Heritability Estimates of Obesity Measures in Siblings With and Without Hypertension


Abstract—The goal of the present study was to evaluate mean values and heritability estimates of 3 global and 11 regional obesity measures in siblings with (HPT, n=209) or without (non-HPT, n=91) early-onset (age ≤55 years) hypertension who originated from the same families. Sixty-one sibships, each having at least 2 HPT siblings, were selected from a French-Canadian population with a known founder effect. Comparison of the mean values showed that HPT siblings are more obese than non-HPT siblings and that the body fat of HPT siblings is more centrally distributed. Significant differences were observed in all global obesity measures (P=0.009 to 0.0001). Among the regional measures, the most prominent differences were seen in waist circumference (P=0.00002), waist/hip ratio (P=0.0001), and suprailiac skinfold (P=0.00008). Comparison of the heritability estimates derived from sibling/sibling correlations (FCOR program, SAGE) suggested that genetic factors play a greater role in HPT (n=357) than in non-HPT (n=93) sib-pairs in determining most obesity measures. Similar to the mean values, these differences were most apparent in global and upper-body measures, with heritabilities ranging from 40% to 70% (P=0.05 to 0.0006) in HPT siblings and from 0% to 32% (P=NS) in non-HPT siblings. In summary, the present results suggest that HPT and non-HPT siblings drawn from the same families differ by the degree and distribution of body fat accumulation and that this difference is determined, at least in part, by genetic factors cosegregating with hypertension. This, in turn, suggests that a genetic link exists between obesity and hypertension in these families. (Hypertension. 2001;38:41-47.)

Key Words: obesity ■ hypertension, essential ■ genetics ■ siblings

Obesity is a major risk factor for the development of essential hypertension. A positive relationship between body weight and blood pressure has been demonstrated in both sexes and in people of different ethnic backgrounds.1–5 Studies suggest that not only the degree but also the distribution of accumulated body fat is an important risk factor for the development of hypertension.$^{6}$ It has long been recognized that the prevalence of hypertension is higher in individuals with upper-body obesity than in individuals with lower-body obesity.7,8 More recently, this difference has been related to the increased quantity of intra-abdominal visceral fat$^{9}$ that is frequently found in individuals with upper-body obesity.$^{10}$ Mechanisms of the relationship between visceral obesity and hypertension are not well understood. It has been proposed that, because visceral fat is characterized by a relatively high lipid turnover,$^{11}$ its accumulation may result in higher levels of free fatty acids in the portal circulation. This, in turn, may contribute to the development of hypertension via a number of disturbances, including the enhancement of lipid synthesis, gluconeogenesis, insulin resistance, and aldosterone production.$^{12–14}$

Genes play a significant role in the development of both obesity and hypertension.$^{14–16}$ In twins, it has been estimated that 29% to 77% of interindividual variance of various global and regional obesity-related traits$^{17–19}$ and 34% to 73% of interindividual variance of blood pressure can be explained by genetic factors.$^{20–22}$ Familial cross-trait correlations carried out in the Quebec Family Study$^{23}$ suggest that some of these genetic factors are involved in the regulation of both obesity-related traits and blood pressure. Consistent with the association of hypertension with upper-body obesity, most significant cross-trait correlations in that study were observed between diastolic blood pressure and measures of upper-body obesity.

The goal of the present study was to evaluate means and heritability estimates of 3 global and 11 regional obesity-related measures in siblings with (HPT) and without (non-HPT) early-onset hypertension. Both groups of siblings originated from the same sibships selected on the basis of having at least 2 HPT siblings with dyslipidemia from a French-Canadian population with a known founder effect.$^{24,25}$

Methods

The sibships investigated in the present study were selected from a geographically isolated population living in the Chicoutimi/Lac St...
Jean region in the Canadian province of Quebec. This population originates from a relatively limited number of ancestors of French descent who migrated to this region in the 19th century. Because of little migration thereafter and relatively high growth rates, this population today represents one of the largest isolated populations in North America. Several monogenic disorders have been shown to have a high prevalence in this population. For some of them, a founder effect has been identified.

