Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Int J Obes (Lond). Author manuscript; available in PMC 2010 March 01.

Published in final edited form as:

Int J Obes (Lond). 2008 December ; 32(12): 1799–1806. doi:10.1038/ijo.2008.194.

Latent common genetic components of obesity traits

BO Tayo[1], **R Harders**[1], **A Luke**[1], **X Zhu**[2], and **RS Cooper**[1]

[1]Department of Preventive Medicine and Epidemiology, Loyola University Chicago, Stritch School of Medicine, Maywood, IL, USA

[2]Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH, USA

Abstract

Background—Obesity is rapidly becoming a global epidemic. Unlike many complex human diseases, obesity is defined not just by a single trait or phenotype, but jointly by measures of anthropometry and metabolic status.

Methods—We applied maximum likelihood factor analysis to identify common latent factors underlying observed covariance in multiple obesity-related measures. Both the genetic components and the mode of inheritance of the common factors were evaluated. A total of 1775 participants from 590 families for whom measures on obesity-related traits were available were included in this study.

Results—The average age of participants was 37 years, 39% of the participants were obese (body mass index ≥ 30.0 kg/m^2) and 26% were overweight (body mass index 25.0 - 29.9 kg/m^2). Two latent common factors jointly accounting for over 99% of the correlations among obesity-related traits were identified. Complex segregation analysis of the age and sex-adjusted latent factors provide evidence for a Mendelian mode of inheritance of major genetic effect with heritability estimates of 40.4% and 47.5% for the first and second factors, respectively.

Conclusions—These findings provide a support for multivariate-based approach for investigating pleiotropic effects on obesity-related traits which can be applied in both genetic linkage and association mapping.

Keywords

African American; Heritability; Latent Genetic Component; Maximum Likelihood Factor Analysis; Obesity Trait; Pleiotropic; Segregation Analysis

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use:http://www.nature.com/authors/editorial_policies/license.html#terms

Correspondence to: BO Tayo.

Correspondence: Bamidele Olusegun Tayo, PhD Department of Preventive Medicine and Epidemiology, Loyola University Medical Center 2106 South First Ave, Bldg 105 Maywood, IL 60153, USA. Tel: +1 708 327 9013 Fax: +1 708 327 9009 E-mail: btayo@lumc.edu.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Introduction

Obesity is becoming a health concern for countries across the range of economic development.1-10 An intensive research effort has been launched to define the social and biologic etiology of this public health problem; however, the practical implications for disease control have not yet been apparent. Modest progress is currently being made in the search for the genetic components of obesity. Highly consistent findings have been reported for the FTO gene, at least in European populations,11,12 and some analyses have supported a role for INSIG2.13,14 Non-replication of many other reported associations demonstrates that much remains to be known about the possible catalogue of the genetic factors contributing to obesity in humans.

Unlike many other complex human diseases, obesity is defined not just by one trait or phenotype, but both separately and jointly by anthropometric and metabolic variables. In addition to research aimed at determining the genetic determinants of each obesity-related measure such as height, weight, body mass index (BMI), fat mass (FM), percent body fat mass (PBFM), adiponectin level, resting metabolic rate (RMR), etc.,15-22 there have also been efforts at identifying possible genetic factors acting on more than one of these measures at the same time.23-27 Beyond the bi-variate approach that has commonly been employed in the search for pleiotropic loci, multivariate techniques such as factor analysis can be applied. Multivariate statistical approach provides the advantage of investigating common effects on an unrestricted number of traits as opposed to a bi- or tri-variate approach. The aim of this study was to apply maximum likelihood factor analysis technique to identify latent (unobserved) common factors underlying observed covariance in multiple obesity-related measures and then evaluate the genetic components and the mode of inheritance of such common factors using data on African-American families.

Methods

Study participants

Participants in this study were self-identified African-American family members recruited from a working class suburb of Chicago, IL. The sampling frame for this study was provided by the International Collaborative Study on Hypertension in Blacks (ICSHIB) and is described in detail elsewhere.28-31 Nuclear families were identified through middle-aged probands and thereafter all available first-degree relatives were enrolled into the study. Study protocols were reviewed and approved by the institutional review board at the Loyola University Chicago Stritch School of Medicine prior to all recruitment activities. Written informed consent was obtained from each participant. This study included 1775 adult participants from 590 families for whom measurements on selected obesity-related traits were available.

Measurements

All measurements were taken during a screening exam in a clinic setting by trained research staff using standardized protocols designed for the study.28 For each participant, information on relationship to the proband was obtained and this was used to established

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

pedigree relationships. Body weight was measured to the nearest 0.2 kg on calibrated electronic scales, while height was obtained using a stadiometer consisting of a steel tape attached to a straight wall and a wooden headboard. The headboard was positioned with the participant shoeless, feet and back against the wall, and head held in the Frankfort horizontal plane and measurement taken to the nearest 0.1 cm. Both waist circumference (WC) and hip circumference (HC) were measured to the nearest 0.1 cm by using inelastic tape. Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters.

