

# Lipid Profiles of Children With Down Syndrome Compared With Their Siblings



**WHAT'S KNOWN ON THIS SUBJECT:** Some researchers have suggested that individuals with Down syndrome (DS) are protected from atherosclerotic disease; however, recent data from 2 large cohort studies of individuals with DS are significant for increased mortality from ischemic heart disease and cerebrovascular disease.



**WHAT THIS STUDY ADDS:** This study compares lipid profiles among children with DS and their siblings, highlighting the presence of a less favorable lipid profile in this high-risk population.

## abstract



**OBJECTIVES:** Our objective was to compare serum lipid profiles, total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), and high-density lipoprotein (HDL) between children with Down syndrome (DS) and their non-DS siblings. We hypothesized that the children with DS would have higher TC, LDL, and TG and lower HDL. The secondary aim was to explore if the difference in lipid profiles could be explained by differences in weight status.

**METHODS:** This was a cross-sectional study. Fasting lipid profile was obtained from 27 children with DS and 31 siblings between 4 and 10 years of age with no severe comorbidities (heart disease, cancer, hypothyroidism, diabetes, or obesity). BMI was calculated and BMI z scores were used to account for differences in BMI throughout childhood.

**RESULTS:** Children with DS had higher TC (difference, 11.2 mg/dL; 95% confidence interval: 2.5–19.9;  $P = .01$ ), LDL (12.8 mg/dL; 7.2–18.4;  $P < .001$ ), TG (33.6 mg/dL; 11.1–56.1;  $P = .003$ ), and lower HDL (–7.6 mg/dL; –12.1 to –3.0;  $P = .001$ ) after adjustment for race, gender, age, and ethnicity. Results remained significant after additional adjustment for BMI z score: TC (14.9 mg/dL; 4.9–24.9;  $P = .003$ ), LDL (16.6 mg/dL; 10.1–23.2;  $P < .001$ ), TG (32.7 mg/dL; 7.7–57.7;  $P = .01$ ), and lower HDL (–6.4 mg/dL; –12.2 to –0.7;  $P = .03$ ).

**CONCLUSIONS:** Children with DS have less favorable lipid profiles than their siblings independent of weight status. These findings may have important implications for the screening and treatment of this large population at increased risk for ischemic heart disease. *Pediatrics* 2012;129:e1382–e1387

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### KEY WORDS

hypercholesterolemia, Down Syndrome, pediatrics, obesity, prevention

### ABBREVIATIONS

CVD—cardiovascular disease  
DS—Down syndrome  
GEE—generalized estimating equations  
HDL—high-density lipoprotein  
ID—intellectual disability  
LDL—low-density lipoprotein  
TC—total cholesterol  
TG—triglyceride

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Down syndrome (DS) is one of the most common causes of developmental disability in the United States with a prevalence of 1 of every 691 live births.<sup>1</sup> Persons born with DS are at increased risk for various health conditions, including thyroid disease, leukemia, congenital heart defects, gastrointestinal tract abnormalities, obesity, and diabetes mellitus.<sup>2</sup> Despite this increased risk of chronic disease, life expectancy for individuals with DS has continued to improve with an estimated mean survival approaching 60 years of age.<sup>3</sup> Increasing life expectancy along with an elevated risk of obesity and diabetes mellitus in individuals with DS, raise concerns about long-term health, in particular, atherosclerotic cardiovascular disease. Obesity and insulin resistance, which are common among individuals with DS, are associated with unfavorable (more atherogenic) lipid profiles, characterized by high triglycerides (TGs) and low high-density lipoprotein (HDL) cholesterol. Previous studies comparing lipid and lipoprotein concentrations in individuals with DS with individuals without DS have produced conflicting results.<sup>4–8</sup> Additionally, it is unclear if individuals with DS have a particularly atherogenic lipid profile before developing obesity and diabetes.