Sibships were selected on the basis of having at least 2 affected siblings. Affected status was defined by the presence of early-onset hypertension and dyslipidemia and by the absence of secondary hypertension, body mass index (BMI) > 35 kg/m², diabetes mellitus, serum creatinine > 180 mmol/L, liver disease, malignancy, pregnancy, and substance abuse. HPT sibships were defined as those with diastolic blood pressure > 90 mm Hg on 2 occasions or those currently taking antihypertensive medication with documented hypertension in their medical records. Sibships with dyslipidemia were defined as those with total cholesterol ≥ 5.2 mmol/L or HDL cholesterol ≤ 0.9 mmol/L or those currently taking lipid-lowering medication with documented dyslipidemia in their medical records. In individuals older than 55 years, the onset of hypertension, dyslipidemia, and diabetes mellitus was determined from medical records. When at least 2 siblings in a sibship satisfied the above criteria, other siblings willing to participate in the study were also included. To ensure genetic homogeneity, only sibships with both parents of Catholic, French-Canadian origin were studied. Using these selection criteria, we collected a total of 61 sibships, with an average size of 4.9 ± 0.32 siblings. The sibships comprised a total of 300 siblings. In this cohort, the prevalence of early-onset hypertension, dyslipidemia, and diabetes mellitus was 69.7%, 69.7%, and 5.6%, respectively. The institutional ethics committee reviewed and approved the study. All subjects gave their informed consent.

The main goal of the present study was to compare mean values and heritability estimates of global and regional obesity measures in HPT siblings (n = 209) and non-HPT siblings (n = 91) originating from the same sibships. Although selection of the sibships was based on a number of inclusion and exclusion criteria (see above), HPT and non-HPT status was defined solely by the presence of early-onset (age ≤ 55 years) hypertension. Early-onset hypertension was chosen as the selection criterion on the basis of previous studies that suggested that genes play a more significant role in hypertension with onset at ≤ 55 years of age than in hypertension with onset at > 55 years. The non-HPT sibships included 82 normotensive siblings and 9 hypertensive siblings who had been diagnosed with hypertension at > 55 years of age. Eighty-three percent of HPT siblings and 60.8% of non-HPT siblings suffered from early-onset dyslipidemia (x² = 14.24, P = 0.0002). The HPT and non-HPT sibships did not differ by age (52.7 ± 0.49 and 51.9 ± 0.49 years, respectively), male/female ratio (97:112 and 46:45, respectively), and the prevalence of early-onset diabetes mellitus (6.2% and 2.2%, respectively).

Three global and 11 regional obesity-related measures were collected by standardized procedures. The global measures included BMI, total body fat (TBF) derived from skinfold measurements, and TBF determined by bioimpedance. Individual global measures were compared by Student’s t test. For HPT and non-HPT concordant sib-pairs, heritability estimates of obesity-related measures were derived from intraclass sibling/sibling correlations (r) computed with the FCOR program (version 2.1, SAGE package, Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio). For discordant sib-pairs (1 HPT and 1 non-HPT sibling), the estimates were determined from interclass sibling/sibling correlations. Statistical significance of r was determined as previously described. Assuming random mating and negligible covariance and interaction between phenotypic value and environmental deviation, heritability can be estimated as follows: ² = 2 x 100. Before correlation analysis, extreme outliers (> 3 SD from the mean) were excluded, and obesity measures were then adjusted for significant covariates by multiple linear regression. As covariates, age and gender were included in the regression of global obesity measures and skinfolds in non-HPT siblings, age, gender, and height were tested in the regression of circumferences.Sibling/sibling correlation analysis was carried out with equal weight to nuclear families.

**Results**

**Mean Values and Heritability Estimates of Obesity Measures in All Siblings**

The whole cohort of 300 siblings originating from 61 sibships was on average moderately overweight, including individuals with a wide range of adiposity (minimum BMI, 16.83 kg/m²; maximum BMI, 40.50 kg/m²) (Table 1). Heritability estimates of most global and regional obesity measures were ~ 40%. Among the global measures, the highest estimate was obtained for BMI (40%); the lowest estimate, for TBF derived from skinfold measurements (20%) (Table 1). The heritability estimates of circumferences ranged from 32% for the distal thigh to 42% for the upper arm and the waist/hip ratio; those of skinfolds, from 12% for the thigh to 54% for suprailiac skinfold (Table 1).

**Mean Values and Heritability Estimates of Obesity Measures in HPT and Non-HPT Siblings**

Analysis of all global and most regional obesity-related phenotypes indicated that HPT siblings are more obese than non-HPT ones. For the global obesity phenotypes, all differences were highly statistically significant, with probability values ranging from 0.009 for TBF determined by bioimpedance to 0.0001 for BMI (Figure 1). In circumferences and skinfolds, differences were more prominent in upper-body than in lower-body measures, with the most significant differences being observed in waist circumference (P = 0.00002) and suprailiac skinfold (P = 0.00008) (Figure 1). The waist/hip ratio, a commonly used index of upper-body obesity, was also significantly greater in HPT than in non-HPT siblings (P = 0.0001) (Figure 1).

