Cardiometabolic Risk and Body Composition in Youth With Down Syndrome

Sheela N. Magge, MD, MSCE,a Babette S. Zemel, PhD,b,c Mary E. Pipan, MD,c,d Samuel S. Gidding, MD,e Andrea Kelly, MD, MSCEf

BACKGROUND AND OBJECTIVES: Whether BMI captures adiposity and cardiometabolic risk in Down syndrome (DS), a condition associated with obesity, short stature, and altered body proportions, is not known. We compared cardiometabolic risk measures in youth with DS and typically developing matched controls.

METHODS: Youth with \( (n = 150) \) and without \( (n = 103) \) DS of comparable age (10–20 years), sex, race, ethnicity, and BMI percentile underwent whole-body dual-energy X-ray absorptiometry, fasting glucose, insulin, lipids, lipoprotein particles, inflammatory factors, and when BMI percentile \( \geq 85 \), an oral glucose tolerance test.

RESULTS: Sixty-four percent of youth with DS had BMI percentile \( \geq 85 \). Among these, no difference in glucose, insulin, or insulin resistance was detected, but prediabetes was more prevalent with DS (26.4% vs 10.3%; \( P = .025 \)) after adjustment for demographics, pubertal status, and BMI \( z \) score (odds ratio = 3.2; \( P = .026 \)). Among all participants, those with DS had higher low-density lipoprotein cholesterol (median 107 [interquartile range 89–128] vs 88.5 [79–103] mg/dL; \( P < .00005 \)), triglycerides (89.5 [73–133] vs 71.5 [56–104] mg/dL; \( P < .00005 \)), non–high-density lipoprotein cholesterol (non-HDL-C; 128 [104–153] vs 107 [92–123] mg/dL; \( P < .00005 \)), and triglycerides/HDL-C (2.2 [1.6–3.4] vs 1.7 [1.1–2.5] mg/dL; \( P = .0003 \)) and lower levels of HDL-C (41 [36.5–47] vs 45 [37–53] mg/dL; \( P = .012 \)). DS youth had higher high-sensitivity C-reactive protein, interleukin-6, small low-density lipoprotein particles (LDL-P), and total LDL-P, but similar LDL-P size. Youth with DS had less visceral fat (VFAT), fat mass, and lean mass for BMI \( z \) score, but greater VFAT at higher fat mass. However, VFAT did not fully explain the increased prevalence of dyslipidemia or prediabetes in youth with DS.

CONCLUSIONS: Despite similar insulin resistance, youth with DS had greater prevalence of dyslipidemia and prediabetes than typically developing youth, which was not fully explained by VFAT.

WHAT'S KNOWN ON THIS SUBJECT: Youth with DS commonly have increased BMI. Conflicting data regarding cardiovascular risk challenge screening and intervention practices, while suggesting DS-specific phenomena may offer cardioprotection. However, metabolic differences related to an extra chromosome 21 may confer increased obesity-related risk.

WHAT THIS STUDY ADDS: This large study of youth with DS compared to typically developing control patients examined relationships between body composition and cardiometabolic risk. Youth with DS had more atherogenic lipid profiles, including increased low-density lipoprotein cholesterol and, among those with BMI \( \geq 85 \) percentile, had greater prediabetes and dyslipidemia prevalence.

METHODS
Adolescents ages 10 to 20 years with DS (n = 150) and youth with non-DS (n = 103) of comparable age, sex, race, ethnicity, and BMI percentile were recruited for a cross-sectional study. The institutional review boards of Children’s Hospital of Philadelphia and the Children’s National Health System approved the protocol. Parental consent and participant consent and/or assent were obtained.

Participants
Exclusion criteria included major organ-system illness not related to DS (except type 2 diabetes mellitus [T2DM]), (eg, polycystic kidney disease, liver disease, sickle cell disease, brain tumor, etc), current or previous oncologic process, cyanotic or symptomatic congenital heart disease, pulmonary hypertension, pregnancy, type 1 diabetes mellitus (T1DM), genetic syndrome known to affect glucose tolerance, familial hypercholesterolemia, or current treatment with medication known to affect insulin sensitivity or lipids (other than diabetes agents in T2DM). Participants were recruited in a staggered manner (those with DS first) to enroll participants with non-DS such that 1 participant with non-DS was similar to 1 to 2 existing participants with DS on the basis of age, sex, race, ethnicity, and BMI percentile. Raw BMI was used for matching if the BMI was in the >99 percentile.

Anthropometrics
Weight (kilograms) was measured by using a digital electronic scale (Scalesicon), and height (centimeters) was measured by using a wall-mounted stadiometer (Holtain), with the participant in light clothing without shoes. Age- and sex-specific BMI z scores were calculated on the basis of Centers for Disease Control and Prevention (CDC) 2000 growth charts for both groups. Zemel et al published new growth charts for DS in 2015. However, the same group also recommended using the standard CDC BMI growth charts for individuals with DS when attempting to identify excess adiposity because the standard CDC growth charts better identified fat mass index in the >80 percentile, a threshold associated with increased CMR, than the DS-specific BMI growth charts. For BMI percentile extremes, the BMI z score was calculated by expressing the BMI relative to the median BMI in units of half the distance between 0 and +2 z scores, as recommended by the CDC. Weight status was categorized as normal weight (BMI in the fifth–85 percentiles), overweight (BMI in the 85th–95th percentile), and obese (BMI in the ≥95th percentile) for those 10 to 20 years. For participants ≥20 years but <21 years, weight status was defined as normal weight (BMI of 18.5–25), overweight (BMI ≥25), and obese (BMI ≥30). Waist and hip circumferences were measured by using standard techniques, with waist circumference measured at the umbilicus. The waist-to-hip ratio, waist-to-height ratio, and tri-ponderal mass index (weight/height$^3$) were calculated.

