Sex Differences in the Contributions of Visceral and Total Body Fat to Blood Pressure in Adolescence

Zdenka Pausova, Amel Mahboubi, Michal Abrahamowicz, Gabriel T. Leonard, Michel Perron, Louis Richer, Suzanne Veillette, Daniel Gaudet, Tomas Paus

Abstract—Excess body fat deposited viscerally rather than elsewhere in the body is associated with higher risk for hypertension; this relationship is stronger in men than in women. Here we investigated whether similar sex dimorphism exists already in adolescence. A population-based sample of adolescent boys (n=237) and girls (n=262), age 12 to 18 years, was studied. Total body fat (TBF) was assessed with multifrequency bioelectrical impedance, and visceral fat (VF) was quantified with MRI. Blood pressure (BP) was measured beat by beat during an hour-long protocol, including supine, sitting, mental stress, and poststress sections. Multivariate mixed-model analysis was used to assess the relative contributions of TBF and VF to BP during these sections. In boys, BP was strongly positively associated with VF (P<0.0001), whereas it was less strongly and negatively associated with TBF (P=0.004); these relationships did not substantially vary during the protocol. In contrast, in girls, BP was strongly positively associated with TBF (P=0.0006), whereas it was not associated with VF (P=0.08); the relationship with TBF varied during the protocol and was most apparent during mental stress (TBF×section interaction: P=0.002). Furthermore, when waist circumference was included in multivariate models instead of VF, it was not associated with BP in either sex; this indicates that waist circumference may not be an appropriate surrogate for VF. Thus, in adolescence, adiposity-related BP elevation is driven mainly by visceral fat in males and by fat deposited elsewhere in females. This dimorphism suggests sex-specific mechanisms of obesity-induced hypertension and the need for sex-specific criteria of its prevention. (Hypertension. 2012;59:572-579.)

Key Words: abdominal obesity ■ blood pressure ■ adolescence ■ sex differences and mental stress

O
verweight and obesity have become a major health problem not only in adults but also in children and adolescents. In Canada and the United States, ≈60% of adults and 30% of adolescents are currently overweight or obese.1–4 In both countries, the proportion of obese adolescents has tripled over the last 30 years.4,5 This is alarming, because obesity is a leading risk factor for hypertension,6,7 which, in turn, is a major risk factor for cardiovascular disease,8–10 still the main cause of death in industrialized countries. It is estimated that, at a population level, 65% to 78% of adult hypertension can be attributed to obesity.11 The prevalence of hypertension is almost double in overweight and obese adults (35% to 50%) compared with normal weight individuals (23%).2 A strong association between excess body fat and high blood pressure (BP) exists already among children and adolescents, with clinical hypertension occurring in 34% of those who are obese (≥95th percentile).12

The association of obesity and hypertension is related not only to excess body fat but also to its distribution. For any given quantity of total body fat (TBF), adults who deposit fat viscerally rather than elsewhere in the body are at higher risk for hypertension,13,14 and this relationship is stronger in men than in women.14 In adolescence, the relative contribution of TBF and visceral fat (VF) to BP variation is not known. Furthermore, although it is well established that 24-hour ambulatory BP monitoring is a better predictor of target-organ damage than standard office BP,15–17 the relative contributions of TBF and VF to BP variation during daily life activities are not known in either adults or adolescents. Therefore, the aim of the present study was 2-fold, to investigate the relative contributions of TBF and VF to BP variation and sex differences and mental stress
hour-long cardiovascular protocol designed to mimic both a clinical setting and daily life activities, such as changes in posture and mental stress.

Methods

Adolescent Sample
Adolescent males (n=237) and females (n=262), all whites and aged 12 to 18 years, were recruited from the Saguenay-Lac St Jean region of Quebec, as part of the Saguenay Youth Study.18 The Saguenay Youth Study is an ongoing, population-based, cross-sectional study of cardiometabolic and mental health and its genetic modifiers in adolescence. All of the participants are recruited via local high schools. The Saguenay Youth Study is family based, focused primarily on recruitment of sibling pairs; this design is motivated by the fact it allows both genetic association and linkage studies.18 Information on parental history of hypertension was not ascertained. Written consent of the parents and assent of the adolescents were obtained before the commencement of data collection. The research ethics committee of the Chicoutimi Hospital approved the study protocol. The current sample consists of subjects recruited and tested between November 2003 and June 2009.

