Intra-abdominal Adiposity and Individual Components of the Metabolic Syndrome in Adolescence

Sex Differences and Underlying Mechanisms

Catriona Syme, MSc; Michal Abrahamowicz, PhD; Gabriel T. Leonard, PhD; Michel Perron, PhD; Alain Pitiot, PhD; Xi Qiu, MSc; Louis Richer, PhD; John Totman, MSc; Suzanne Veillette, PhD; Yongling Xiao, MSc; Daniel Gaudet, MD, PhD; Tomas Paus, MD, PhD; Zdenka Pausova, MD

Objective: To investigate the association between intra-abdominal adiposity and individual components of the metabolic syndrome (MS) in adolescent males and females.

Design: Cross-sectional study of a population-based cohort.

Setting: Saguenay Youth Study, Quebec, Canada.

Participants: A total of 324 adolescents, aged 12 to 18 years.

Intervention: Measures were compared between males and females with “high” or “low” intra-abdominal fat (IAF).

Main Outcome Measures: Intra-abdominal fat was quantified with magnetic resonance imaging. Primary outcome measures were blood pressure (BP) and fasting serum glucose, insulin, lipids, and C-reactive protein levels. Secondary mechanistic measures were cardiovascular variability indexes of autonomic nervous system function, pubertal development, and serum levels of cortisol, leptin, and sex hormones.

Results: The MS was completely absent in adolescents with low IAF and was present in 13.8% of males and 8.3% of females with high IAF. Excess IAF was associated with a higher homeostasis model assessment index (0.5 [95% confidence interval (CI), 0.3 to 0.8]; P < .001) and triglycerides level (17.7 mg/dL [to convert to millimoles per liter, multiply by 0.0113] [95% CI, 9.7 to 25.7 mg/dL]; P < .001), lower high-density lipoprotein cholesterol level (−3.9 mg/dL [to convert to millimoles per liter, multiply by 0.0259] [95% CI, −6.2 to −1.5 mg/dL]; P = .003), and higher C-reactive protein level (0.03 mg/L [to convert to nanomoles per liter, multiply by 9.524] [95% CI, 0.01 to 0.05 mg/L]; P = .003). High IAF was associated with elevations of BP and sympathetic activity in males only (higher systolic BP, 6 mm Hg [95% CI, 1 to 11 mm Hg]; P = .02 and low-frequency power of diastolic BP, 629 mm Hg2 [95% CI, 37 to 1222 mm Hg2]; P = .04).

Conclusions: Our results suggest that, already in adolescence, accumulation of IAF may promote development of the MS, affecting the metabolic and inflammatory components similarly in both sexes but influencing BP adversely only in males. The latter may be attributed, in part, to the augmentation of sympathetic activity also seen only in males.


Obesity is a leading cause of the metabolic syndrome (MS), defined by the co-occurrence of intra-abdominal obesity, atherogenic dyslipidemia, raised blood pressure (BP), insulin resistance and/or glucose intolerance, and a proinflammatory state. In the industrialized world, its prevalence is increasing. Based on criteria proposed by the World Health Organization and the Third Report of the National Cholesterol Education Program’s Adult Treatment Panel, an estimated 47 million individuals in the United States have the syndrome. Moreover, the syndrome, typically regarded as a middle- to late-adulthood disorder, is now present in childhood and adolescence. Population-weighted estimates from a study conducted between 1988-1994 indicate that, in the United States, nearly 30% of obese adolescents have the MS.

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It has long been recognized that upper-body compared with lower-body obesity is more closely associated with cardiovascular and metabolic abnormalities of the MS. More recently, this difference has been re-
lated to the increased quantity of intra-abdominal fat (IAF) that is frequently found in individuals with upper-body obesity. Underlying mechanisms linking intra-abdominal obesity to development of the MS are not well understood. Accumulation of visceral fat, characterized by a relatively high lipid turnover, may result in higher levels of free fatty acids in the portal circulation. This, in turn, may contribute to the development of individual components of the MS via, for example, enhanced lipid synthesis, gluconeogenesis, and insulin resistance. Furthermore, IAF correlates positively with activation of the sympathetic nervous system, which may further enhance free fatty acid release into portal circulation. Sympathoactivation may also contribute to the elevation of BP through its effects on vasculature and renal handling of sodium and water.

