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Cardiometabolic profiles in children and adults with overweight and obesity and down syndrome

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Abstract

Individuals with Down syndrome (DS) are at increased risk for being overweight/obese, but the associated cardiometabolic risk (CR) is not clear. Cross-sectional anthropometric and clinical laboratory data from a multi-site, international cohort of individuals with DS were analyzed to determine cardiometabolic risk by reporting observed distributions of cardiometabolic biomarkers in overweight/obese individuals with DS throughout the lifespan. Descriptive statistics and regression analyses by age categories determined the distributive percentiles for cardiometabolic biomarkers and tested for adiposity as a predictor of CR. Across seven DS clinics, data were collected on 240 patients between the ages of 3 and 63 years, with one quarter overweight and three quarters obese among children and nearly all adults being obese. In children and adults, most cardiometabolic biomarker profiles showed distributive values within normal ranges. Blood lipids were positively associated with body mass index (BMI) in children (high density lipid-cholesterol, $p = 0.01$; low density lipid-cholesterol, $p = 0.02$). Levels of hs-CRP were elevated in both children and adults, with BMI positively associated with hs-CRP in adults with DS ($p = 0.04$). Liver enzyme values were positively associated with BMI in children and adults. The data suggest that in contrast to the general population, in individuals with Down syndrome, being overweight and obese does not appear to confer a significantly increased risk for cardiometabolic disease by biomarker profile. Individuals with DS who are overweight/obese appear to have unique cardiometabolic profiles unrelated to adiposity, notable for increased hs-CRP and normal HA1c levels.

KEYWORDS
cardiometabolic, Down syndrome, obesity, trisomy 21

Abbreviations: BMI, body mass index; DS, Down syndrome; HA1c, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein.

1 | BACKGROUND

Overweight and obesity is associated with an increased risk of developing diabetes, elevated blood pressure, nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease. Individuals with Down syndrome (DS) are at increased risk for being overweight/obese due to constitutional, behavioral, and metabolic differences including generalized hypotonia, short stature, unhealthful dietary patterns, decreased resting energy expenditure with low levels of physical activity, presence of comorbidities and gait disorders, and increased circulating leptin concentration and reduced adiponectin expression (Bertapelli et al., 2016; Moreau et al., 2021; Ptomey et al., 2020). Some studies, however, indicate that the rates of Type 2 diabetes, hypertension, and coronary artery disease may be lower in people with DS than in the general population (Chicoine et al., 2021; Santoro et al., 2020). A better understanding of cardiometabolic risk has been identified as a key knowledge gap among researchers in the DS community (Hendrix et al., 2021). The aim of this research was to assess cardiometabolic risk in individuals with DS identified as overweight/obese by reporting their observed distribution of clinical cardiometabolic biomarkers.

Levels of high-sensitivity C-reactive protein (hs-CRP), a bioactive molecule produced by the body when blood-vessel walls are inflamed, increase during periods of inflammation in the body. High levels of hs-CRP have been shown to predict risk of cardiovascular disease and adverse cardiovascular events in the general population (Lagrand et al., 1999). Adults with DS may have an increased risk for cardiovascular events compared to the general population, although the underlying etiology of increased risk can vary with cardiovascular events occurring alongside congenital vascular anomalies in individuals with DS while cardiovascular disease is related to increased cardioembolic stroke risk in the general population (Santoro et al., 2018; Bello et al., 2017; Powell-Wiley et al., 2021; Sobey et al., 2015), One recent study in children with DS showed increased levels of hs-CRP (Magge et al., 2019), yet the range of values across the lifespan and the predictive utility of using hs-CRP to determine cardiovascular risk in the theoretically increased at-risk population of individuals with DS who are overweight and obese remains unknown.

Elevated cholesterol and dysregulated blood lipid profiles are a long established risk for cardiovascular disease and an important modifiable risk factor for coronary heart disease, heart attack, and stroke (American Heart Association, n.d.). Prior studies looking at blood lipid levels in individuals with DS have shown mixed results, with studies finding altered blood lipid levels in children with DS (Magge et al., 2019; Adelekan et al., 2012; Buonuomo et al., 2016), while a study found adults with DS to have normal blood lipid levels (Tansley et al., 2012).