Like the mean values, the heritability estimates of all global and most regional obesity measures were greater in HPT sib-pairs (sib-pairs concordant for the presence of early-onset hypertension, n = 249 to 357) than in non-HPT sib-pairs (sib-pairs concordant for the absence of early-onset hypertension, n = 46 to 93). Individual global measures were all virtually the same, being ~ 50% in HPT sib-pairs and 0% in non-HPT sib-pairs (Figure 2). Considering regional obesity measures, the heritability estimates were greater in HPT than in non-HPT sib-pairs for upper-body but not for lower-body measures (Figure 2). Thus, among circumferences, heritabilities of the upper arm, waist, hip, and waist/hip ratio were higher in HPT than in non-HPT sib-pairs; heritabilities of the proximal thigh and middle thigh did not differ; and heritability of the distal thigh was, in contrast, greater in non-HPT than in HPT sib-pairs (Figure 2). Among skinfolds, the heritability estimates of upper-body measures (ie, biceps, triceps, subscapular, and suprailiac skinfolds) were again higher in HPT than in non-HPT sib-pairs, and estimates of thigh skinfold did not differ between the 2 groups (Figure 2).

The heritability estimates of obesity-related measures obtained in discordant sib-pairs (1 HPT and 1 non-HPT sibling)
further supported the existence of a difference in genetic effects between HPT and non-HPT siblings. For most global and upper-body measures, the magnitude of genetic effects increased as the number of HPT siblings in the comparison increased (i.e., \( h^2_{\text{non-HPT,non-HPT}} < h^2_{\text{HPT,non-HPT}} < h^2_{\text{HPT,HPT}} \)) (Figure 2). This pattern of sibling/sibling correlations is typical for inferring dimorphism in genetic effects between 2 classes of siblings,23 which, in this case, are HPT and non-HPT siblings. Among global and upper-body measures, this dimorphic pattern was not observed for BMI and upper-arm circumference. It is noteworthy that these 2 obesity measures reflect not only the mass of adipose tissue but also the mass of other tissues, such as muscle and bone (Figure 2).

Taken together, the above results demonstrate that HPT siblings compared with non-HPT siblings are characterized by both a greater degree of obesity and a greater tendency for upper-body fat distribution. Furthermore, the heritability estimates of most global and upper-body measures, which ranged from 40% to 70% (\( P<0.05 \)), and 0% to 32% (\( P=\text{NS} \)) in HPT siblings and from 0% to 32% (\( P=\text{NS} \)) in non-HPT siblings, indicate that these differences may be explained by genetic factors existing mainly in HPT siblings.

Previous studies6 have suggested that the degree and distribution of body fat accumulation contribute independently to the development of hypertension. To test whether the differences in regional measures observed between HPT and non-HPT siblings in the present study are independent of overall obesity, individual circumferences and skinfolds were analyzed after adjustment for BMI (used as a surrogate for overall obesity). After this manipulation, most obesity measures were no longer significantly different. Only the waist/hip ratio, waist circumference, and suprailiac skinfold remained significantly greater in HPT siblings than in non-HPT siblings (Table 2). After adjustment for overall obesity, the heritability estimates of the waist/hip ratio and suprailiac skinfold also remained greater in HPT (44%, \( P<0.05 \), and 70%, \( P<0.001 \), respectively) than in non-HPT (0%, \( P=\text{NS} \), and 38%, \( P=\text{NS} \), respectively) sib-pairs. In discordant sib-pairs, the estimates were intermediate to those obtained in HPT and non-HPT sib-pairs (26%, \( P=\text{NS} \), and 64%, \( P<0.01 \)), suggesting again that a dimorphism in the genetic effects influencing central obesity exists between the 2 groups of siblings. The heritability estimate of waist circumference did not reach statistical significance in either HPT or non-HPT sib-pairs (Table 2). These results indicate that, when regional measures of adiposity are adjusted for overall obesity, the only differences between HPT and non-HPT siblings in body fat distribution are seen in measures of abdominal obesity. In addition, the results suggest that genetic factors play a more important role in determining this difference in HPT than in non-HPT siblings.

**Discussion**

The results of the present study demonstrate that HPT and non-HPT siblings drawn from the same families differ significantly by both degree and distribution of body fat accumulation and that genetic factors, which appear to exist mainly in HPT siblings, may be determinants of the difference. This suggests that a genetic link exists between hypertension and obesity in these families.

