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Genetic epidemiology of cardiometabolic risk ractors and their clustering patterns in Mexican American children and adolescents: The SAFARI Study

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Abstract

Pediatric metabolic syndrome (MS) and its cardiometabolic components (MSCs) have become increasingly prevalent, yet little is known about the genetics underlying MS risk in children. We examined the prevalence and genetics of MS-related traits among 670 non-diabetic Mexican American (MA) children and adolescents, aged 6–17 years (49 % female), who were participants in the San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) study. These children are offspring or biological relatives of adult participants from three well-established Mexican American family studies in San Antonio, Texas, at increased risk of type 2 diabetes. MS was defined as ≥ 3 abnormalities among 6 MSC measures: waist circumference, systolic and/or diastolic blood pressure, fasting insulin, triglycerides, HDL-cholesterol, and fasting and/or 2-h OGTT glucose. Genetic analyses of MS, number of MSCs (MSC-N), MS factors, and bivariate MS traits were performed. Overweight/obesity (53 %), pre-diabetes (13 %), acanthosis nigricans (33 %), and MS (19 %) were strikingly prevalent, as were MS components, including abdominal adiposity (32 %) and low HDL-cholesterol (32 %). Factor analysis of MS traits yielded three constructs: adipo-insulin-lipid, blood pressure, and glucose factors, and their factor scores were highly heritable. MS itself exhibited 68 % heritability. MSC-N showed strong positive genetic correlations with obesity, insulin resistance, inflammation, and acanthosis nigricans, and negative genetic correlation with physical fitness. MS trait pairs exhibited strong genetic and/or environmental correlations. These findings highlight the complex genetic architecture of MS/MSCs in MA children, and underscore the need for early screening and intervention to prevent chronic sequelae in this vulnerable pediatric population.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Introduction

The twin epidemics of obesity and type 2 diabetes mellitus (T2DM) have become global public health crises (Must et al. 1999; Zimmet 2003; Smyth and Heron 2006). Linked inexorably to them, metabolic syndrome (MS) – a clustering of cardiometabolic abnormalities including obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, and hypertension – strongly predicts both T2DM and cardiovascular disease (CVD), and has itself become a third pandemic, with profound impact worldwide (Reaven 1988; DeFronzo 1995; Grundy 2007; DeBoer 2011). Obesity, insulin resistance and associated inflammatory processes are major underlying mechanisms of MS (DeFronzo 1995; Cruz et al. 2005; Yang and Ming 2011), which affects an estimated 77 to 86 million adults in the US, among whom minority groups, including Mexican Americans (MAs), bear a disproportionate burden (Ford et al. 2010).

A global surge in the prevalence of obesity among children and adolescents has pushed the prevalence of MS and its correlates among youth to unprecedented levels (Goran et al. 2004; Cruz et al. 2005; Ogden et al. 2010; DeBoer 2011). An estimated 8.6 % of the National Health and Nutrition Examination Survey (NHANES) 2001–2006 sample of adolescents aged 12–19 years were found to have MS; by extrapolation, approximately 2.5 million adolescents exhibited this condition nationally (Johnson et al. 2009). Minority youths were affected disproportionately with both obesity and MS (Johnson et al. 2009; Ogden et al. 2010). The overall prevalence of MS in NHANES was highest in Hispanics [11.2 %], followed by non-Hispanic European Americans [8.9 %] and non-Hispanic African Americans [4.0 %] (Johnson et al. 2009). Once MS and its risk factors develop in childhood, they may track into adulthood, with long-term health and economic consequences, including T2DM, CVD, and their sequelae (Weiss et al. 2004; Steinberger et al. 2009; Birnbaum et al. 2011). For this reason, the identification of children and adolescents at elevated risk of developing MS and related complications is critical for initiating early interventions to minimize future morbidity and mortality (Steinberger et al. 2009).

Defining MS for children and adolescents is challenging, however (Ford and Li 2008; DeBoer 2010; Kassi et al. 2011), and the utility of MS as a clinical construct has engendered ongoing debate (Simmons et al. 2010; Tenenbaum and Fisman 2011; Golden et al. 2012). Some investigators have suggested focusing instead on individual cardiometabolic risk factors, such as obesity, insulin resistance, dyslipidemia, glucose intolerance, and hypertension (Schutte et al. 2009; Steinberger et al. 2009; Hoffman 2009). Yet detailed knowledge of the genetic basis of cardiometabolic risk factors and phenotypic correlations between these factors in children has been extremely limited (Butte et al. 2005). Several studies, including our own, have shown that multiple correlated traits involved in MS may be influenced by common genetic (Duggirala et al. 2001; Arya et al. 2002; Farook et al. 2012) and environmental factors and their interactions.

Over the past 20 years, we have examined the genetics of obesity, T2DM, CVD, MS, and related traits in Mexican American adults in San Antonio, TX, using data from several studies of well-characterized families at increased risk of T2DM. There is evidence for a strong relationship between family history of T2DM and development of MS-related traits in children (Cruz et al. 2002; Goran et al. 2004; Valdez et al. 2007). We therefore conducted a genetic epidemiologic investigation of MS-related cardiometabolic risk factors in 673 MA children aged 6–17 years, who are the offspring or biological relatives of adult participants from three well-established MA family studies.

The major objectives of this study are: (1) to examine the prevalence of MS and related cardiometabolic risk factors in children and adolescents without T2DM, from these same

T2DM-enriched MA families; (2) to examine the genetic basis of MS and related traits; (3) to investigate the genetic basis for correlations between the number of MS components (MSC-N) and measures of obesity, insulin resistance, inflammation, acanthosis nigricans and physical fitness; and (4) to assess the extent to which the clustering of MS-related risk factors is influenced by common genetic factors.