Body Fat Quantity and Distribution
Weight (0.1-kg precision), height (1-mm precision), and waist circumference (1-mm precision) were measured. Adolescents were defined as obese or overweight if their body mass index was ≥85th age- and sex-specific percentile of the Centers for Disease Control and Prevention body mass index curves (http://www.cdc.gov/growthcharts). TBF was assessed using multifrequency bioimpedance analysis (Xitron Technologies, San Diego, CA). Adolescents were asked to refrain from caffeine, alcohol, and vigorous activity 24 hours before the measurement. The measurement was made after a 20-minute stabilization period, during which the participants were resting in a supine position. Further details on the bioimpedance method of determining TBF are provided in the online-only Data Supplement. Correlations of TBF with other measures of body fat are presented in Figure S1 of the online-only Data Supplement.

VF and subcutaneous abdominal fat were measured with MRI, which is currently the only noninvasive (ie, without injection) method that can distinguish between VF and subcutaneous abdominal fat in population-based studies of children and adolescents.19,20 T1 relaxation time for adipose tissue is much shorter than that of most other tissues, and, thus, T1-weighted MRI produces images on which fat is very bright and easy to segment by semiautomated or automated techniques.21 Therefore, we measured volumes of VF and subcutaneous abdominal fat from a heavily T1-weighted, spin-echo scanner, as described previously.22 Adolescents were asked to refrain from caffeine, alcohol, and vigorous activity 24 hours before the measurement. The measurement was made after a 20-minute stabilization period, during which the participants were resting in a supine position. Further details on the bioimpedance method of determining TBF are provided in the online-only Data Supplement. Correlations of TBF with other measures of body fat are presented in Figure S1 of the online-only Data Supplement.

BP at Rest and in Response to Physical and Mental Challenges
All of the subjects underwent a 52-minute cardiovascular protocol, performed in a hospital setting on Saturdays between 8:00 AM to 12:00 PM. The protocol was not timed to any particular phase of the female menstrual cycle. The protocol, designed to mimic daily life activities, included a posture test (supine, standing, and sitting sections, each lasting 10 minutes) and a math stress test (2-minute stress and 10-minute stress recovery).23 Averages of these 5 consecutive sections were used in statistical analyses. Throughout the protocol, a noninvasive hemodynamic monitor, Finometer (FMS Finapres, Amsterdam, the Netherlands), was used to continuously record finger blood flow. The Finometer derives beat-to-beat brachial systolic and diastolic BPs (SBP and DBP, respectively) from the reconstructed and level-corrected finger blood flow waveform. Finometer is a reliable device for tracking BP in adults and children ≥6 years of age.24,25 Adolescents were defined as hypertensive if their sitting SBP or DBP was ≥95th age-, sex-, and height-specific percentile reported in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.26

Serum Estradiol
Blood samples were taken between 8:00 and 9:00 AM after overnight fasting. Serum concentration of estradiol was assayed at the clinical biochemistry department of the Hôtel-Dieu Hospital (Montreal, Quebec, Canada). Note that, because of menstrual cycle-related variations in serum estradiol in females, serum estradiol was measured only in males.

Questionnaires
Subjects completed a self-report of pubertal development using the Puberty Development Scale,27 which is an 8-item self-report measure of physical development based on the Tanner stages with separate forms for males and females. For this scale, there are 5 categories of pubertal status: (1) prepubertal; (2) beginning pubertal; (3) midpubertal; (4) advanced pubertal; and (5) postpubertal. Participants answer questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males. Shirkiff et al28 compared self-ratings and physician ratings of pubertal development and found significant correlations between adolescent self-rating and physician’s rating, ranging from 0.63 to 0.68. In addition, serum-free testosterone, which reflects gonadal development, correlates with self-rated pubertal stage in boys (r=0.66; P<0.0001).29 Therefore, the self-rated puberty development scale likely provides a valid measure of pubertal development. In addition, parents completed questionnaires ascertaining information on, among others, socioeconomic status (family income). The questionnaire was administered by a research nurse during a home visit.18