HPT siblings, compared with non-HPT siblings, were on average more obese and their body fat was more centrally

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**Table 1.** Mean Values and Heritability Estimates of Obesity-Related Measures in All Siblings

<table>
<thead>
<tr>
<th>Obesity-Related Measures</th>
<th>No. of Siblings</th>
<th>Mean ± SEM</th>
<th>No. of Sib-Pairs</th>
<th>Heritability Estimates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global obesity measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>297</td>
<td>27.59±0.26</td>
<td>898</td>
<td>40†</td>
</tr>
<tr>
<td>TBF, skinfolds</td>
<td>262</td>
<td>31.88±0.56</td>
<td>731</td>
<td>20</td>
</tr>
<tr>
<td>TBF, bioimpedance</td>
<td>211</td>
<td>28.85±0.76</td>
<td>517</td>
<td>36*</td>
</tr>
<tr>
<td><strong>Circumferences</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper arm, cm</td>
<td>290</td>
<td>32.89±0.24</td>
<td>809</td>
<td>42†</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>296</td>
<td>91.69±0.78</td>
<td>809</td>
<td>38*</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>293</td>
<td>101.02±0.48</td>
<td>809</td>
<td>42†</td>
</tr>
<tr>
<td>Waist/hip, cm/cm</td>
<td>296</td>
<td>0.90±0.01</td>
<td>809</td>
<td>42†</td>
</tr>
<tr>
<td>Proximal thigh, cm</td>
<td>286</td>
<td>58.07±0.32</td>
<td>809</td>
<td>38*</td>
</tr>
<tr>
<td>Middle thigh, cm</td>
<td>289</td>
<td>52.84±0.29</td>
<td>809</td>
<td>38*</td>
</tr>
<tr>
<td>Distal thigh, cm</td>
<td>286</td>
<td>40.40±0.24</td>
<td>809</td>
<td>32*</td>
</tr>
<tr>
<td><strong>Skinfolds, mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>258</td>
<td>17.53±0.67</td>
<td>678</td>
<td>16</td>
</tr>
<tr>
<td>Triceps</td>
<td>263</td>
<td>26.81±0.79</td>
<td>678</td>
<td>34*</td>
</tr>
<tr>
<td>Subscapular</td>
<td>260</td>
<td>26.14±0.64</td>
<td>678</td>
<td>40*</td>
</tr>
<tr>
<td>Suprailiac</td>
<td>262</td>
<td>24.96±0.66</td>
<td>678</td>
<td>54†</td>
</tr>
<tr>
<td>Thigh</td>
<td>259</td>
<td>31.03±1.01</td>
<td>678</td>
<td>11</td>
</tr>
</tbody>
</table>

*\( P<0.05 \); †\( P<0.01 \).
distributions. Significant differences were observed for all
global obesity measures. With respect to body fat distribu-
tion, most significant differences were seen in the waist/hip
ratio, waist circumference, and suprailiac skinfold. This was
the case both before and after adjustment for overall obesity.
These results are consistent with previous investigations6 that
demonstrated that both overall obesity and central distribu-
tion of body fat are independent risk factors for the develop-
ment of hypertension. They are also consistent with the
suggested role of intra-abdominal fat in hypertension, be-
cause the waist/hip ratio, waist circumference, and suprailiac
skinfold have been shown previously to be one of the best
anthropometric predictors of intra-abdominal visceral fat.31,32

In contrast to previous studies, which involved unrelated
individuals, the present investigation includes HPT and non-
HPT siblings originating from the same families. Such a
design allowed us to compare the 2 groups of siblings not
only with respect to mean values but also with regard to
heritability estimates. The latter analyses showed that most
global and upper-body measures demonstrate a greater heri-
tability in HPT than in non-HPT sib-pairs, whereas lower-
body measures either did not differ or showed a higher
heritability in non-HPT than in HPT sib-pairs. This indicates
that genetic factors play a greater role in determining the
degree of obesity in HPT than in non-HPT sib-pairs. They
also indicate that with respect to body fat distribution, these
factors make HPT siblings more susceptible to the develop-
ment of upper-body obesity. Heritability estimates of obesity-
related measures have not previously been compared in
siblings with and without hypertension. They have, however,
been determined in a Utah study33 that, like the present
investigation, involved families with 2 or more hypertensive
individuals. In the Utah study, all anthropometric measures
demonstrated a significant genetic component with a low and
insignificant family-shared environmental effect. The herita-
bility estimates, ranging from 17% to 36%, were similar to
those obtained here when both HPT and non-HPT siblings
were analyzed together (Table 1).