Historically, individuals with DS were considered protected from atherosclerotic disease and, in fact, some researchers had proposed DS as an “atheroma-free” model of disease.<sup>4</sup> Results of postmortem studies that found individuals with DS to have no atherosclerotic plaques, decreased frequency of arteriosclerosis, or decreased total area of raised lesions compared with non-DS controls are cited in the literature.<sup>4,9,10</sup> However, there are conflicting reports that do not support describing DS as an atheroma-free model of disease. In examining autopsy material of institutionalized children <21 years of

age with intellectual disability (ID), slightly more atherosclerosis was found in the coronary arteries and aortas of persons with DS in comparison with other residents with ID.<sup>11</sup> Another study found fatty streaks and early fibromuscular lesions in aortic segment autopsy material obtained from both the DS and control group, concluding that there was no decrease in prevalence of preatherosclerotic lesions in persons with DS compared with a control group that comprised persons with ID but without DS.<sup>12</sup>

Recent data from 2 large epidemiological studies of individuals with DS suggest that they may actually have an increased risk of mortality from ischemic heart disease and cerebrovascular disease compared with the general population.<sup>13,14</sup> In 1 study of >4800 individuals from Sweden and Denmark, individuals with DS were found to have a 3.9-fold increased incidence of mortality due to ischemic heart disease. The authors of the study acknowledged that participants were selected through a hospital-based registry and may constitute a population with a greater risk for mortality.<sup>13</sup> However, another epidemiological study of >14 000 individuals in California found a similar 4.3-fold increased incidence of mortality due to ischemic heart disease. In this study, participants were selected from a state department of developmental services registry.<sup>14</sup>

The aim of this study was to compare lipid profiles of nonobese, nondiabetic children with DS with their non-DS siblings to assess if DS is associated with an unfavorable lipid profile, independent of weight status. Because lipid profile is strongly associated with genetic and lifestyle factors, this sibling design is particularly useful to investigate the effect of DS on lipids, while reducing the between-group difference in familial variables. We hypothesized that children with DS would

have higher total cholesterol (TC), higher low-density lipoprotein (LDL) cholesterol, higher TG, and lower HDL cholesterol compared with sibling controls. Additionally, we expected the DS group, even if nonobese, to have a greater BMI; therefore, the secondary aim of the study was to determine if differences in lipid profiles were mediated by BMI.

## METHODS

### Participants

This cross-sectional study used participants from a 3-year prospective cohort study of growth and changes in body composition in children with DS and their siblings. Thirty-six families were recruited from the Philadelphia metropolitan area through physician referrals and information circulated to local DS parent groups. Families who had 1 child with DS and 1 child without DS were screened by telephone for eligibility. Inclusion criteria for the larger cohort study were as follows: (1) participants between 4 and 10 years of age, (2) prepubertal, (3) BMI below the 95th percentile for age and gender,<sup>15</sup> based on parental telephone report of subject's weight and height. For the current study, participants at or above the 95th BMI-for-age percentile when they presented at the study visit were also excluded. Children <4 years were excluded secondary to concerns about compliance with some of the measurements of the larger cohort study and children >10 years were excluded in an effort to limit the sample to prepubertal children. The following conditions were used as exclusion criteria: (1) history of congenital cardiac defect requiring open heart surgery; (2) history of intestinal anomalies requiring bowel resection and/or ongoing medical intervention; (3) history of hypothyroidism requiring medication or other chronic conditions known to affect energy balance or growth (including diabetes); and (4) history of cancer. If >1

sibling met eligibility criteria, the caregiver selected one to participate based on the child's interest. Written informed consent from parent/guardian and assent from participants were obtained, and all procedures were reviewed and approved by the Institutional Review Board at The Children's Hospital of Philadelphia.

## Procedures

Demographic information was obtained via questionnaire during the families' initial visit to the Clinical and Translational Research Center at The Children's Hospital of Philadelphia. Anthropometric measurements were also obtained at the Clinical and Translational Research Center. Participants were weighed without shoes, wearing a light-weight gown on a daily calibrated Scaletronix digital scale (Scaletronix, White Plains, NY). Standing height was obtained via wall-mounted stadiometer (Holtain, Inc, Crymych, UK). Weight and height were measured in triplicate by a trained anthropometrist with the use of research-standard methods.<sup>16</sup> All participants were measured by 1 single highly trained anthropometrist whose reliability was regularly assessed. BMI, defined as weight in kilograms divided by height in meters squared, was calculated. Because BMI varies with age and differs by gender, BMI z score was calculated by using age-, race-, and gender-specific BMI reference data.<sup>17</sup> After a 12-hour supervised inpatient overnight fast with 24-hour nursing staff present, blood samples were drawn for TC, direct HDL, and TG. TC and TG levels were analyzed by the colorimetric method, with a reportable dynamic range of 50 to 325 mg/dL for cholesterol and 10 to 525 mg/dL for triglycerides. HDL was quantitatively measured by using a 2-point rate analysis via spectrophotometer with a reportable dynamic range of 3 to 110 mg/dL. LDL cholesterol was calculated by using the Friedewald equation.<sup>18</sup>

## Statistical Analysis

Descriptive analyses were performed. Mean TC, LDL, HDL, and TG values were then analyzed for the 2 groups and compared by using generalized estimating equations (GEEs).

