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Risk Ratios for Obesity in Families of Obese African-American and Caucasian Women

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Key Words

Risk ratio · Lambda · Overweight · Obesity · Body mass index · Extreme sampling · Discordant pairs

Abstract

We examined age- and sex-standardized risk ratios (SRRs) in matched samples of 1,185 families of obese African-American and Caucasian women. Familial risk ratios increased with body mass index (BMI) of proband and BMI thresholds of relative. Ratios were higher in Caucasian than African-American families, apparently because Caucasian probands were more extreme relative to their population mean. Risk ratios for moderate obesity (BMI $\geq$ 30) were around 2 for African-Americans and were a little higher in Caucasians. Ratios for extreme obesity (BMI $\geq$ 40) ranged from 3 to 5 in African-Americans and from about 5 to 9 in Caucasians. Thin relatives were rare in families of both races. Risk ratios appear high enough in both racial groups to facilitate the identification of quantitative trait loci underlying common obesity phenotypes. The high population prevalence of obesity in African-American women will require particularly high selection thresholds to achieve risk ratios comparable to those for Caucasians. The scarcity of thin siblings in both groups will greatly increase the effort required in sample recruitment for discordant pair designs.

Introduction

Overweight and obesity are very common health problems, currently affecting one third to one half of adults in the United States [1]. Obesity affects women in particular, especially those of African descent. For example, approximately two thirds of African-American women are at least mildly overweight [1].

Numerous studies indicate that genes play a role in the determination of individual differences in obesity [2, 3], accounting for 40–70% of the total trait variance. Most studies have focused on Caucasians, but the few that have studied African-Americans reported similar levels of family correlations [4–9] and genetic influence [10] as have been reported for Caucasians.

Identifying genetic loci influencing a multigenic trait such as obesity depends on many factors, particularly the trait prevalence and heritability, which together determine the relative risk or λ [11] for each of the causal genes. In the absence of information about the specific number of genes and gene effect sizes, overall standardized risk ratios provide a good indicator of relative feasibility of identifying quantitative trait loci. To date, four published studies have reported risk ratios or λ values for obesity-related phenotypes. The first examined adiposity ranging from the 10th to 90th percentile and found very low risk ratios [12]. The second paper examined extreme obesity in a sample of Caucasian women and found ratios of 5 or

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more [13]. The third [14] summarized ratios for 11 different samples for moderate obesity (90th percentile) and thinness (10th percentile). The fourth [15] reported familial risk ratios for BMI and fat distribution (sum of 5 skinfolds and trunk-to-extremity skinfolds) in the Canadian general population to be 5, 4, and 3, respectively. Although not reported directly, ratios may be calculated from two other published reports [5, 16] and others have been estimated indirectly through segregation analyses [17]. Only one study examined African-Americans [5, 14], and that sample was extremely small.

It has been estimated that on average 77–88% of genes in African-Americans are of west-African origin, with most of the remainder having originated in Europe [18]. This genetic admixture, combined with an approximate doubling of the obesity prevalence in African-Americans relative to Caucasians, suggests that studies of African-Americans may also offer the possibility of identifying genes contributing to the mean difference between races [19].

In this paper, we report standardized familial risk ratios for obesity in a large sample of African-American and Caucasian families ascertained through BMI- and age-matched obese probands. We consider the implications of our results for gene identification strategies.

Methods

Subjects

Families were recruited for a genetic study of obesity over a 7-year period beginning in 1992. The recruitment process has been described previously [9, 20]. Briefly, subjects were respondents to advertisements and direct mailings aimed at individuals 50 or more pounds overweight. Respondents received a screening interview in which they reported their height, weight and age and estimated height weight and age (or age at death) of spouses and first degree relatives (parents, siblings, and children). Most respondents were women.