Statistical Methods
Descriptive statistics used to characterize the study population included means and SEs for continuous variables and proportions for categorical variables. Our main analyses focused on estimating the relative contributions of TBF and VF to the variations in SBP and DBP during a cardiovascular protocol consisting of 5 consecutive sections (ie, supine, standing, sitting, stress, and poststress), while adjusting for interindividual differences in age and height and, in addition, models, also in puberty stage and subcutaneous abdominal fat. Age and height were included in all of the models, because they are standard clinical correlates of BP in children and adolescents.30,31 In all of the analyses, we relied on the multivariable mixed linear model to account for clustering of observations within families (ie, for the correlations of the outcomes between siblings). The mixed linear model extends the conventional linear regression of continuous outcomes to correlated data.32 In addition, the mixed linear-model analyses of repeated-measure data handle well any data that are missing because of subject failure to complete some of the repeated-measure assessments.33 For each outcome, a preliminary analysis involved assessing the normality assumption, on which the statistical inference about the mixed linear model estimates relies. TBF, VF, and subcutaneous abdominal fat had positively skewed distributions and were log transformed, using logarithm with base 10, which improved the fit. Analyses were done separately in boys and girls. SBP and DBP were measured repeatedly over 5 experimental sections (ie, supine, standing, sitting, stress, and stress recovery). In addition to accounting for sibling clustering within families, the mixed-model analyses of these repeated measures had to account for the interdependence of repeated outcome measures for the same subject. This was achieved by specifying the assessment time (ie, “section”) as a repeated factor in the mixed model and assuming autoregressive order 1 covariance structure of the within-subject residuals, which implied that measurements that were closer in time correlated more strongly.34 Furthermore, we considered a possibility that the putative effects of TBF and VF might also differ among the 5 sections. Therefore, for each repeated-measures outcome, we have
Results

Relevant characteristics of adolescent boys (n=237) and girls (n=262) are provided in Table 1 and Table S1 (available in the online-only Data Supplement). The prevalence of overweight or obesity (≥85th age- and sex-specific percentile) was 29% in boys and 21% in girls, which is similar to that in the Canadian adolescent population at large (2004 Canadian Community Health Survey). The prevalence of hypertension (sitting SBP or DBP ≥95th age, sex- and height-specific percentile) was 7.1% in boys and 3.3% in girls, which is also similar to that in the Canadian adolescent population at large.35

The main aim of the current study was to investigate, in males and females, the relative contributions of TBF and VF expanded the multivariable mixed model by including a series of 2-way interactions between either TBF or VF and indicators of each section. Then, an “omnibus” Wald-like test, on 4 degrees of freedom, was used to test the significance of the joint effect of the 4 interaction terms involving the same characteristic (TBF or VF). If the omnibus test yielded a 2-tailed P value <0.05, this was considered as evidence of significant differences between the section-specific effects of the variable on a given outcome. Then, we assessed the change in the respective estimates to examine whether and to what extent the effects of TBF and VF on these outcomes might be modified by additional adjustment for puberty stage and subcutaneous abdominal fat.

To evaluate usefulness of waist circumference as a possible surrogate for VF, we then reran all of the previous analyses replacing VF by waist circumference, log transformed using logarithm with base 10. The goodness of fit of the 2 alternative models was then compared to assess which variable was better in capturing the hypothesized associations.
to BP variation, while adjusting for interindividual differences in age and height, standard clinical correlates of BP in children and adolescents. These multivariate analyses showed that, in boys, SBP was positively associated with VF ($P<0.0001$), whereas at the same time, it was negatively albeit less strongly associated with TBF ($P=0.004$; Figure 1). In girls, a very different pattern was observed. SBP was related to TBF only ($P=0.0006$), and this relationship was, in contrast to boys, positive (Figure 1). These results indicate that, in boys, VF is a substantially more important predictor of SBP than TBF and remains highly significant even after adjusting for TBF; VF itself explains $4.3\%$ of the total variation in SBP, whereas TBF explains only $1\%$ of this variation. In girls, in contrast, TBF is a more important predictor of SBP.
Table 2. Univariate Associations Between Systolic Blood Pressure and Each Total Body Fat and Visceral Fat in Boys and Girls

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Body Fat*</td>
<td>Visceral Fat*</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>SBP supine</td>
<td>3.21</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP standing</td>
<td>1.45</td>
<td>0.15</td>
</tr>
<tr>
<td>SBP sitting</td>
<td>1.49</td>
<td>0.14</td>
</tr>
<tr>
<td>SBP stress</td>
<td>3.37</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP stress recovery</td>
<td>2.81</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data were analyzed with univariate mixed-linear model. SBP indicates systolic blood pressure.