Body composition was determined using bioelectrical impedance analysis (BIA), as described in detail elsewhere.32,33 Briefly, a tetrapolar placement of electrodes was used with current electrodes placed on dorsal surfaces of the right hand and foot at the distal metacarpals and metatarsals, respectively, and the detector electrodes placed on the pisiform prominence of the wrist and between the medial and lateral malleoli of the right ankle34. BIA measurements were then taken using a single-frequency (50 kHz) battery-powered analyzer (model BIA 101Q; RJL Systems, Clinton Township, MI). Total body water was estimated from BIA resistance measurements, weight and height by using an equation derived from this population.33 To obtain an estimate of fat-free mass (FFM), total body water was divided by a hydration standard (0.73),35 and fat mass (FM) was calculated as the difference between weight and FFM. Percent body fat mass (PBFM) was calculated as the product of FM and the inverse of weight in kilograms multiplied by 100. Body surface area (BSA) and resting metabolic rate (RMR) were calculated according to the formulas listed below. The standardized Du Bois and Du Bois36,37 formula which has been evaluated in similar populations24 was used for the BSA. For the RMR calculation, we used the predictive equation of Mifflin et al,38 viz,

$$\text{BSA} = 0.20247*[(\text{height in m})^{0.725}]*[(\text{weight in kg})^{0.425}]$$

$$\text{RMR (males)} = (9.99*\text{weight in kg})+(6.25*\text{height in cm})-(4.92*\text{age in years})+5$$

$$\text{RMR (females)} = (9.99*\text{weight in kg})+(6.25*\text{height in cm})-4.92*\text{age in years})-161$$

Statistical analysis

Descriptive characteristics of the study participants were calculated using the statistical software package SAS/STAT®, version 9.1 (SAS Institute Inc., Cary, NC). Pair-wise correlations of the obesity-related traits (BMI, FM, PBFM, RMR, BSA, WC, & HC) were estimated. To capture unobservable factors contributing to the observed correlations among the obesity-related traits, we performed maximum likelihood factor analysis. Factor analysis (FA) assumes that the observed relationships between variables as measured by their correlations or covariances are due to the relationships of the variables to some latent common variables or factors. Factor analysis enables the identification and separation of latent common factors and the unique factors which account for observed covariation and variation, respectively, among the traits. A unique factor, which is made up of a specific factor and errors of measurement, contributes to the variance of only one variable, whereas latent common factor contributes to the variance of at least two variables. Let us assume a set of m, variables, $Y' = [y_1, y_2, \ldots, y_m]$, linked to a finite number of unobserved latent

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

common factor, f_1, f_2,…, f_k where $k < m$, then the factor analysis model to find the k latent common factors can be represented as

$$y_{ij}=\lambda_{i1}f_{1j}+\lambda_{i2}f_{2j}+\cdots+\lambda_{ik}f_{kj}+e_{ij}$$

where

y_{ij} is the value of the ith observation on the jth variable

λ_{ik} is the value of the ith observation on the kth latent common factor

f_{kj} is the regression coefficient or loading of the kth latent factor for predicting the jth variable

e_{ij} is the jth variable's unique factor, which is similar to a residual

Although principal common factor analysis is perhaps the most popular method of common factor analysis, we chose to use the maximum likelihood FA because this method has the desirable asymptotic properties39,40 and the possibility to test hypotheses about the number of common factors. The inclusion of traits in the FA model was based on Kaiser's Measure of Sampling Adequacy41 value being greater than 0.5. The extracted factors were age- and sex-adjusted prior to their use in segregation analysis.

Segregation analysis

To estimate the heritability of each latent common factor as well as determine the mode of inheritance for each factor in our sample of African-American families, we fitted different hypothesis-based mathematical models and estimated all model parameters by method of maximum likelihood as implemented in the computer software program Pedigree Analysis Package for Java (jPAP).42 Depending on the hypothesis being tested, each model assumed an autosomal segregating locus with allele frequencies $_{qA}$and 1-$_{qA}$ for allele A and allele B, respectively, at the locus. The three possible genotypes at the locus are AA, AB and BB with their trait means designated as μ_{AA}, μ_{AB} and μ_{BB}, and the corresponding standard deviations as σ_{AA}, $\sigma_{AB,}$ and σ_{BB}, respectively. The transmission probability (τ) is defined as the probability of a parent transmitting an allele A, the putative disease allele, to an offspring and this is represented as τ_{AA}, $\tau_{AB,}$ and τ_{BB} for parent with genotype AA, AB or BB, respectively. The polygenic heritability, here defined as the residual polygenic heritability after accounting for the contribution of the major locus,43 was modelled and designated as h^2.

Genetic and transmission models evaluated include sporadic, environmental, no polygene, general and Mendelian - codominant, additive, dominant and recessive. Details of each model are presented below.

Sporadic model—This model assumed no major gene, no intergeneration transmission, and no within-genotype variance due to polygenes (h^2=0). Genotype-specific trait means

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and, similarly, genotype-specific trait standard deviations were correspondingly estimated as equal to one another (i.e., $\mu_{AA}=\mu_{AB}=\mu_{BB}$ and $\sigma_{AA}=\sigma_{AB}=\sigma_{BB}$).

Environmental model without generation effects ($\tau = q_A$)—This model assumes independence of offspring genotypes from parental genotypes without major gene, and transmission probabilities are all equal to the frequency of the disease allele irrespective of the genotypes ($\tau_{AA} = \tau_{AB} = \tau_{BB} = q_A$). In this model, population heterogeneity is assumed by allowing the genotype-specific effects to differ from one another.

No polygenic model—In this model a major gene segregating without other polygene effects is assumed (i.e., $h^2=0$). The putative disease allele frequency, transmission probabilities, genotype-specific trait means and standard deviations are all estimated without any constraint.