Materials and methods

Study population

The **S**an **A**ntonio **F**amily **A**ssessment of Metabolic **R**isk **I**ndicators in Youth–the SAFARI study–was designed to evaluate cardiometabolic risk factors in children and teenagers, aged 6–17 years old, from predominantly lower-income extended MA families whose adult members had previously participated in one of three community-based genetic epidemiologic studies in San Antonio, TX: the San Antonio Family Diabetes/Gallbladder Study (SAFDGS), the San Antonio Family Heart Study (SAFHS), and the Veterans Administration Genetic Epidemiology Study (VAGES) (Mitchell et al. 1996; Puppala et al. 2006; Coletta et al. 2009). These children represent the youngest of multiple generations from their families to have taken part in our studies. All research procedures were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. Written informed consent was obtained from one or both parents of each child, and signed assent was obtained from children ≥7 years old, prior to the initiation of study assessments.

Family history, demographic, phenotypic, behavioral, and environmental data were obtained for SAFARI participants through both home and clinic questionnaires. Physical, clinical, and laboratory assessments were performed at the Children's Center of the Texas Diabetes Institute (TDI), San Antonio, TX, USA, where blood samples were collected after a 10-h fast to measure glucose, insulin, lipids, and inflammatory markers. When possible, an oral glucose tolerance test (OGTT) was performed; plasma glucose was measured at −15 and 0 min before and at 30, 60, 90, and 120 min after an oral glucose load (1.75 g/kg body weight, to a maximum of 75 g). Plasma glucose was measured by glucose-oxidase method (Beckman Glucose Analyzer 2, Beckman, Fullerton, CA, USA). Serum samples were analyzed at Texas Biomedical Research Institute, San Antonio, using the following kits for: fasting (FI) and post-load specific serum insulin (30, 60, 90, and 120 min): RIA, Millipore, Billerica, MA, USA; total cholesterol (TC): H/P Reagent, Boehringer Mannheim, Indianapolis, IN, USA; HDL-cholesterol (HDL-C): H/P Reagent, Boehringer Mannheim, Indianapolis, IN, USA; triglycerides (TG): Stanbio Liquicolor Triglycerides, Boerne, TX, USA. LDL-cholesterol (LDL-C) was estimated using the Friedewald formula. Inflammatory markers, including serum high-sensitivity C-reactive protein (hs-CRP) (ELISA, Alpco immunoassay, Salem, NH, USA), and plasma C-peptide (Luminex, Millipore, Billerica, MA, USA) were also measured.

Anthropometric data, including height, weight, waist circumference, and systolic and diastolic blood pressure, were obtained using standard protocols. Body composition (fat mass, lean-body mass, percent body fat) was measured using dual-energy-X-ray absorptiometry (DXA Hologic). Pubertal status was assessed using Tanner staging. Presence/severity of acanthosis nigricans (AN) on the neck was evaluated using a scale previously developed and validated by our group (Burke et al. 1999). AN severity score (AN-SS) ranged from 0 to 5; the dichotomous trait AN was defined as AN-SS ≥2. A modified Harvard Step Test (Treviño et al. 2004) physical fitness score (PFS) was calculated as total duration of exercise in seconds × 100, divided by the sum of three post-exercise heart rates.

T2DM diagnosis required either fasting plasma glucose (FPG) ≥126 mg/dl or 2-h post-load plasma glucose (2-h PG) ≥200 mg/dl (WHO 1999; ADA 2002). MS was defined as presence of ≥3 of the following 6 dichotomized MSCs: increased waist circumference/abdominal obesity (≥90th percentile for age, sex, MA ethnicity) (Fernández et al. 2004); hyperinsulinemia (>75th percentile for total SAFARI cohort: ≥16.25 μIU/ml) (Goodman et al. 2004); glucose intolerance [impaired fasting glucose (IFG: FPG ≥100 and <126 mg/dl) or impaired glucose tolerance (IGT: 2-h PG ≥140 and <200 mg/dl), or both] (ADA 2003; Nathan et al. 2007); hypertriglyceridemia (≥110 mg/dl) (Cook et al. 2003); low HDL-cholesterol (≤40 mg/dl) (Cook et al. 2003); and elevated systolic and/or diastolic blood pressure (≥90th percentile for height, age and sex) (NHBPEP 2004). In addition, the number of MS components (range: 0–5 in our data) was used as a semi-quantitative trait (MSC-N). Measures of insulin resistance (HOMA-IR) and insulin sensitivity were derived using the University of Oxford Diabetes Trials Unit HOMA2-IR calculator (Matthews et al. 1985; http://www.dtu.ox.ac.uk/homacalculator) and the Matsuda composite whole-body insulin sensitivity index (ISI) (Matsuda and DeFronzo 1999), respectively. To assess early-phase insulin secretion, the insulinogenic index was calculated as the ratio of the increment in serum insulin to the increment in plasma glucose from 0 to 30 min post-load (Abdul-Ghani et al. 2009). BMI percentiles by sex and age were obtained from NHANES III. Participants below the ≥85th percentile were classified as normal, those >85th percentile and <95th percentile as overweight, those ≥95th percentile and <99th percentile as obese, and those >99th percentile as severely obese.

Statistical analyses

The genetics of MS-related quantitative traits were evaluated with a variance-components approach. In a simple model, variances or covariances between relatives as a function of the genetic relationships can be specified, and heritability (h^2), defined as the proportion of phenotypic variance that is attributed to additive genetic effects, can be estimated from the components of variance (Falconer 1989; Almasy and Blangero 1998). A likelihood-ratio test was used to determine whether the heritability of a given phenotype was significant ($P < 0.05$). Covariates such as age, sex, age^2, age × sex, age^2 × sex, and pubertal status (defined using two dummy variables, with pre-pubertal status as the reference) were included in all analyses, if found to be significant. This variance-components method was extended to discrete traits such as MS, using a threshold or liability model (Duggirala et al. 1997).

