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Acanthosis nigricans predicts the clustering of metabolic syndrome components in Hispanic elementary school-aged children

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Abstract

Background—Acanthosis nigricans (AN) is a dermatologic condition associated with hyperinsulinemia, a marker of insulin resistance that is the principal abnormality in metabolic syndrome (MetS). We examined the association of AN with the clustering of MetS components.

Methods—A cross-sectional study was conducted in an urban school-based health center in New Mexico. Students without diabetes were evaluated for AN, a family history of type 2 diabetes, body mass index (BMI), and MetS components. The clustering of MetS components by BMI category and AN status was assessed by comparing the group means of summed average z-scores of fasting insulin, triglycerides, high-density lipoprotein- cholesterol, and systolic blood pressure among the students. A multivariate model with BMI category and AN status controlling for Tanner stage was performed to identify the variables associated with the clustering of MetS components.

Results—Complete data were available for 90 children (age, 9.7 ± 1.4 years; 94 % Hispanic; 60 % female). In multivariate modeling of MetS cluster z-score, significant differences were found

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between the students with BMI < 85th percentile [−0.27; 95 % confidence interval (95 % CI) = − 0.42 to − 0.11] and (a) the students with BMI 85th – 94.9th percentile with AN (0.74; 95 % CI = 0.17 – 1.31) and (b) the students with BMI ≥ 95th percentile with AN (0.86; 95 % CI = 0.54 – 1.18). No significant differences in the MetS cluster z-score were seen between the students with BMI < 85th percentile and those with BMI 85th – 94.9th percentile without AN (0.24; 95 % CI = − 0.33 to 0.81) or those with BMI ≥ 95th percentile without AN (0.31; 95 % CI = − 0.13 to 0.75).

Conclusions—Overweight/obese Hispanic elementary school-aged children with AN exhibit clustering of MetS components and could benefit from early intervention.

Keywords

Acanthosis nigricans; children; Hispanic; insulin resistance; metabolic syndrome; obesity; school health services

Introduction

Obesity in association with hypertension, elevated levels of triglycerides, reduced levels of high-density lipoprotein-cholesterol (HDL-C), insulin resistance, or glucose intolerance is a widely recognized constellation of risk factors for heart disease and type 2 diabetes known as the metabolic syndrome (MetS). Although the MetS has long been recognized as a precursor to cardiovascular disease and type 2 diabetes in adults (1 – 3), the evidence for an increase in the prevalence of the MetS in US adolescents has been accumulating (4 – 6). To address concerns about the growing prevalence of the MetS and to prevent the disease in adolescents, it is important to identify the high-risk children.

The implications of the MetS in children are more severe than in adults for at least two reasons. First, the morbidities associated with type 2 diabetes initiating in adolescence would result in many more decades of morbidity than in an adult. Second, an extended period of morbidity would certainly translate into higher medical costs over the course of a lifetime. A study that investigated healthcare utilization and costs associated with the MetS in three health plans in Seattle, WA, found that the average annual total costs between patients with the MetS and those without the MetS differed by a factor of 1.6 ($5732 vs. $3581) (7). Furthermore, for those with the MetS who go on to develop type 2 diabetes, the costs were nearly twice that of prediabetic patients. Another study involving 4188 working adults in Michigan found that the health costs for employees with the MetS and associated diseases were nearly four-fold greater than those without the MetS and who were disease-free (8).

Acanthosis nigricans (AN) may serve as a marker for identifying children at risk of developing the MetS. AN is a dermatologic condition characterized by hyperpigmentation, hyperkeratosis, and papillomatosis and is strongly associated with hyperinsulinemia (9 – 15). The typical areas of involvement in AN include the posterior neck, the axilla, the elbows, and the knees, with the neck being involved 93 % – 99 % of the time (16, 17). In populations where traditional risk factors, such as obesity and a family history of diabetes are especially common, AN may aid in rapidly identifying a subgroup of individuals who are at an increased risk for future disease, particularly type 2 diabetes (18). Although several studies have found AN to be an independent predictor of hyperinsulinemia (10, 13, 19), others have not (20, 21).