The aim of the present study was to investigate the impact of IAF, assessed with magnetic resonance imaging (MRI), on individual components of the MS in a population-based cohort of 324 adolescent males and females. We also examined whether the autonomic nervous system, assessed with power spectral analysis of beat-to-beat BP and interbeat interval (IBI), contributes to these effects.

METHODS

STUDY SITE AND POPULATION

Adolescents, aged 12 to 18 years, were recruited in a remote, French-Canadian population as part of the Saguenay Youth Study; all subjects were white. This is an ongoing, cross-sectional, family-based (adolescent sibships) investigation of the long-term consequences of prenatal exposure to maternal cigarette smoking (PEMCS) on cardiovascular and metabolic health and on the brain and behavior in adolescence; details on subject ascertainment are described elsewhere. Adolescence was chosen as a period when initial stages of cardiovascular and metabolic abnormalities may become apparent and are not yet altered by confounding variables such as medication. The outcomes studied in this article were not prespecified but were included in the Saguenay Youth Study protocol from its outset. Because PEMCS has been implicated in increasing the risk for obesity, we included PEMCS as a covariate in all analyses. The Research Ethics Committee of the Chicoutimi Hospital approved the study protocol.

CURRENT SAMPLE

The current sample consists of 324 subjects recruited and tested between November 2003 and December 2006. At the time of analysis, 408 subjects had undergone the study protocol, but 63 subjects were excluded because of technical issues, 17 subjects did not or could not complete the protocol (eg, following dizziness due to postural hypotension or need to urinate), and 2 subjects had poor-quality recordings throughout the protocol.

QUANTITATIVE PHENOTYPING

Quantity and distribution of body fat were assessed with (1) MRI, (2) anthropometry, and (3) bioelectrical impedance. Ten axial slices, 10-mm thick, were acquired in a Phillips 1.0-T magnetic resonance scanner. Adipose tissue was imaged with a heavily T1-weighted, single breath-hold spin-echo sequence. A single slice at the level of the umbilicus was selected for quantification of abdominal fat. Images were smoothed using an adaptive bilateral filter to remove image noise while preserving edge information. An initial fat classification map was obtained using a standard region-growing algorithm. An iterative refinement procedure corrected false positives and false negatives using a battery of morphological operators, including hysteresis, thresholding over small neighborhoods, and median filtering to remove salt and pepper noise. The resulting classification map was manually segmented into subcutaneous abdominal fat (SAF) and IAF. Subcutaneous abdominal fat was defined as areas of adipose tissue lying between the skin surface and the outer aspect of the muscle layer of the abdominal cavity, and IAF was defined as adipose tissue lying within the innermost aspect of the abdominal cavity and not contained within other abdominal organs or muscles. A histogram counting algorithm computed the total number of voxels for each type of fat. This semiautomated method was validated against manual segmentation in 20 randomly selected subjects (SAF, r² = 0.99; IAF, r² = 0.97). (2) Trained nurses measured weight (0.1-kg precision), height (0.1-cm precision), waist and hip circumferences (0.1-cm precision), and suprailiac skinfold (1-mm precision) 3 times. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. (3) Multifrequency bioimpedance analysis was used to estimate total body fat (Xitron Technologies, Inc, San Diego, California). Subjects were asked to refrain from caffeine, alcohol, and vigorous activity 24 hours before the measurement.

SERUM BIOCHEMICAL ANALYSES

A fasting blood sample was drawn between 8 AM and 9 AM. The sample was evaluated for glucose and lipid metabolism (glucose [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0555], insulin [to convert microinternational units to picomoles per liter, multiply by 6.945], triglycerides [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0113], and high-density lipoprotein [HDL] cholesterol [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259]), and creatinine (to convert milligrams per deciliter to micromoles per liter, multiply by 88.4). Serum proinflammatory state (C-reactive protein [CRP] level [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0113], triglycerides [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259], and high-density lipoprotein [HDL] cholesterol [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259]), and creatinine (to convert milligrams per deciliter to micromoles per liter, multiply by 88.4). Serum proinflammatory state (C-reactive protein [CRP] level [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0113], triglycerides [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259], and high-density lipoprotein [HDL] cholesterol [to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259]), and creatinine (to convert milligrams per deciliter to micromoles per liter, multiply by 88.4).
CARDIOVASCULAR MEASUREMENTS

All subjects underwent a 53-minute cardiovascular protocol involving simple physical and mental challenges intended to evoke cardiovascular responses. The physical challenge was a change in posture from supine (10 minutes) to standing (10 minutes) and from standing to sitting (10 minutes). The mental challenge was a sequence of 46 simple arithmetic problems to be solved aloud. The level of difficulty progressively increased to ensure some failure for all subjects.32 Throughout the protocol, conducted in a hospital setting on Saturdays between 8 AM and 12 PM, a noninvasive hemodynamic monitor (Finometer; FMS Nijmegen, Amsterdam, the Netherlands) was used to continuously record finger blood flow. The Finometer derives beat-to-beat brachial systolic BP (SBP) and diastolic BP (DBP), IBI, and its inverse, heart rate (HR).