Blood pressure, an important marker of risk for future cardiovascular events, has been shown to be lower in children with DS than reported values in the general population. While age, sex, and race were not predictive of blood pressure in one recent study, the study did not assess for weight, an important modifier of blood pressure (Santoro et al., 2020).

A few studies have reported on liver function values in children with DS and indicate a possible increased risk for nonalcoholic fatty liver disease in children with DS who are overweight or obese (de Matteo & Vajro, 2017; Valentini et al., 2017, 2020). Whether this co-occurring association is a result of obesity or simply an association related to other metabolic drivers is unclear.

While an increased prevalence of Type 1 diabetes mellitus has been reported in individuals with DS, thought to be related to immune system dysregulation, risk for Type II diabetes mellitus in overweight and obese individuals with DS is less clear. Type II diabetes is typically related to adiposity and metabolic profile in the neurotypical population (Moreau et al., 2021).

Risk for metabolic syndrome in individuals with DS remains an ongoing area of research with recent studies reporting the condition in children, adults and elderly (de Asua et al., 2014; de Winter et al., 2011; Valentini et al., 2020). Though individuals with DS share common risk factors and associated clinical conditions, the prevalence of metabolic syndrome in this population remains unclear at this time.

Given that adiposity is a known risk factor for Type II diabetes, nonalcoholic fatty liver disease, hyperlipidemia, and cardiovascular disease in the neurotypical population, we aimed to describe these risks in individuals with DS. In this large, multi-site study, we assess cardiometabolic risk for individuals with DS who are overweight/obese by reporting the distribution of clinical biomarkers and measurements, including hemoglobin A1c, liver function, blood lipids, hs-CRP, thyroid stimulating hormone, blood pressure, heart rate, body mass index, and waist circumference.

2 | METHODS

2.1 | Sites and participants

All data were collected as part of the International Down Syndrome Patient Database (IDSPD), a multi-center voluntary registry containing provider entered data (Lavigne et al., 2015). Seven sites participated in the collection of data for this study including Massachusetts General Hospital (Boston, MA), Boston Children's Hospital (Boston, MA), Duke University Medical Center (Durham, NC), Children's Hospital of Pittsburgh (Pittsburgh, PA), Geisinger Medical Center (Danville, PA), Mater Hospital (South Brisbane, Australia), and The Bambino Gesu' Children's Hospital (Rome, Italy). Institutional Review Board approval was obtained from each participating site. Consent or a waiver of consent was obtained for participants in the IDSPD to allow review of medical records and extraction of data into a shared database. A single study protocol was collaboratively developed and used at all sites to ensure that data collection and measurement procedures were the same across all sites and countries. Data were collected on patients ages 3 years and older presenting at their routine DS specialty clinic visits; all sites agreed on the need for the clinical data to be collected, and no additional tests or procedures outside of standard of care were collected. Given the established association between excess adiposity and alterations in serum clinical biomarkers in the general population, including HA1c, liver and thyroid function, blood lipids, and hs-CRP, we collected data on these clinical biomarkers in overweight/obese

individuals with DS to assess for the similar presence of biomarker dysregulation. Given the well-established associated between excess adiposity and cardiometabolic disease and mortality risk in the general population, enrollment in this study was limited to subjects who were classified as overweight and obese. As our main objective was to assess the distribution of metabolic biomarkers in overweight/obese patients followed at DS specialty clinics, the study included patients ages 3 years and older with Down syndrome who were overweight or obese by body mass index (BMI) criteria (BMI ≥85 percentile for age and sex in children and BMI ≥25 in patients 18 years and older).

2.2 | Data

Cross sectional data were collected, with each subject's data collected once. Data were collected during or after subjects' scheduled DS specialty clinic visits between January 1, 2018, and December 31, 2019. Data collected included clinical and electronic health records data. Clinical data obtained from the day of the visit included (1) physiologic, (2) anthropometric, and (3) laboratory data. In addition, demographic and medical history data were obtained from patients' electronic health records.