The MetS in children is a cause for special concern because it is a well-established precursor of cardiovascular disease and type 2 diabetes in adults (22 – 24). Only recently have attempts been made to characterize the MetS in the pediatric population (4, 25, 26). Because data that track individuals from childhood to adulthood are limited, little is known about

how well pediatric MetS predicts adult disease; however, the evidence of this sort is beginning to emerge. In a follow-up study of 771 children ages 6 – 19, the Princeton Lipid Research Clinics found that children with the clustering of the MetS risk factors were significantly more likely to have cardiovascular disease 25 years later when compared with their peers (27). Franks et al. (28) found from the longitudinal data for 1604 non-diabetic 5 – 19-year-old American-Indian children that the strategies targeting obesity, dysregulated glucose homeostasis, and low HDL during childhood support the prevention of type 2 diabetes. Recently, Nguyen et al. reported data from the Bogalusa Heart Study, which show that indicators of poor glucose homeostasis, such as plasma glucose and insulin levels and insulin resistance index [homeostasis model assessment-insulin resistance (HOMA-IR)] in childhood not only persisted into adulthood but also predicted who would develop adult prediabetes and type 2 diabetes (29).

The main aim of the present study was to investigate the association between AN and the components of the MetS in school-aged children. To accomplish this goal, we enrolled students attending an urban elementary school in New Mexico and obtained their health history, anthropometric measures, and serum biomarkers of the MetS, which included glucose, insulin, triglyceride, and HDL-C. In addition, we collected demographic information that included age, sex, and race/ethnicity. These data were used to address several questions. First, we were interested in knowing the prevalence of AN in these children. Second, we wanted to compare the levels of biomarkers and cardiometabolic risks by body mass index (BMI) and AN status of the children. Specifically, we compared insulin levels, HOMA-IR, triglycerides, HDL-C, systolic blood pressure (SBP), and the clustering of these in children stratified by BMI and AN status.

Materials and methods

Study participants

In spring 2006, we recruited a convenience sample of 117 children ages 5 – 11 to provide a cross-sectional study for evaluating the prevalence of AN and its association with insulin resistance and the clustering of the MetS components. Children were from an elementary school located in the zip code area, with the highest percentage of families under 185 % of the federal poverty level in Albuquerque, NM, and where most of the students were Hispanic. Students were recruited through classroom presentations about prevention of type 2 diabetes. Packets containing an informational letter, consent/assent form describing the aims and methods of the study, and a health history survey were given to students to take home to their parents. Students and parents interested in participating in the study returned the completed consent/assent form and health history survey to the school's health center. A modest prize consisting of pencils, erasers, and stickers was given to all students who returned the study packet regardless of whether they participated in the study. All study procedures were conducted at the elementary school's health center under the aegis of the University of New Mexico (UNM) School-based Health Center (SBHC) program. SBHC physicians (two pediatricians and one family medicine doctor) reviewed the students' risks of type 2 diabetes and provided counseling to the children and their parents on the risk reduction as a benefit of participation.

Inclusion criteria included the enrollment in the collaborating elementary school and students who had been diagnosed previously with diabetes (type 1 or 2) were excluded from the study. The study was approved by the UNM Human Research Review Committee and the School Districts' Research, Development and Accountability Department.

Biomarkers

A UNM Clinical and Translational Science Center (CTSC) research nurse drew fasting blood by venipuncture into serum separator tubes. Blood was allowed to clot at room temperature for 30 min and then centrifuged for 10 min in a clinical centrifuge. The serum fraction was aliquoted into cryovials and stored at − 80 ° C. Glucose was measured using the ACE Glucose Reagent kit (Alfa Wassermann Diagnostic Technologies, LLC, West Caldwell, NJ, USA), whereas insulin was measured using the Immulite/Immulinte 100 Insulin kit (Siemens Healthcare Diagnostics Products Ltd., Llanberis, Gwynedd, UK). Triglyceride and HDL-C were measured using ACE Chemistry System (Alfa Wassermann Diagnostic Technologies, LLC, West Caldwell, NJ, USA). Breakfast was provided to students after blood sampling.