ASSESSMENTS OF AUTONOMIC NERVOUS SYSTEM FUNCTION

Power spectral analysis of IBI and DBP is a well-established means of estimating cardiovascular autonomic nervous system activity.16,27 Power spectral analysis of IBI and DBP was carried out for 8 two-minute periods of the cardiovascular protocol: supine, standing 1, standing 2, sitting 1, sitting 2, sitting 3 (pre–math test), math test, and post–math test. For each period, beat-to-beat time series of IBI and DBP were interpolated using a piecewise cubic spline method, resampled at a frequency of 5 Hz and detrended before being transformed by a 1024-point fast Fourier transform,26 using standard Matlab functions (Matlab 7.3.0; MathWorks, Inc, Natick, Massachusetts). Low-frequency (LF) and high-frequency (HF) spectral powers were determined by integrating the power spectrum between 0.04 and 0.15 Hz and between 0.15 and 0.4 Hz, respectively; HFIBI and LFDBP were considered proxies of parasympathetic27 and sympathetic nervous system activity,20,30 respectively.

DEFINING THE MS

Subjects were classified as having the MS if they had 3 or more of the following 5 conditions: (1) SBP and/or DBP in the 95th (age-, sex-, and height-specific) percentile or higher,31 using the US Centers for Disease Control and Prevention growth charts (http://www.cdc.gov/growthcharts); (2) BMI in the 95th (age- and sex-specific) percentile or higher of the Centers for Disease Control and Prevention BMI curves4; (3) fasting glucose and sex-specific) percentile or higher,31 using the US Centers for Disease Control and Prevention BMI curves5; (3) fasting glucose and sex-specific) percentile or higher,31 using the Centers for Disease Control and Prevention growth charts of parasympathetic27 and sympathetic nervous system activities change rapidly to meet the demands made on the heart and vasculature in response to physical and mental challenges, such as those presented in our protocol.34 Accordingly, LFIBI and HFIBI were analyzed separately for each period. We used a multiple linear regression model including IAF, sex, their interaction, and the covariates menarche, or food intake (Table 1).

RESULTS

CHARACTERIZATION OF ADOLESCENTS WITH HIGH OR LOW IAF

Males and females were classified as having high or low IAF based on the median IAF: 14 050 mmHg in males and 19 507 mmHg in females. Subjects with high vs low IAF (both males and females) were significantly older, taller, and more advanced in terms of sexual maturation (Table 1) but did not differ by SES, PEMCS, physical activity, or food intake (Table 1).