A subset of the female respondents who had complete data for height, weight and age for the respondent and both parents were selected as probands for the present study. Further, only a subset of families included in the present study was eligible for our linkage study [20]. African-American and Caucasian probands with BMI $\geq$ 30 and with complete data on families were then individually matched for BMI (BMI: weight in kilograms divided by the square of height in meters) and were group matched for age. Specifically, probands were individually matched for BMI within one BMI unit. When possible, we also matched individuals by age within BMI. When an exact match was not available, we selected individuals as close in age as possible. Finally, we excluded potential probands if no good age match could be found in order to achieve similar frequency distributions for age in the two samples. This matching process resulted in samples of 1,185 African-American and 1,185 Caucasian families of probands with BMI $\geq$ 30. Of these, a subset of 801 families of each race was selected through a proband with BMI $\geq$ 40.

Descriptive statistics for this sample have been reported previously [9]. For probands selected for a BMI $\geq$ 30, the means of African-American and Caucasian probands match exactly for the BMI variable (mean $\pm$ SD = 45.1 $\pm$ 9 kg/m^2) and mean age did not differ significantly (mean $\pm$ SD = 36 $\pm$ 8 years and mean $\pm$ SD = 37 $\pm$ 9 years for African-Americans and Caucasians, respectively; $F(1, 2{,}369) = 0.16$, $p = 0.69$). Likewise, for probands selected for a BMI $\geq$40, the African-American and Caucasian probands match exactly for the BMI variable (mean $\pm$ SD = 49.5 $\pm$ 7.5 kg/m^2) and mean age did not differ (both mean $\pm$ SD = 36 $\pm$ 8 years). Proband BMI values ranged from 30 to 73 and were identically distributed in the two racial groups because of the matching process. Age ranged from 18 to 65 in African-Americans and from 18 to 63 in Caucasians. Ages were similar in the two groups across the whole distribution [9]. Correlations between respondent BMI and age were low and did not differ between the African-American and Caucasian groups ($r = -0.07$ and -0.15, respectively, $n = 1{,}185$, $Z = 1.82$, $p = 0.07$).

Accuracy and Bias in Self and Informant Reports

For a subset of these probands whose families entered our genetic linkage studies, we compared estimated and measured heights and weights of family members for the two racial groups. As reported previously for this sample [9], both racial groups tended to overestimate height (on average 1/2 inch), underestimate weight (on average 10 lb) and underestimate BMI (on average 1.6 units, kg/m^2). There were no differences in the over- and underestimates based on the race of the informant. For African-Americans, the correlations were 0.93 for height and 0.94 for weight and BMI. For Caucasians, the value was 0.95 for height, weight and BMI. These results are very similar to those from an earlier study of a nonoverlapping sample of Caucasians [21]. Because of the consistency of the reporting bias and the high correlations between estimated and measured values, inaccuracy or bias should not differentially influence the familial risk ratios for the two races.

Obesity and Thinness Thresholds

Probands were grouped according to level of obesity in two ways. We used non-overlapping intervals of BMI ($30 \leq$ BMI < 40 and BMI ≥ 40) representing moderate and extreme obesity, respectively, and overlapping thresholds (BMI $\geq$ 30 and BMI $\geq$ 40). Obesity thresholds in relatives were defined as BMI $\geq$ 30 and BMI $\geq$ 40, whereas thinness was defined as BMI $<$ 20. These thresholds (BMI $<$ 20, BMI $\geq$ 30 and BMI $\geq$ 40) correspond to the 8th, 73rd and 95th percentiles for BMI, respectively, in African-Americans and to the 8th, 79th and 98th percentiles for BMI, respectively, in Caucasians.

Standardization of Obesity Prevalence and Computation of Risk Ratios

Age- and sex-standardized prevalences were estimated by computing obesity prevalence within the six age (20–34, 35–59, and 60+ years) and sex categories, then giving equal weight to each category within race [22]. The standardized risk ratio (SRR) was computed by taking the ratio of the age- and sex-standardized rates for this sample to age- and sex-standardized rates estimated from the first phase of the third National Health and Nutrition Examination Survey (NHANES III) [23]. Standard errors were approximated by $1/b[(p(1 - p)/n]$, where b is the baseline risk of reaching the obesity threshold in the population, p is the proportion of relatives who