*Data were log transformed.

predictor of SBP than VF and remains highly significant even after adjusting for VF; TFV itself explains ≈1.8% of the total variation in SBP, whereas VF explains only <1.0% of this variation. Interestingly, these sex-specific contributions of TFV and VF to SBP may not be driven by sex differences in the quantity of the 2 fat depots, because, for example, the quantity of VF did not significantly differ between boys and girls (Table 1), and yet it was positively associated with SBP in boys and not in girls (in both multivariate [Figure 1] and univariate [Table 2] analyses).

In boys, the opposing relationships of SBP with TFV and VF remained similar across all 5 of the sections of our protocol (supine, standing, sitting, stress, and poststress), as indicated by a modest interaction of TFV with section (P=0.04) and no interaction of VF with section (P=0.27; Figure 1). In girls, the positive relationship of SBP with TFV varied across the protocol (TFV* section interaction: \( P=0.0002 \)), being most pronounced during mental stress (Figure 1).

The multivariate relationships of SBP with TFV and VF were similar after additional adjustment for puberty stage in boys (TFV: \( P=0.02 \); VF: \( P<0.0001 \)) and girls (TFV: \( P=0.003 \)) and remained significant even after additional adjustment for subcutaneous abdominal fat in boys (TFV: \( P=0.02 \); VF: \( P=0.002 \)) and not in girls (TFV: \( P=0.54 \)). Finally, the multivariate relationships of SBP with TFV and VF were similar but less pronounced for DBP (Figure S2).

Waist circumference is considered a clinically useful proxy of visceral adiposity. Therefore, we examined whether there is the same relationship between BP and waist circumference as seen with VF. These analyses showed that, when waist circumference instead of VF is included, SBP is not associated with either waist circumference or TFV in either boys or girls (Figure 2). These results indicate that waist circumference, as a clinical measure of abdominal obesity, does not capture the BP variance associated with visceral adiposity and, as such, may not be an appropriate surrogate of VF in adolescence.

Finally, we examined whether the inverse association of BP with TFV that we observed in the multivariate model in boys could be related to findings of previous studies suggesting that, in obese boys, peripheral adipose tissue may be an important source of estradiol,36,37 which can lower BP.38 We found that boys with “high” versus “low” peripheral adiposity (defined as TFV adjusted for VF) had higher serum estradiol (\( P=0.036 \)) and similar SBP (\( P=0.10 \); Figure S3). On the other hand, boys with high versus low visceral adiposity (defined as VF adjusted for TFV) had similar serum estradiol (\( P=0.40 \)) but higher SBP (\( P=0.0007 \); Figure S3). These findings give some credence to the possible protective effect of estradiol (produced by peripheral fat) vis-à-vis BP in adolescent boys.

Discussion

Our results provide evidence of a marked sexual dimorphism in the relationships of visceral and peripheral fat to BP variation in adolescence: in boys, adiposity-associated elevation in BP is enhanced by excess visceral adiposity and attenuated by excess peripheral adiposity, whereas in girls, it is not influenced by visceral adiposity and it is enhanced by excess peripheral adiposity. Our results suggest that waist circumference, when included in multivariate models instead of VF, is not associated with BP and, as such, may not be an appropriate surrogate for VF in adolescence.