Body Composition
Whole-body scans were acquired by using dual-energy X-ray absorptiometry (DXA) to measure percentage of body fat, whole-body lean mass, whole-body fat mass, and visceral fat area with Hologic Horizon and Discovery A models and were analyzed with Hologic Enhanced Whole-Body software versions 13.3 to 13.6 (Hologic, Bedford, MA). Lean BMI and fat mass index were calculated as lean body mass/height$^2$ and fat mass/height$^2$.

Collected Variables
Demographic information and medical history were obtained from the guardian and participant. Breast development in girls and testicular volume in boys were assessed by
a pediatric endocrinologist in an examination for pubertal staging in all but a limited number of participants \((n = 9\) total, \(n = 3\) with DS, and \(n = 6\) with non-DS) for whom a validated self-assessment measure was used.\(^{17}\)

Blood pressure was measured after \(\geq5\) minutes of rest in a seated position by using automatic oscillometry (Dynamap; GE Healthcare, Chicago, IL). After a 10- to 12-hour overnight fast, a blood sample was obtained for glucose, insulin (Human Insulin Enzyme-Linked Immunosorbent Assay [ELISA] kit; ALPCO Diagnostics, Salem, NH), and lipoprotein subclass particle analysis by using nuclear magnetic resonance spectroscopy (Vantera Clinical Analyzer; LipoScience, Inc, Morrisville, NC) and for lipoprotein insulin resistance index (LP-IR; a composite marker of insulin-resistant dyslipoproteinemia, calculated by using an algorithm weighting the 6 lipoprotein parameters by concentration and size and calculating the sum\(^{18}\)), leptin (Leptin ELISA kit; ALPCO Diagnostics), high–molecular-weight adiponectin (Chemiluminescence ELISA kit; ALPCO Diagnostics), free fatty acids (colorimetric assay; Wako, Mountain View, CA), PAI-1 (Protein Simple Human Serpin-E1 Ella kit), interleukin-6 (IL-6) (Protein Simple Human Ella kit), and high-sensitivity C-reactive protein (hs-CRP).

Hemoglobin A1c (HbA1c), plasma glucose, and the lipid profile were measured by using a colorimetric assay on the Vitros 5600 integrated system (Ortho Clinical Diagnostics, Raritan, NJ). Insulin resistance was reported as the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated as (fasting insulin [micro international units per milliliter] \(\times\) fasting glucose [millimoles per liter])/22.5.\(^{19}\)

Participants categorized as having overweight or obesity underwent an oral glucose tolerance test and were instructed to ingest a glucose solution (1.75 g/kg; maximum 75 g) over 2 minutes. Consideration was given for participants with DS who could not comply with these instructions, and oral glucose tolerance test results were included if the glucose solution was drunk in \(\leq15\) minutes. Blood was drawn for glucose (Statstrip Nova Glucose Meter System) and insulin at 30, 60, 90, and 120 minutes. If the oral glucose tolerance test was not tolerated or if the family refused, an attempt was made to draw fasting glucose and insulin at times 0 and 120 minutes. Participants with impaired fasting glucose (fasting glucose level \(\geq100\) mg/dL) and/or impaired glucose tolerance (2-hour glucose level of 140–199 mg/dL) had a confirmatory plasma glucose test performed in the hospital laboratory and were categorized as having prediabetes if hyperglycemia was confirmed.\(^{20}\) Participants who had impaired fasting glucose and did not have a 2-hour glucose drawn were categorized as having prediabetes. HbA1c was not used to define prediabetes in this study. Any subject found to have diabetes (fasting glucose level \(\geq125\) mg/dL and/or 2-hour glucose level \(\geq200\) mg/dL) was excluded from the analysis because the participant would not have been on diabetes treatment and because lipids could be affected by a lack of glucose control. The insulinogenic index, (insulin at 30 min − insulin at 0 min)/ (glucose at 30 min − glucose at 0 min); the disposition index, (1/fasting insulin) \(\times\) (insulinogenic index); and the Matsuda index, \((10 000/\text{square root of } [\text{fasting glucose } \times \text{ fasting insulin}]) \times \text{oral glucose tolerance test mean glucose} \times \text{oral glucose tolerance test mean insulin} \) were calculated. The Matsuda index was calculated for those with data at a minimum for time of 0 minutes and 120 minutes (agrees well with the original Matsuda calculation\(^{21}\)).