Laboratory data included blood serum and clinical biomarkers for cardiometabolic disease. Specifically, biomarkers were collected for diabetes (Hemoglobin A1c), thyroid dysregulation (TSH), electrolyte dysregulation (basic metabolic panel), cardiovascular disease (blood lipids, hs-CRP, blood pressure, heart rate), and kidney disease (BUN, creatinine, and estimated glomerular filtration rate). An anion gap was calculated for each subject, a marker for metabolic dysregulation seen in organ dysfunction, including kidney disease, lung disease, heart disease, and other organ disorders. Missing data were coded as missing values and subjects with missing data were retained in the final analysis as long as complete data on age, BMI, and clinic site were available.

2.3 | Anthropometric and physiologic data

All sites were provided with visual and written instruction on how to measure height and weight, obtain waist circumference, and measure blood pressure (Williams et al., 2009). Height, weight, waist circumference, and blood pressure were obtained on each patient, each measured in duplicate and averaged. Weight status was determined by BMI, calculated as weight in kilograms divided by height in meters squared for adults and by using age- and sex-specific BMI percentiles for children according to the Centers for Disease Control growth references (US Department of Health and Human Services, n.d.). While growth charts for youth with DS are available, their use remains controversial, and DS-specific charts have not been shown to provide superior weight status classification compared to CDC growth charts (Hatch-Stein et al., 2016). The presence or absence of acanthosis nigricans was assessed clinically by a physician and documented for each patient.

2.4 | Clinical laboratory data

Non-fasting blood hemoglobin A1c (HA1c), lipid cholesterol levels (total cholesterol, high density lipid-cholesterol/HDL-C, low density lipid-cholesterol/LDL-C, triglycerides), thyroid stimulating hormone (TSH), serum electrolytes (sodium, potassium, bicarbonate, chloride, glucose, calcium, magnesium, phosphate, anion gap), renal function (creatinine, blood urea nitrogen), liver function (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), Alkaline Phosphatase, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin), and high sensitivity C-reactive protein (hs-CRP) were collected on each patient.

2.5 | Analysis

We used descriptive statistics to report patient characteristics, including demographic, as well as all clinical data. Data were grouped by age categories and reported separately for children and adults, with mean values along with standard deviation (SD) calculated for continuous variables. Distributive percentiles were also calculated for each metabolic biomarker. Separate linear regressions with BMI percentile in children and BMI in adults as the independent variable and each cardiometabolic biomarker as the dependent variable and adjusted for age, sex, and country tested for adiposity as a predictor of cardiometabolic risk in DS (regression results are provided in the Supplementary Index materials).

3 | RESULTS

The study sample includes 240 patients between the ages of 3 and 63 years, with 157 pediatric patients and 83 adult patients (Table 1). Half (50%) of the study sample was female, with 75% White, 3% Black, 2% Asian, and 6% identifying as Latinx. Among pediatric patients, 38 were preschool aged (3–5 years old), 78 were grade school aged (6–12 years old), and 41 were middle and high school aged (13–18 years old). Roughly one quarter of pediatric patients were overweight with three quarters obese, while the majority (94%) of adult patients were obese.

3.1 | Children

3.1.1 | Anthropometric and physiologic data

Table 2 provides the minimal, maximal, mean and SD values for the anthropometric, physiologic, and laboratory data for children by age group. Percentile values are provided in Table S1. Blood pressures in children with DS increased with age while heart rate decreased with age, with values in similar ranges to pediatric reference values (Hughes & Kahl, 2018). One subject had a diagnosis of hypertension. Ten children (6%) had documented acanthosis nigricans. We found no