Mendelian models—The models assume Mendelian transmission under the assumption of Hardy-Weinberg equilibrium. Under this assumption, the probability distributions for the three putative genotypes are then p^2, $2pq$ and q^2. The transmission probabilities for AA, AB, and BB genotypes are therefore fixed at 1.0, 0.5, and 0.0, respectively. Contribution from polygenes is assumed and hence heritability is estimated along with allele frequency, genotypic means and standard deviations. The effects of the three genotypes are assumed to be independent under a codominant model. In an additive model, the effect of the disease allele is assumed to be additive such that the effects of all three genotypes are different and can be ordered as AA > AB > BB (genotypic effect increases with increasing number of the disease allele A). The effect of genotype AB is also assumed to be centered mid-way between genotypes AA and BB. The transforming growth factor type beta-1 (TGFB1)44 is an example of autosomal additive Mendelian gene. The dominant model assumes the effects of the two disease-allele carrying genotypes AA and AB are the same (AA = AB) and different from that of the BB genotype. An example is the coloboma-obesity-hypogenitalism-mental retardation syndrome.45 In the recessive model, the genotypic effects of BB and AB are assumed to be the same and different from that of the AA genotype.

General model—This model makes no assumption about the disease allele frequency at the putative locus or the genotypes and their corresponding effects or transmission. All parameters are set to be free and allowed to adjust to the empirical data thereby providing the best fit to the data. The general model serves as baseline for other models with one or more constrained parameters in the likelihood ratio tests.

Results

Descriptive statistics

A total of 1775 adult participants from 590 families for whom measurements on obesity-related traits were available were included in this study. Table 1 presents the characteristics of the study participants. Women were significantly older than the men (38.0 and 35.4 years for women and men, respectively). The women were also significantly heavier (BMI: 30.4 vs. 27.0 kg/m^2), had higher fat mass and percentage body fat mass (FM: 35.0 vs. 23.1 kg;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

PBFM: 41.0 vs. 25.6 %), and larger hip circumference (HC: 111.6 vs. 104.5 cm) than the men. However, the men on average had significantly higher resting metabolic rate and body surface area (RMR: 1772 vs. 1486 Kcal/d; BSA: 2.0 vs. 1.9 m^2). There was no significant difference in waist circumference between men and women. Furthermore, the distribution of BMI in the entire study sample of women and men showed that 39% and 26% of the participants were obese (BMI ≥ 30.0 kg/m^2) and overweight (BMI 25.0 - 29.9 kg/m^2), respectively.

Identification and extraction of latent common factors

The maximum likelihood factor analysis procedure was used to identify latent factors common to the obesity-related quantitative measures. Since factor analysis is a multivariate statistical technique used to identify latent (unobserved) factors underlying observed correlations among measured variables, the correlations among the seven obesity-related traits in this study were first estimated and are presented in the lower triangle of Table 2. The high correlations between these traits provided justification for their inclusion in the factor analysis. Kaiser's Measure of Sampling Adequacy (MSA) for individual trait (Table 3, second column) showed that none was at an unacceptable level for retention in the analysis.

Likelihood ratio tests of hypotheses about the number of common factors indicated that two factors sufficiently explained the observed co-variation among the traits. A model of two factors was subsequently fitted to the data and the first factor (Factor1) explained 86% of the observed covariance of the traits, while the second factor (Factor2) explained the remaining 14%. The proportion of variance in each trait accounted for by Factor1 and Factor2 are presented in the last three columns of Table 3. The two factors jointly accounted for more than 78% of any trait-specific variance.

The partial correlations controlling for the effects of Factor1 and Factor2 are presented in the upper triangle of Table 2. The correlations showed that the two factors together captured mostly the positive co-variances in the selected obesity-related traits. The individual trait loadings or regression coefficients on the two factors indicated that Factor1 represented a latent common factor contributing to the observed covariance in BMI, FM, PBFM, WC and HC; while Factor2 represented a latent common factor underlying the observed covariance in RMR and BSA (Figure 1). Prior to the segregation analyses, the effects of age and sex on the extracted Factor1 and Factor2 were adjusted for in fitted polygenic models. The residualized Factor1 and Factor2 were then used in segregation analysis.

Segregation analysis results

The segregation analysis results for Factor1 and Factor2 are shown in Tables 4 and 5, respectively. No proband adjustment was carried out since study families were not ascertained through a proband defined on a trait related to obesity. The tables present the maximum likelihood estimates of the model parameters, −2lnL values, Akaike Information Criterion (AIC) values, χ^2 values, degrees of freedom, and the respective p-values for the different hypotheses examined for each trait (latent factor). For each trait, eight genetic models were fitted, namely, sporadic, Mendelian, dominant, recessive, additive, no polygene

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(major gene only), environmental, and general. The first seven models on the list are nested in the general and thus each of them was compared to the general model.

First we tested the hypothesis of no major effect by comparing the sporadic model with the general model. The null hypothesis of "no major effect" was rejected for both Factor1 (χ^2=245.51, 8 df, p <0.001) and Factor2 (χ^2=215.78, 8 df, p <0.001). The hypothesis of "no transmission of major effect" was next assessed by comparing the environmental model, i.e., a model that assumes independence of offspring genotypes from parental genotypes, with the general model in which all transmission probabilities were estimated. This hypothesis was rejected for both traits (χ^2=11.94, 3 df, p=0.008 for Factor1; χ^2=30.43, 3 df, p <0.001 for Factor2). Having rejected the null hypotheses of "no major effect" and "no transmission of major effect", the hypothesis of "no polygene effects" was consequently tested by comparing the model in which heritability was not estimated with the general model. Again, the null hypothesis of no polygene effects for the two factors could not be supported (p <0.001). Finally, the hypothesis of "Mendelian transmission" was assessed for both traits by comparing a set of Mendelian models (codominant, dominant, recessive, and additive) in which the transmission probabilities were fixed (τ_{AA}=1.0, τ_{AB}=0.5, τ_{BB}=0.0) with the general model in which transmission probabilities were estimated along with other parameters.

