Interaction of Body Mass Index and Framingham Risk Score in Predicting Incident Coronary Disease in Families

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Background—Siblings of individuals with premature coronary heart disease (CHD) have a marked excess risk of CHD risk factors and premature CHD. The impact of body mass index (BMI) on incident CHD in these families and the extent to which it may be mediated by associated risk factors are unknown. The aim of this study was to examine the effect of high BMI on incident CHD in white and black families with premature CHD and to estimate the heritability of BMI.

Methods and Results—Risk factors, BMI, and Framingham Risk Score (FRS) were assessed at baseline and incident CHD was determined prospectively in 827 apparently healthy siblings of probands with premature CHD aged <60 years. During a mean follow-up of 8.7 years, 13.3% of siblings had incident CHD events. Event rates were higher in obese and overweight siblings than in those with normal weight (15.3% and 16.0% versus 8.1%, respectively; \( P = 0.01 \)). Multivariable Cox proportional hazards analyses demonstrated the independent prognostic value of BMI when added to FRS (\( P = 0.02 \)). A marked interaction between obesity (BMI \( \geq 30 \) kg/m²) and high FRS (>20%) was seen for incident CHD (\( P \) for interaction\( =0.008 \)), with an adjusted hazard ratio compared with low-FRS/normal-weight siblings of 14.63 (95% CI, 6.40 to 33.44; \( P < 0.0001 \)). BMI heritability (\( h^2 \)) was moderate for whites and low for blacks (52% and 29%, respectively).

Conclusions—High BMI contributed independently and significantly to incident CHD, beginning in the overweight range, and was most notable for obese siblings with a high-risk FRS. (Circulation. 2005;111:1871-1876.)

Key Words: body mass index \( \blacktriangleright \) risk factors \( \blacktriangleright \) coronary disease

Overweight and obesity continue to increase substantially both in the United States and worldwide, affecting all ages, sexes, and races.\(^1\)\(^-\)\(^3\) The relationship between obesity and the potentially attendant increase in cardiovascular risk may have its origins very early in life, in that weight gain in infancy and childhood appears to have substantial effects on the later propensity for development of cardiovascular risk factors and atherosclerosis.\(^4\)\(^-\)\(^7\) Increased body weight in adulthood has also been strongly associated with many individual cardiovascular risk factors\(^8\)\(^-\)\(^10\) and with increased overall cardiovascular risk in many epidemiological studies.\(^9\)\(^-\)\(^11\)

In families known to be at high risk for premature coronary heart disease (CHD), the cardiovascular risk of overweight and obesity may be even more salient. Premature CHD likely has a strong genetic component,\(^12\)\(^-\)\(^13\) and siblings of individuals with a history of premature CHD have a marked excess risk of CHD themselves,\(^14\)\(^-\)\(^15\) which may be accounted for by known risk factors, lifestyle, unknown genetic factors, and gene–lifestyle interactions. We and others have previously shown that cardiovascular risk factors tend to cluster in these high-risk families.\(^16\)\(^-\)\(^20\) The extent to which CHD risk in families with premature CHD is modified by an increased body mass index (BMI) independent of Framingham Risk Score (FRS) remains unknown. In addition, it is not known whether there is a BMI threshold associated with actual incident CHD in these families that may predispose certain individuals to premature CHD events on the basis of their BMI. We designed this study to determine the role of high BMI in incident CHD in families with known premature CHD. We also sought to determine the extent to which adult BMI was heritable in both black and white siblings.

Methods

Study Population
The Johns Hopkins Sibling Study is an ongoing prospective cohort study of siblings of probands with known premature CHD.\(^19\) Appar-ently healthy asymptomatic siblings were identified at the time of a CHD event in an index individual at the time of hospitalization in any of 10 Baltimore hospitals for acute myocardial infarction, a
coronary revascularization procedure, or unstable/stable angina with angiographically documented coronary artery disease before age 60 years.19 Siblings were excluded if they had clinically evident CHD, were aged >60 years, or had functional limitations that precluded exercise testing, organ transplantation, concurrent chronic glucocorticosteroid use, or a life-threatening comorbidity with estimated life expectancy <5 years. At the time of the index event, all eligible siblings were invited for a baseline evaluation that consisted of a comprehensive cardiovascular history and physical examination, anthropometric measurements, and fasting blood tests for lipids and glucose. Siblings were accrued from 1983 to 1996. At the time of screening, siblings and their physicians received detailed individualized recommendations on weight management and cardiovascular risk factor modification.