Data collection and measurements

Before collecting the data, the participating physicians were trained by the principal investigator to identify AN. The validation of the training program is described elsewhere (18). SBHC physicians reviewed the health history survey with the participating students and their parents at the study visit. Health history items queried included student's family history of diabetes and student's personal history of diabetes. A physical examination that included AN evaluation of the posterior neck and pubertal status according to the methods of Tanner (30, 31) was performed by the SBHC physicians. Student's blood pressure in a seated position on the right arm was measured by a UNM CTSC pediatric research nurse with a Welch Allen (Skaneateles Falls, NY, USA) aneroid sphygmomanometer in accordance with the Fourth Task Force Recommendations for technique and cuff sizes (32). Participant's height and weight were measured twice by the UNM CTSC bionutritionist using the method described by Gordon et al. (33). Participants were weighed to the nearest 0.1 kg on a portable strain-gauge digital scale (Seca Model 770, Seca North America West, Chino, CA, USA) and height was measured to the nearest 0.1 cm using a Schorr vertical measuring board (Schorr Productions, Olney, MD, USA). BMI was calculated as kg/m^2. A program from the Centers for Disease Control and Prevention was used to calculate the BMI percentile and z-score for children based on their height (cm), weight (kg), sex, and age (in months) (34).

Data analysis

Descriptive statistics, including frequency distributions, for all variables were calculated. As insulin and HOMA-IR values were skewed, the data were log transformed. Analysis of variance was used to evaluate bivariate relationships for HOMA-IR and the MetS cluster z-score compared with age, gender, family history of diabetes, AN, Tanner stage, and BMI category.

The MetS components included in the cluster z-score were insulin, SBP, triglycerides, and HDL-C (35). BMI was not included in the cluster analysis because it was used to categorize comparison groups. Glucose concentration was not used because of the narrow and normal range of values found in these children, as expected for their young age. The z-score for each of the four components was calculated by first determining the difference between each participant's value for the respective component and the sex-specific mean value for that component (35). Then, the result was divided by the corresponding SD. Finally, for each participant, the average of the z-scores for the four components was computed (with reversed sign for HDL-C); higher z-score indicates that the four components tend to cluster in the higher distributions implicating higher risk.

BMI and AN were grouped as follows: (a) students with BMI < 85th percentile, (b) students with BMI 85th – 94.9th percentile (overweight) with AN, (c) students with BMI 85th –

94.9th percentile (overweight) without AN, (d) students with BMI ≥ 95th percentile (obese) with AN, and (e) students with BMI ≥ 95th percentile (obese) without AN. One-way analysis of variance was performed between the five groupings of BMI and AN status and the outcomes of the MetS cluster z-score, HOMA-IR, insulin, triglycerides, HDL-C, and SBP. All analyses were performed with the aid of the software program SAS 9.2 (SAS Institute, Cary, NC, USA).

Three-factor analysis of variance was conducted to determine the variables associated with the clustering of the MetS components (the MetS cluster z-score) and also with insulin resistance (HOMAIR). Independent variables were included in the model when $p < 0.20$ in the bivariate analysis and were then retained in the model if they were significant at $p < 0.05$ in the multivariate model. Due to the collinearity relationship between age and Tanner stage, final models were calculated without age and contained sex, Tanner stage, and BMI/AN categories.

Results

Population

Ninety students between ages 5 and 12 had complete data for the analysis. Sixty percent were female and almost all were of Hispanic descent. Among these Hispanic students, a family history of diabetes in the first- or second-degree relative was high (52 %) as were overweight and obesity (36 %). AN was identified in 22 % of subjects. Some students already manifested the components of the MetS, such as hypertriglyceridemia (6 % with trigly ceride levels ≥ 1.695 mmol/L or 150 mg/dL), low HDL-C (37 % with HDL-C levels < 1.036 mmol/L or 40 mg/dL), and impaired fasting glucose (8 % with glucose levels ≥ 5.55 mmol/L or 100 mg/dL). None were identified with type 2 diabetes (Table 1).

Insulin resistance and clustering of the MetS components

As shown in Table 2, both insulin resistance reported as HOMA-IR and the clustering of the MetS components reported as the MetS cluster z-score were found to be significantly related to age, sex, Tanner stage, AN, and BMI status. A family history of diabetes in the first- or second-degree relative was not associated with insulin resistance or the clustering of the MetS components.

Students who were not overweight or obese did not have AN. As shown in Table 3, in the heavier BMI categories, mean insulin, triglycerides, HDL-C, HOMA-IR, and the MetS cluster z-score all worsened. The geometric mean insulin for obese students with AN was 118.76 pmol/L, which was significantly greater than the geometric mean insulin levels for students in all groups: for those who were not overweight or obese (38.89 pmol/L), for those students who were overweight regardless of AN status (without AN 47.92 pmol/L and with AN 61.81 pmol/L), and for those students who were obese but without AN (53.48 pmol/L). HOMA-IR exhibited a similar trend to insulin when subjects were stratified according to the BMI/AN categories. However, when evaluating the clustering of the MetS components, obese students with AN had a statistically significant higher mean MetS cluster z-score (0.97) when compared with obese students without AN (0.13) and also overweight students without AN (0.02) but was not significantly different from overweight students with AN (0.5).