As shown in Table 4, the hypothesis of Mendelian transmission could not be rejected for Factor1. To determine the best fitting Mendelian model for Factor1, all the Mendelian models were compared with each other using the AIC values since the models were non-hierarchical. The Mendelian Additive model had the least AIC value and was judged the best fitting among all the Mendelian models fitted to Factor1. This implies that the inheritance of Factor1 follows additive mode with heritability of 40%. The estimate of the putative allele frequency of the segregating genetic effect indicated a common gene with allele frequency equal to 64%. Similarly, when compared with the general model, none of the Mendelian models could be rejected at a significance level of 0.01 for Factor2. The inspection of the AIC values showed that the Mendelian dominant model with the least AIC provided the best fit (Table 5), implying that the inheritance of Factor2 follows a dominant mode. Maximum likelihood estimates for the allele frequency was 34% and the heritability was 48%.

Discussion

We have performed maximum likelihood factor analysis using seven obesity-related traits measured on 1775 participants from 590 African-American families. The purpose of our study was to use multivariate statistical technique to identify unobserved common underlying factors contributing to the observed correlations among obesity-related traits, and to determine the extent to which genetics plays a role in and the mode of inheritance of such factors.

The high correlations between the traits and their individual sampling adequacy measures underscored the suitability of the multivariate analytical technique used in this study. Using factor analysis approach, we were able to separate unobserved common factors that

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

influence these traits collectively from those factors unique to each trait and thus separately influenced the individual trait variances. By implication, the genetic component of such latent factors can be referred to as pleiotropic, since the latent factors are components of multiple traits. To capture the full range of genetic factors underlying correlation among traits, a number of multivariate methods have been proposed and eventually applied to linkage and association mapping46-49. Multivariate methods are consistently more powerful than single-trait methods for gene mapping50-53. In addition to providing the strategy for dimension reduction, the multivariate approach used in this study provides the flexibility to study correlated traits jointly, and identify and extract latent factors contributing to the traits collectively. The latent factors extracted from the correlated traits provide the opportunity to map pleiotropic factors influencing the expression of the traits. An advantage that arises from using latent factors over a single-trait is the ability to localize pleiotropic loci. With the exception where, in addition to being pleoitropic, a locus also influences a trait's unique expression, use of single-trait linkage and association mapping may well fail to detect these pleiotropic loci.

We recognize that results of latent factor analysis could be difficult to interpret biologically, especially when these factors are extracted from many traits. This difficulty often arises from both determining how many factors are appropriate and how to interpret the trait's loadings-also referred to as the traits' beta coefficients on each factor. The method of maximum likelihood factor analysis used in this study provides an easy means of deciding the appropriate number of factors because the method makes it possible to test hypotheses about how many best fits the data. In essence, hypotheses about different numbers of factors can be tested, and from inferences based on likelihood ratio test, the number of factors that best fits the data is identified. Some other rules not based on statistical inference also exist that can be used in determining the appropriate number of factors. These include the “Guttman-Kaiser Criterion” that involves extracting the number of factors with eigenvalues greater than unity54, extracting as many factors as required to explain a specific percentage of the variance in the traits, and the use of the Scree55 plot to identify the number of factors corresponding to the last eigenvalue before they start to level off. Likewise, to overcome the difficulty in interpretation, rotated factor loadings are often used instead of the unrotated. Rotation involves shifting the factors in the factor space so as to maximize the interpretation of the loadings on the factors. Depending on whether the latent factors can be assumed to be correlated or uncorrelated, the oblique or orthogonal method can be employed, respectively, to accomplish the factor rotation.

For a complex human disorder such as obesity, it is known that environmental and genetic factors plus their interactions play a coordinated role. In the absence of molecular genetic markers, heritability estimates provide information on the proportion of the total variances of a trait that can be attributed to genetic components. In the present study, the heritability estimates of 40% and 48% for the first and second latent factors, respectively, were an indication of high genetic components in the two factors. Our results also showed that the segregation of the genetic component of the first latent factor for these obesity traits is consistent with Mendelian additive mode of inheritance while that for the second factor is significantly consistent with dominant mode of inheritance.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Given the complex nature of obesity both in terms of phenotype definition and measurement, it is less surprising that the two latent factors reported in this study differ in their mode of inheritance. However, we anticipate that inclusion of data on molecular genetic marker in this type of analysis would provide further insight to the pleitropic effects on obesity in this population. We recognize the limitations of this study arising from the lack of molecular data, but our findings provide strong support and justification for such a desired independent follow-up study with molecular data. Overall, we have applied multivariate analytical technique to identify common latent factors with pleitropic effects on obesity-related traits, and have also reported the mode of inheritance of these factors to be under the influence of major effect in African-American families.