BODY-FAT QUANTITY AND DISTRIBUTION IN ADOLESCENTS WITH HIGH OR LOW IAF

As expected, subjects with high vs low IAF demonstrated higher values of all indexes of adiposity (Table 2). The difference in IAF only was greater in males than females (37 183 mmHg vs 39 499 mmHg); P < .001 and 28 076 mmHg vs 33 105 mmHg); P < .001, respectively; IAF × sex interaction, P = .04).
Table 1. Comparison of the Characteristics of Adolescent Males and Females With “High” vs “Low” IAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males</th>
<th>Females</th>
<th>High IAF (n=80)</th>
<th>Low IAF (n=77)</th>
<th>High IAF (n=85)</th>
<th>Low IAF (n=82)</th>
<th>P Value</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>15.0 (1.9)</td>
<td>14.4 (1.7)</td>
<td>15.0 (2.0)</td>
<td>14.4 (1.9)</td>
<td>.05</td>
<td>.6 (0.2 to 1.0)</td>
<td>.007</td>
<td>0 (−0.4 to 0.4)</td>
<td>.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.1 (10.5)</td>
<td>166.3 (10.1)</td>
<td>160.9 (7.0)</td>
<td>160.1 (7.4)</td>
<td>.12</td>
<td>2.3 (0.3 to 4.2)</td>
<td>.02</td>
<td>7.7 (5.8 to 9.7)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income, Can$</td>
<td>[54 083.66] [22 788.93]</td>
<td>[56 329.46] [22 635.36]</td>
<td>[51 402.60] [23 192.26]</td>
<td>[57 540.36] [23 345.86]</td>
<td>.47</td>
<td>−4915</td>
<td>.10</td>
<td>695</td>
<td>.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner stage</td>
<td>40/40</td>
<td>36/41</td>
<td>45/39</td>
<td>35/47</td>
<td>.18</td>
<td>0.3 (−0.1 to 0.7)</td>
<td>.10</td>
<td>−0.1</td>
<td>.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity, sessions/wk</td>
<td>3.6 (0.9)</td>
<td>3.4 (0.8)</td>
<td>4.2 (0.7)</td>
<td>4.0 (0.8)</td>
<td>.77</td>
<td>0.2 (0.1 to 0.4)</td>
<td>.01</td>
<td>−0.65</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h kcal intake</td>
<td>9 (9)</td>
<td>11 (8)</td>
<td>9 (8)</td>
<td>11 (11)</td>
<td>.78</td>
<td>−1 (−3 to 1)</td>
<td>.39</td>
<td>0 (−2 to 3)</td>
<td>.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat, %d</td>
<td>35 (9)</td>
<td>33 (9)</td>
<td>31 (8)</td>
<td>32 (8)</td>
<td>.18</td>
<td>1 (−1 to 2)</td>
<td>.58</td>
<td>2 (−1 to 4)</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, %d</td>
<td>15 (4)</td>
<td>16 (5)</td>
<td>14 (4)</td>
<td>15 (4)</td>
<td>.65</td>
<td>−1 (−2 to 0)</td>
<td>.15</td>
<td>0 (−1 to 2)</td>
<td>.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrates, %d</td>
<td>51 (9)</td>
<td>52 (11)</td>
<td>54 (10)</td>
<td>53 (9)</td>
<td>.31</td>
<td>0 (−2 to 2)</td>
<td>.99</td>
<td>−2 (−5 to 1)</td>
<td>.29</td>
<td></td>
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</table>

Abbreviations: CI, confidence interval; IAF, intra-abdominal fat; PEMCS, prenatal exposure to maternal cigarette smoking.

a Variables were analyzed with a mixed linear model, including sex, IAF × sex interaction, family clustering, and potential confounding variables (age, height, Tanner stage, household income, and PEMCS) in the model. Estimated IAF difference is positive when high IAF is greater than low IAF. Estimated sex difference is positive when males are more than females.


c Twenty-four–hour food-recall energy intake.

d Diet composition with respect to relative fat, protein, and carbohydrates content.

IMPACT OF IAF ON INDIVIDUAL COMPONENTS OF THE MS AND RELATED VARIABLES

In both males and females, subjects with high vs low IAF had higher levels of fasting insulin and triglycerides and HOMA index and lower levels of HDL cholesterol (Table 3). The values of insulin, HOMA index, and triglycerides were higher by 20% to 30% and those of HDL cholesterol were lower by 7%. When analyzing SBP measured at rest while seated, we found a significant IAF × sex interaction (P = .01). Males with high vs low IAF had significantly higher SBP (6 mm Hg [95% CI, 1 to 11 mm Hg]; P = .02), but there was no difference in females (−1 mm Hg [95% CI, −5 to 2 mm Hg]; P = .45) (Table 3). Intra-abdominal fat showed no significant effect on fasting glucose level or DBP (measured at rest while seated) in either males or females (Table 3). With respect to the MS-related variables, in both males and females, subjects with high vs low IAF showed higher CRP levels and no significant difference in morning cortisol, total testosterone, and estradiol levels (Table 3). In addition, subjects with high vs low IAF demonstrated higher leptin levels, but the difference was significantly greater (IAF × sex interaction, P < .001) in females (8.7 ng/mL [95% CI, 6.2 to 11.1 ng/mL]; P < .001) than in males (2.8 ng/mL [95% CI, 1.9 to 3.7 ng/mL]; P < .001) (Table 3). Subjects with high vs low IAF also exhibited higher bioavailable testosterone levels, and this difference (IAF × sex interaction, P = .008) was greater in males (34.7 ng/dL [95% CI, 0 to 72.3 ng/dL]; P = .06) than in females (2.9 ng/dL [95% CI, 0 to 5.8 ng/dL]; P = .06) (Table 3).