**Sample Size and Statistical Analysis**

Non–high-density lipoprotein cholesterol (non-HDL-C) (total cholesterol − HDL-C) was chosen as the primary study outcome because it has been shown in multiple studies to be predictive of cardiovascular disease.\(^{22–25}\) It has been proposed as a strong cardiovascular disease risk marker because it incorporates not only low-density lipoprotein cholesterol (LDL-C) but also very low-density lipoprotein cholesterol and thus includes all of the apolipoprotein B–containing lipoproteins.\(^{25}\) The primary outcome was used to calculate sample size. By assuming 150 children with DS and 100 youth without DS for analysis and conservatively using nonparametric methods for comparison of cardiovascular disease risk factors, study power exceeded 0.85 to detect a between-group difference of 0.4 SD. For non-HDL-C, 0.4 SD corresponds to an 8-mg/dL difference. A difference of 10 mg/dL is considered clinically relevant.\(^{26}\)

Normally distributed continuous variables were summarized as mean \(\pm\) SD, and between-group comparisons were made by using Student’s \(t\) test. If deviating from normality, variables were summarized as median (interquartile range), and the Wilcoxon rank test was used for between-group comparisons. Categorical variables were summarized as count and percentage and compared by using Fisher’s exact test. Linear and/or logistic regression was used (as appropriate) for comparison, with adjustment for potential confounding variables such as age, sex, race, ethnicity, and pubertal stage. For regression analyses, puberty status was dichotomized (pubertal stages 1–2 versus pubertal stages 3–5) by using breast development in girls and testicular volume in boys. There were few participants of color, so participants were dichotomized as white participants and participants of
color. When analyzing relationships between cardiometabolic outcomes and adiposity measures, testing was performed for effect modification by group.

To determine which clinically available measure of adiposity (BMI, BMI z score, tri-ponderal mass index, waist circumference, waist-to-height ratio, and waist-to-hip ratio) was most strongly associated with non-HDL-C and triglycerides/high-density lipoprotein (HDL), linear regression models were performed, with adjustment for age, sex, race, ethnicity, and pubertal status. Each adiposity measure was added to the model individually, and its significance level and the adjusted $R^2$ were examined. The $R^2$ of the various models was used to assess the amount variance described by the components of that particular regression model.

The fit of each linear regression model was assessed through the adjusted $R^2$ value. The linear regression models were assessed further through graphical checks, the Shapiro-Wilk test of normality of the residuals, and the Cook-Weisberg test for heteroscedasticity. Logistic regression models were assessed by using the Hosmer-Lemeshow goodness-of-fit test. In cases in which outliers that influenced the linear regression model were identified, sensitivity analysis was performed after removing the outliers. If the regression models were not substantially different, the original model was presented. Otherwise the original model was replaced by the model after removing the outliers.

$P < .05$ was considered statistically significant. Statistical analyses were performed by using Stata (version 15.0; Stata Corp, College Station, TX).

**RESULTS**

Consistent with study design, DS ($n = 150$) and non-DS ($n = 103$) groups were similar in age, sex, race, ethnicity, pubertal stage, BMI, BMI z score, and BMI percentile (Table 1). Groups were also similar in waist circumference. The waist-to-height ratio, waist-to-hip ratio, and tri-ponderal mass index were higher in DS (Table 1).

**Lipid Parameters**

Participants with DS had higher concentrations of LDL-C, triglycerides, non-HDL-C, and triglycerides/HDL and a lower concentration of HDL-C. Consistent with increased LDL-C levels, the group with DS had a lipoprotein particle pattern of higher concentrations of small low-density lipoprotein particles (LDL-Ps) and total LDL-Ps and similar LDL-P size. Consistent with their higher triglyceride levels, large very low-density lipoprotein particles (VLDL-Ps) and large VLDL-P size were higher in participants with DS (Table 2). These relationships persisted after adjusting for demographics, pubertal stage, and BMI z score (Table 3). Among participants with over-weight and obesity, youth with DS had a higher prevalence of dyslipidemia than youth with non-DS. Among those with normal BMI, the group with DS had numerically greater dyslipidemia prevalence, but only non-HDL-C reached borderline statistical significance (Fig 1). With increasing BMI z score, the difference in the non-HDL-C level between youth with DS and non-DS was magnified ($\beta = .049$ for log-transformed non-HDL-C; $P = .033$ for effect modification), as was the difference in the LDL-C level between youth with DS and non-DS ($\beta = .052$ for log-transformed LDL-C; $P = .032$ for interaction) (Fig 2 A and B). Higher concentrations of non-HDL-C, triglycerides/HDL, LDL-C, triglycerides, large VLDL-P, total LDL-P, and small LDL-P persisted in participants with DS compared with control patients, with substitution of visceral fat for BMI z score ($P < .0005$ in all linear regression models). Concentrations of IL-6 and hs-CRP, but not PAI-1, were higher in the group with DS (Table 2).

**Body Composition**

Fat mass index, percentage of body fat, and lean BMI were similar in youth with and without DS (Table 4). Those with DS had lower lean body mass for a given BMI z score. Youth with DS also had less visceral fat for a given BMI z score compared with youth with non-DS, which persisted

<table>
<thead>
<tr>
<th>TABLE 1 Demographics and Anthropometric Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>DS (n = 150)</strong></td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>African American race, n (%)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnicity, n (%)</td>
</tr>
<tr>
<td>Pubertal stage, n (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², median (IQR)</td>
</tr>
<tr>
<td>BMI z score, mean ± SD</td>
</tr>
<tr>
<td>BMI percentile (for age and sex), mean ± SD</td>
</tr>
<tr>
<td>Waist circumference, cm, median (IQR)</td>
</tr>
<tr>
<td>Waist-to-height ratio, median (IQR)</td>
</tr>
<tr>
<td>Waist-to-hip ratio, median (IQR)</td>
</tr>
<tr>
<td>Tri-ponderal mass index, kg/m³, median (IQR)</td>
</tr>
</tbody>
</table>