Acknowledgements

This work was supported by National Heart, Lung, and Blood Institute (NHLBI) grant number HL53353-10.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000; 894(i-xii):1–253.
2. Caballero B. The Global Epidemic of Obesity: An Overview. Epidemiol Rev. 2007
3. Cheung BM, Thomas GN. The metabolic syndrome and vascular disease in Asia. Cardiovascular & hematological disorders drug targets. 2007; 7:79–85. [PubMed: 17584042]
4. Horvath Z, Pankotai MG, Szabolcs I. Stakeholder appraisal of policy options for responding to obesity in Hungary. Obes Rev. 2007; 8(Suppl 2):75–81. [PubMed: 17371310]
5. Kruger HS, Puoane T, Senekal M, van der Merwe MT. Obesity in South Africa: challenges for government and health professionals. Public health nutrition. 2005; 8:491–500. [PubMed: 16153330]
6. Moon G, Quarendon G, Barnard S, Twigg L, Blyth B. Fat nation: Deciphering the distinctive geographies of obesity in England. Social science & medicine (1982). 2007; 65:20–31. [PubMed: 17467130]
7. Newell A, Zlot A, Silvey K, Arail K. Addressing the obesity epidemic: a genomics perspective. Preventing chronic disease. 2007; 4:A31. [PubMed: 17362622]
8. Pender JR, Pories WJ. Epidemiology of obesity in the United States. Gastroenterology clinics of North America. 2005; 34:1–7. [PubMed: 15823434]
9. Urek R, Crncevic-Urek M, Cubrilo-Turek M. [Obesity--a global public health problem]. Acta Med Croatica. 2007; 61:161–164. [PubMed: 17585471]
10. Wyatt SB, Winters KP, Dubbert PM. Overweight and obesity: prevalence, consequences, and causes of a growing public health problem. The American journal of the medical sciences. 2006; 331:166–174. [PubMed: 16617231]
11. Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nature genetics. 2007; 39:724–726. [PubMed: 17496892]
12. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science (New York, NY. 2007; 316:889–894.
13. Herbert A, Gerry NP, McQueen MB, et al. A common genetic variant is associated with adult and childhood obesity. Science (New York, NY. 2006; 312:279–283.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

14. Lyon HN, Emilsson V, Hinney A, et al. The association of a SNP upstream of INSIG2 with body mass index is reproduced in several but not all cohorts. PLoS genetics. 2007; 3:e61. [PubMed: 17465681]
15. Ginsburg E, Livshits G, Yakovenko K, Kobyliansky E. Major gene control of human body height, weight and BMI in five ethnically different populations. Annals of human genetics. 1998; 62:307–322. [PubMed: 9924609]
16. Zhao LJ, Xiao P, Liu YJ, et al. A genome-wide linkage scan for quantitative trait loci underlying obesity related phenotypes in 434 Caucasian families. Human genetics. 2007; 121:145–148. [PubMed: 17115187]
17. Wu X, Cooper RS, Borecki I, et al. A combined analysis of genomewide linkage scans for body mass index from the National Heart, Lung, and Blood Institute Family Blood Pressure Program. American journal of human genetics. 2002; 70:1247–1256. [PubMed: 11923912]
18. Feitosa MF, Borecki IB, Rich SS, et al. Quantitative-trait loci influencing body-mass index reside on chromosomes 7 and 13: the National Heart, Lung, and Blood Institute Family Heart Study. American journal of human genetics. 2002; 70:72–82. [PubMed: 11713718]
19. Luke A, Wu X, Zhu X, Kan D, Su Y, Cooper R. Linkage for BMI at 3q27 region confirmed in an African-American population. Diabetes. 2003; 52:1284–1287. [PubMed: 12716766]
20. Mukhopadhyay N, Finegold DN, Larson MG, Cupples LA, Myers RH, Weeks DE. A genome-wide scan for loci affecting normal adult height in the Framingham Heart Study. Human heredity. 2003; 55:191–201. [PubMed: 14566097]
21. Wu X, Luke A, Cooper RS, et al. A genome scan among Nigerians linking resting energy expenditure to chromosome 16. Obesity research. 2004; 12:577–581. [PubMed: 15090624]
22. Zhu X, Cooper RS, Luke A, et al. A genome-wide scan for obesity in African-Americans. Diabetes. 2002; 51:541–544. [PubMed: 11812767]
23. Deng HW, Deng H, Liu YJ, et al. A genomewide linkage scan for quantitative-trait loci for obesity phenotypes. American journal of human genetics. 2002; 70:1138–1151. [PubMed: 11923910]
24. Li X, Quinones MJ, Wang D, et al. Genetic effects on obesity assessed by bivariate genome scan: the Mexican-American coronary artery disease study. Obesity (Silver Spring, Md. 2006; 14:1192–1200.
25. Livshits G, Otremski I, Kobyliansky E. Genetics of human body size and shape: complex segregation analysis. Annals of human biology. 1995; 22:13–27. [PubMed: 7762972]
26. Livshits G, Roset A, Yakovenko K, Trofimov S, Kobyliansky E. Genetics of human body size and shape: body proportions and indices. Annals of human biology. 2002; 29:271–289. [PubMed: 12031137]
27. Livshits G, Yakovenko K, Ginsburg E, Kobyliansky E. Genetics of human body size and shape: pleiotropic and independent genetic determinants of adiposity. Annals of human biology. 1998; 25:221–236. [PubMed: 9624461]
28. Ataman SL, Cooper R, Rotimi C, et al. Standardization of blood pressure measurement in an international comparative study. Journal of clinical epidemiology. 1996; 49:869–877. [PubMed: 8699206]
29. Cooper R, Rotimi C, Ataman S, et al. The prevalence of hypertension in seven populations of west African origin. American journal of public health. 1997; 87:160–168. [PubMed: 9103091]
30. Hicks C, Zhu X, Luke A, et al. A genome-wide scan of loci linked to serum adiponectin in two populations of African descent. Obesity (Silver Spring, Md. 2007; 15:1207–1214.
31. Luke A, Guo X, Adeyemo AA, et al. Heritability of obesity-related traits among Nigerians, Jamaicans and US black people. Int J Obes Relat Metab Disord. 2001; 25:1034–1041. [PubMed: 11443503]
32. Luke A, Durazo-Arvizu R, Rotimi C, et al. Relation between body mass index and body fat in black population samples from Nigeria, Jamaica, and the United States. American journal of epidemiology. 1997; 145:620–628. [PubMed: 9098179]
33. Luke AH, Rotimi CN, Cooper RS, et al. Leptin and body composition of Nigerians, Jamaicans, and US blacks. The American journal of clinical nutrition. 1998; 67:391–396. [PubMed: 9497181]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

34. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol. 1986; 60:1327–1332. [PubMed: 3700310]
35. Wang Z, Deurenberg P, Wang W, Pietrobelli A, Baumgartner RN, Heymsfield SB. Hydration of fat-free body mass: review and critique of a classic body-composition constant. The American journal of clinical nutrition. 1999; 69:833–841. [PubMed: 10232621]
36. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition (Burbank, Los Angeles County, Calif. 1989; 5:303–311. discussion 312-303.
37. Martin AD, Drinkwater DT, Clarys JP. Human body surface area: validation of formulae based on a cadaver study. Human biology; an international record of research. 1984; 56:475–488.
38. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. The American journal of clinical nutrition. 1990; 51:241–247. [PubMed: 2305711]
39. Bickel, PJ.; Doksum, KA. Mathematical Statistics. Holden-Day; San Francisco: 1977.
40. Lawley, DN.; Maxwell, AE. Factor Analysis as a Statistical Method. Macmillan Publishing Co., Inc.; New York: 1971.
41. Cerny BA, Kaiser HF. A Study of a Measure of Sampling Adequacy for Factor-Analytical Correlation Matrices. Multivariate Behavioral Research. 1977; 12:43–47. [PubMed: 26804143]
42. Hasstedt SJ. jPAP: Document-Driven Software for Genetic Analysis. Genetic epidemiology. 2005; 6:255.
43. Wijsman EM. Monte Carlo Markov chain methods and model selection in genetic epidemiology. Computational Statistics & Data Analysis. 2000; 32:349–360.
44. Grainger DJ, Heathcote K, Chiano M, et al. Genetic control of the circulating concentration of transforming growth factor type beta1. Hum Mol Genet. 1999; 8:93–97. [PubMed: 9887336]
45. Verloes A, Temple IK, Bonnet S, Bottani A. Coloboma, mental retardation, hypogonadism, and obesity: critical review of the so-called Biemond syndrome type 2, updated nosology, and delineation of three “new” syndromes. Am J Med Genet. 1997; 69:370–379. [PubMed: 9098485]
46. Blangero J, Konigsberg LW. Multivariate segregation analysis using the mixed model. Genetic epidemiology. 1991; 8:299–316. [PubMed: 1761203]
47. Goodman E, Dolan LM, Morrison JA, Daniels SR. Factor analysis of clustered cardiovascular risks in adolescence: obesity is the predominant correlate of risk among youth. Circulation. 2005; 111:1970–1977. [PubMed: 15837951]
48. Xiao J, Wang X, Hu Z, Tang Z, Xu C. Multivariate segregation analysis for quantitative traits in line crosses. Heredity. 2007; 98:427–435. [PubMed: 17392707]
49. Almasy L, Dyer TD, Blangero J. Bivariate quantitative trait linkage analysis: pleiotropy versus co-incident linkages. Genetic epidemiology. 1997; 14:953–958. [PubMed: 9433606]
50. Schmitz S, Cherny SS, Fulker DW. Increase in power through multivariate analyses. Behav Genet. 1998; 28:357–363. [PubMed: 9926617]
51. Evans DM. The power of multivariate quantitative-trait loci linkage analysis is influenced by the correlation between variables. Am J Hum Genet. 2002; 70:1599–1602. [PubMed: 11992269]
52. Amos C, de Andrade M, Zhu D. Comparison of multivariate tests for genetic linkage. Hum Hered. 2001; 51:133–144. [PubMed: 11173964]
53. Ott J, Rabinowitz D. A principal-components approach based on heritability for combining phenotype information. Human heredity. 1999; 49:106–111. [PubMed: 10077732]
54. Guttman L. Some necessary conditions for common factor analysis. Psychometrika. 1954; XIX: 149–161.
55. Carttel RB. The Scree test for the number of factors. Multivariate Behavioral Research. 1966; 1:245–276. [PubMed: 26828106]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