TABLE 1 Demographic characteristics of study sample, $N = 240$

	Pediatric ($N = 157$)	Adult ($N = 83$)	Total ($N = 240$)
Age (yr): Mean (SD)	9.4 (4.5)	32.0 (11.9)	16.7 (13.1)
USA ($N = 162$)	9.0 (4.9)	31.7 (11.9)	19.1 (14.3)
Italy ($N = 72$)	9.7 (3.9)	40.0 (0.0)	10.1 (5.3)
Australia ($N = 6$)	–	33.7 (13.4)	33.7 (13.4)
Sex: *N* (%)			
Male	74 (47.1)	43 (51.8)	117 (48.8)
Female	82 (52.2)	38 (45.8)	120 (50.0)
Missing	1 (0.6)	2 (2.4)	3 (1.2)
Race: *N* (%)			
White	123 (78.3)	57 (67.7)	180 (75.0)
Black	5 (3.2)	2 (2.4)	7 (2.9)
Asian	5 (3.2)	0 (0)	5 (2.1)
Native American	1 (0.6)	0 (0)	1 (0.4)
Ethnicity: *N* (%)			
Latinx	8 (5.1)	6 (7.2)	14 (5.8)
Medical history: *N* (%)			
Overweight	34 (22.7)	5 (6.0)	39 (16.3)
Obese	123 (77.3)	78 (94.0)	201 (83.7)
Thyroid disease	41 (26.1)	39 (47.0)	80 (33.3)
Diabetes type 1	1 (0.6)	–	1 (0.4)
Diabetes type 2	–	1 (1.2)	1 (0.4)
Hypertension	1 (0.6)	4 (4.8)	5 (2.1)
Hyperlipidemia	3 (1.9)	10 (12.0)	13 (5.4)

[a]Hypertension, high blood pressure; hyperlipidemia, high blood cholesterol profile.

association between BMI and heart rate or blood pressure in children. Waist circumference in children was associated with BMI, with each 1-unit increase in BMI percentile increasing waist circumference by 2.3 cm ($p < 0.0001$) (Table S4).

3.1.2 | Clinical laboratory data

The mean HA1c values were normal in all age groups. One child had a diagnosis of Type 1 diabetes. The 95th percentile of HA1c was elevated falling within the prediabetic range at 5.9% for children ages 6–12 years, while the corresponding values were within normal ranges for children ages 3–5 and 13–18 years. Body mass index was not associated with HA1c in children.

The mean levels of blood lipids, including total cholesterol (TC), LDL-C, HDL-C, and triglycerides, were within normal recommended ranges in all age groups. Three children had a diagnosis of hyperlipidemia. Total cholesterol values surpassed recommended ranges starting at the 95th percentile in children with DS (201 mg/L in 3–5 years, 224 mg/L in 6–12 years, and 214 mg/L in 13–18 years). LDL-C was above recommended values at the 95th percentile for children 6–12 years (153 mg/L) and at the 85th percentile for children 13–18 years (133 mg/L), while HDL-C was below a recommended level of 40 mg/L in half of children ages 3–5 years, and up to three quarters of children ages 6 years and older. Triglycerides levels were above recommended ranges at the 85th percentile for children 3–5 years (185 mg/L) and 13–18 years (168 mg/L) and at the 95th percentile for 6–12 years (222 mg/L). Adiposity was significantly associated with both HDL-C and LDL-C in children, with a 1-unit increase in BMI percentile corresponding to a 0.8 mg/L decreased in HDL-C ($p = 0.01$) and a 1.7 mg/L increase in LDL-C ($p = 0.02$).

The mean (SD) TSH values were 3.9 (2.0) uIU/mL, 5.2 (8.5) uIU/mL, and 4.3 (3.4) uIU/mL in children ages 3–5, 6–12, and 13–18 years, respectively. At the 85th percentile of the population values, TSH levels were found to be within elevated ranges across all pediatric age groups, at 6.3 uIU/mL in 3–5 years, 6.0 uIU/mL in 6–12 years, and 6.6 uIU/mL in 13–18 years. Forty-one children had a current or previous thyroid disorder diagnosis. Thyroid function was not associated with calculated adiposity.

The ranges for serum electrolyte values in children with DS corresponded to published reference ranges for neurotypical children, without any large variations by age group. Calculated adiposity was positively associated with glucose level, with each 1-unit increase in BMI percentile increasing glucose by 0.5 mmol/L, $p < 0.0001$.

All measures of renal function likewise fell within normal ranges for children. Renal function was not associated with BMI percentile.

For liver function biomarkers, all mean values were within normal ranges. The 85th and 95th percentiles for GGT in adolescents 13–18 years were 74 and 81 U/L, respectively, and each 1-unit increase in BMI percentile was associated with a 1 U/L increase in GGT in

TABLE 2 Distribution of metabolic biomarkers in children with down syndrome who are overweight or obese, $N = 157$.