Table 1. Age-adjusted percentage of relatives with a BMI ≥ 30, BMI ≥ 40, or BMI <20, grouped by race, sex, and BMI of proband, with NHANES III population prevalences for comparison

	African-Americans				Caucasians			
	proband BMI 30–39	proband BMI ≥ 30	proband BMI ≥ 40	NHANES III	proband BMI 30–39	proband BMI ≥ 30	proband BMI ≥ 40	NHANES III
Risk for BMI ≥ 30 in relatives								
Female relatives	66.50	70.12	71.98	33.92	52.84	59.62	62.90	24.14
Male relatives	39.48	44.58	47.22	20.36	39.50	47.86	52.10	18.56
All relatives	52.98	57.35	59.60	27.14	46.17	53.74	57.50	21.36
Risk for BMI ≥ 40 in relatives								
Female relatives	24.52	32.52	36.60	6.52	16.54	24.76	28.80	3.70
Male relatives	9.30	13.22	15.28	3.78	7.02	13.08	16.12	1.10
All relatives	16.91	22.87	25.94	5.15	11.78	18.92	22.47	2.40
Risk for BMI <20 in relatives								
Female relatives	2.46	1.90	1.64	8.10	5.62	4.38	3.78	9.68
Male relatives	1.58	2.62	3.16	8.86	2.54	2.30	2.18	5.40
All relatives	2.02	2.26	2.40	8.48	4.08	3.34	2.98	7.54

reached the threshold, and n is the total number of relatives in the group. The standard error estimates are anticonservative in that family members are assumed to be independent. It is also assumed that the NHANES III prevalence is a constant. SRRs were statistically evaluated by computing 95% confidence intervals (95% CI), and two SRRs were considered different when the 95% CIs did not overlap.

Results

Age-adjusted rates of moderate obesity (BMI ≥ 30), extreme obesity (BMI ≥ 40), and thinness (BMI < 20) in relatives of probands with moderate or extreme obesity are given in table 1. Comparative population rates are presented based on NHANES III. For obesity, all the familial rates are high relative to population values. Compared with the NHANES data, the rates of obesity in women are particularly high, reaching a maximum for moderate obesity in female relatives of extremely obese African-American probands of 72%, if the age and sex categories are evenly distributed. A total of 37% of these African-American women had a BMI ≥ 40. For thinness, on the other hand, familial rates are lower in all relatives than in the population, reaching a minimum of 2% in African-American male relatives, if age and sex categories are evenly distributed.

SRRs are presented for proband intervals (30 ≤ BMI < 40 and BMI ≥ 40) in figure 1 and for proband thresholds (BMI ≥ 30 and BMI ≥ 40) in figure 2.

For the African-American relatives, risk for moderate obesity (BMI ≥ 30) increased with proband classification from 2.0 to 2.2 for the nonoverlapping intervals and from 2.1 to 2.2 for the overlapping thresholds (fig. 1, 2). Differences in SSRs for proband intervals were significant but those for thresholds were not. Risk for extreme obesity (BMI ≥ 40) increased from 3.3 to 5.0 for the nonoverlapping intervals and from 4.4 to 5.0 for the overlapping thresholds. Differences in SRRs for proband intervals and thresholds were significant. Risk for thinness (BMI < 20) was low in all groups (0.2–0.3), and all SRRs overlapped. There were no significant differences in SRRs for thinness between the two groups.

For the Caucasian relatives, risk for moderate obesity (BMI ≥ 30) increased with proband classification from 2.2 to 2.7 for the nonoverlapping intervals and from 2.5 to 2.7 for the overlapping thresholds (Fig. 1, 2). Risk for extreme obesity (BMI ≥ 40) increased from 4.9 to 9.4 for the non-overlapping intervals and from 7.9 to 9.4 for the overlapping thresholds. Differences in SRRs for proband intervals and thresholds were significant for both moderate and extreme obesity. Risk for thinness (BMI < 20) was low in all groups (0.4), and all the 95% CIs for the SRRs overlapped.