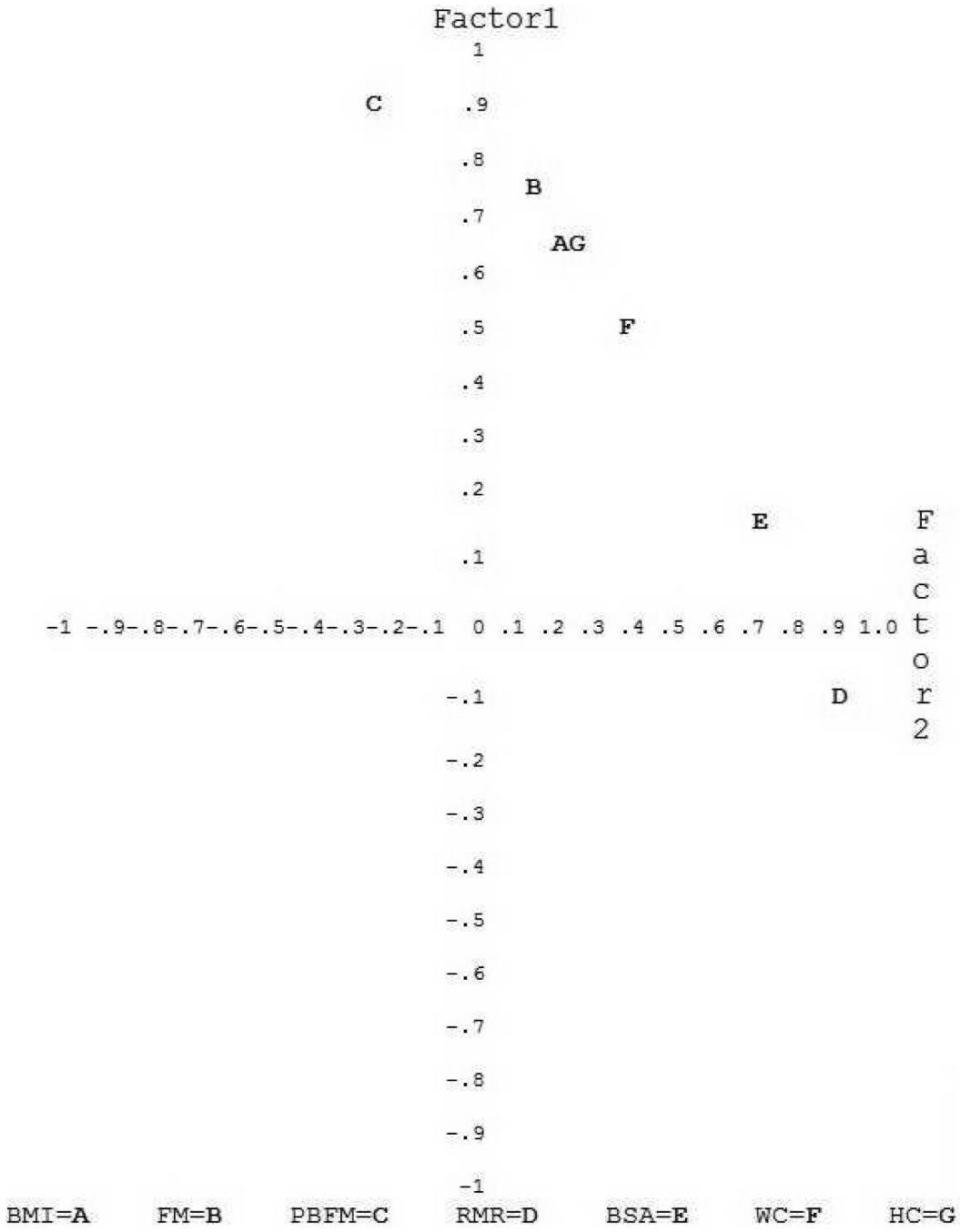

Figure 1.

Pattern of Factor1 and Factor2 loadings for the seven obesity traits. Factor1 displayed high loadings on BMI, FM, PBFM, WC and HC; while Factor2 is marked by high loadings on RMR and BSA.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Descriptive characteristics[¶] of participants

	Women (n=1122)	Men (n=653)	All (n=1775)
Age (years)	38.04±15.44	35.44±13.52	37.08±14.81
BMI (kg/m^2)	30.36±8.10	27.03±6.46	29.13±7.71
FM(kg)	34.97±15.94	23.07±13.89	30.59±16.26
PBFM (%)	40.99±8.72	25.55±9.00	35.31±11.55
RMR (Kcal/d)	1486.09±231.97	1771.65±231.90	1591.15±269.71
BSA (m^2)	1.86±0.23	1.99±0.24	1.91±0.24
WC (cm)	91.54±17.31	90.91±16.29	91.30±16.94
HC (cm)	111.63±15.81	104.48±12.46	109.00±15.06

Abbreviations: BMI, body mass index; FM, fat mass; PBFM, percent body fat mass; RMR, resting metabolic rate; BSA, body surface area; WC, waist circumference; HC, hip circumference.

[¶]Values are significantly different between women and men except for WC

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Adjusted and unadjusted correlations[¶] between obesity traits

	BMI	FM	PBFM	RMR	BSA	WC	HC
BMI		**0.008**	**−0.366**	**−0.066**	**−0.214**	**0.413**	**0.379**
FM	0.942		**0.047**	**0.028**	**−0.016**	**−0.064**	**−0.044**
PBFM	0.768	0.886		**−0.035**	**0.158**	**−0.103**	**−0.088**
RMR	0.579	0.534	0.158		**0.033**	**−0.146**	**−0.085**
BSA	0.728	0.726	0.416	0.917		**0.179**	**0.032**
WC	0.884	0.845	0.640	0.655	0.800		**0.277**
HC	0.933	0.933	0.775	0.593	0.757	0.864	

Abbreviations: BMI, body mass index; FM, fat mass; PBFM, percent body fat mass; RMR, resting metabolic rate; BSA, body surface area; WC, waist circumference; HC, hip circumference.

[¶]Values in the lower triangle are unadjusted correlations, and those in the upper triangle are correlations adjusted for effects of Factor 1 and Factor2.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Traits sampling adequacy and percentage variance of traits explained by both Factor1 and Factor2

	Kaiser's Measure of Sampling Adequacy	Percent variance explained by		
		Factor1	Factor2	Both Factors
BMI	0.832	89.43	0.37	89.81
FM	0.782	99.72	0.13	99.85
PBFM	0.716	76.02	16.75	92.77
RMR	0.712	31.76	65.91	97.67
BSA	0.788	56.12	36.97	93.08
WC	0.921	73.08	5.09	78.17
HC	0.961	87.98	0.72	88.70

Abbreviations: BMI, body mass index; FM, fat mass; PBFM, percent body fat mass; RMR, resting metabolic rate; BSA, body surface area; WC, waist circumference; HC, hip circumference.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4