If continuous variables were normally distributed, then the $t$ test was used (listed as mean ± SD); if not, then the Wilcoxon rank test was used (listed as median [IQR]). Fisher’s exact test was used for categorical variables. IQR, interquartile range.
TABLE 2 Cardiometabolic Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>DS (n = 147)</th>
<th>Control Patients (n = 103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL, median (IQR)</td>
<td>92 (85–96)</td>
<td>89 (84–93)</td>
<td>.009</td>
</tr>
<tr>
<td>Insulin, μU/mL, median (IQR)</td>
<td>7.7 (4.7–12.3)</td>
<td>8.8 (4.7–15.8)</td>
<td>.34</td>
</tr>
<tr>
<td>HbA1c, %, mean ± SD</td>
<td>5.0 ± 0.29</td>
<td>5.2 ± 0.29</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>HOMA-IR, median (IQR)</td>
<td>1.8 (1.0–2.7)</td>
<td>1.95 (0.92–3.4)</td>
<td>.58</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg, median (IQR)</td>
<td>105.5 (98.5–114.5)</td>
<td>109 (101.5–114.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg, median (IQR)</td>
<td>59 (53.5–64.5)</td>
<td>60 (57–65.5)</td>
<td>.08</td>
</tr>
<tr>
<td>hs-CRP, ng/mL, median (IQR)</td>
<td>2.5 (0.64–6.9)</td>
<td>1.0 (0.32–4.5)</td>
<td>.006</td>
</tr>
<tr>
<td>PAI-1, ng/mL, median (IQR)</td>
<td>20.4 (13.2–32.7)</td>
<td>25.4 (14.7–38.5)</td>
<td>.07</td>
</tr>
<tr>
<td>IL-6, pg/mL, median (IQR)</td>
<td>2.3 (1.4–3.5)</td>
<td>1.5 (1.4–2.9)</td>
<td>.003</td>
</tr>
<tr>
<td>Adiponectin, μg/mL, median (IQR)</td>
<td>2055 (1412–2030)</td>
<td>2056 (1252–2839)</td>
<td>.41</td>
</tr>
<tr>
<td>Leptin, ng/mL, median (IQR)</td>
<td>25.3 (9.7–54.9)</td>
<td>17.5 (6.9–47.2)</td>
<td>.17</td>
</tr>
<tr>
<td>LDL-C, mg/dL, median (IQR)</td>
<td>107 (89–128)</td>
<td>88.5 (79–103)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (IQR)</td>
<td>89.5 (73–133)</td>
<td>71.5 (56–104)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>HDL-C, mg/dL, median (IQR)</td>
<td>41 (36.5–47)</td>
<td>45 (37–53)</td>
<td>.012</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL, median (IQR)</td>
<td>128 (104–153)</td>
<td>107 (92–123)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Triglyceride/HDL ratio, median (IQR)</td>
<td>2.2 (1.9–3.4)</td>
<td>1.7 (1.1–2.5)</td>
<td>.003</td>
</tr>
<tr>
<td>LPIR, mean ± SD</td>
<td>45.4 ± 15.5</td>
<td>38.2 ± 17.2</td>
<td>.004</td>
</tr>
<tr>
<td>Total LDL-P, nmol/L, median (IQR)</td>
<td>977 (806–1193)</td>
<td>850 (683–987)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Total LDL-P size, nm, median (IQR)</td>
<td>26.7 (20.3–21.2)</td>
<td>20.7 (20.2–21.1)</td>
<td>.29</td>
</tr>
<tr>
<td>Small LDL-P, nmol/L, median (IQR)</td>
<td>518 (401–639)</td>
<td>420 (315–529)</td>
<td>.0002</td>
</tr>
<tr>
<td>Total HDL-P, μmol/L, median (IQR)</td>
<td>28.3 (25.8–30.8)</td>
<td>23.5 (26.9–32.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Total HDL-P size, nm, median (IQR)</td>
<td>9.6 (9.2–9.9)</td>
<td>9.6 (9.1–9.9)</td>
<td>.83</td>
</tr>
<tr>
<td>Total HDL-C, μmol/L, mean ± SD</td>
<td>9.5 ± 5.4</td>
<td>11.6 ± 4.9</td>
<td>.002</td>
</tr>
<tr>
<td>Large VLDL-P, nmol/L, median (IQR)</td>
<td>3.9 (2.3–5.7)</td>
<td>2.4 (1.5–4.1)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Small VLDL-P, nm, median (IQR)</td>
<td>49.2 (45.8–53.6)</td>
<td>47.1 (44.2–50.7)</td>
<td>.0007</td>
</tr>
</tbody>
</table>

If continuous variables were normally distributed, then the t test was used (listed as mean ± SD); if not normally distributed, then the Wilcoxon rank test was used (listed as median (IQR)). HDL-P, high-density lipoprotein particles; IQR, interquartile range.

after adjustment for demographics and pubertal stage (β = −.75 [visceral fat square root transformed]; P < .0005), and had lower total fat mass (β = −.29 [fat mass log transformed]; P < .0005) for the BMI z score after adjusting for covariates (Fig 3A).