From figures 1 and 2 it can be seen that the CIs for the SRRs for African-American and Caucasian families overlapped for only one group of comparisons, for thinness in relatives of extremely obese probands. Caucasian families have higher risk ratios for all levels of obesity and the dif-

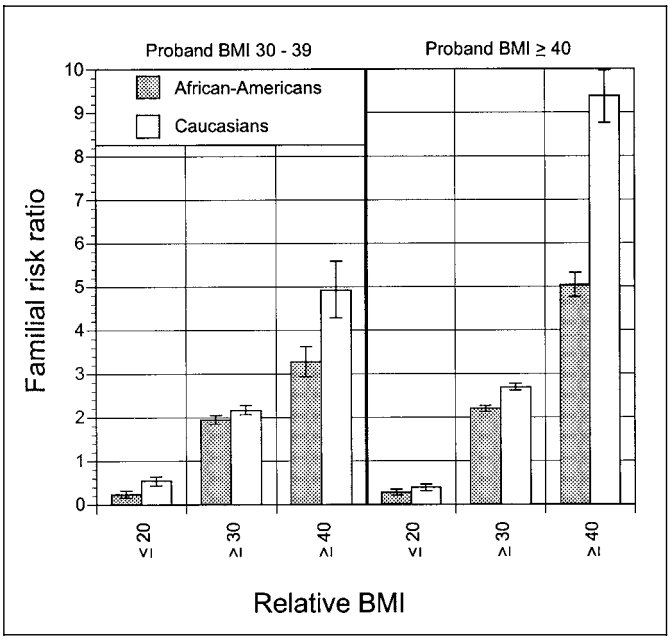

Fig. 1. SRRs and CIs for moderate obesity (BMI ≥ 30), extreme obesity (BMI ≥ 40), and thinness (BMI < 20) in relatives of probands with 30 ≤ BMI < 40 or BMI ≥ 40 compared with population rates. SRRs are given for African-American (shaded bars) and Caucasian (open bars) relatives.

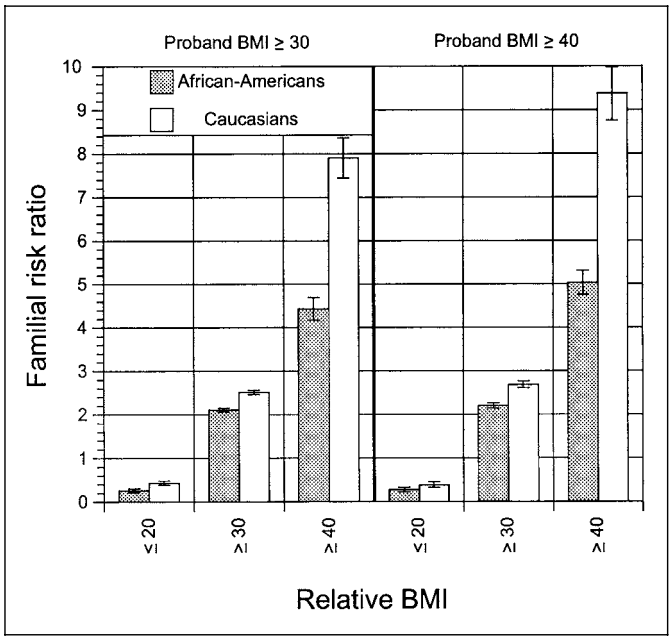

Fig. 2. SRRs and CIs for moderateobesity (BMI ≥ 30), extreme obesity (BMI ≥ 40), and thinness (BMI <20) in relatives of probands with thresholds of BMI ≥ 30 or BMI ≥ 40 compared with population rates. SRRs are given for African-American (shaded bars) and Caucasian (open bars) relatives.

ference in risk increases with increasing levels of proband BMI. African-American families have lower ratios for thinness than do Caucasian families. Whereas thinness is less common in both sets of families than in the population, the rates are especially low in the African-American families.