In multivariate modeling, after adjusting for the variables associated with HOMA-IR, such as sex, Tanner stage, and BMI/AN categories, pubertal status was associated with almost a two-fold increase in HOMA-IR and a fivefold increase in the MetS cluster z-score when compared with prepubertal students. Obese students with AN were different with a two-fold increase in HOMA-IR when compared with students who were not overweight and obese.

Students with AN, regardless if they were overweight or obese, had a higher MetS cluster z-score when compared with overweight or obese students without AN. However, overweight and obese students without AN did not have statistically different MetS cluster z-score when compared with students who were not overweight or obese.

Discussion

As the epidemic of obesity and the MetS continues to increase in U.S. adolescents, it becomes critical to identify the high-risk children for lifestyle modification to reduce the risk of early onset of premature cardiovascular disease and type 2 diabetes. AN is a reliable dermatologic marker of hyperinsulinemia (10, 12). The findings in the present study support that overweight and obese children with AN have higher cardiometabolic risks than children without AN. The finding that one in five of the elementary school students in our study already had AN is an alarming indicator of an impending marked increase of type 2 diabetes. Insulin resistance by HOMA-IR and the MetS cluster z-score were increased in the overweight (BMI 85th – 94.9th percentile) and obese (BMI ≥ 95th percentile) groups. Although there was an overlap in some confidence intervals of the HOMA-IR and the MetS cluster z-score by BMI and AN status, it is clear that the values of these dependent variables increased when children had AN (Table 4). A student whose BMI was ≥ 95th percentile and who had AN was more than twice as likely to be insulin resistant compared with students whose BMI was < 85th percentile and who did not have AN. The MetS cluster z-score was nearly four-fold higher in students with BMI ≥ 95th percentile and AN when compared with students whose BMI was < 85th percentile and who did not have AN. Even students with BMI in the 85th – 94.9th percentile and AN had a MetS cluster z-score that was more than three-fold higher than students with a BMI < 85th percentile.

In a study of 113 obese children in Hungary, 57 of whom were obese but without AN and 58 of whom were obese with AN, insulinemia was more marked in the obese children with AN than those who did not have AN (36). Insulin resistance was also correlated with the degree of AN as measured by the intensity of pigmentation. In addition, these same investigators found that triglycerides were higher and HDL-C concentrations were lower in the obese children with AN compared with obese children without AN. In the present study, we too found that obese students with AN had higher levels of insulin, were more insulin resistant, and had higher levels of triglycerides and lower levels of HDL-C than students without AN (Table 3). In a study of 236 ethnically diverse (60 % Hispanic, 30 % African American) children ages 8 – 14 years with AN and 51 children without AN, Brickman et al. (37) reported that AN was a predictor of insulin resistance and abnormal glucose homeostasis as determined by oral glucose tolerance testing and suggested that AN confers an increased risk of insulin resistance beyond that attributable to adiposity alone. Consistent with these two previously mentioned studies, our results also showed an interaction effect between obesity and AN. Other investigators have also documented that AN further exacerbates the differences seen in insulin, insulin resistance, and triglycerides in obese children (19, 38). In contrast, however, Nguyen et al. (20) and Hirschler et al. (21) did not find AN to be an independent marker of insulin resistance when they controlled for adiposity. The seemingly contradictory results between the Nguyen et al. study and ours may be due to the fact that the children in his study were African American or White, whereas our subjects were primarily Hispanic. Furthermore, whereas in our study we made comparisons stratified by BMI and AN status, Nguyen et al. did not do so. With regards to the study by Hirschler et al., they did not log transform the HOMA-IR and insulin data. As it is widely recognized that these variables are usually skewed, failure to log-transform the data may have prevented them from detecting significant differences between AN and insulin resistance.

