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Obesity, Central Adiposity and Cardiometabolic Risk Factors in Children and Adolescents: a Family-based Study

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Abstract

Objective—Assess genetic and phenotypic correlations of obesity-related cardiometabolic risk factors in a family-based cohort.

Methods—Anthropometric, body composition and biochemical measurements were collected on 999 members of 111 extended Midwestern US families of Northern European origin. Forward stepwise regression was used to identify which of Tanner stage, sex, Tanner stage by sex, BFMI, body fat percent (BF%) (DXA), VF/SubQF (CT scan for adults or MRI for children), VF, SubQF, BMI% and waist to height ratio (WHtR) most influence HOMA, HDL-c, TG, and LDL-c.

Results—In children and adolescents, subcutaneous adiposity was the most significant covariate for HOMA ($p<0.001$) and TG ($p=0.001$) and BMI percentile for HDL-c ($p=0.002$) and LDL-c ($p<0.001$). In adults, waist-height ratio ($p<0.001$), visceral/subcutaneous fat ratio ($p=0.001$) and BMI ($p=0.02$) were most significant for HOMA; visceral fat ($p<0.001$) and BMI ($p=0.02$) for TG and visceral fat for LDL-c ($p=0.001$).

Conclusion—Subcutaneous adiposity at the waist is a more significant predictor of MetS traits in children and adolescents than it is in adults.

Keywords

Central adiposity; adolescent obesity; metabolic syndrome; insulin resistance; dyslipidemia

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Introduction

Studies in adults show central adiposity increases the likelihood of finding metabolic abnormalities and this risk is mostly attributed to visceral fat (1-4). The few pediatric studies of this issue show conflicting results, (5-11) and even when there is an association with central adiposity, it is not clear whether visceral fat (VF) or subcutaneous fat (SubQF) plays a larger role in the observed association (11-13). We examined the influence of central adiposity and abdominal fat depots on cardiometabolic traits in a large and well-characterized multi-generational family-based cohort.

Methods

Participants

The study cohort consists of 999 individuals ranging in age from 6 to 90 years, from 111 extended families who were recruited via the membership of the Take Off Pounds Sensibly (TOPS) club. Details of their recruitment and ascertainment procedures have been previously described (14). The recruitment period was between 1995-2010 and all families lived in the Midwestern United States and were of Northern European ethnicity by self-reporting. All study procedures for adults, adolescents and children were approved by the Institutional Review Boards of the Medical College of Wisconsin and Children's Hospital of Wisconsin, respectively.

All phenotypic measurements were made as previously described (14). A list of these measurements and their mean values are given in the Supplementary Table 1. Height was measured without shoes and weight was measured with the subjects wearing light clothing and without shoes. Waist circumference (WC) was the minimal measurement at the navel region, and hip circumference (HC) was the widest measurement at the hip and buttocks. Body mass index (BMI) was calculated by dividing weight in kg by the square of height in meters. BMI percentiles were calculated for children and adolescents using CDC standards. Tanner staging was performed by self-assessment based on standard pictures. In case of any doubt or confusion, a physician member of the team was available to explain the procedure and to perform the assessment directly if needed. Fat mass and fat free mass were determined by whole-body DXA scan (15). Body lean mass is derived from total fat free mass by subtracting bone mineral content. Body fat mass index (BFMI) and lean mass index (LMI) were then calculated by the following equations:

$$BFMI = \text{fat mass (kilogram)} / \text{height}^2 \left(m^2 \right) ;$$

$$LMI = \text{lean mass (kilogram)} / \text{height}^2 \left(m^2 \right) .$$

Total abdominal fat (TAF), VF and SubQF were measured by CT scans of the fourth lumbar spine (16) in adults, and by MRI at the same level in children and adolescents (17). Fasting glucose (FG), fasting insulin (FI), HDL-c, LDL-c, adiponectin, leptin, TNF-alpha,

interleukin 1 beta and interleukin 6 were measured using immunoassays as described previously (18).