IMPACT OF IAF ON CARDIOVASCULAR AND AUTONOMIC NERVOUS SYSTEM FUNCTIONS

The Figure shows 53 one-minute means of SBP, DBP, and HR calculated throughout the entire protocol and 8 two-minute calculations of LFDBP and HFms computed for specific periods. When analyzing these measures, SBP was significantly higher in males with high vs low IAF but not females (IAF × sex interaction, P < .001) (Figure). In males, the mean estimated difference between the 2 groups over the entire protocol was 5 mm Hg (95% CI, 3 to 8 mm Hg; P < .001), reaching up to 9 mm Hg during both physical and mental challenges (Figure). A similar but less pronounced pattern was also observed for DBP (IAF × sex interaction, P = .009); in males, the estimated mean difference was 2 mm Hg (95% CI, 0 to 4 mm Hg; P = .02), exceeding 3 mm Hg during and in between the challenges (Figure). No significant effect of intra-abdominal adiposity on HR was observed in either males or females (Figure).

Multiple linear regression analyses of LFDBP, a surrogate for sympathetic activity, revealed significant IAF × sex interactions during the first and second sitting periods (P = .04 for both), when males with high vs low IAF demonstrated higher LFDBP (Figure). The adjusted difference was significant for the second sitting period (629 mm Hg² [95% CI, 37 to 1222 mm Hg²]; P = .04) and marginally nonsignificant for the first sitting period (310 mm Hg² [95% CI, −127 to 1098 mm Hg²]; P = .12). In contrast, the LFDBP differences between females with high and low IAF during both periods were nonsignificant (sitting...
The present study is one of the first to examine the relationship between intra-abdominal obesity and the MS directly using MRI. With this method, we found that the MS was completely absent in adolescents with low IAF while it was present in 13.8% of males and 8.3% of females with high IAF. Overall, these results are consistent with recent population-based reports indicating that the MS, traditionally regarded as an adult disorder, is now emerging during adolescence.5,36 Our results suggest that intra-abdominal obesity may be a driving force behind its development.

In the present investigation, SBP and DBP were elevated in males with high vs low IAF. A similar pattern was also observed for LF\textsubscript{DBP}, an index of sympathetic activity, suggesting that sympathoactivation may be involved in the observed BP elevations. Consistently, IAF, but not SAF, has been previously related to increased sympathetic activity in adult males.12,37 Sympathoactivation is thought to be a key underlying mechanism of obesity-related hypertension38; augmented sympathetic outflow to the kidneys and vasculature can increase sodium and water reabsorption and peripheral vascular resistance, respectively, and hence BP. Previous research suggests that obesity-induced hyperleptinemia and hyperinsulinemia

![Table 2. Comparison of Body-Fat Quantity and Distribution in Adolescent Males and Females With “High” vs “Low” IAF\textsuperscript{a}](chart.png)

**Abbreviations:** BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; IAF, intra-abdominal fat; PEMCS, prenatal exposure to maternal cigarette smoking; SAF, subcutaneous abdominal fat; WC, waist circumference.

\textsuperscript{a}Variables were analyzed with a mixed linear model, including sex, IAF × sex interaction, family clustering, and potential confounding variables (age, height, Tanner stage, household income, and PEMCS) in the model. Estimated IAF difference is positive when high IAF is greater than low IAF. Estimated sex difference is positive when males are more than females. A posteriori power estimations: the mean unadjusted differences between high and low IAF groups detectable in the pooled analyses of males and females with 80% power by 2-tailed \( t \) tests at .05 significance level) are 12 964 and 9058 mm\(^3\) for IAF, respectively.

\textsuperscript{b}Percentage of fat by bioimpedance.

1, −194 mm Hg\(^2\) [95% CI, −567 to 178 mm Hg\(^2\)]; \( P = .30 \); sitting 2, −132 mm Hg\(^2\) [95% CI, −652 to 389 mm Hg\(^2\)]; \( P = .62 \). For other periods, the main effect of IAF on LF\textsubscript{DBP} was nonsignificant (\( P \) values \( > .10 \)) (Figure). High-frequency IBI, a proxy for parasympathetic activity,32 did not show any significant IAF × sex interactions (\( P \) values \( > .30 \)) (Figure) or differences between subjects with high and low IAF (\( P \) values \( > .10 \)) (Figure).