The finding that genetic factors determining obesity mea-
sures that have previously been related to an increased risk of
hypertension are present mainly in HPT siblings suggests that
a genetic link between hypertension and obesity exists in the

Figure 1. Comparison of global and regional
(circumferences and skinfolds) obesity mea-
sures in HPT and non-HPT siblings. Adjusted
values (mean±SEM) are shown as a percent-
age of the mean of the total sample. Statisti-
cally significant results of the 2-tailed Stu-
dent’s t test are indicated as follows:

*P<0.05, **P<0.01, ***P<0.001, and
****P<0.0001.
families investigated here. Such a link has been demonstrated previously. A common latent factor mediating the clustering of obesity, hypertension, and diabetes was identified in a sample of 2508 male twin pairs. Using multivariate genetic modeling, it was estimated that this common factor includes both genetic (59%) and environmental (41%) determinants. The environmental determinants appeared to be specific rather than shared by co-twins. In addition, the existence of genes with pleiotropic effects on both blood pressure and body fat accumulation was indicated in a study that, like the present investigation, involved French Canadians. There, significant familial cross-trait correlations have been observed between blood pressure and upper-body fat in primarily normotensive, nonobese families. Furthermore, a candidate gene study also investigating French Canadians identified a significant effect of the tumor necrosis factor-α gene locus on both obesity and obesity-associated hypertension in families selected for hypertension and dyslipidemia.

In addition to genetic factors, a significant impact of environmental influences on adiposity has been demonstrated in some studies. In the present investigation, heritability estimates of obesity-related traits were derived from sibling/sibling correlations. Heritability estimated in this way may reflect an impact of both genetic and family-shared environmental influences. The environmental influences are usually derived from mother/father correlations, because it is assumed that parents living in the same household (1) share environmental influences, including dietary and cultural habits, but (2) possess a different genetic makeup. The subjects of the present study were individuals who were 50 years old and who were drawn from families affected with early-onset hypertension and dyslipidemia. Both these disorders are associated with increased mortality; in most sibships, parents were not available for the study, and therefore, family-shared environmental influences could not be determined directly. Despite that, the results of our study provided some indirect evidence indicating that family-shared environment may not have a significant impact on certain obesity measures. For example, the heritability estimates of specific global and upper-body measures demonstrated a significant role of genetic factors in HPT but not in non-HPT siblings, even though both types of siblings originated from the same families and therefore were exposed to the same familial and cultural influences. A low and negligible impact of family-
shared environment on obesity-related phenotypes has been shown previously in some twin and family investigations. In our study, these investigations also involved age groups most likely living in separate households.

In summary, the results of the present study suggest that, in hypertensive families of French-Canadian origin, the presence of hypertension is associated with both an increased degree of adiposity and central distribution of body fat, and genetic factors cosegregating with hypertension appear to play a significant role in this association.

Acknowledgments

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References


### Table 2. Measures of Regional Body-Fat Distribution Adjusted for Overall Obesity in HPT and Non-HPT Siblings

<table>
<thead>
<tr>
<th>Regional Measures</th>
<th>Mean Values ± SEM</th>
<th>Heritability Estimates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPT Siblings</td>
<td>Non-HPT Siblings</td>
</tr>
<tr>
<td></td>
<td>(n=178–205)</td>
<td>(n=79–90)</td>
</tr>
<tr>
<td>Circumferences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper arm, cm</td>
<td>32.87±0.12</td>
<td>32.71±0.12</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>91.88±0.37</td>
<td>90.71±0.60</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>100.77±0.26</td>
<td>101.20±0.47</td>
</tr>
<tr>
<td>Waist/hip, cm/cm</td>
<td>0.909±0.004</td>
<td>0.895±0.006</td>
</tr>
<tr>
<td>Proximal thigh, cm</td>
<td>57.84±0.22</td>
<td>58.18±0.28</td>
</tr>
<tr>
<td>Middle thigh, cm</td>
<td>52.70±0.20</td>
<td>52.77±0.33</td>
</tr>
<tr>
<td>Distal thigh, cm</td>
<td>40.34±0.18</td>
<td>40.32±0.20</td>
</tr>
<tr>
<td>Skinfolds, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>17.39±0.58</td>
<td>17.69±0.90</td>
</tr>
<tr>
<td>Triceps</td>
<td>26.73±0.63</td>
<td>26.74±0.97</td>
</tr>
<tr>
<td>Subscapular</td>
<td>26.10±0.53</td>
<td>25.86±0.70</td>
</tr>
<tr>
<td>Suprailiac</td>
<td>25.60±0.37</td>
<td>23.00±0.95</td>
</tr>
<tr>
<td>Thigh</td>
<td>30.87±0.74</td>
<td>31.33±1.07</td>
</tr>
</tbody>
</table>

Statistical significance of both the 1-sided Student’s t test and heritability estimates derived from sibling/sibling correlations is indicated as follows: *P<0.05, †P<0.01, ‡P<0.001.


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