Discussion

Familial risk ratios increased with proband BMI and were higher in Caucasian than African-American families. Because rates of obesity are higher in African-Americans than in Caucasians, the Caucasian probands are more extreme relative to their population mean. Risk ratios for moderate obesity (BMI ≥ 30) were around 2 for African-Americans and were a little higher in Caucasians. Ratios for extreme obesity were considerably higher, ranging from 3 to 5 in African-Americans and from about 5 to 9 in Caucasians. Thin relatives were rare in families of both races.

Our results are consistent with those of Allison et al. [12], who found lower overall ratios for milder forms of obesity, which increased with increasing threshold. Using thresholds similar to those used in the present study, we previously reported ratios of 1.5–2 for moderate obesity and from 3 to 5.5 for extreme obesity [13]. Unstandardized ratios may also be estimated from data given in an earlier report on Princeton School District Study [5]. For probands with BMI at or above the 90th percentile, which at that time corresponded roughly to our classification of moderate obesity, the ratio for a combined sample of families ascertained randomly and through hyperlipidemic probands the ratio was a little over 2 (2.3). λ values estimated from segregation analysis [17] were in the same range for the 90th percentile (λ 1.4–2.5 for siblings). Allison et al. [14] also used the 90th percentile as an obesity threshold and found λ values in the range of approximately 1.5–3.5 for American and European Caucasians, East Indians, Native Americans, and African-Americans. For most samples, the values were in the range of 2.5–3.5. The Princeton study [5, results also cited in ref. 14] is the only one to have reported data on which risk ratios may be estimated for African-Americans. An estimated ratio of 1.5 is similar to but somewhat lower than SRRs found in the current study for moderate obesity. However, it

should be noted that the earlier study was based on only 13 families compared with 1,185 in the present study.

Results presented in the paper by Risch [11] suggested that it should be practical to collect samples of sufficient size to identify genes with λ values of 2 or greater. Even with a high overall risk ratio, λ for a particular gene will depend on the number of causative genes and their relative effects. Since it is not possible to know these factors in advance, power estimation requires many assumptions. For example, we reported earlier that to achieve a one-sided p value of 10^{-4} with 80% power, 767 affected sibling pairs would be needed. This estimate assumed an overall risk ratio of 5, five genes contributing equally, and markers having an average PIC value 0.8 and an average inter-marker distance of 10 cM [13]. Given these estimates, it appears that it should be feasible to identify genes for extreme obesity in both African-Americans and Caucasians.

It has been suggested that extremely discordant relative pairs may be especially useful in identifying genes for complex traits [24]. However, the enhanced power comes at the cost of increased effort needed to identify unusual pairs. It is obvious that, when an index case from the extreme upper end of the phenotype is chosen (e.g., BMI $\geq$ 40), the likelihood of finding a concordant sibling (e.g., BMI $\geq$ 30) is much higher than finding a discordant sibling (e.g., BMI $<$ 20) as we have shown in this paper. Thus, the gain in power by ascertaining extreme discordant sib pairs must outweigh the cost of recruitment and screening.

According to the sample size calculations by Ziegler and Hebebrand [25], the required sibling pairs differ widely by parameters obtained from segregation analysis. To achieve α of 0.0001 and 1 – β of 0.8, for example, either 285 extremely discordant sibling pairs (top 97%-bottom 40%) or 299 extreme-concordant sibling pairs (top 97%-top 90%) are needed when the parameters from Price et al. [26] are used for the power calculation. Whereas the sample sizes are similar, the availability of concordant sibling pairs appears to be three times that for discordant pairs (0.24 and 0.07, respectively). As the authors cautioned [25], these numbers are only meant to be heuristic in comparing relative magnitudes of the estimates, as different sets of parameters yield different results. Further, Risch and Zhang [24] showed that the number of required extreme concordant sibling pairs can be reduced by requiring that parents have phenotypes in the bottom 70th percentile – especially when residual correlations are substantial. This strategy reduces the available families somewhat; however, the gain in power may be considerable for certain models (e.g., recessive mode of inheritance, rare allele). Another alternative that appears to retain some of the increased power associated with discordant pairs involves raising the lower threshold [27] so that recruitment cost is reduced by including a greater number of relatives with average weight.

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