Phenotypic (ρ_P), genetic (ρ_G), and environmental (ρ_E) correlations between MS-related continuous traits were determined using bivariate genetic analysis (Lange and Boehnke 1983). This approach can be extended to conduct bivariate analysis of quantitative and dichotomous traits (Williams et al. 1999). Phenotypic correlation (ρ_P) between a pair of traits is given by:

$$\rho_P = \sqrt{h_1^2 h_2^2}\,\rho_G + \sqrt{e_1^2 e_2^2}\,\rho_E$$

where ρ_P is the phenotypic correlation; ρ_G, the additive genetic correlation; ρ_E, the random environmental correlation; h^2_1 is the heritability of trait 1; h^2_2 is the heritability of trait 2; e^2_1 is equal to $1-h^2_1$; and e^2_2 is equal to $1-h^2_2$. Using likelihood-ratio tests, the significance ($P < 0.05$) of the phenotypic, additive genetic, and random environmental correlation was determined, respectively. Trait-specific significant covariates were included in bivariate analyses; pubertal status was included irrespective of its significance, for comparability across the trait-pairs examined. Univariate and bivariate procedures are incorporated in the program SOLAR (Almasy and Blangero 1998). We employed a principal component factor analysis (PCFA) (Arya et al. 2002) using SPSS19 to extract the underlying factors of 8 MS-

related continuous traits that were used to define MS and its 6 MSCs. Factors with eigenvalues ≥1 were extracted and rotated using varimax rotation with Kaiser normalization. Factor correlations with the original trait, with factor loadings >0.40, were examined to determine which variables were important constituents of each factor. We estimated the heritability of each factor using the factor-specific scores as a quantitative trait, after adjusting for significant covariate influences.

Results

A total of 673 children and adolescents (SAFHS 373, SAFDGS 126, VAGES 174) participated in SAFARI. They came from 401 nuclear families/sibships, each of which contained an average of approximately 2 (range: 1–5) children. These sibships were embedded within the original SAFHS, SAFDGS, and VAGES extended families. SAFARI children generated a total of 3,664 relative pairs: 383 sibling pairs, 550 first-cousin pairs, 661 second-cousin pairs, and 662 third-cousin pairs (Table 1). Of the 673 examined participants, only 3 (0.45 %) met T2DM criteria. These 3 children were excluded from all analyses related to MS. Table 2 shows characteristics of the 670 children without T2DM. The mean age of the children was 11.5 years; 49.3 % were girls. In our sample, 52.7 % were overweight, obese, or severely obese (BMI ≥85th percentile); 33.6 % were either obese or severely obese (BMI ≥95th percentile); and 10.9 %, were severely obese (BMI ≥99th percentile). Prevalences of IFG, IGT, and prediabetes (IFG, IGT, or both) were 5.9 %, 12.0 %, and 13.2 %, respectively; 33.1 % exhibited AN. As reported in Table 2, data availability differed from trait to trait; data were transformed, when needed, using log-transformation or inverse normal transformation. All traits were significantly heritable ($P < 0.05$), except for 2-h insulin and 2-h PG, which were marginally significant. After adjusting for any significant covariate effects, significant heritability estimates ranged from 0.34 (hs-CRP) to 1.00 (AN).

Prevalence of the 6 individual MS components (MSCs), based on available data, ranged from 11.9 % (elevated blood pressure) to 31.9 % (low HDL-C) (Table 3; Fig 1). Abdominal adiposity, low HDL-C, hypertriglyceridemia, and hyperinsulinemia were more prevalent in girls than in boys, who exhibited higher prevalence of glucose intolerance and elevated blood pressure. MS prevalence overall was 18.7 %, with girls (21.0 %) affected more than boys (16.6 %). MS prevalence increased substantially with rising BMI percentile category (Table 4), from 1.4 % among normal-weight to 8.9 % among overweight, 39.7 % among obese, and 67.7 % among severely obese children. Similarly, the prevalence of MSCs increased dramatically with rising BMI. In particular, the transition from overweight to obesity was associated with dramatic increases in cardiometabolic components, including a tripling of the prevalence of abdominal adiposity, 140 % greater prevalence of hyperinsulinemia, and 70 % higher prevalence of glucose intolerance. The prevalence of MS itself was quadrupled among obese, compared with overweight, children. Even among children categorized as normal-weight, however, a substantial proportion already were found with elevated blood pressure (7.9 %), hyperinsulinemia (10.7 %), low HDL-C (18.1 %), and glucose intolerance (10.8 %).

As shown in Table 2, both MS and the number of its components exhibited by a child (MSC-N) were under strong additive genetic influences: h^2 for MS = 0.68, for MSC-N = 0.54. We also examined the extent to which MSC-N correlated with measures of obesity (overweight and obese), body composition (fat mass, lean mass, and % body fat), insulin action and secretion (HOMA-IR, Matsuda ISI, insulinogenic index, and C-peptide), inflammation (hs-CRP), acanthosis nigricans (AN-SS), and physical fitness (PFS). We partitioned phenotypic correlations (ρ_Ps) between MSC-N and the above traits into their genetic (ρ_G) and environmental (ρ_E) correlations. The ρ_Ps between MSC-N and these traits

ranged from −0.26 (Harvard PFS) to 0.73 (obese), and were highly statistically significant (Table 5). As expected, MSC-N is inversely correlated with both Matsuda ISI and PFS, while positively correlated with the other traits. All ρ_Ps were largely and significantly influenced by common genetic factors; ρ_Gs ranged from −0.45 (PFS) to 0.84 (obesity). Only the ρ_Es between MSC-N and fat mass, % body fat, HOMA-IR, and Matsuda ISI were significant; these influenced the ρ_Ps substantially.

Using PCFA, we examined factor structures that underlie correlations among the 8 quantitative traits (WC, FI, FPG, 2-h PG, HDL-C, TG, SBP, and DBP) used to define MSCs. By comparison, we analyzed the same 8 traits from non-T2DM adults from the three parental cohorts of SAFARI. Data for both children and adults were log-transformed, for comparability. Since data for all traits are required for PCFA and 2-h PG data were not available for all children, these analyses were based on a reduced SAFARI sample (N = 412). For adults, data for all 8 traits were available for 1,803 individuals. PCFA yielded three very similar factors for children and adults (Table 6). Among factor loadings >0.40, the first extracted factor (Factor 1) exhibited high positive correlations with WC, FI, and TG, and negative correlation with HDL-C, as expected; we have interpreted this factor as an adipo-insulin-lipid factor. Factor 2 showed high positive correlations with only DBP and SBP and thus represents a blood pressure factor. Factor 3, which exhibited high positive correlations with FPG and 2-h PG, represents a glucose factor. These three factors together explained approximately 65.0 % of variation in both data sets. After adjusting for significant covariate effects, significant heritabilities ($P < 0.05$) were found for these factors in both children and adults, respectively: adipo-insulin-lipid factor: 0.76 and 0.58; blood pressure factor: 0.68 and 0.41; and glucose factor: 0.36 and 0.46 (Table 6).