	3–5 years				6–12 years				13–18 years			
	Mean	Min	Max	SD	Mean	Min	Max	SD	Mean	Min	Max	SD
Physiologic/vital signs												
SBP (mmHg)	104	86	121	10	110	75	141	11	119	99	137	9
DBP (mmHg)	63	48	82	9	67	40	89	10	71	46	91	11
HR (bpm)	101	73	137	14	88	62	115	14	85	62	116	12
WC (cm)	59	43	76	7	79	27	110	13	100	51	148	19
BMI percentile	97	87	100	4	96	72	100	5	97	86	100	3
Metabolic												
TSH (ulU/mL)	3.9	1.3	11	2.0	5.2	1.5	72.8	8.5	4.3	1.2	18.9	3.4
HA1c (%)	4.9	4.4	5.3	0.3	5.1	4.3	6.7	0.4	5.2	4.5	5.6	0.3
hs-CRP (mg/L)	2.9	0.03	45.2	8.0	2.6	0.1	22	3.6	4.6	0.3	34.8	6.9
Blood lipids												
TC (mg/L)	160	123	220	24	163	108	269	31	168	105	219	28
HDL-C (mg/L)	46	16	71	11	50	22	86	11	45	9	62	10
LDL-C (mg/L)	96	48	132	21	100	48	186	27	100	46	164	28
TG (mg/L)	135	56	459	83	99	30	379	57	113	39	295	61
Electrolytes												
Sodium (mmol/L)	140	137	144	2	140	132	145	2	140	135	144	2
Potassium (mmol/L)	4.4	3.8	5.5	0.4	4.5	3.2	6.3	0.5	4.3	3.4	5.6	0.5
Bicarbonate (mmol/L)	24	14	30	4	24	17	62	5	25	18	30	3
Chloride (mmol/L)	104	98	109	3	103	94	118	3	103	97	110	3
Glucose (mg/dL)	85	66	113	10	90	67	123	10	89	22	121	14
Calcium (mg/dL)	9.3	8.2	10.4	0.6	9.4	8.5	10.5	0.4	9.2	8.5	9.8	0.4
Magnesium (mg/dL)	2.2	1.2	2.6	0.3	2.2	1.8	4.1	0.3	2.1	1.2	4.7	0.5
Phosphate (mg/dL)	5.1	3.9	6.4	0.5	4.8	3.4	7.4	0.7	3.9	3.1	5.3	0.5
AG (mmol/L)	15	6	29	7	16	4	30	7	15	4	24	6
Renal function												
Creatinine (mg/dL)	0.4	0.3	0.6	0.1	0.5	0.4	0.8	0.1	0.8	0.5	1.2	0.1
BUN (mg/dL)	15	9	26	4	15	7	30	4	15	7	24	4
eGFR (mL/min/BSA)	83	0	120	39	97	75	118	10	89	60	120	18
Liver function												
ALT (U/L)	24	11	58	10	24	11	59	10	31	14	79	14
AST (U/L)	31	23	60	7	26	17	46	5	23	10	39	7
AP (U/L)	226	2	370	69	244	93	390	67	109	5	81	18
GGT (U/L)	14	3	22	4	19	3	47	8	28	9	81	18
TP (g/dL)	6.7	1	7.6	1.1	7.1	0.3	8	0.9	7.4	6.6	8.6	0.5
Albumin (g/dL)	4.1	3.2	4.8	0.4	4.3	3.5	5.1	0.3	4.1	3.1	4.7	0.4
TB (mg/dL)	0.3	0.1	1.1	0.2	0.4	0.1	1.1	0.2	0.4	0.1	0.9	0.2
DB (mg/dL)	0.1	0	0.4	0.1	0.1	0.1	0.4	0.1	0.1	0.1	0.3	0.1

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, hear rate; bpm, beats per minute; WC, waist circumference; BMI, body mass index; TSH, thyroid stimulating hormone; HA1c, hemoglobin A1c; hs-CRP, high sensitivity c-reactive protein; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; AG, anion gap; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TP, total protein; TB, total bilirubin; DB, direct bilirubin.

children. There were no other significant associations between BMI percentile and other liver function biomarkers in children.