Our study demonstrates that not only is insulin resistance associated with AN but also the clustering of cardiometabolic risk factors too are also associated with AN. Given that AN presents early in childhood where the components of the MetS may still be within normal limits and are beginning to cluster, identifying these young children is important because they would benefit from lifestyle modification that would decrease the future risk of developing the MetS and type 2 diabetes. AN is a convenient and readily recognizable skin marker that can be quickly assessed in a clinical setting by a medical provider. In the present study, although no children were found to have developed type 2 diabetes, 8 % of all participants did have evidence of impaired glucose homeostasis. This means that many more of our subjects with AN but who had yet to express indicators of prediabetic state would benefit from the early intervention and prevention.

This study has several implications for public health that are worth considering. First, as it was conducted in an elementary school that houses a SBHC, the opportunity exists for health professionals to work collaboratively with teachers to implement programs aimed at reducing the risk of type 2 diabetes. The study demonstrates the feasibility of AN screening and type 2 diabetes risk reduction counseling in a captive audience. Second, AN screening of young children has the potential to prevent dyslipidemia, hypertension, the MetS, and type 2 diabetes. Last, behavioral lifestyle modifications introduced during early childhood are likely to be continued in adulthood.

One limitation of our study is the relatively small sample size. Nevertheless, despite the small number of participants, we were able to observe statistically significant differences in cardiometabolic risks in obese children with and without AN. Second, with regard to study design, a longitudinal study as opposed to a cross-sectional study would have been preferred. Our future studies will utilize a larger sample size and longitudinal design, which will permit us to gain more definitive answers to causality visà-vis the development of type 2 diabetes.

In conclusion, our study underscores the gravity of the growing prevalence of the MetS in youth. AN is a reliable skin marker for insulin resistance and cardiometabolic risk that can be used to identify young children for early preventive therapy. Future studies should evaluate the prevention strategies for lifestyle modification that can be implemented in collaboration with schools.

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Table 1

Summary of the characteristics of the 90 students.

Parameter	n (% of total)
Age, years	
5 – 9	45 (50)
10 – 12	45 (50)
Sex	
Female	54 (60)
Male	36 (40)
Race/ethnicity	
Hispanic	84 (93)
Other	4 (4)
Missing	2 (2)
Family history of diabetes	
Yes	47 (52)
No	36 (40)
Missing	7 (8)
BMI	
< 85th percentile	57 (63)
85th – 94.9th percentile	12 (13)
≥ 95th percentile	21 (23)
Tanner stage	
I	49 (54)
II – V	34 (38)
Missing	7 (8)
AN	20 (22)
SBP ≥ 95th percentile	0 (0)
DBP ≥ 95th percentile	4 (4)
Triglycerides ≥ 1.695 mmol/L or 150 mg/dL	5 (6)
HDL-C < 1.036 mmol/L or 40 mg/dL	33 (37)
Glucose ≥ 5.55 mmol/L or 100 mg/dL	7 (8)

Table 2

HOMA-IR and MetS cluster z-score by age, sex, Tanner stage, AN, BMI, and family history of diabetes.

Parameter	HOMA-IR, geometric mean (95 % CI)	MetS cluster z-score, mean (95 % CI)
Age, years		
5 – 9	1.13 (0.92 – 1.40)	− 0.29 (− 0.49 to − 0.09)
10 – 12	2.13 (1.71 – 2.66)	0.29 (0.06 – 0.51)
p-Value	< 0.001	< 0.001
Sex		
Female	1.77 (1.45– 2.16)	Not applicable
Male	1.27 (0.96– 1.68)	
p-Value	0.05	
Tanner stage		
I	1.17 (0.95 – 1.44)	− 0.27 (− 0.45 to − 0.08)
II – V	2.44 (1.93 – 3.10)	0.35 (0.07 – 0.63)
p-Value	< 0.001	< 0.001
AN		
No	1.28 (1.08 – 1.51)	− 0.24 (− 0.37 to − 0.10)
Yes	3.11 (2.31 – 4.19)	0.83 (0.45 – 1.20)
p-Value	< 0.001	< 0.001
BMI		
< 85th percentile	1.22 (1.01– 1.46)	− 0.31 (− 0.45 to − 0.16)
85– 94.9 percentile	1.67 (1.14– 2.43)	0.26 (− 0.12 to 0.64)
≥ 95th percentile	2.92 (2.09– 4.07)	0.69 (0.31– 1.06)
p-Value	< 0.001 [a]	< 0.001 [b]
Family history of diabetes		
No	1.56 (1.20 – 2.02)	− 0.04 (− 0.25 to 0.17)
Yes	1.53 (1.21 – 1.95)	0.04 (− 0.21 to 0.29)
p-Value	0.93	0.65

[a] The geometric mean for the ≥ 95th percentile group is significantly different from the geometric means of the other groups.