**IMPACT OF IAF ON THE PREVALENCE OF THE MS IN ADOLESCENT MALES AND FEMALES**

The MS was not present in any subjects with low IAF. Among subjects with high IAF, the MS (defined by the presence of at least 3 of 5 components) was found in 13.8% of males and 8.3% of females; this sex difference was not statistically significant. Since obesity is a component of the MS and, to a certain degree, was used to categorize subjects as having high or low IAF (BMI and IAF were correlated [males with high IAF, \( r = 0.56 \); females with high IAF, \( r = 0.56 \]) we also assessed the prevalence of the MS without including obesity as a component. This analysis showed that the MS (defined by the presence of at least 3 of 4 components) was present in 7.5% of males with high IAF and 3.9% of females with high IAF; again, the sex difference was not significant.
Females and males increase generation of estradiol prior to ing adolescence. Males increase production of testosterone vs females. The mechanisms of this difference pathoactivation (and possibly BP) observed only in males. The mechanisms of this difference pathoactivation, have been implicated in these effects. Testosterone enhances vasoconstriction in response to adrenergic agonists. In addition, levels of plasma norepinephrine, which is primarily derived from sympathetic nerve endings, increase in males with advancing puberty and testosterone levels. In the current study, we observed that bioavailable testosterone levels significantly increased in subjects with high vs low IAF, with the difference being greater in males than females. These results suggest that testosterone could play a role in sympathoactivation and BP elevation observed in males with high compared with low IAF. No significant differences may play a role in sympathoactivation. In our study, leptin and insulin serum levels were higher in subjects with high vs low IAF, with the former difference being greater in females than males and the latter difference being similar in both sexes. These results do not support the involvement of leptin and insulin in high IAF—associated sympathoactivation (and possibly BP) observed only in males.

Adolescence is a period of sexual development when a number of physiological differences between males and females emerge; one such difference is an elevation of BP in males vs females. The mechanisms of this difference are not clear at present, though a large body of research implicates sex hormones that change dramatically during adolescence. Males increase production of testosterone and females increase generation of estradiol prior to menarche, after which estradiol cycles with the menstrual cycle at levels constantly higher than in males. Long-term exposure to testosterone is thought to promote BP elevation; it may compromise renal function and impair vascular reactivity. Multiple abnormalities, including sympathoactivation, have been implicated in these effects. Testosterone enhances vasoconstriction in response to adrenergic agonists. In addition, levels of plasma norepinephrine, which is primarily derived from sympathetic nerve endings, increase in males with advancing puberty and testosterone levels. In the current study, we observed that bioavailable testosterone levels significantly increased in subjects with high vs low IAF, with the difference being greater in males than females. These results suggest that testosterone could play a role in sympathoactivation and BP elevation observed in males with high compared with low IAF. No significant differences
Figure. Cardiovascular and autonomic nervous system at rest and in response to postural and mental challenges in males and females with “high” or “low” intra-abdominal fat (IAF). One-minute means of beat-to-beat systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during a 53-minute cardiovascular protocol, including a posture test (minutes 1-30) and math stress test (minutes 31-53), are shown. In addition, indexes of sympathetic and parasympathetic activity (low-frequency power of DBP [LFDBP] and high-frequency power of interbeat interval [HFIBI], respectively) are presented for 8 two-minute periods: supine (minutes 9-10), standing 1 (minutes 11-12), standing 2 (minutes 17-18), sitting 1 (minutes 21-22), sitting 2 (minutes 27-28), sitting 3 (pre–math test, minutes 34-35), math test (minutes 42-43), and post–math test (minutes 49-50). The data are all adjusted for potential confounding variables, including age, height, Tanner stage, household income, and prenatal exposure to maternal cigarette smoking. They are presented as mean (SEM); solid squares indicate the mean for individuals with high IAF and open squares show the mean for individuals with low IAF. The dashed vertical line indicates the end of the posture test. The 53 one-minute means of SBP, DBP, and HR were analyzed with mixed-model regression analyses. Statistics show the $P$ value of the IAF $\times$ sex interaction and the estimated difference (95% confidence interval [CI]) and $P$ value for high vs low IAF in males (A) and in females (B). The 8 estimates of sympathetic (LFDBP) and parasympathetic (HFIBI) nervous system functions, calculated for specific 2-minute periods, were analyzed using multiple linear regression analysis. Statistical significance for a difference between males with high and low IAF is indicated with * ($P<.04$).
between subjects with high and low IAF were identified in estradiol, which is thought to be cardioprotective.