Statistical Analysis

Each trait was first inverse normalized using the pedigree based genetic analysis package SOLAR (19). Using linear mixed models in SOLAR to account for kinship, a forward stepwise regression procedure was used to predict the factors influencing serum levels of key MetS components: HOMA (as a measure of insulin resistance) and HDL-c, LDL-c and plasma triglycerides (TG) (as measures of dyslipidemia). Independent variables in the children and adolescents analysis included Tanner stage, sex, Tanner stage by sex, BFMI, body fat percent (BF%), VF/SubQF, VF, SubQF, BMI%, and waist to height ratio (WHtR). In adults, age was used in place of tanner stage. A significance level for inclusion in the model was specified at $p < 0.05$.

Results

We used SOLAR to assess the genetic and phenotypic correlation between various traits. Figure 1 shows their correlation genetically (the left wing) or phenotypically (the right wing) ($p < 0.05$). Phenotypic correlation (Figure 1) analysis showed that BMI is strongly correlated with fat mass ($\rho_p = 0.86 \pm 0.01$) and BFMI ($\rho_p = 0.88 \pm 0.01$) as well as with truncal subcutaneous fat ($\rho_p = 0.84 \pm 0.02$), though less so with VF ($\rho_p = 0.70 \pm 0.03$). BMI and measures of central adiposity (WC and WHR) had modest correlations with FG, FI and HOMA (range ρ_p of 0.16 to 0.43). BMI and WC were also modestly correlated with TG ($\rho_p = 0.31$ and 0.28 , respectively) and HDL-c ($\rho_p = -0.28$ and -0.27 , respectively). BMI, BF%, BFMI and WC were not correlated with total cholesterol (TC) ($p > 0.05$) and only weakly correlated with LDL-c (ρ_p range 0.08-0.14).

We then used forward step-wise regression to assess which of the measures of adiposity and fat distribution are the most significant influence on HOMA, HDL-c, TG and LDL-c (children and adolescents Table 1a and adults Table 1b). In children and adolescents, SubQF remained highly significant as an independent covariate for HOMA and TG, while BMI% remained the most significant covariate for HDL-c and LDL-c. Sex was also an independently significant variable for TG levels. In contrast, in adults WHtR, VF/SubQF ratio and BMI remained the most significant variables for HOMA; VF and BMI for TG and VF for LDL-c; only sex remained significant for HDL-c.

Discussion

We found that subcutaneous adiposity at the waist, rather than visceral fat, remained in the stepwise regression models as a significant predictor of HOMA and of TG in children and adolescents. In contrast, VF, VF/SubQF ratio and WHtR remained significant as independent effectors of HOMA, TG and LDL-c in adults. This finding suggests that the influence of body fat distribution on MetS risk in children and adolescents is not the same as that seen in adults. In adults, most studies implicate VF stores as the most significant influence on insulin resistance and dyslipidemia (20) and we too identified VF as the most significant factor influencing HOMA and TG levels in adults, but this was not the case in

children and adolescents. This indicates that body fat depots may differ in their pathogenic significance at different stages of the life cycle. Further studies will be needed to replicate our findings and to determine their underlying pathophysiological mechanism. If confirmed, these findings may impact research and health education priorities in the adolescent age group and could lead to a better understanding of the pathophysiology of obesity-related comorbidities.

We also found that BMI is strongly correlated with measures of central adiposity, fat distribution, insulin resistance and dyslipidemia (Figure 1). The convenience and ease of use of BMI and its broad correlation with other measures of adiposity supports the use of BMI as a surrogate measure for those phenotypes in clinical practice. Neither BMI nor measures of central adiposity showed any strong association with TC or LDL-c, supporting the notion that genetic and lifestyle factors play a larger role in determining LDL-c levels than BMI *per se*.

This study was restricted to subjects of European origin and these results must await replication in other populations before we can generalize these findings. This is also a cross-sectional study whereas a longitudinal design would be ideal for tracking changes across pubertal stages and with advancing age.