Baseline Cardiovascular Evaluations
During the baseline evaluation, data were obtained by standardized methods administered by trained personnel using the same protocols. A detailed history was recorded and physical examination was performed by a study cardiologist using standardized protocols. All comorbidities reported by the siblings were verified with question probes. In the case of a possible CHD event, medical record documentation was obtained to ensure that the sibling was free of clinically manifest CHD at baseline. Smoking status was defined as any self-reported smoking within 1 month and was confirmed by expired carbon monoxide levels. Individuals who claimed to be nonsmokers but who had expired carbon monoxide levels >8 ppm on 2 readings were considered current smokers.

The mean of 3 blood pressure measurements taken over an 8-hour interval at standardized times was used to define screening blood pressure levels.21 Hypertension was defined as mean resting blood pressure ≥140/90 mm Hg or the use of antihypertensive medication.21 After participants fasted for 12 hours overnight, levels of glucose, triglycerides, total cholesterol, and HDL cholesterol were measured in a Centers for Disease Control–standardized laboratory. For individuals with triglyceride levels ≤4.49 mmol/L (400 mg/dL), the Friedewald equation was used to estimate LDL cholesterol.22 Diabetes was defined as fasting glucose >6.88 mmol/L (125 mg/dL) or the use of antidiabetic medication.

Anthropometric Measurements and Definitions
Body weight was measured on a balance scale twice, and the mean of the 2 values was taken. Body height in inches was measured with a stadiometer. BMI was calculated as weight divided by the square of the height (kg/m²) and used to define categories of overweight and obesity according to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.23 BMI categories were defined as normal (BMI <25 kg/m²), overweight (BMI 25 to 29.9 kg/m²), and obese (BMI ≥30 kg/m²).

Framingham Risk Scores
The 1998 Framingham sex-specific risk equations for estimating 10-year total CHD events (angina, myocardial infarction, or CHD death) for asymptomatic individuals were used to estimate CHD risk at baseline.24 FRS equations included age, total cholesterol, HDL cholesterol, blood pressure, diabetes, and smoking status.24

CHD End Points
Siblings were recontacted from 1998 to 2002, and a standardized health status questionnaire was administered by a trained interviewer. Individuals reporting possible cardiovascular events were asked to sign a medical release to retrieve all relevant medical records. In the event of a participant’s death, the nearest living relative gave permission for access to medical records, and death records and/or autopsy reports were obtained. Records were then reviewed independently for classification of a CHD event with the use of standardized criteria by 3 investigators and another nonstudy Johns Hopkins cardiologist. All were blinded to the participants risk factor status. For any discordance in CHD event classification, the medical records were sent to an external academic cardiologist for blinded review. Incident CHD events included sudden cardiac death, myocardial infarction, unstable/stable angina with a documented flow-limiting stenosis, or angina requiring revascularization during follow-up. Event classification was nearly identical to that of the Framingham Heart Study.25 Only 28 siblings (3.3%) were completely lost to follow-up.

Measures of Heritability
Heritability (h²) is the proportion of the total variance in a trait that is due to additive gene effects and is an estimate primarily of the genetic control of a trait.26 The heritability of BMI was estimated as follows: h² (%) = 2r × 100, or 2 times the intraclass correlation coefficient of BMI among siblings.26 Heritability estimates for BMI were examined by race and adjusted for age and sex.

Statistical Analyses
Statistical analyses were done with the use of SAS version 8.2, 2000 (SAS Institute). Means and SDs were calculated for continuous variables, and statistical comparisons were made with Student t tests. Tests of normality used the Kolmogorov-Smirnov statistic. Pearson correlation coefficients were calculated for the correlation of BMI with FRS and individual risk factors. Categorical variables were compared with contingency table arrays and the χ² statistic. BMI was examined both as a continuous and categorical variable, the latter in order to examine for a threshold effect. Siblings were stratified into 9 FRS-BMI categories based on 3 FRS categories (low risk <10%, intermediate risk 10% to 20%, high risk >20%) and 3 BMI categories (normal, overweight, obese). Cox proportional hazards regression analyses with the use of generalized estimating equations (GEE) to adjust for familial correlations were used to determine independent predictors of the outcome variables.27 Likelihood ratio tests were used to determine whether GEE-adjusted Cox regression models that included BMI or BMI-FRS interaction terms provided a significantly better fit than did Cox regression models limited to FRS alone.