In males, we saw that excess IAF was associated with increased BP throughout the entire cardiovascular protocol, whereas augmented sympathetic activity was observed only during recovery from a physical challenge (10-minute standing). These results suggest that excess IAF affects the sympathetic nervous system mainly by diminishing its expected withdrawal after a physical challenge (as seen in females) (Figure). This finding may be important, as clinical studies have found that delayed cardiovascular recovery from exercise is a significant predictor of mortality in subjects with cardiovascular disease.

Based on our current data, we cannot determine the exact causes of the differences in IAF quantity between subjects with high and low IAF, as they did not differ in food intake or physical activity. We speculate they may vary in metabolic rate and/or genetic predisposition for body fat distribution (eg, intra-abdominal rather than subcutaneous). It is also possible that subjects with higher IAF were less active and/or had higher energy intake in the past or that a false-negative finding occurred because of a measurement error.

This study has certain limitations, including (1) a cross-sectional design, (2) the use of power spectral analysis of cardiovascular variability to assess autonomic nervous system function, (3) a lack of dose-response analyses, and (4) a potential for type I error inflation. (1) A longitudinal design would facilitate examination of a causal relationship between, eg, age-related changes in IAF, SBP, and LFDBP. Usefulness of cross-sectional studies, however, should not be underestimated, as they have generated many clinically significant associations. (2) Further studies should assess continuous dose-response relationships between IAF and different components of the MS. These studies will have to be carried out in larger samples and, if possible, designed specifically for this type of investigation. (4) The total number of results reported in Table 2, Table 3, and the Figure (primary and secondary mechanistic outcomes) equals 80. About 4 tests would be expected to yield $P < 0.05$ by chance alone ($80 \times 0.05 = 4$), but we found 18 significant results. Although these calculations are only approximate, as they assume independence of the 80 tests, they clearly indicate that a vast majority of the significant associations reported reflect genuine effects of IAF rather than type I errors.

In summary, our results suggest that intra-abdominal obesity is associated with adverse cardiovascular and metabolic consequences in male and female adolescents. Already in this age category, it appears to increase the risk for the MS, affecting insulin resistance, dyslipidemia, and a proinflammatory state similarly in males and females but influencing BP adversely only in males. The latter may be related in part to an intra-abdominal obesity–induced augmentation in sympathetic activity also seen only in males.

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Author Affiliations: Brain and Body Centre, University of Nottingham, Nottingham, England (Ms Syme, Drs Pitiot, Paus, and Pausova, and Messrs Totman and Qiu); and Department of Epidemiology and Biostatistics, McGill University (Drs Abramowicz, Leonard, and Paus and Ms Xiao) and Research Centre—CHUM (Centre hospitalier de l’Université de Montréal) (Dr Pausova), Montreal; Groupe ÉCOBES (d’étude des conditions de vie et des besoins de la population) (Drs Perron and Veillette), Université de Québec (Dr Richer), and Community Genomic Centre, Université de Montréal, Chicoutimi Hospital (Dr Gaudet), Chicoutimi, Quebec, Canada.

Correspondence: Zdenka Pausova, MD, Brain and Body Centre, University of Nottingham, University Park, Nottingham NG7 2RD, England (zdenka.pausova@nottingham.ac.uk).

Author Contributions: Dr Pausova had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Leonard, Veillette, Gaudet, Paus, and Pausova. Acquisition of data: Syme, Leonard, Perron, Richer, Gaudet, and Pausova. Analysis and interpretation of data: Syme, Abramowicz, Pitiot, Qiu, Totman, Xiao, and Pausova. Drafting of the manuscript: Syme, Abramowicz, Pitiot, and Pausova. Critical revision of the manuscript for important intellectual content: Abramowicz, Leonard, Perron, Qiu, Richer, Totman, Veillette, Xiao, Gaudet, Paus, and Pausova. Statistical analysis: Syme, Abramowicz, Xiao, and Pausova. Obtained funding: Paus and Pausova. Administrative, technical, and material support: Syme, Leonard, Perron, Pitiot, Qiu, Richer, Totman, Veillette, Paus, and Pausova.

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