[b] The means for all groups are significantly different from each other. 95 % CI, 95 % confidence interval.

Table 3

MetS cluster z-score, HOMA-IR, glucose, insulin, triglycerides, HDL-C, and SBP according to BMI percentile and AN status.

Variable	BMI < 85th percentile	BMI 85th – 94.9th percentile (overweight)		BMI ≥ 95th percentile (obese)		p-Value
	− AN (n = 57)	−AN (n = 6)	+ AN (n = 6)	−AN (n = 7)	+ AN (n = 14)	
MetS cluster z-score	− 0.31 (− 0.45 to − 0.16)	0.02 (− 0.45 to 0.49)	0.50 (− 0.21 to 1.21) [b]	0.13 (− 0.34 to 0.60)	0.97 (0.49 – 1.45) [a]	< 0.001
HOMA-IR	1.2 (1.0 – 1.5)	1.5 (0.7 – 3.1)	1.8 (1.1 – 3.2)	1.6 (0.8 – 3.2)	3.9 (2.8 – 5.4) [c]	< 0.001
Insulin, pmol/L	38.89 (32.64 – 45.84)	47.92 (24.31 – 95.84)	61.81 (36.81 – 103.48)	53.48 (28.47 – 102.09)	118.86 (88.9 – 159.04) [c]	< 0.001
Glucose, mmol/L	4.94 (4.83 – 5.05)	4.88 (4.55 – 5.27)	4.66 (4.44 – 4.88)	4.77 (4.55 – 5.0)	5.11 (4.88 – 5.33)	0.10
Triglyceride, mmol/L	0.82 (0.76 – 0.90)	0.97 (0.71 – 1.31)	1.07 (0.69 – 1.67)	1.12 (0.96 – 1.32)	1.27 (0.99 – 1.62)	< 0.001
HDL-C, mmol/L	1.27 (1.19 – 1.35)	1.17 (1.04 – 1.27)	0.98 (0.83 – 1.11)	1.01 (0.91 – 1.11)	0.91 (0.80 – 1.04) [b]	< 0.001
SBP, mm Hg	99 (97 – 101)	103 (91 – 115)	108 (101 – 116)	98 (87 – 109) [d]	107 (103 – 111)	0.001

Total cholesterol and LDL cholesterol were not measured as they are not components of the MetS. Values are mean (95 % CI) for MetS cluster z-score, HDL-C, and SBP; values are geometric mean (95 % CI) for HOMA-IR, insulin, and triglycerides.

[a] Significantly different from BMI < 85th percentile, overweight BMI with no AN, and obese BMI with no AN.

[b] Significantly different from BMI < 85th percentile.

[c] Significantly different from all other groups.

[d] Significantly different from overweight BMI with AN.

Table 4

Multivariate model of HOMA-IR and MetS cluster z-score.

	Log HOMA model	p-Value	MetS cluster z-score model	p-Value
Sex				
Male	2.2 (1.6– 3.1)	0.91	Not applicable	
Female	2.2 (1.7– 2.8)			
Tanner stage				
I	1.6 (1.3 – 2.0)	< 0.001	0.12 (− 0.09 to 0.34)	< 0.001
II – V	3.1 (2.2 – 4.3)		0.63 (0.37 – 0.89)	
BMI and AN				
BMI < 85th percentile	1.3 (1.1– 1.6)	< 0.001 [a]	− 0.27 (− 0.42 to − 0.11)	< 0.001 [b]
BMI 85th– 94.9th percentile with −AN	2.2 (1.2 – 4.1)		0.24 (− 0.33 to 0.81)	
BMI 85th– 94.9th percentile with + AN	2.7 (1.4– 4.9)		0.74 (0.17– 1.31)	
BMI ≥ 95th percentile with −AN	2.1 (1.3 – 3.4)		0.31 (− 0.13 to 0.75)	
BMI ≥ 95th percentile with + AN	3.4 (2.4– 4.9)		0.86 (0.54– 1.18)	

[a] The BMI < 85th percentile group is significantly different from the BMI ≥ 95th percentile + AN group.

[b] The BMI < 85th percentile group is significantly different from the BMI 85th – 94.9th percentile with + AN group and the BMI ≥ 95th percentile + AN group.