In addition, we conducted bivariate genetic analyses to determine ρ_Ps, ρ_Gs, and ρ_Es among the same 8 MS-related traits in SAFARI children; Table 7 displays results for 28 trait-pairs. Except for DBP:FPG, all ρ_Ps were statistically significant ($P < 0.05$); as expected, HDL-C was negatively correlated with other traits. Nine trait-pairs exhibited significant ρ_Gs: WC with HDL-C (−0.45), TG (0.52), FI (0.53), and 2-h PG (−0.69); SBP with DBP (0.88) and TG (0.32); DBP with HDL-C (−0.28) and TG (0.34); and HDL-C with TG (−0.43); ρ_G is marginally significant for WC:SBP (0.25). These findings reflect potential pleiotropic influences on these MS trait-pairs. The following 5 trait-pairs were found to be under significant common non-shared environmental influences (ρ_Es): WC:2-h PG (0.82), TG:FI (0.58), TG:2-h PG (0.49), FPG:FI (0.32), and FI:2-h PG (0.36). The ρ_Es involving SBP:DBP (0.47) and FPG:2-h PG (0.26) were marginally significant. Of the trait-pairs that exhibited significant ρ_Gs or ρ_Es, only ρ_P of the trait pair WC:2-h PG is influenced by both ρ_G and ρ_E, while the other trait pair ρ_Ps were largely influenced by ρ_Gs or ρ_Es as discussed above.

Discussion

SAFARI children bear substantial cardiometabolic and related burdens: 53 % were overweight/obese; 34 %, obese; 19 % had MS; 13 %, pre-diabetes; and 33 %, acanthosis nigricans. Although several adult genetic studies of MS using family data have been conducted, comparable data are rare for pediatric populations (Butte et al. 2005). Yet such data are of special interest, because complex traits among children and adolescents are less subject to long-term aging-related influences. Our results indicate substantial additive genetic influences on MS-related traits. The moderate-to-high heritability estimates we observed (Table 2) are comparable to those available from two other pediatric studies (Butte et al. 2005; Beardsall et al. 2009).

As discrete traits, MS and its components have been examined within a number of pediatric studies, including selected samples of high-risk children and/or nationally representative

data sets such as NHANES. Although its prevalence has varied with the definitions used (Cook et al. 2008; Kassi et al. 2011), MS prevalence has been shown to increase with rising BMI, and is highest among overweight and obese children and adolescents (Weiss et al. 2004; Cruz et al. 2004; Butte et al. 2005). In SAFARI data, MS increased dramatically from 1.4 % in normal-weight children to 67.7 % in severely obese children. Striking elevations in the prevalence of both MS and individual components occurred in obese, compared with overweight, children. The prevalence of glucose intolerance exhibited remarkable increases in this transition, despite corresponding but dramatically higher prevalence of hyperinsulinemia among obese, compared with overweight, children. Even the very young were affected: one third of SAFARI children with MS were less than 10 years old, and even three 6-year-olds were affected.

Comparison of MS prevalence among different study populations is complicated by differences in participants' ages, weight, and ethnicity, and in the definition of MS. Weiss et al. (2004) found that pediatric MS prevalence varied from 38 to 49 %, depending on participant obesity level. Cook et al. (2008), analyzing data for obese adolescents in NHANES (1999–2002), reported MS prevalences ranging from 12.4 % to 44.2 %, depending upon MS definition. Among Hispanic youth in NHANES (2001–2006), the prevalence of MS was 11.2 % (Johnson et al. 2009). Among overweight Hispanic children in *Viva La Familia* (age 4 to 19 years), the prevalence of MS was 28 % in boys, and 27 % in girls (Butte et al. 2005). In a study of overweight Hispanic children (8–13 years), the prevalence was 30 % (Cruz et al. 2004). By comparison, the prevalence of MS in SAFARI was 18.7 %., but was higher in girls (21.0 %) than in boys (16.6 %).

In contrast to population-based studies of MS and its components, the uniqueness of the SAFARI study is its ability to disentangle the genetic architecture of cardiometabolic risk represented by MS and its components. We found evidence for strong additive genetic factors influencing the MS phenotype (h^2 = 68 %), as well as overall cardiometabolic burden, as measured by number of MS components (MSC-N: h^2 = 54 %) in children and adolescents. In bivariate genetic analyses of MSC-N and its correlates, we found evidence of pleiotropy: substantial contribution of common additive genetic factors to the positive phenotypic correlations between MSC-N and measures of obesity (overweight, obese, fat mass, lean mass, % body fat), insulin resistance (HOMA-IR) and secretion (insulinogenic index, C-peptide), inflammation (hs-CRP), and acanthosis nigricans, and to the negative phenotypic correlations between MSC-N and both whole-body insulin sensitivity (Matsuda ISI) and physical fitness (Harvard PFS). These correlation estimates should be interpreted with caution, however, because of redundancies between insulin resistance measures and the MS component based on fasting insulin, and between abdominal obesity and measures of overweight and obesity based on BMI percentile categories. Several other studies also have observed positive phenotypic associations with MSC-N or MS for both inflammation and acanthosis nigricans, and inverse phenotypic associations between MS prevalence and both insulin sensitivity and low physical activity (Weiss et al. 2004; Cruz et al. 2004; Shaibi et al. 2008; Ice et al. 2009; Brambilla et al. 2011; DeBoer 2011). Our bivariate genetic analyses, however, signify the strong common genetic basis for the complex associations between increasing number of MS components and the concomitant risks associated with the examined correlates of MS. In general, the main contribution to observed phenotypic correlations is genetic, and the magnitude of these genetic correlations is most pronounced for obesity-related variables, with somewhat lower genetic correlations for insulin resistance and sensitivity measures.