GEEs were implemented by using the xtgee procedure in Stata software (version 7.0; Stata Corp., College Station, TX). GEE extends linear regression and logistic regression to nonindependent data by specifying a working correlation structure that describes the pattern of association among the non-independent measurements, in addition to the usual linear or logistic model for the expected value of the outcome variable. GEE was used to account for a lack of independence between the 2 groups and to adjust for confounding variables of age, gender, race, and ethnicity. The association of DS status with TC, HDL, LDL, and TG level was first analyzed unadjusted, then adjusting for confounding variables. To determine if BMI mediated any difference in lipid profile variables between the 2 groups, adjusted analyses were then performed with additional adjustment for BMI z score. The goal was to assess differences in TC, HDL, LDL, and TG between children with DS and the sibling control group, to adjust for potentially confounding variables, and to determine whether BMI mediated the observed difference. All analyses were performed by using Stata software and a *P* value of <.05 was accepted as statistically significant.

## RESULTS

Of the 36 children with DS enrolled in the study, one was excluded secondary to a new diagnosis of hypothyroidism requiring treatment with hormone replacement therapy. Of the 36 siblings enrolled, 3 refused phlebotomy; therefore, no lipid samples were available. In addition, 8 subjects with DS and 2 control subjects were excluded because their BMI for age was at or above the 95th

percentile at the measurement visit. Therefore, data were analyzed for 27 children with DS and 31 sibling controls. Descriptive information on study participants is reported in Table 1, including height and weight percentile ranges on DS growth curves for the children with DS.<sup>19</sup> As expected, the children in the DS group were shorter and had higher BMI z scores compared with the sibling group.

Mean TC, LDL, TG, and HDL values for the DS group and the sibling groups are reported in Table 1. None of the lipid profiles obtained had any immediate clinical implications requiring medical or nutritional intervention. Mean TC, LDL, and TG levels were higher in the DS group than the sibling control group, and HDL levels were lower, although these differences were not statistically significant in the unadjusted analysis for TC and LDL. Unadjusted and adjusted analyses of the difference in mean lipid values between the study groups are presented in Table 2. Potentially confounding variables (gender, age, race, and ethnicity), identified a priori, were used to adjust differences in lipid levels. The differences in lipid concentrations were essentially unchanged after additional adjustment for BMIz (Table 2).

## DISCUSSION

Results from this study suggest that the lipid profile of nonobese prepubertal children with DS is less favorable than that of their siblings, with higher concentrations of TC, LDL, and TG and lower concentrations of HDL after adjustment for important confounding factors. Our findings of increased TC, LDL, TG, and decreased HDL in individuals with DS are similar to 1 previous report by Zamorano et al<sup>20</sup> in Chile in 1991. In that study, lipid profiles of 72 children with DS were compared with 66 controls without DS. Children with DS were

**TABLE 1** Descriptive Characteristics ( $\pm$  SD) of Study Participants

	Subjects with Down Syndrome	Siblings	Unadjusted <i>P</i>
Subject characteristics			
<i>n</i>	27	31	NS
Age, y	6.6 $\pm$ 2.1	7.2 $\pm$ 2.3	NS
Gender, % female	48.1	48.4	NS
Race			
% African American	0	9.7	NS
% Asian	3.7	3.2	
% White	96.3	87.1	
Ethnicity			
% Hispanic	11.1	12.9	NS
% Non-Hispanic	88.9	87.1	
Anthropometric measures			
Height, cm	108.7 $\pm$ 10.6	122.7 $\pm$ 15.6	<.001
Height for age percentile on DS growth chart	60.8th (4.7th to 99.0th)	N/A	
Weight, kg	20.6 $\pm$ 5.6	25.3 $\pm$ 9.1	.01
Weight for age percentile on DS growth chart	42.9th (2.9th to 91.9th)	N/A	
BMi <sub>z</sub>	0.75 $\pm$ 0.7	-0.1 $\pm$ 0.1	<.001
Lipid profile, mean value (SD)			
TC	173.2 $\pm$ 24.3	166.1 $\pm$ 19.1	NS
HDL	48.3 $\pm$ 13.8	54.2 $\pm$ 16.4	.001
LDL	103.8 $\pm$ 20.3	96.6 $\pm$ 15.2	NS
TG	105.7 $\pm$ 53.6	76.5 $\pm$ 33.2	.003

N/A, not applicable; NS, not significant.