Results
The 827 siblings came from 469 families with mean (±SD) number of siblings 1.8 (±1.1) per family. The sibling population was middle-aged; half were women, and one fifth were black (Table 1). The group was generally well educated and had a high prevalence of hypertension, hypercholesterolemia, and smoking. The prevalence of diabetes was similar to that of the general population. Mean levels of total and LDL cholesterol as well as triglycerides were all in the border-line-high range, whereas the mean HDL cholesterol level was within normal range. The mean (±SD) FRS value was 8.9% (±7.1%), which is considered low risk.28 The majority of siblings (69%) were either overweight or obese at baseline.

Association of BMI With Cardiovascular Risk Factors
When the risk factors were examined individually, BMI was most closely correlated with diastolic blood pressure (r = 0.30), glucose (r = 0.29), HDL cholesterol (r = –0.23), triglycerides (r = 0.19) (all P < 0.0001), and education (r = –0.12, P = 0.0005). There was no correlation between BMI and age (r = 0.04, P = 0.21). There was a modest but statistically significant positive unadjusted correlation between BMI and FRS (r = 0.19, P = 0.0001).

Predicted and Observed CHD Event Rates in Siblings
Compared with siblings with normal weight (Figure 1A), those who were overweight or obese had increased predicted
10-year estimated FRS risk at baseline (sex-adjusted
P<0.001). During a follow-up of 8.7 years (±3.3), 13.3% of
siblings had incident CHD events (Figure 1B), with most of
these events (77%) occurring in siblings aged <60 years at
the time of the event. Event rates were higher in obese and
overweight siblings than in those with normal weight (15.3%
and 16.0% versus 8.1%, respectively; P<0.01).

Incremental Prognostic Value of BMI to FRS
BMI and FRS were each strongly associated with incident
CHD events (P<0.0001) in separate univariable Cox propor-
tional regression analyses that adjusted for familial correla-
tions. In a multivariable model that adjusted for FRS, race,
and familial correlations, BMI remained a significant predic-
tor of incident CHD events (Table 2). In this fully adjusted
model, for every 1-kg/m² increase in BMI, there was an
associated 4% increase in incident CHD events (P<0.02),
independent of FRS, race, and familial correlations. In 2
separate multivariable models of high BMI (categorical
variable defined as either ≥25 or ≥30 kg/m²) that adjusted
for FRS, race, and familial correlations, the independent
effect of overweight and obesity on incident CHD was of
similar magnitude. The adjusted hazard ratio for BMI ≥25
was 1.59 (95% CI, 0.99 to 2.55), and the hazard ratio for BMI
≥30 was 1.58 (95% CI, 1.07 to 2.31). In a Cox proportional
regression model that included BMI and triglycerides in the
same model, BMI remained significantly associated with
CHD risk (P<0.001).

When the siblings were stratified by baseline FRS risk
categories (Figure 2), overweight and obesity did not signif-
cantly alter CHD risk for siblings with FRS ≤20% (P>0.5
for both). However, a marked interaction between obesity and

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### TABLE 1. Baseline Characteristics of Siblings by Weight Categories

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (BMI 18.5–24.9)</th>
<th>Overweight (BMI 25–29.9)</th>
<th>Obese (BMI ≥30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.7±7.3</td>
<td>46.2±7.2</td>
<td>46.5±7.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.0±2.8</td>
<td>12.9±2.9</td>
<td>12.1±2.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Women, %</td>
<td>63</td>
<td>34</td>
<td>56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black, %</td>
<td>14</td>
<td>16</td>
<td>29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>41</td>
<td>27</td>
<td>27</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>24</td>
<td>44</td>
<td>67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>1</td>
<td>5</td>
<td>16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol medication, %</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.74±1.22</td>
<td>6.01±1.26</td>
<td>6.24±1.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.71±1.18</td>
<td>3.94±1.09</td>
<td>4.13±1.24</td>
<td>0.0004</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.45±0.44</td>
<td>1.27±0.39</td>
<td>1.20±0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.24±0.74</td>
<td>1.83±1.46</td>
<td>2.16±1.94</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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### Figure 1.