Lower fat mass, lean body mass, and visceral fat for a given BMI z score revealed that youth with DS were smaller overall than their unaffected peers. However, with increasing fat mass, the relationship between visceral fat and fat mass varied by group; at higher levels of fat mass, youth with DS had greater visceral fat (β = .0004 [visceral fat square root transformed]; P = .002 for interaction, with adjustment for covariates) compared with control patients.(Fig 3B). The relationship is weak, given the small β coefficient, but reveals a slightly increased slope in the association for DS.

**Metabolic Parameters**

In the full cohort, youth with DS had higher fasting glucose levels than youth with non-DS. No differences in fasting insulin or HOMA-IR were found, but LPIR was higher in youth with DS. HbA1c levels were lower in youth with DS compared with youth with non-DS (Table 2).

Among participants with overweight and obesity (Table 5), HbA1c levels were lower in those with DS (P < .0005), and no differences in fasting glucose, insulin, HOMA-IR, insulinoenic index, disposition index, or Matsuda index were detected. Yet, the prevalence of prediabetes was higher in youth with DS compared with control patients (Fisher’s exact test, P = .025), resulting in an odds ratio (OR) of 3.2 (logistic regression, P = .025) for those with DS having prediabetes compared with control patients, with adjustment for demographics and pubertal stage.

With additional adjustment for BMI z score, the increased odds (OR = 3.1; P = .03) persisted. To determine if the increased prediabetes prevalence in participants with DS was explained by visceral adiposity, visceral fat was substituted for BMI z score, and the

TABLE 3 Youth With DS Have a More Atherogenic Lipoprotein Profile Compared With Control Patients (Adjustment for Potential Confounding Variables)

<table>
<thead>
<tr>
<th>Lipids and/or Lipoproteins</th>
<th>Adjustment for Demographics + Pubertal Stage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adjusted for Demographics + BMI z Score&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient for Group Difference</td>
<td>SE</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.27</td>
<td>0.06</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides/HDL</td>
<td>0.36</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.16</td>
<td>0.07</td>
</tr>
<tr>
<td>Small LDL-P</td>
<td>9.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Total LDL-P</td>
<td>0.73</td>
<td>0.04</td>
</tr>
<tr>
<td>Small VLDL-P</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Large VLDL-P</td>
<td>0.42</td>
<td>0.10</td>
</tr>
<tr>
<td>VLDL-P size</td>
<td>&lt; 0.0005</td>
<td>0.0003</td>
</tr>
<tr>
<td>LPIR</td>
<td>0.85</td>
<td>2.1</td>
</tr>
</tbody>
</table>

HDL-P, high-density lipoprotein particles.
<sup>a</sup> Demographics include age, sex, race, and ethnicity.
increased odds for prediabetes in participants with DS remained higher (OR = 3.4; \( P = .024 \)).

**Clinical Adiposity Measures and CMR Outcomes**

Each clinical adiposity measure (BMI, BMI \( z \) score, tri-ponderal mass index, waist circumference, waist-to-height ratio, and waist-to-hip ratio) was highly associated (\( P < .0005 \)) with both non-HDL-C and triglycerides/HDL in those with DS. For non-HDL-C, all models had a similar adjusted \( R^2 \) (13.6%–19.2%). For triglycerides/HDL, the model-adjusted \( R^2 \) (19.2%–21.4%) was similar for all models except for waist-to-hip ratio (14.2%). No 1 clinical adiposity measure emerged as the strongest predictor of non-HDL-C or triglycerides/HDL for participants with DS.

**DISCUSSION**

With the achievement of longer life spans for individuals with DS, the occurrence of obesity-related comorbidities and the measures that best capture their risk in DS need to be better defined.\(^2\) In this study, we demonstrated that youth with DS had more atherogenic lipid and lipoprotein particle profiles, including higher LDL-C levels, compared with youth without DS of comparable age, sex, race, ethnicity, pubertal stage, and BMI percentile. Among participants with overweight and obesity, youth with DS had a higher prevalence of dyslipidemia. The group with DS also had a higher prevalence of prediabetes but no detectable difference in HOMA-IR. Youth with DS had decreased visceral fat, fat mass, and lean body mass for a given BMI \( z \) score compared with youth with non-DS but had increased visceral fat at higher fat mass levels. However, visceral fat did not fully explain the increase in dyslipidemia and prediabetes in youth with DS. Finally, our analyses revealed that other clinical measures of adiposity did not predict non-HDL-C or triglycerides/HDL levels significantly better than BMI in youth with DS.

Dyslipidemia, typically seen in obesity and metabolic syndrome, involves elevated levels of triglycerides, decreased HDL-C levels, relatively normal LDL-C levels, and increased small, dense LDL-Ps.\(^2\) Our results reveal these findings in youth with DS but also show elevated levels of LDL-C. Previous studies of cardiovascular disease risk in individuals with DS have been limited by small sample sizes. A previous study from our group in which 27 prepubertal children with DS were compared with 31 unaffected siblings also revealed that children with DS had a more dyslipidemic profile than their siblings after adjustment for socioeconomic factors and BMI \( z \) score.\(^2\) Some adult studies support our findings of increased dyslipidemia in individuals with DS, whereas others do not.\(^2\) In a large cohort of 390 Mexican participants with DS of various ages, 73.4% had elevated LDL-C levels, 3.5% had elevated triglyceride levels, and 21% had both.\(^22\) Authors of few studies have measured lipoprotein subclass particles in individuals with DS. Compared with youth with non-DS, youth with DS had a more atherogenic lipoprotein particle pattern, with greater small LDL-Ps and total LDL-Ps. LPIR was significantly higher in the group with
DS, reflecting greater insulin-resistant dyslipoproteinemia. Our finding of increased inflammatory factors also supports a higher atherosclerotic risk in individuals with DS.