Conclusion

Our analysis suggests that the relative influence of body fat depots on cardiometabolic traits may be different at different developmental stages. In children and adolescents, unlike in adults, subcutaneous adiposity at the waist is a stronger predictor of cardiometabolic risk than visceral fat.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

OA conceived the study, assisted in the phenotyping procedures, contributed to the discussion, wrote and revised the manuscript. YZ conceived the study, performed statistical analyses, contributed to the discussion, wrote and revised the manuscript. JWK contributed to the data analysis and discussion and revised the manuscript. DC performed statistical analyses. RJ contributed to subject recruitment and phenotyping. JB contributed to the study design. The late Dr. Ahmed H. Kissebah was the principal investigator on the various NIH funded studies that led to the collection of this unique family-based cohort. He contributed to the study design and provided valuable advice about all aspects of the study until the day he passed away in 2012.

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Abbreviations

HDL-c	HDL-cholesterol
TG	plasma triglycerides
WC	waist circumference
WHR	waist to hip ratio
BMI	body mass index
BMI%	body mass index percentile
VF	visceral fat
SubQF	subcutaneous fat
MetS	Metabolic Syndrome
HC	hip circumference
DXA	dual-energy X-ray absorptiometry
Bodpod	air-displacement plethysmography
HOMA	homeostasis model assessment
LDL-c	LDL-cholesterol
sBP	systolic blood pressure
dBp	diastolic blood pressure
BFMI	body fat mass index
LMI	lean mass index
TAF	total abdominal fat
HMED	HDL median diameter
LMED	LDL-cholesterol median diameter
LDLppd	LDL-cholesterol dominant peak diameter
BMED	apoB-containing non-HDL median diameter
IL-β	interleukin-1beta
IL-6	interleukin-6
WHtR	waist to height ratio
BF%	body fat percent
FG	fasting glucose
FI	fasting insulin
TC	total cholesterol
IGR	insulin to glucose ratio

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What's Known on This Subject

- Cardiometabolic risk factors are present in childhood, increase during puberty, and impact future morbidity and mortality.
- Their prevalence are affected by age, sex, body mass index (BMI), fat distribution and pubertal stage, but data about these interactions, especially in children and adolescents, is limited and sometimes contradictory.

What This Study Adds

- We examined the prevalence and interactions of cardiometabolic risk factors in a well-characterized U.S. Midwestern family-based cohort of Northern European origin.
- We found that in children and adolescents, unlike in adults, subcutaneous adiposity, not visceral adiposity, is the strongest predictor of insulin resistance and hypertriglyceridemia.

Figure 1. Phenotypic and genetic correlation between body composition traits and metabolic risk factors

Genetic correlations (ρ_g) are shown on the left and phenotypic (ρ_p) on the right. Colored tones indicate statistically significant ($p < 0.05$) correlations, with red strongest and yellow weakest for positive correlations; deep blue strongest and light blue weakest for negative correlations.

Table 1
Multivariate regression analysis of selected variables* influencing cardiometabolic risk factors in (A) children and adolescents and (B) adults

A) Children and adolescents

Risk Factor	Variable	p value
HOMA	SubQF	8.40×10^{-12}
HDL-c	BMI percentile	0.002
TG	SubQF	0.001
	Sex	0.04
LDL-c	BMI percentile	0.0008

B) Adults

Risk Factor	Variable	p value
HOMA	Waist to Height	2.60×10^{-16}
	VF/SubQF	0.001
	BMI	0.02
HDL-c	Sex	0.02
TG	VF	2.67×10^{-14}
	BMI	0.02
LDL-c	VF	0.001

* Independent variables: Tanner stage (for children and adolescents), age (for adults) and Tanner stage by sex, sex, BFMI, body fat percent (BF%), VF/SubQF, VF, SubQF, BMI% , waist to height ratio (WHtR)