The marked sex differences in the relative contributions of VF and TFV to BP that we observed here in adolescents have not been reported previously; we showed that VF (independent of TFV) is associated with BP only in boys and that the association between TFV (independent of VF), and BP is of the opposite direction in boys and girls, respectively (Figure 1). VF is rarely measured directly (with MRI) in adolescents in sample sizes exceeding tens of participants,20,39,40 and the relative contributions of VF and TFV to BP have not been studied separately in adolescent boys and girls but only when pooled together.39 In the latter case, it was shown that neither TFV nor VF is significantly related to BP when the 2 variables are considered together and sex is treated as a confounding variable.39 Given our findings, these results are not surprising, because the opposite direction of these relationships in males and females would cancel each other in sex-pooled samples. Consistent with this prediction, we found no significant relationship between TFV and BP and only modest relationship between VF and BP when males and females were pooled together and sex was considered as a confounder (Figure S4).

The mechanisms of the observed sex differences are not clear at present, although previous research suggests that sex hormones may be involved. In the present study, VF was associated with BP in male but not female adolescents.
This difference could be related to the stronger VF-associated sympathoactivation\textsuperscript{41,42} seen in young boys versus girls\textsuperscript{22,43}, perhaps driven by raising levels of testosterone during male puberty\textsuperscript{44}. Thus, for example, a functional variant in the androgen receptor gene, which mediates androgenic effects testosterone, has been associated not only with higher VF but also with higher sympathetic vasomotor tone and BP in adolescent males but not females\textsuperscript{45}.

In the present study, we observed that excess peripheral fat (defined here as TBF adjusted for VF) in boys attenuates the overall positive association between body fat and BP (Table 2). This observation is consistent with a previous study demonstrating that elevated peripheral fat reduces the risk for metabolic syndrome, which includes hypertension as its component, in adult men with high VF\textsuperscript{46}. Although the underlying mechanisms are not clear, excess peripheral fat...
has been associated with higher serum estrogens in obese adult men,37,47 and estrogens have BP-lowering effects.38 In men, adipose tissue can produce estrogens by converting testosterone to estradiol by aromatase, which is an enzyme found at higher concentrations in peripheral compared with VF.39 Consistent with this previous research, our preliminary results showed that, in males with high versus low peripheral adiposity, serum estradiol is higher and SBP does not differ, whereas in males with high versus low visceral adiposity, serum estradiol does not differ and SBP is higher by >5 mm Hg (Figure S3). Further research is required into the role of adipose tissue-produced estrogens in BP regulation in males.

Our results, demonstrating that waist circumference, when included in multivariate models instead of VF, is not associated with BP in either sex, suggest that waist circumference may not be an appropriate surrogate for VF in adolescence. This finding is consistent with previous studies in adults showing that VF quantified directly with MRI or computed tomography is associated with BP above and beyond traditional anthropometric measures of obesity, including waist circumference.13,14,46,48,49

Finally, we showed that, in boys, adiposity-BP relationships were present during both physical and mental challenges, whereas, in girls, they were seen mainly during mental challenges. Active standing, which we used as a physical challenge, is expected to activate the sympathoadrenal system, whereas the math stress, which we used as a mental challenge, is assumed to activate both the sympathoadrenal and hypothalamo-pituitary-adrenal systems. It has been shown previously that the hypothalamo-pituitary-adrenal axis is hyperresponsive to stress in obese premenopausal women.50,51 Whether this characteristic contributes to the adiposity-BP relationship that we observed in females during mental stress requires further research.

Perspectives

Our results suggest that, in adolescence, BP elevation associated with excess body fat is driven mainly by VF in males and by fat deposited elsewhere in females. The presence of this sexual dimorphism suggests sex-specific mechanisms of obesity-induced hypertension, thus indicating the need for sex-specific prevention and treatment strategies of this disease in this age category.

Acknowledgments

We thank the following individuals for their contributions in acquiring data: Manon Bernard (database architect, Hospital for Sick Children), Jacynthe Tremblay and her team of research nurses (Saguenay Hospital), Helene Simard and her team of research assistants (Cégep de Jonquière), and Rosanne Aleong (program manager, Rotman Research Institute).

Sources of Funding

The Canadian Institutes of Health Research (Z.P., T.P.), Heart and Stroke Foundation of Quebec (Z.P.), and the Canadian Foundation for Innovation (Z.P.) fund the Saguenay Youth Study. M.A. is a James McGill Professor of Biostatistics at McGill University.

Disclosures

None.