Atherosclerotic disease prevalence data in DS have also been conflicting. In 1977, DS was found to be an “atheroma-free” condition on the basis of the absence of coronary artery atherosclerosis found during autopsies of 5 adults with DS who were institutionalized compared with adults without DS who were institutionalized. In contrast, another study of adults with DS who were hospitalized revealed that the standardized mortality ratio was 6.2 for “diseases of the circulatory system” and 3.9 for “ischemic heart disease” after known congenital heart disease was excluded. Adults with DS also have a high risk of stroke, driven largely by high cardioembolic risk. Authors of other adult studies have examined surrogate markers of cardiovascular disease such as carotid intima media thickness (cIMT) and aortic stiffness by pulse wave velocity (PWV). One study revealed no difference in carotid-femoral PWV between individuals with DS and non-DS, possibly because of chronic lower blood pressure in individuals with DS. cIMT was lower in a group of 52 adults with DS compared with age- and sex-matched control patients. Furthermore, cardiovascular disease risk factors predicting cIMT differed in individuals with DS versus non-DS, suggesting that DS may involve a unique atherogenesis model. In their study of adults with DS living in a Mediterranean setting, Parra et al. found lower PWV and lower systolic blood pressure in groups with DS (n = 51) versus non-DS (n = 51). After adjustment for systolic blood pressure, age, and sex, no significant differences in PWV or cIMT were identified between groups. These authors found that some traditional cardiovascular disease risk factors associated with PWV and cIMT in individuals with non-DS were not operative in those with DS, again suggesting a unique model of cardiovascular disease risk in those with DS.

Despite the possibility of lower blood pressure in those with DS offering a protective cardiovascular disease effect, the increased LDL-C level in our large cohort of youth with DS reveals an increased risk of atherosclerosis. Increased LDL-C levels may have other implications. Individuals with DS are at an increased risk for Alzheimer disease; ~30% of adults with DS have Alzheimer disease by their 50s, and 50% have Alzheimer disease by their 60s. The gene for the amyloid protein, which plays a key pathologic role in Alzheimer disease, is located on chromosome 21 and is present in trisomic in DS. Other genes involved in aging are also located on chromosome 21, increasing the risk for Alzheimer disease. In fact, the neuropathology of Alzheimer disease is present in almost all adults with DS older than 40 years. Elevated cholesterol levels have also been associated with dementia. Atherosclerosis of the intracranial arteries is an important independent risk factor for dementia. In a series of in vitro and in vivo measures, Granic and Potter showed evidence of a cholesterol-dependent cell-cycle defect that may be involved in both atherosclerosis and/or cardiovascular disease risk and Alzheimer disease. The role of dyslipidemia in exacerbating Alzheimer disease risk in individuals with DS needs further study.

TABLE 4 Body Composition

<table>
<thead>
<tr>
<th></th>
<th>DS (n = 147)</th>
<th>Control Patients (n = 103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral fat, cm², median (IQR)</td>
<td>54.6 (39.9–81.9)</td>
<td>60.4 (41.2–104.1)</td>
<td>.052</td>
</tr>
<tr>
<td>Whole-body fat mass, kg, median (IQR)</td>
<td>18.7 (12.0–27.6)</td>
<td>22.4 (16.1–39.7)</td>
<td>.0007</td>
</tr>
<tr>
<td>Whole-body lean mass, kg, median (IQR)</td>
<td>36.2 (28.8–42.8)</td>
<td>36.3 (29.7–44.8)</td>
<td>.41</td>
</tr>
<tr>
<td>Whole-body lean mass, kg, median (IQR)</td>
<td>35.1 (27.6–42.4)</td>
<td>44.1 (32.4–52.2)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>FMI, kg/m², median (IQR)</td>
<td>9.3 (6.1–13.0)</td>
<td>9.0 (6.1–14.7)</td>
<td>.81</td>
</tr>
<tr>
<td>FMI z score, median (IQR)</td>
<td>0.90 (0.17–1.5)</td>
<td>0.76 (0.13–1.7)</td>
<td>.89</td>
</tr>
<tr>
<td>Lean BMI, median (IQR)</td>
<td>16.1 (13.6–18.6)</td>
<td>15.5 (13.2–17.9)</td>
<td>.27</td>
</tr>
<tr>
<td>Lean BMI z score, mean ± SD</td>
<td>0.55 ± 1.1</td>
<td>0.32 ± 1.2</td>
<td>.12</td>
</tr>
</tbody>
</table>

If continuous variables were normally distributed, then the t test was used (listed as mean ± SD); if not, then the Wilcoxon rank test was used (listed as median [IQR]). FMI, fat mass index; IQR, interquartile range.
We hypothesized that increased CMR in youth with DS would be associated with increased adiposity. Although previous research has indicated decreased resting energy expenditure in youth with DS compared with their unaffected siblings, this decrease did not explain the increased adiposity in youth with DS. In the current study, our results revealed decreased visceral fat, fat mass, and lean body mass for a given BMI z score. Although the BMI z score is a relative measure of adiposity, visceral fat, fat mass, and lean body mass are quantitative; this finding reveals that youth with DS are, overall, smaller than their typically developing peers. However, as fat mass increased, those with DS had greater visceral fat compared with those with non-DS (Fig 3 A and B). This higher level of visceral fat, however, did not fully explain the increased prevalence of dyslipidemia and prediabetes in youth with DS. This finding suggests that DS-specific phenomena may impart a predisposition to dyslipidemia.