A, FRS by BMI categories. Sex-adjusted pairwise analyses showed that there was a significant difference in estimated FRS risk between normal and overweight, normal and obese, and overweight and obese groups (P<0.001 for all 3 comparisons). B, Observed CHD events during study follow-up (8.7±3.3 years) by baseline weight categories of the siblings (P=0.01). Sex-adjusted pairwise analyses showed that there was a significant difference between normal and overweight (P=0.04) and between normal and obese groups (P=0.02) for observed CHD events. There was no significant difference between overweight and obese groups (P=0.38).

### Table 2. Multivariable Cox Proportional Hazard Model* Predicting Incident CHD Events (n=827)

<table>
<thead>
<tr>
<th>Variable</th>
<th>ß-Coefficient (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>0.037 (0.016)</td>
<td>0.02</td>
</tr>
<tr>
<td>FRS, %</td>
<td>0.075 (0.009)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The multivariable model included BMI and FRS as continuous variables and race as a categorical variable and was GEE adjusted for nonindependence of families. Race was not a significant predictor of events. ß-Coefficients and SEs shown are per unit increment in BMI (kg/m²) and per unit increment in FRS (1% increase in 10-year predicted risk of CHD events).
TABLE 3. Multivariable Cox Proportional Hazard Model* Predicting Incident CHD Events in Siblings by Categories of FRS and BMI (n=827)

<table>
<thead>
<tr>
<th>FRS Category</th>
<th>BMI Category</th>
<th>No. of CHD Events/n</th>
<th>Hazard Ratios* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (FRS &lt;10%)</td>
<td>Normal weight</td>
<td>12/212</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>20/206</td>
<td>1.88 (0.92–3.83)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>8/124</td>
<td>1.67 (0.70–3.98)</td>
<td>0.24</td>
</tr>
<tr>
<td>Intermediate risk (FRS 10%–20%)</td>
<td>Normal weight</td>
<td>9/41</td>
<td>4.29 (1.86–9.91)</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>25/95</td>
<td>4.49 (2.27–8.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>18/86</td>
<td>5.41 (2.65–11.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High (FRS &gt;20%)</td>
<td>Normal weight</td>
<td>0/7</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>8/31</td>
<td>5.15 (2.17–12.19)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>10/25</td>
<td>14.63 (6.40–33.44)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The multivariable model was GEE adjusted for nonindependence of families and included the 9 BMI-FRS groups (represented as dummy variables) and race.
†Normal weight/low FRS was the reference group for all other groups.

Discussion

Our study is the first to show the adverse and independent impact of high BMI on CHD outcomes in apparently healthy siblings from families with premature CHD, particularly in those with the greatest FRS and clustering of multiple risk factors. BMI is not currently included in Framingham risk equations. High BMI was an independent predictor of increased CHD risk in our study, providing incremental prognostic value to FRS risk estimates. We also found that obesity, compared with overweight, carried similar increased relative risk for incident CHD risk in these apparently healthy siblings until they had a high FRS (>20%). In siblings who were high risk on the basis of having several risk factors, obesity resulted in a 14-fold increase in risk compared with normal-weight, low-risk siblings. Interestingly, the magnitude of genetic control of BMI in this population was found to be at most in the moderate range and even less so for blacks, suggesting that a large proportion of the variance in BMI can be explained by nongenetic or other factors that are not highly clustered. Thus, potentially modifiable factors that derive from lifestyle or environment may be contributing considerably to adult BMI in these families, particularly for blacks.

We have previously shown clustering of cardiovascular risk factors, including increased body weight, in these siblings. However, the extent to which overweight and obesity may contribute to their overall increased CHD risk was not known until this study. Excess body weight has previously been found to be a moderately strong risk factor for CHD in most population-based studies, in part through its impact on individual risk factors such as hypertension, diabetes, and dyslipidemia, but also independently. Prior data from the Framingham Study suggested that obesity may predispose to premature cardiovascular disease, although measures of adiposity are currently not included in FRS equations. In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, obesity was associated with accelerated atherosclerosis in autopsies of young men. Recently, obesity has been shown to affect the early development of atherosclerosis and shorten life expectancy.