To detect the underlying structure among the correlated MS-related cardiometabolic traits, several studies used either factor analysis or a confirmatory factor analysis (Ford and Li 2008; Gurka et al. 2012). Reviewed by Ford and Li (2008), such studies used definitions

which included a wide range of MS components (5–19) and 1–5 derived factors. Using data from 8 MS traits, our analyses yielded three factors - adipo-insulin-lipid, blood pressure, and glucose – which were essentially replicated using data from non-diabetic adult family members. Such structural patterns reveal complex interrelationships among these cardiometabolic risk factors, which are already evident very early in life in our SAFARI children. In both data sets, the factor-specific scores were influenced by substantial additive genetic factors.

We employed bivariate genetic analyses of the eight phenotypically correlated traits in SAFARI children to provide additional insights into their complex interrelationships. In general, these traits exhibited significant phenotypic correlations, some of which were predominantly influenced by genetic correlations, and others by environmental correlations. The four traits (WC, FI, TG, and HDL-C) loaded on factor 1 (adipo-insulin-lipid factor) exhibited significant genetic correlations, including negative correlations between HDL-C and certain traits. While the blood pressure measures (SBP and DBP) loaded on factor 2 were strongly genetically correlated, it is evident that they also shared common genetic influences with lipid traits, including the inverse genetic association between DBP and HDL-C. Glucose traits (factor 3: FPG and/or 2-h PG) were environmentally correlated with obesity, insulin, and lipids in these children, but the positive phenotypic correlation between WC and 2-h PG was largely influenced by negative genetic correlation and positive environmental correlation, in turn suggesting that genetic and environmental sources of variation influence these traits through different physiological mechanisms (Falconer 1989). It is plausible that the observed inverse genetic correlation between WC and 2-h PG is related to the cascade of events related to hyperinsulinemia, reactive hypoglycemia, hyperphagia, and obesity (Ludwig 2002; Chaput et al. 2008).

In recent years, numerous genome-wide association studies of individual traits related to MS have successfully localized susceptibility variants/genes for such phenotypes as obesity, T2DM, dyslipidemia, and hypertension, as well as childhood obesity; a few studies have also localized variants/genes with potential pleiotropic influences on MS (McCarthy 2010; Zeller et al. 2012; Fall and Ingelsson 2012; Norris and Rich 2012; Manco and Dallapiccola 2012). Our immediate plans are to conduct genome-wide screenings for the identification of genetic variants influencing individual MS traits - most importantly, those pleiotropically influencing multivariate MS traits in our data. Such efforts should yield significant insights into the genetic mechanisms underlying the complex metabolic pathways related to MS trait clustering patterns.

Obesity and insulin resistance are the major intertwined underlying processes of MS. Insulin resistance represents a core component of metabolic risk which precedes, and lays the groundwork for, the later development of such life-threatening diseases as T2DM and CVD. By the time glucose levels have risen to the diagnostic threshold of glucose intolerance, β-cell function has already become severely compromised (Abdul-Ghani and DeFronzo 2009). One in every 8 SAFARI participants has already reached this stage. The high rate of prediabetes in this and other studies (Abdul-Ghani and DeFronzo 2009; Li et al. 2009) strongly suggests that –by screening high-risk children for insulin resistance – lifestyle and/or pharmacologic interventions could be initiated during the closing window of opportunity in late adolescence and early adulthood, to prevent later development of T2DM and vascular dysfunction.

Limitations of our study include the following: our estimate of the prevalence of IGT/pre-diabetes may be biased, since OGTT data were available for only 62 % of SAFARI children. It is possible that heritability estimates may have been inflated since shared environmental influences were not accounted for in our analyses. Such influences, however, appear to be

minimal in this study, since the children are distributed across large pedigrees, represented by a wide variety of relative pairs, and sib-pairs account for only 10 % of the relative pairs examined. In addition, SAFARI children are from families residing predominantly in lower-income neighborhoods, and higher heritability can be expected when environmental conditions are relatively uniform. It should be reiterated that no definition of MS in children and adolescents has been fully validated; in fact, there have been continued concerns about the diagnostic criteria for pediatric MS, including their usefulness for treatment purposes, and the degree to which estimates of the prevalence of MS vary with the definitions used (Ford and Li 2008; Brambilla and Pietrobelli 2009; DeBoer 2010; Kassi et al. 2011).

In conclusion, we have demonstrated dramatic increases in the prevalence of MS and its individual risk components with increasing age and adiposity. Even very young SAFARI participants, however, and those categorized as normal-weight, exhibited cardiometabolic risk indicators, including dyslipidemia, hyperinsulinemia, and glucose intolerance. Our findings highlight the complex genetic architecture of MS and its risk components in MA children, and underscore the need to identify early-warning cardiometabolic risk indicators, and to screen normal-weight, as well as overweight and/or obese, children for them (Steinberger et al. 2009; Goodman et al. 2009; May et al. 2012). Early detection of cardiometabolic risk could provide a life-changing window of opportunity in which to intervene to interrupt the cascade of metabolic dysfunction which these conditions all too often bring in their wake. Given the observed burden of MS and its risk factors in our SAFARI children, our goals for the near future include implementation of effective intervention strategies in this vulnerable population. In addition, identification of specific genetic factors underlying the phenotypic expressions of MS risk factors may increase the potential to identify genetic predictors of an individual's response to dietary, physical activity, and other lifestyle interventions, and thus facilitate the tailoring of individualized programs for both prevention and treatment interventions. Such targeted early-life interventions could have significant clinical impact on cardiometabolic risk, not only in childhood but also in adulthood.