Given the altered body proportions characteristic of DS, we considered whether BMI is truly the best clinical adiposity measure to predict CMR in youth with DS. Authors of a 2013 study examined the specificity and sensitivity of BMI to predict increased percentage of body fat by using DXA in 32 adolescents and young adults with DS and found that the obese, but not the overweight category, predicted an increased percentage of body fat well. In separate models, using non-HDL-C and triglycerides/HDL as outcomes, we added BMI, BMI z score, tri-ponderal mass index, waist circumference, waist-to-height ratio, or waist-to-hip ratio to our adjusted model. None of the other measures clearly performed better than BMI.

The reason for decreased HbA1c levels among participants with DS in our study is not clear. Wachtel and Pueschel reported macrocytosis in individuals with DS as well as increased red blood cell turnover. If the latter is confirmed, a shortened red blood cell life span could cause a factitious decrease in HbA1c levels. This finding warrants further investigation to inform appropriate screening methods in individuals with DS.

Although DS is associated with increased risk for T1DM, little is known about the risk for insulin resistance and T2DM, which are often consequences of obesity in individuals with non-DS. Hill et al demonstrated an elevated standardized mortality ratio of 11.4 for diabetes in individuals with DS but did not differentiate between diabetes types. Among youth with overweight and obesity, we identified an elevated prevalence of prediabetes (26.4% vs 10.3%; P = .025) in participants with DS compared with those with non-DS. This finding could potentially be explained by increased insulin resistance or by decreased pancreatic β-cell secretory capacity. Our results did not detect a difference in insulin resistance by HOMA-IR or Matsuda index between groups. Other studies have also revealed no difference in HOMA-IR among adults with and without DS. However, 1 report revealed that adults with DS had a higher waist-to-height ratio.

**TABLE 5 Metabolic Indices in Participants With Overweight or Obesity**

<table>
<thead>
<tr>
<th></th>
<th>DS (n = 96)</th>
<th>Control Patients (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL, median (IQR)</td>
<td>92.0 (85.0–97.0)</td>
<td>91.5 (85.0–93.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Insulin, μU/mL, median (IQR)</td>
<td>10.7 (6.9–15.1)</td>
<td>13.9 (7.6–20.1)</td>
<td>.07</td>
</tr>
<tr>
<td>HbA1c, %, mean ± SD</td>
<td>5.0 ± 0.29</td>
<td>5.5 ± 0.32</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>IFG, n (%)</td>
<td>12 (12.8)</td>
<td>3 (4.7)</td>
<td>.10</td>
</tr>
<tr>
<td>IGT, n (%)</td>
<td>10 (14.5)</td>
<td>3 (5.2)</td>
<td>.14</td>
</tr>
<tr>
<td>AGT, n (%)</td>
<td>19 (26.4)</td>
<td>6 (10.3)</td>
<td>.025</td>
</tr>
<tr>
<td>HOMA-IR, median (IQR)</td>
<td>2.4 (1.5–3.4)</td>
<td>3.0 (1.8–4.6)</td>
<td>.11</td>
</tr>
<tr>
<td>Insulinogenic index, median (IQR)</td>
<td>2.1 (1.1–4.1)</td>
<td>2.4 (1.2–4.3)</td>
<td>.63</td>
</tr>
<tr>
<td>DI, median (IQR)</td>
<td>0.25 (0.14–0.34)</td>
<td>0.19 (0.12–0.28)</td>
<td>.21</td>
</tr>
<tr>
<td>Matsuda index, median (IQR)</td>
<td>6.3 (5.0–11.1)</td>
<td>6.4 (4.2–11.3)</td>
<td>.42</td>
</tr>
</tbody>
</table>

Because of missing time points during the oral glucose tolerance test, for IGT, AGT, insulinogenic index, DI, and Matsuda index, n = 46–72 for those with DS and n = 56–78 for control patients. If continuous variables were normally distributed, then the t test was used (listed as mean ± SD); if not, then the Wilcoxon rank test was used (listed as median [IQR]). For categorical variables, Fisher’s exact test was used. AGT, abnormal glucose tolerance; DI, disposition index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range.
indicative of increased abdominal obesity, and that those with abdominal obesity had increased HOMA-IR. Some studies have revealed increased T2DM, high fasting glucose, and insulin resistance in individuals with DS. Given the numerous comparisons made in this study, we consider the increase in prediabetes prevalence to be preliminary data requiring verification in future studies. If future research confirms our findings of increased prediabetes prevalence and a lack of difference in insulin resistance in individuals with DS, dysglycemia could be attributable to a defect in β-cell secretory capacity. Although our study did not detect differences in insulinogenic index or disposition index among those with and without DS, these results may not be valid given missing data points during the oral glucose tolerance test. In a recent publication linking T2DM and DS, Peiris et al. sought genes that were involved in T2DM pathophysiology by focusing on the oxidative stress and mitochondrial dysfunction associated with β-cell dysfunction and impaired glucose-stimulated insulin secretion. Because islets from fetal tissue in those with DS also reveal β-cell mitochondrial dysfunction and impaired insulin secretion, Peiris et al. used a trisomy 21 screening approach, mouse models, and human gene expression studies to find new T2DM genes and identified regulator of calcineurin 1. This gene is involved in β-cell mitochondrial dysfunction associated with T2DM in the general population. Further studies are needed to determine the potential role of this gene in the increased diabetes risk in individuals with DS (T1DM and/or T2DM).