**TABLE 2** Mean Differences (95% CI) in Lipid Profile Variables Between Subjects With Down Syndrome and Their Siblings (Reference Group)

	Unadjusted	<i>P</i>	Adjusted ( <sup>a</sup> )	<i>P</i>	Adjusted ( <sup>b</sup> )	<i>P</i>
TC	7.1 (-2.3 to 16.5)	.14	11.2 (2.5-19.9)	.01	14.9 (4.9-24.9)	.003
HDL	-6.8 (-10.8 to -2.8)	.001	-7.6 (-12.1 to -3.0)	.001	-6.4 (-12.2 to -0.7)	.03
LDL	7.4 (-0.5 to 15.2)	.07	12.8 (7.2-18.4)	<.001	16.6 (10.1-23.2)	<.001
TG	29.4 (9.8-49.1)	.003	33.6 (11.1-56.1)	.003	32.7 (7.7-57.7)	.01

Values are given in milligrams per deciliter. CI, confidence interval.

<sup>a</sup> Adjusted for age, gender, race, ethnicity, and income.

<sup>b</sup> Additional adjustment for BMI z score.

found to have higher TG, TC, LDL, and lower HDL compared with controls. Weight, BMI, age, and gender were not controlled for in that study. Other studies of lipid and lipoprotein concentrations in individuals with DS have produced varying results ranging from no significant difference in cholesterol, triglycerides, and lipoprotein levels between DS and non-DS groups to reports of increased serum cholesterol, triglycerides and oxidatively modified LDL.<sup>4-8,21</sup> Our study is the first to use exclusively sibling controls to show all measured lipid parameters to be less favorable in the DS group after adjustment for important confounding factors.

Our findings of less favorable lipid profiles in the DS group are also significant in light of a recent study on obesity in children with DS. In that study, the authors concluded that, given the high rates of obesity in children with DS, obesity laboratory assessment protocols for the general pediatric population should also be applied to children with DS.<sup>22</sup> Although current DS health supervision guidelines encourage the monitoring of BMI and emphasize education to prevent obesity, there are no specific recommendations for obesity-related laboratory assessment.<sup>23</sup>

The mechanism by which individuals with DS develop a less favorable lipid

profile than their siblings is unclear, but, based on our results, this mechanism does not appear to be explained by overall adiposity, as measured by BMI. Differences observed in lipid profile may be related to fat distribution, but, because the current study was not designed to answer this question, anatomic distribution of fat was not measured. In the general population, increased waist circumference and waist-to-height ratio are associated with an unfavorable lipid profile; however, to our knowledge, no studies of adipose tissue distribution in individuals with DS have been performed. In addition, there is a known association between hypothyroidism and hyperlipidemia, and many individuals with DS have hypothyroidism; however, hypothyroidism requiring treatment was one of the exclusion criteria for this study. In their epidemiological study, Hill et al<sup>13</sup> postulated that the excess mortality from cardiovascular disease (CVD) in DS may be related to unrecognized congenital heart defect, increased BMI, and tendency toward diabetes mellitus in persons with DS. However, these conditions were excluded or adjusted for in our study, suggesting that an unfavorable lipid profile may also play a role in the increased CVD mortality of individuals with DS.