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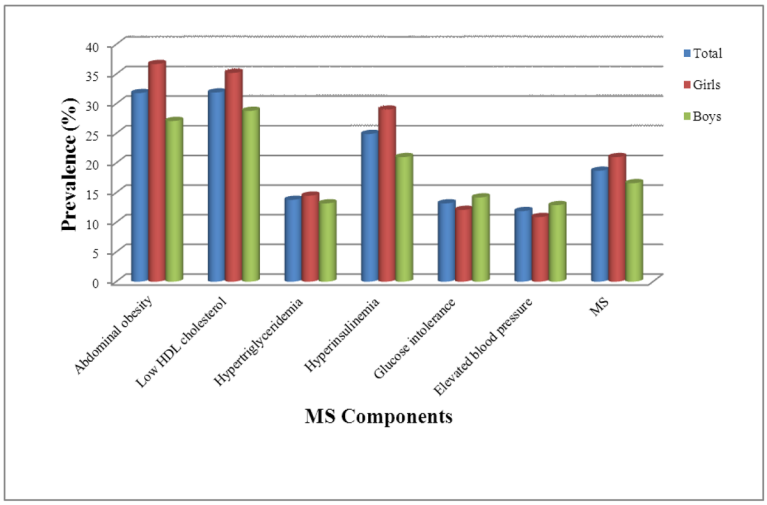

Figure 1.
Prevalence of MS and its six cardiometabolic components, overall and by sex, among 670 SAFARI children and adolescents, aged 6 to 17 years old, without diabetes

Table 1

Types and numbers of relative pairs among 673 SAFARI children and adolescents, aged 6 to 17 years old

Type of Relative Pair	No. of Pairs
Siblings	383
Avuncular	9
Half-sibs	86
Half-avuncular	5
1st cousins	550
1st cousins, 1 rem	234
Half first cousins	74
1st cousins, 2 rem	2
Half first cousins, 1 rem	36
2nd cousins	661
2nd cousins, 1 rem	512
Half second cousins	178
3rd cousins	662
Half second cousins, 1 rem	10
2nd cousins, 2 rem	6
3rd cousins, 1 rem	137
Half third cousins	6
4th cousins	30
Other relatives (third and fourth cousins, double third cousins and 2nd cousins, half-avuncular, and others)	83
Total	3,664

Table 2

Characteristics of 670 SAFARI children and adolescents, aged 6 to 17 years old, without diabetes, and heritability estimates for MS-related traits

Variable*	N†	Mean ± SD or %	h^2 ± SE‡	*P* value	Significant covariates‡
Girls	670	49.3	-	-	
Age (years)	670	11.5 ± 3.5	-	-	
Pre-pubertal (Tanner 1)	635	49.8	-	-	
Pubertal (Tanner 2–4)	635	24.3	-	-	
Post-pubertal (Tanner 5)	635	26.0	-	-	
BMI (kg/m^2)§	670	22.7 ± 6.5	0.75 ± 0.11	1.1×10^{-11}	age, puberty
BMI z-score	670	1.0 ± 1.1	0.73 ± 0.11	4.1×10^{-11}	age, sex, puberty
Overweight	670	52.7	0.91 ± 0.16	2.1×10^{-8}	sex, age^2, puberty
Obese	670	33.6	0.78 ± 0.19	6.9×10^{-6}	sex, puberty
Waist circumference (mm)	664	764.5 ± 179.7	0.63 ± 0.12	3.0×10^{-8}	age, age^2, puberty
Fat mass (kg)§,‖	634	16.0 ± 11.1	0.69 ± 0.12	1.8×10^{-9}	age, age^2, puberty
Lean mass (kg)§,‖	634	33.1 ± 13.4	0.61 ± 0.11	3.3×10^{-8}	age, sex, age × sex, age^2 × sex, puberty
% Body fat‖	634	30.2 ± 9.9	0.78 ± 0.11	1.6×10^{-12}	sex, age × sex, age^2, age^2 × sex
Fasting insulin (μIU/ml)§	626	13.6 ± 9.4	0.55 ± 0.11	2.0×10^{-7}	age^2, puberty
2-h insulin (μIU/ml)§	415	69.4 ± 65.4	0.21 ± 0.15	0.0744	age^2
Fasting glucose (mg/dl)§	630	89.5 ± 7.5	0.39 ± 0.11	6.3×10^{-5}	age^2
2-h glucose (mg/dl)§	418	115.4 ± 21.2	0.21 ± 0.14	0.0633	-
Pre-diabetes#	630	13.2	0.47 ± 0.25	0.0273	puberty
HOMA-IR¶	622	2.0 ± 1.3	0.60 ± 0.11	1.8×10^{-8}	age^2, puberty
Matsuda ISI¶	390	3.7 ± 1.7	0.56 ± 0.16	0.0001	age^2
Insulinogenic index¶	396	2.1 ± 1.7	0.70 ± 0.15	9.0×10^{-6}	-
C-peptide (ng/ml)¶	514	1.0 ± 0.9	0.72 ± 0.13	1.0×10^{-7}	puberty
hs-CRP (ng/ml)¶	553	1620.1 ± 3220.6	0.34 ± 0.12	0.0009	age, sex, age^2, age^2 × sex, puberty
HDL cholesterol (mg/dl)	623	45.8 ± 10.9	0.64 ± 0.12	2.9×10^{-8}	age × sex, puberty

Variable*	N†	Mean ± SD or %	h^2 ± SE‡	*P* value	Significant covariates‡
LDL cholesterol (mg/dl)	623	87.1 ± 23.6	0.61 ± 0.12	1.0×10^{-7}	age, puberty
Total cholesterol (mg/dl)	623	147.9 ± 27.1	0.61 ± 0.12	3.1×10^{-8}	puberty
Triglycerides (mg/dl)§	623	74.9 ± 39.8	0.77 ± 0.11	8.8×10^{-13}	age × sex
SBP (mm Hg)	670	104.1 ± 9.7	0.66 ± 0.11	1.0×10^{-10}	age, sex, age × sex
DBP (mm Hg)	670	63.2 ± 7.0	0.64 ± 0.11	9.7×10^{-10}	age, puberty
Harvard PFS	501	47.7 ± 24.8	0.64 ± 0.14	2.7×10^{-6}	age, sex, age × sex, age^2
Acanthosis nigricans (AN)	661	33.1	1.00	1.0×10^{-9}	-
AN severity score (AN-SS)	660	1.3 ± 1.7	0.75 ± 0.11	3.6×10^{-12}	puberty
MS**	625	18.7	0.68 ± 0.28	0.0078	puberty
MSC-N**	613	1.3 ± 1.4	0.54 ± 0.13	1.1×10^{-5}	puberty