References

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_Hypertension_. 2012;59:572-579; originally published online January 30, 2012; doi: 10.1161/HYPERTENSIONAHA.111.180372

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Sex differences in the contributions of visceral and total body fat to blood pressure in adolescence

Running title: Visceral fat and blood pressure in adolescence

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Multi-frequency bioimpedance analysis

The multi-frequency bioimpedance system we employed uses a 500μA current and measures resistance and reactance at frequencies between 4 kHz and 1 MHz. Complex bioimpedance is determined according to the Cole-Cole (1) model extended by De Lorenzo (2) as follows:

\[
Z_{obs} = \left( \frac{R_E}{R_E + R_i} \right) \left[ R_i + \frac{R_E}{1 - (j \omega C_M (R_E + R_i))^\alpha} \right] e^{j \omega T_0}
\]

where \(Z_{obs}\) is the observed complex impedance; \(R_E, R_i\) and \(C_M\) are the component values of the circuit; \(\omega\) is frequency in radians/sec; \(j\) is \(\sqrt{-1}\); volumes are predicted from the modeled \(R_E\) and \(R_i\), using equations formulated from Hanai mixture theory (3).
REFERENCES


Table S1. Non-normally distributed characteristics of adolescent males and females

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males (n=237)</th>
<th>Females (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>60.5 (28.8-110.9)</td>
<td>54.3 (28.2-99.0)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>21.0 (13.9-35.6)</td>
<td>20.7 (14.2-34.9)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>72.5 (55.0-118.0)</td>
<td>68.0 (52.0-11.0)</td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>8.6 (1.7-39.0)</td>
<td>12.7 (1.7-41.8)</td>
</tr>
<tr>
<td>Visceral fat (cm$^3$)</td>
<td>15.7 (2.9-144.7)</td>
<td>19.0 (2.9-89.8)</td>
</tr>
<tr>
<td>Subcutaneous abdominal fat (cm$^3$)</td>
<td>57.0 (12.0-518.2)</td>
<td>109.4 (22.0-439.8)</td>
</tr>
</tbody>
</table>

Median (minimum-maximum) values are shown.
Figure S1: Pair-wise correlations of total body fat determined by bioimpedance, visceral fat measured with magnetic resonance imaging and other measures of body fat in males (A) and females (B).
Figure S2: Multivariate relationships of diastolic blood pressure (DBP) with total body fat and visceral fat in males and females. Multivariable mixed linear model was used to estimate the relative contribution (model coefficient with 95% confidence interval) of total body fat and visceral fat to DBP, while adjusting for inter-individual differences in height. DBP means of 5 consecutive sections of a 52-minute cardiovascular protocol (i.e. supine, standing, sitting, stress and post-stress) were included in these analyses as repeated measures. Representative scatter plots of the multivariate associations of DBP with visceral fat and total body fat are also shown; for this purpose, the sitting section of the protocol was chosen.
Figure S3: Morning serum estradiol and systolic blood pressure (SBP) in males with “high” versus “low” peripheral and visceral adiposity. Males with above median (“high”) and below median (“low”) peripheral and visceral adiposity were compared; the differences were adjusted for age and puberty (and height in case of SBP). Peripheral adiposity was defined as total body fat (TBF) adjusted for visceral fat (VF), and visceral adiposity was defined as VF adjusted for TBF. Blood samples were taken between 8:00 and 9:00 AM after overnight fasting. Serum concentration of estradiol was assayed at the Clinical Biochemistry Department of the Hôtel-Dieu Hospital, Montreal, Canada. SBP means of 5 consecutive sections of a 52-minute cardiovascular protocol (i.e. supine, standing, sitting, stress and post-stress) were included in these analyses as repeated measures.
Figure S4: Multivariate relationships of systolic blood pressure (SBP) with total body fat and visceral fat in males and females together. Multivariable mixed linear model was used to estimate the relative contribution (model coefficient with 95% confidence interval) of total body fat and visceral fat to SBP, while adjusting for inter-individual differences in height. SBP means of 5 consecutive sections of a 52-minute cardiovascular protocol (i.e. supine, standing, sitting, stress and post-stress) were included in these analyses as repeated measures. Representative scatter plots of the multivariate associations of SBP with visceral fat and total body fat are also shown; for this purpose, the sitting section of the protocol was chosen.