study confirms previous cross-sectional findings of an association between obesity and increased prevalence of hearing loss in adolescents. After adjusting for potential confounding factors, high TG was associated with increasing odds of hearing impairment in speech frequency (OR 10.87; 95% CI: 1.98, 59.74) compared with those without it. Although the OR of this magnitude may seem to be a large effect size; the wide confidence interval of OR reflects a low precision of this study. On the other hand, if the study was repeated multiple times on other samples, the calculated OR would be any value between 2 (small effect size) and 60 (large effect size). Hence, we are uncertain due to the wide CI. Children with high TG compared with those without it, may have higher rates of HFHL (OR 2.32; 95% CI: 0.97, 5.52). However, the strength of the

association was not significant with a wide CI. There are few epidemiological studies about the association between hearing loss and MetS components in adolescents. Kohlberg et al.³² revealed that obesity was associated with a 1.73-fold increase in the odds of SNHL. In a recent study, Wang et al.³³ found that fat mass index consistently predicted higher hearing threshold in children (OR 1.2). In a cross-sectional study, Lalwani et al.³⁴ suggested that obesity in adolescents was associated with elevated pure tone hearing thresholds and greater prevalence of unilateral low-frequency SNHL (OR 1.85). In an analysis of adolescents who participated in the National Health and Nutrition Examination Survey (NHANES) 2007–2010, Scinicariello²⁸ found that obesity was associated with increased odd of having audiometric notches and HFHL, but not with speech frequency HL. In contrast with our findings, Anbari et al.³⁵ observed no association between dyslipidemia and SNHL in children and adolescents.

Dyslipidemia disrupts blood flow through the processes of plaque formation, vascular remodeling, and vascular luminal obstruction, leads to endothelial dysfunction and vascular inflammation and increases the accumulation of lipid and cholesterol on the intima of vessel walls. This disorder ultimately impairs oxygen supply in target organs such as the cochlea.³⁶ It has been shown that dyslipidemia in guinea pigs caused severe edema in the stria marginal layer and mild edema in the outer hair cell, mainly in the basal turn.³⁷

Notably, central adiposity is associated with dyslipidemia, hypertension and hypercoagulability.³⁸ Obesity is a systemic chronic inflammatory condition.³⁹ Excessive macronutrients in adipose tissues stimulate the release of inflammatory mediators, such as tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6), as well as the production of adiponectin. Adiponectin is an adipocytokine, which is synthesized and released by adipose tissue and presents in low concentrations in obese people⁴⁰ and those with MetS.⁴¹ A meta-analysis by Reilly et al. showed that low levels of adiponectin were often observed in obese children.⁴² The results of two animal studies further confirm the potential role of adiponectin in the development of hearing loss. The first study⁴³ demonstrated the expression of adiponectin receptor 1 in the auditory system of mice. Another study⁴⁴ showed that adiponectin deficiency exacerbated hearing loss, particularly in the high frequency range in knockout mice. Adiponectin

deficiency leads to endothelial changes in the wall of cochlear blood vessels and cochlear hair cells damage, particularly in the basal turn of the cochlea. In addition, hearing impairment could be a result of incorrect expression of C-reactive protein, decreased activation of TNF- α -induced NF- κ B, and reduced I κ B kinase (I κ B) phosphorylation.⁴⁵

The present study revealed that the more MetS components a patient has, the higher the hearing impairment. In a cross-sectional study from the LIPGENE cohort, Yubero-Serrano et al.⁴⁶ confirmed that MetS subjects with more components exhibited higher oxidative stress, which led to increased activity of antioxidant enzymes (superoxide dismutase [SOD] and glutathione peroxidase [GPx]) and several other biomarkers. The SOD and GPx activities were lower in subjects with 2 MetS components than in subjects with 4 or 5 MetS components. The authors found the SOD was the most relevant oxidative stress biomarker in patients with MetS. Similarly, Sánchez-Rodríguez et al.⁴⁷ found that subjects with 5 MetS components had a 10-times higher risk of developing oxidative stress than subjects with 1 component.

The present study has several limitations. First, its cross-sectional design makes it impossible to draw causal conclusions. Children with MetS received regular medical support and health care compared with those without, and they may take various medications, which may be protective or a hazard to hearing loss. These can affect the associations between MetS components and the incidence of hearing loss. This remains to be validated in a prospective cohort study. Secondly, we used self-reported history of other risk factors, such as otitis media, smoking, and hands-free usage. Misinformation may change the association in favor or away from the null hypothesis. Third, the pure-tone audiogram offers limited insight into functional hearing and should be viewed only as a test of hearing sensitivity. The financial constraints prevented us from assessing cochlear damage with autoacoustic emission. Monitoring the development of hearing and emission loss in children with MetS is recommended in future works. Another limitation of our study is that we did not include children under 12 years old. Therefore, the results from our study cannot be applied to children in this age group. Finally, the duration of MetS in the children with this condition was relatively short. While it was difficult to have participants with a longer duration of MetS, this would be optimal.

Conclusion

The present case-control study showed that children with MetS had increased odds of minimal/mild hearing loss at SFHL (OR 8.94) and HFHL (OR 5.28) compared with control participants. The present case-control study provided new insights into the possible association of high TG and central obesity with the hearing impairment at SFHL in adolescence, even after adjustment for other MetS components and several hearing-related covariates. The rapid rise in the prevalence of obesity may lead to increased hearing threshold in adolescents. Based on the findings of the present

study, further studies about the possible effects of central obesity and dyslipidemia on hearing loss are needed.

Conflict of interests

The authors declare that they have no conflict of interests.

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