Hyperglycemia and insulin resistance are also known to be related to dyslipidemia. Hyperglycemia can cause increased oxidative stress, glycosylation of proteins such as LDL cholesterol (making it more atherogenic), decreased nitric oxide production, and increased coagulability, leading to endothelial injury and increased atherogenic risk.<sup>24</sup> In addition, insulin resistance at the level of the adipocyte can increase free fatty acids, and result in increased small, dense LDL cholesterol.<sup>25</sup> In a previous publication by our group, we compared obesity-related hormones between the same 2 study groups (children with DS and sibling controls).<sup>26</sup>

We found no significant difference in glucose ( $83.4 \pm 7.7$  mg/dL in the DS group and  $80.5 \pm 11.0$  mg/dL in the sibling group,  $P = .095$ ) or insulin ( $10 \pm 10.3$   $\mu$ U/mL in DS group vs  $7.7 \pm 2.2$   $\mu$ U/mL in the sibling group,  $P = .3$ ) between the 2 groups in the unadjusted comparison. When the comparison was adjusted for age, gender, race, and ethnicity, the difference in insulin was still not significant ( $P = .1$ ), but the difference in glucose became statistically significant ( $P = .007$ ). Despite the statistical significance, the authors do not believe the difference between 83.4 mg/dL and 80.5 mg/dL to be clinically significant. They are both well within the normal fasting glucose range. Although the relationship between glucose and the risk for diabetes is considered to be a continuum (even if glucose is in the normal range), the authors do not know of any such data for the relationship between glucose and dyslipidemia.

Given our study design and results, congenital heart defects, hypothyroidism, weight status, glucose, and insulin levels are unlikely to explain the difference in lipid profile in these children with DS compared with their siblings, and the question of whether overexpression of chromosome 21 directly influences lipid profile can be raised. In a study screening for additional familial combined hyperlipidemia genes, a locus conferring susceptibility to elevated apoB levels was identified on chromosome 21.<sup>27</sup> A study performed on fetuses with DS was suggestive of abnormalities of lipid metabolism in utero, before other factors could influence lipid levels. DS fetuses were also found to have increased TC and increased apolipoprotein A levels compared with controls.<sup>28</sup>

Another possible mechanism for increased dyslipidemia in children with DS involves leptin, a hormone secreted

by adipose tissue that correlates with percentage of fat mass in humans.<sup>29</sup> In a previous study, we found that children with DS had increased leptin levels for percentage of body fat when compared with their siblings, suggesting increased leptin resistance at the same fat level with DS.<sup>26</sup> Leptin is also significantly associated with total cholesterol and triglycerides, even after adjusting for BMI.<sup>30</sup> Therefore, it is possible that increased leptin resistance in DS may play a role in the lipid profile of the children with DS observed here.

The strengths of this study included the use of biological siblings as a control group, reducing the effect of potential familial and environmental factors, as well as the recruitment bias of healthy controls. The limitations of this study include its relatively small sample size and exclusion of individuals with DS who have comorbid disease, which reduces the generalizability to most children with DS. This design, however, decreased the risk of confounding by these conditions and increased the chances to identify an effect of DS alone. Because there is no national DS registry, our sample of patients with DS does not represent a population-based sample of all persons with DS. We acknowledge the possibility that the families willing to participate in our study may have children with more complex medical needs. We acknowledge the possibility that families willing to participate in our study may have children with more complex medical needs. Additional limitations include the failure to control for blood sugar levels, insulin levels, or hemoglobin A1c because blood sugar, insulin, and hemoglobin A2c can potentially affect lipid levels.

## CONCLUSIONS

Our findings of unfavorable lipid profiles in young, prepubertal, nonobese

children with DS are significant in light of recent epidemiological studies showing increased mortality from ischemic heart disease and CVD in persons with DS. It will be important to conduct long-term surveillance of children with DS to determine whether these differences in lipid profile translate into increased morbidity and mortality from CVD. A scientific statement from the American Heart Association presented guidelines for more aggressive cardiovascular risk management in pediatric patients with conditions associated with increased risk of CVD.<sup>31</sup> DS is not included among these conditions. If our findings are confirmed by longitudinal data linking lipid profile with CVD morbidity and mortality among people with DS, they would suggest that children with DS also constitute a group at high risk for dyslipidemia and ischemic heart disease and should be considered for early routine screening and treatment, similar to other children at higher risk. As with other populations, treatment should start with therapeutic lifestyle changes and additional pharmacology therapy as needed. Children with DS constitute a large population at high risk for obesity, diabetes and, based on our data, a less favorable lipid profile, which is an additional risk factor for adult CVD. With the increased life expectancy of individuals with DS and the increasing importance of adult chronic disease in this population, optimal CVD prevention is necessary in children and adults with DS.

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