Adipose tissue is metabolically active, secreting various adipocytokines such as leptin and tumor necrosis factor-α, which may influence the expression of CHD by promoting insulin resistance, chronic inflammation, thrombosis, oxidant stress, or chronic upregulation of sympathetic tone.
study of Finnish families with premature CHD, the clustering of risk factors associated with insulin resistance was more common in siblings who developed early-onset CHD compared with those who did not.37 Excess adiposity is also associated with atherogenic lipoprotein profiles (elevated triglycerides and low HDL cholesterol), although our study findings suggest that BMI predicts increased CHD risk independent of atherogenic remnant–rich lipoproteins.38 Interestingly, the relationship between the degree of obesity and the extent of metabolic abnormalities is heterogeneous, with largely unknown environmental, genetic, and gene–environment interactions that may potentially modify the effects of obesity on CHD risk.39

Obesity was highly prevalent in these families with premature CHD that constituted our study. Compared with a nationally representative American population in which the overall prevalence of overweight and obesity was 32.0% and 22.5%, the prevalence in these siblings was 40.1% and 28.4%, respectively, and was especially prevalent in women and blacks.23

To our knowledge, our study is the first to suggest that obesity may substantially increase the risk of CHD for siblings of probands with premature CHD, specifically for those with the highest FRS risk profiles. Overall, the observed event rates in the FRS categories were consistent with predicted estimates, suggesting that the use of FRS models in this biracial cohort was consistent with other cohorts of similar ethnic and racial composition.40 Incident CHD rates were higher in overweight than in normal-weight siblings, but being obese did not confer much excess risk beyond that conferred by overweight until a high FRS co-occurred together with obesity. One potential limitation to our study is that most of the siblings had low or intermediate FRS, with a small proportion of siblings in the high-FRS category. However, the interaction that we found between obesity and high FRS was highly statistically significant and improved the identification of siblings who were at higher risk of developing CHD. Because this was a relatively young population, the high-risk FRS siblings may also potentially be more enriched with multiple risk factors than a comparably high-risk population-based group, although data from Framingham also support the finding that there is a markedly increased risk when obesity and risk factor clusters coexist.41

Heritability estimates of weight or BMI have been derived predominantly from population- or family-based studies that were not enriched with familial CHD.42–46 Given the large proportion of blacks in our study, we were able to give estimates for the heritability of BMI not just in the white families but also in blacks. Our overall BMI heritability estimates were remarkably similar to estimates of heritability in population studies (40% to 50%).44,47 Although sharing a common familial environment may inflate the estimates of heritability, we found low to moderate heritability for BMI, which in turn represents the maximal possible contribution of additive genes. Thus, although genetic influences may account for up to half the variance of BMI, they are unlikely to account for substantially more than that. This suggests that the excessive prevalence of high BMI that was present in these families with premature CHD has a relatively small contribution from additive genes unique to these families. Instead, lifestyle and environmental factors, or gene–environment interactions, appear to be much more implicated in the development of overweight and obesity.

The important interaction between obesity and markedly increased global risk represents an opportunity for targeting those siblings who are at highest risk for CHD for the prevention and treatment of overweight and obesity as well as modifying other risk factors that place them at high risk. If this interaction between obesity and high global risk for developing CHD is demonstrated in other studies, then the potential public health implications may be far-reaching, especially for the millions of Americans who are becoming increasingly overweight and prone to the development of risk factors at younger ages.

In conclusion, siblings from families with premature CHD demonstrated a high prevalence of high BMI, which was independently associated with incident CHD events. When obesity co-occurred with multiple risk factors, there was a remarkable increase in CHD events. On the basis of measures of heritability, our study suggests that the genetic influence on adult BMI was in the moderate range. Nongenetic factors related to lifestyle and environment are likely to be much more influential in determining adult BMI in families with premature CHD. The findings in our study raise the possibility of a putative link between obesity and premature CHD that, if confirmed in future studies, may have important public health implications for the prevention of CHD in families.

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References


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