Levels of hs-CRP in children with DS were elevated, with mean (SD) values of 2.9 (8.0) mg/L, 2.6 (3.6) mg/L, and 4.6 (6.9) mg/L in children ages 3–5, 6–12, and 13–18 years, respectively. The 95th percentile for hs-CRP was 22.4 mg/L in children ages 3–5 years and 9.1 mg/L in children ages 6–12 years, while the 85th percentile was 11.5 mg/L and the 95th percentile was 19.3 mg/L in children ages

13–18 years. The hs-CRP was not associated with calculated adiposity in children.

3.2 | Adults

3.2.1 | Anthropometric and physiologic data

Table 3 provides the minimal, maximal, mean and SD values for the anthropometric, physiologic, and laboratory data for adults. Table S2 lists the percentile values for adults. Mean blood pressure and heart rate values in adults with DS were within normal ranges. Four adults had a diagnosis of hypertension. The mean waist circumference in adults with DS was 112 cm (44 in.) (Table S2), with means of 113 cm (44 in.) in women and 110 cm (42 in.) in men (Table S3). The 50th, 75th, and 95th percentile for waist circumference in adults were 107 cm (42 in.), 120 cm (47 in.), and 154 cm (61 in.), respectively. Four adults (5%) had documented acanthosis nigricans.

3.2.2 | Clinical laboratory data

The mean (SD) HA1c was within normal range at 5.3 (0.9) % in overweight and obese adults with DS, reaching an elevated prediabetic range of 5.7% at the 85th percentile, and 6.1% at the 95th percentile. One adult had a diagnosis of Type 2 diabetes. Body mass index did not predict HA1c level (Table S5).

Mean levels of all blood lipids, as well as electrolytes, renal function, and liver function markers were all within normal ranges in adults with DS. Ten adults had a diagnosis of hyperlipidemia. The mean (SD) triglyceride level in adults were within normal range at 126 (63) mg/L, however, triglyceride level was associated with adiposity with each 1-unit increase in BMI correlated with a 3 mg/L triglyceride increase. The mean (SD) serum glucose level in adults was within normal range at 90 (15) mmol/L, however, BMI was found to be positively associated with glucose, with glucose increasing by 0.7 mmol/L for each 1-unit increase in BMI percentile, $p = 0.02$. The mean (SD) AST and TP levels in adults were likewise within normal range at 22 (7) U/L and 7.4 (0.5) g/dL, respectively, however, adiposity was also associated with AST and total protein with each 1-unit increase in BMI predicting a 0.3 U/L increase in AST ($p = 0.04$) and a 0.03 g/dL increase in TP ($p = 0.002$). There were no other observed association between BMI and serum electrolytes, renal, or liver biomarkers.

The mean (SD) TSH was 2.7 (2.6) ulU/mL in adults, with 75th, 85th, and 95th percentile values of 3.5, 4.3, and 5.8 ulU/mL, respectively. Thirty-nine adults had a current or previous thyroid disorder diagnosis. Calculated adiposity measured by BMI did not predict thyroid function.

The mean (SD) hs-CRP in adults with DS was 5.9 (5.3) mg/L, with the 75th, 85th, and 95th percentile being 8.0, 12.0, and 18.8 mg/L, respectively. In adults with DS, BMI was positively associated with hs-

TABLE 3 Distribution of metabolic biomarkers in adults ages 19 years and older with Down syndrome who are overweight or obese, $N = 83$.