Our study has limitations. Obstructive sleep apnea, increased in both obesity and DS, is associated with greater insulin resistance and inflammation. However, the expense of polysomnography studies makes testing for obstructive sleep apnea infeasible. Our study involves many statistical comparisons, increasing the chance of type I error; but the analyses performed were necessary to address the specific aims of the study. Moreover, the majority of primary lipid outcomes were highly significant (P < .0005), decreasing the likelihood of false-positives. Our outcome of increased prevalence of prediabetes in DS should be considered preliminary and will need to be reassessed.

CONCLUSIONS

In this large study of youth with DS compared with their typically developing peers, we combined rigorous metabolic and cardiovascular disease risk testing with body composition measurements by using DXA. Our findings support a more atherogenic lipid and lipoprotein profile in those with DS, particularly higher LDL-C levels, after adjustment for demographics, puberty status, and BMI z score. These findings will be important to consider when designing specific screening recommendations for youth with DS, a topic highly relevant for general pediatricians caring for these children. Further longitudinal studies are needed to elucidate whether increased dyslipidemia in youth with DS translates into increased cardiovascular disease during adulthood and future risk for Alzheimer disease. Our preliminary data revealing an increased prevalence of prediabetes in youth with DS are intriguing, suggesting the need for studies of insulin secretion in individuals with DS. Continued research is needed to provide evidence-based guidelines for clinical care of youth and adults with DS.

ACKNOWLEDGMENTS

We thank the research assistants and coordinators, Divya Prasad, Rachel Walega, and Claire Cochran, for their efforts in recruiting study participants and performing study visits. We also thank all of the research participants and their families for making this work possible.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
cIMT: carotid intima media thickness
CMR: cardiometabolic risk
DS: Down syndrome
DXA: dual-energy X-ray absorptiometry
ELISA: enzyme-linked immunosorbent assay
HbA1c: hemoglobin A1c
HDL: high-density lipoprotein
HDL-C: high-density lipoprotein cholesterol
HOMA-IR: homeostasis model assessment of insulin resistance
hs-CRP: high-sensitivity C-reactive protein
IL-6: interleukin 6
LDL-C: low-density lipoprotein cholesterol
LDL-P: low-density lipoprotein particle
LPIR: lipoprotein insulin resistance index
OR: odds ratio
PWV: aortic stiffness by pulse wave velocity
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
VLDL-P: very low-density lipoprotein particle
and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Dr Magge's current affiliation is Division of Pediatric Endocrinology and Diabetes, School of Medicine, Johns Hopkins University, Baltimore, MD.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01821500).

DOI: https://doi.org/10.1542/peds.2019-0137

Accepted for publication May 17, 2019

Address correspondence to Sheela N. Magge, MD, MSCE, Division of Pediatric Endocrinology and Diabetes, School of Medicine, Johns Hopkins University, 200 N Wolfe St, Rubinstein Building, Room 3120, Baltimore, MD 21287. E-mail: smagge3@jhmi.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2019 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development grant R01HD071981-01A1 (Cardiometabolic Risk Factors and Obesity in Adolescents With Down Syndrome [multiple principal investigators: Drs Kelly and Magge]), by the National Institutes of Health National Center for Research Resources and National Center for Advancing Translational Sciences through grant UL1TR000003, and by Research Electronic Data Capture. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

21. DeFronzo RA, Matsuda M. Reduced time points to calculate the composite index. Diabetes Care. 2010;33(7):e93
22. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular


32. De la Garza-Hernandez NE, Gonzalez Cantu A, Zavala LGM, Rodriguez-Romo A. Descriptive analysis of anthropometric parameters, lipid profile, glucose and insulin in Mexican population with Down syndrome. In: Proceedings from the 98th Annual Meeting of the Endocrine Society, April 1–4, 2018; Boston, MA


Cardiometabolic Risk and Body Composition in Youth With Down Syndrome
Sheela N. Magge, Babette S. Zemel, Mary E. Pipan, Samuel S. Gidding and Andrea Kelly

*Pediatrics* 2019;144;
DOI: 10.1542/peds.2019-0137 originally published online July 17, 2019;

Updated Information & Services
including high resolution figures, can be found at:
hp://pediatrics.aappublications.org/content/144/2/e20190137

References
This article cites 55 articles, 11 of which you can access for free at:
hp://pediatrics.aappublications.org/content/144/2/e20190137#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
*Endocrinology*
http://www.aappublications.org/cgi/collection/endocrinology_sub

*Diabetes Mellitus*
http://www.aappublications.org/cgi/collection/diabetes_mellitus_sub

*Obesity*
http://www.aappublications.org/cgi/collection/obesity_new_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
hp://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
Cardiometabolic Risk and Body Composition in Youth With Down Syndrome
Sheela N. Magge, Babette S. Zemel, Mary E. Pipan, Samuel S. Gidding and Andrea Kelly

Pediatrics 2019;144;
DOI: 10.1542/peds.2019-0137 originally published online July 17, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/144/2/e20190137