* See text for definitions. BMI: body mass index; HOMA-IR: Homeostasis Model of Assessment - Insulin Resistance; Matsuda ISI: Matsuda Insulin Sensitivity Index; hs-CRP: high sensitivity C-reactive proetin; PFS: Physical fitness score;

† values ± 4 SD from the mean were excluded from genetic analyses;

‡ all traits were adjusted for significant covariate effects;

§ traits were log-transformed for genetic analyses;

|| as assessed by DXA;

¶ traits were inverse-normalized for genetic analyses;

IFG: impaired fasting glucose (prevalence: 5.9 % [37/630]); IGT: impaired glucose tolerance (12.0 % [50/418]); pre-diabetes: IFG, IGT or both: (13.2 %);

** The MSC-N analysis included 613/625 children since 12 children were lacking data for some of the examined MSCs. However, these 12 children were included in the MS analysis because they were found with 3 or more risk factors of the available data.

Table 3

Prevalence of MS and its six criterion cardiometabolic components, among 670 SAFARI children and adolescents, aged 6 to 17 years old, without diabetes

Variable	N	Prevalence (%)		
		Total	Girls	Boys
Abdominal obesity	664	31.8	36.7	27.1
Low HDL cholesterol	623	31.9	35.2	28.8
Hypertriglyceridemia	623	13.8	14.5	13.2
Hyperinsulinemia	626	24.9	29.0	21.0
Glucose intolerance	630	13.2	12.1	14.2
Elevated blood pressure	670	11.9	10.9	12.9
MS	625	18.7	21.0	16.6

Table 4

Prevalence of MS and its six criterion cardiometabolic components among SAFARI children and adolescents, aged 6 to 17 years old, without diabetes, by BMI percentile category

	MS prevalence (%) by BMI percentile:							
	<85th		≥85th –<95th		≥95th –<99th		>99th	
	Normal		Overweight		Obese		Severely Obese	
MS Components	N	%	N	%	N	%	N	%
Abdominal obesity	313	1.0	127	18.9	152	74.3	72	98.6
Low HDL cholesterol	288	18.1	123	27.6	146	47.3	66	66.7
Hypertriglyceridemia	288	3.5	123	16.3	146	22.6	66	34.8
Hyperinsulinemia	291	10.7	124	18.5	146	44.5	65	56.9
Glucose intolerance	296	10.8	124	10.5	145	17.9	65	18.5
Elevated blood pressure	317	7.9	128	9.4	152	14.5	73	28.8
MS (≥ 3 MS components)	290	1.4	124	8.9	146	39.7	65	67.7

Table 5

Phenotypic (ρ_P), genetic (ρ_G), and environmental (ρ_E) correlations between number of MS components (MSC-N) and measures of obesity and body composition, insulin resistance and insulin secretion, inflammation, acanthosis nigricans and physical fitness, among SAFARI children and adolescents, aged 6 to 17 years old, without diabetes

Trait Pair[a]	ρ_P	*P* value	$\rho_G \pm$ SE	*P* value	$\rho_E \pm$ SE	*P* value
MSC-N: Overweight	0.66	5.2×10^{-37}	0.83 ± 0.13	6.5×10^{-6}	0.49 ± 0.30	0.2261
MSC-N: Obese	0.73	4.6×10^{-49}	0.84 ± 0.11	1.5×10^{-5}	0.59 ± 0.22	0.0711
MSC-N: Fat mass[b]	0.64	6.7×10^{-52}	0.73 ± 0.11	3.3×10^{-5}	0.54 ± 0.15	0.0183
MSC-N: Lean mass[c]	0.46	5.6×10^{-27}	0.58 ± 0.13	0.0009	0.31 ± 0.17	0.1263
MSC-N: %Body fat	0.60	9.0×10^{-44}	0.58 ± 0.11	0.0003	0.67 ± 0.15	0.0091
MSC-N: HOMA-IR[c]	0.56	5.7×10^{-42}	0.60 ± 0.11	0.0007	0.51 ± 0.14	0.0180
MSC-N: Matsuda ISI[c]	−0.56	1.5×10^{-28}	−0.58 ± .015	0.0060	−0.53 ± 0.16	0.0176
MSC-N: Insulinogenic index[c]	0.32	7.5×10^{-10}	0.41 ± 0.19	0.0499	0.20 ± 0.23	0.4057
MSC-N: C-peptide[c]	0.32	1.0×10^{-11}	0.49 ± 0.15	0.0055	0.04 ± 0.26	0.8937
MSC-N – hs-CRP[c]	0.37	1.6×10^{-17}	0.59 ± 0.17	0.0082	0.22 ± 0.14	0.1761
MSC-N: AN-SS	0.46	3.4×10^{-26}	0.54 ± 0.14	0.0007	0.37 ± 0.21	0.1267
MSC-N: Harvard PFS	−0.26	2.9×10^{-8}	−0.45 ± 0.16	0.0063	0.06 ± 0.24	0.8078

[a] All traits were adjusted for the covariate effects as described in the text;

[b] data were log-transformed;

[c] data were transformed using inverse normal transformation.