Segregation analysis of latent common Factor1, adjusted for age and sex in 1775 relatives from 590 pedigrees[¶]

Model	q_A	τ_{AA}	τ_{AB}	τ_{BB}	u_{AA}	u_{AB}	u_{BB}	σ_{AA}	σ_{AB}	σ_{BB}	h^2	−2lnL	AIC	x^2	df	P
Sporadic	0.689	-	-	-	−0.057	$=u_{AA}$	$=u_{AA}$	0.819	$=\sigma_{AA}$	$=\sigma_{AA}$	-	4274.65	4282.65	245.51	8	<.001
Mendelian	0.670	[1.0]	[0.5]	[0.0]	−0.522	0.322	0.189	0.487	0.887	0.651	0.503	4036.94	4054.94	7.80	3	.050
Dominant	0.321	[1.0]	[0.5]	[0.0]	−0.459	$=u_{AA}$	0.378	0.526	$=\sigma_{AA}$	0.860	0.460	4037.03	4051.03	7.89	5	.162
Recessive	0.715	[1.0]	[0.5]	[0.0]	−0.476	0.351	$=u_{AB}$	0.516	0.859	$=\sigma_{AB}$	0.471	4038.27	4052.27	9.13	5	.104
Additive	0.641	[1.0]	[0.5]	[0.0]	0.384	−0.274	−0.809	0.896	0.562	0.336	0.404	4031.29	4049.29	2.15	3	.542
No polygenes	0.902	0.970	0.084	0.0	0.164	−0.611	1.197	0.734	0.467	0.842	-	4090.82	4112.82	61.68	1	<.001
Environmental	0.820	$=q_{AA}$	$=q_{AA}$	$=q_{AA}$	0.096	−0.596	1.247	0.797	0.428	1.035	0.720	4041.08	4059.08	11.94	3	.008
General	0.267	1.0	0.298	0.785	−0.569	0.129	0.555	0.457	0.762	0.977	0.543	4029.14	4053.14	-	-	-

[¶]Values in square brackets indicate parameters set to given values in the models; q_A = frequency of putative disease allele A; τ_{AA}, τ_{AB} and τ_{BB} = the probability that a parent of type AA, AB and BB transmits allele A to offspring, respectively; u_{AA}, u_{AB} and u_{BB} = genotypic effects for type AA, AB and BB, respectively; $<_{AA}$, $<_{AB}$ and $<_{BB}$ = genotype-specific standard deviations; h^2 = heritability estimate; −2lnL = minus twice the natural log-likelihood; AIC = Akaike Information Criteria (−2lnL + 2*number of parameters estimated in model); X^2 =difference between −2lnL of the model and −2lnL of the General model; df = difference between number of parameters estimated in particular model and the General model; P = p-value of chi-square value.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 5

Segregation analysis of latent common Factor2, adjusted for age and sex in 1775 relatives from 590 pedigrees

Model	q_A	τ_{AA}	τ_{AB}	τ_{BB}	u_{AA}	u_{AB}	u_{BB}	σ_{AA}	σ_{AB}	σ_{BB}	h^2	−2lnL	AIC	x^2	df	P
Sporadic	0.932	-	-	-	−0.064	$=u_{AA}$	$=u_{AA}$	0.870	$=\sigma_{AA}$	$=\sigma_{AA}$	-	4481.12	4489.12	215.78	8	<.001
Mendelian	0.866	[1.0]	[0.5]	[0.0]	−0.358	0.725	1.129	0.664	0.892	0.087	0.438	4273.98	4291.98	8.62	3	.035
Dominant	0.337	[1.0]	[0.5]	[0.0]	−0.470	$=u_{AA}$	0.419	0.603	$=\sigma_{AA}$	0.893	0.475	4274.29	4288.29	8.93	5	.112
Recessive	0.711	[1.0]	[0.5]	[0.0]	−0.494	0.347	$=u_{AB}$	0.585	0.901	$=\sigma_{AB}$	.488	4275.47	4289.47	10.11	5	.072
Additive	0.327	[1.0]	[0.5]	[0.0]	0.307	0.307	−0.546	0.620	0.941	0.555	.496	4273.76	4291.76	8.4	3	.038
No polygenes	0.872	1.00	0.373	1.00	−0.393	0.762	1.173	0.644	0.817	0.142	-	4306.10	4328.10	40.74	1	<.001
Environmental	0.898	$=q_{AA}$	$=q_{AA}$	$=q_{AA}$	.279	0.750	1.170	0.720	0.922	0.032	0.660	4295.79	4313.79	30.43	3	<.001
General	0.796	1.00	0.50	1.00	−0.384	0.647	1.121	0.647	0.903	0.175	0.487	4265.36	4289.36	-	-	-

¶Values in square brackets indicate parameters set to given values in the models; q_A = frequency of putative disease allele A; τ_{AA}, τ_{AB} and τ_{BB} = the probability that a parent of type AA, AB and BB transmits allele A to offspring, respectively; u_{AA}, u_{AB} and u_{BB} = genotypic effects for type AA, AB and BB, respectively; σ_{AA}, σ_{AB} and σ_{BB} = genotype-specific standard deviations; h^2 = heritability estimate; −2lnL = minus twice the natural log-likelihood; AIC = Akaike Information Criteria (−2lnL + 2*number of parameters estimated in model); χ^2 =difference between −2lnL of the model and −2lnL of the General model; df = difference between number of parameters estimated in particular model and the General model; P = p-value of chi-square value.

Int J Obes (Lond). Author manuscript; available in PMC 2010 March 01.