Table 6

Principal-component factor analyses of MS-related quantitative traits in SAFARI children and adolescents, and comparison of SAFARI factor structures with those obtained from non-diabetic adult relatives who had previously participated in SAFHS, SAFDGS, or VAGES

	Factor loadings*					
Phenotype*	**SAFARI Children†**			**Adults (SAFHS/SAFDGS/VAGES) ‡**		
	Factor 1	**Factor 2**	**Factor 3**	**Factor 1**	**Factor 2**	**Factor 3**
WC	**0.706**	0.358	0.042	**0.543**	0.390	0.287
HDL-C	**−0.786**	−0.011	0.070	**−0.779**	0.062	0.042
TG	**0.744**	0.056	0.156	**0.706**	0.211	0.096
FI	**0.619**	0.134	0.314	**0.631**	0.066	0.350
FPG	0.096	0.108	**0.744**	0.175	0.337	**0.797**
2-h PG	0.080	−0.041	**0.764**	0.076	0.122	**0.836**
SBP	0.194	**0.905**	0.094	0.088	**0.845**	0.221
DBP	0.084	**0.906**	−0.003	0.104	**0.874**	0.030
Eigenvalue	2.1	1.8	1.3	2.9	1.2	1.0
Variance **e**xplained (%)	26.4	22.5	16.0	36.3	15.4	13.0
Cumulative **v**ariance (%)	26.4	48.9	64.9	36.3	51.6	64.6
Construct	adipo-insulin-lipid factor	blood pressure factor	glucose factor	adipo-insulin-lipid factor	blood pressure factor	glucose factor
h^2 ± S.E (*P* value)	0.76 ± 0.15 (9.0×10^{-7})	0.68 ± 0.14 (5.0×10^{-7})	0.36 ± 0.15 (4.8×10^{-3})	0.58 ± 0.05 (2.6×10^{-49})	0.41± 0.05 (2.4×10^{-22})	0.46 ± 0.05 (3.5×10^{-34})
Significant covariates	age × sex puberty	age	age^2	age sex age^2	age sex age × sex age^2	age sex

* Factor loadings in bold type are >0.40, factors in adults are shown for comparison; all traits in children and adults were log-transformed;

† Sample sizes for trait-specific analyses varied from 418 for 2-h PG to 670 for SBP and DBP. However, data for all 8 traits were available for only 412 children, because of number of participants for whom OGTT could be performed (N = 418);

‡ Only non-diabetic individuals included and sample sizes of the traits varied from 1,941 for 2-hr glucose to 2,061 for SBP and DBP. However, data for all 8 traits were available for 1,803 individuals.

Table 7

Phenotypic (ρ_P), genetic (ρ_G), and environmental (ρ_E) correlations among 8 MS-related quantitative traits used for MS factor analysis in SAFARI children and adolescents without diabetes

Trait Pair*	ρ_P	*P* value	$\rho_G \pm$ SE	*P* value	$\rho_E \pm$ SE	*P* value
WC: SBP	0.26	6.3×10^{-10}	0.25 ± 0.14	0.0772	0.28 ± 0.20	0.1975
WC: DBP	0.19	5.8×10^{-6}	0.20 ± 0.14	0.1566	0.17 ± 0.20	0.4083
WC: HDL-C	−0.36	2.2×10^{-17}	−0.45 ± 0.13	0.0034	−0.21 ± 0.21	0.3735
WC: TG†	0.41	6.7×10^{-22}	0.52 ± 0.11	0.0002	0.15 ± 0.29	0.6285
WC: FPG†	0.10	0.0150	0.04 ± 0.18	0.8334	0.18 ± 0.17	0.2774
WC: FI†	0.42	3.0×10^{-24}	0.53 ± 0.12	0.0007	0.27 ± 0.17	0.1808
WC: 2-h PG†	0.18	0.0004	−0.69 ± 0.40	0.0221	0.82 ± 0.20	1.8×10^{-5}
SBP: DBP	0.74	6.6×10^{-89}	0.88 ± 0.05	8.8×10^{-10}	0.47 ± 0.15	0.0642
SBP: HDL-C	−0.12	0.0045	−0.14 ± 0.14	0.3439	−0.10 ± 0.22	0.6502
SBP: TG†	0.19	9.2×10^{-6}	0.32 ± 0.12	0.0140	−0.16 ± 0.32	0.6009
SBP: FPG†	0.14	0.0009	0.03 ± 0.17	0.8619	0.28 ± 0.16	0.0943
SBP: FI†	0.20	3.0×10^{-6}	0.19 ± 0.14	0.1904	0.22 ± 0.18	0.2626
SBP: 2-h PG†	0.16	0.0024	0.10 ± 0.32	0.7591	0.24 ± 0.18	0.1958
DBP: HDL-C	−0.14	0.0015	−0.28 ± 0.14	0.0485	0.13 ± 0.22	0.5538
DBP: TG†	0.18	3.6×10^{-5}	0.34 ± 0.13	0.0115	−0.22 ± 0.31	0.4339
DBP: FPG†	0.07	0.1216	0.06 ± 0.17	0.7453	0.08 ± 0.16	0.6106
DBP: FI†	0.13	0.0036	0.14 ± 0.15	0.3341	0.10 ± 0.18	0.5964
DBP: 2-h PG†	0.10	0.0455	0.01 ± 0.34	0.9775	0.18 ± 0.17	0.2912
HDL: TG†	−0.42	1.1×10^{-22}	−0.43 ± 0.11	0.0019	−0.43 ± 0.24	0.1682
HDL: FPG†	−0.09	0.0293	−0.004 ± 0.18	0.9844	−0.20 ± 0.17	0.2445
HDL: FI†	−0.22	2.9×10^{-7}	−0.17 ± 0.15	0.2897	−0.30 ± 0.18	0.1302
HDL: 2-h PG†	−0.13	0.0142	−0.10 ± 0.34	0.7608	−0.18 ± 0.18	0.3111
TG†: FPG†	0.12	0.0042	0.004 ± 0.17	0.9818	0.36 ± 0.23	0.1136

Trait Pair*	ρ_P	*P* value	$\rho_G \pm SE$	*P* value	$\rho_E \pm SE$	*P* value
TG†: FI†	0.30	1.2×10^{-11}	0.18 ± 0.14	0.2032	0.58 ± 0.22	0.0280
TG†: 2-h PG†	0.18	0.0004	−0.04 ± 0.31	0.8956	0.49 ± 0.24	0.0324
FPG†: FI†	0.19	7.1×10^{-6}	0.05 ± 0.18	0.7976	0.32 ± 0.14	0.0280
FPG†: 2-h PG†	0.21	6.5×10^{-5}	0.08 ± 0.40	0.8421	0.26 ± 0.13	0.0580
FI†: 2-h PG†	0.22	6.0×10^{-6}	−0.004 ± 0.36	0.9911	0.36 ± 0.14	0.0181

* All data were adjusted for covariate effects as discussed in the text;

† data were log-transformed.