	Mean	Min	Max	SD
Physiologic/vital signs				
SBP (mmHg)	113	83	148	12
DBP (mmHg)	68	39	92	10
HR (bpm)	74	45	112	13
WC (cm)	112	71	238	25
BMI	33	25	50	6
Metabolic				
TSH (ulU/mL)	2.7	0.1	20.6	2.6
HA1c (%)	5.3	4.4	12.6	1.0
hs-CRP (mg/L)	5.9	0.2	22.7	5.3
Blood lipids				
TC (mg/dL)	179	121	267	31
HDL-C (mg/dL)	51	22	86	13
LDL-C (mg/dL)	104	15	198	31
TG (mg/dL)	126	39	301	63
Electrolytes				
Sodium (mmol/L)	140	132	145	2
Potassium (mmol/L)	4.3	3.7	5.2	0.4
Bicarbonate (mmol/L)	27	20	32	3
Chloride (mmol/L)	102	95	107	2
Glucose (mg/dL)	90	49	148	15
Calcium (mg/dL)	9.4	8.7	10.2	0.4
Magnesium (mg/dL)	2.1	1.7	2.5	0.2
Phosphate (mg/dL)	3.6	2.5	5.6	0.7
AG (mmol/L)	12	4	18	3
Renal function				
Creatinine (mg/dL)	0.9	0.4	1.8	0.2
BUN (mg/dL)	16	3	28	4
eGFR (mL/min/BSA)	86	32	120	20
Liver function				
ALT (U/L)	29	8	118	18
AST (U/L)	24	14	45	7
AP (U/L)	97	46	412	59
GGT (U/L)	25	8	72	14
TP (g/dL)	7.4	6.2	8.8	0.5
Albumin (g/dL)	4.1	3.2	4.9	0.3
TB (mg/dL)	0.5	0.2	1.8	0.3
DB (mg/dL)	0.2	0	0.3	0.1

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, hear rate; bpm, beats per minute; WC, waist circumference; BMI, body mass index; TSH, thyroid stimulating hormone; HA1c, hemoglobin A1c; hs-CRP, high sensitivity c-reactive protein; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; AG, anion gap; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TP, total protein; TB, total bilirubin; DB, direct bilirubin.

CRP, with hs-CRP increasing by 0.3 mg/L for each 1-unit increase in BMI, $p = 0.04$.

4 | DISCUSSION

We report in this study on the distribution of values of cardiometabolic biomarkers in overweight and obese children and adults with Down syndrome. Given the impact of weight gain on clinical measures and biomarkers of cardiometabolic disease and the accompanying increased risk for cardiovascular disease in the general population, and given known metabolic dysregulations in individuals with DS, understanding the distribution of values for cardiometabolic biomarkers in the DS population is of great import. Importantly, this multi-site international study helps clarify risk for cardiometabolic disease in this population by providing an expected distribution of values for cardiometabolic markers in overweight and obese individuals with DS throughout the lifespan. To our knowledge, this is the first study to provide the distributive ranges for both children and adults in this population. In contrast to the general population, we found that in individuals with DS, being overweight and obese does not seem to confer a notably greater risk for cardiometabolic disease by biomarker profile.

While many biomarkers were within similar ranges to reported values in neurotypical populations, we did find some biomarkers to be elevated in overweight and obese individuals with DS. While being overweight/obese did not appear to be associated with elevated blood pressure values in DS, blood pressures is known to be diminished in individuals with DS and using population-based reference cut off values for classification of elevated blood pressure and hypertension may not appropriately identify risk for future cardiovascular disease in DS (Santoro et al., 2020; Whelton & Carey, 2018).

While renal disease can co-occur in individuals with DS, we did not find any relationship between BMI and renal function, and nearly all children and adults in the study had normal renal function levels. These findings suggest that an altered renal function should not be considered normal in DS, and findings of abnormal renal function tests warrant further clinical evaluation.

Waist circumference values in overweight and obese adults with DS were increased compared to general population averages. Increased abdominal girth and truncal adiposity are known to accompany weight gain. Despite this common pathway, the observed waist circumference values in the top quartile of adults with DS remain high in comparison to the top quartile of waist circumference values reported in the general population (Center for Health Statistics, 2015). While waist-to-height ratio has recently been proposed as a useful predictor of cardiometabolic risk by better accounting for visceral fat (Schneider et al., 2011), and may likewise represent an accurate measure of adiposity in individuals with DS (Beck et al., 2021), we chose to report BMI to place our findings within the context of the broader existing literatures on DS and cardiometabolic risk and disease.

Interestingly, we found being overweight/obese predicted cardiometabolic risk measured in several biomarkers for children and adults with DS. Body mass index was associated with higher glucose levels in both children and adults with DS, and glucose was the only cardiometabolic biomarker to be related to weight status in DS across the lifespan. This is consistent with the known risk of increased glucose with weight gain in the neurotypical population. Interestingly, however, while calculated adiposity predicted glucose levels, we found no association between BMI and HA1c. The finding of a lack of association between BMI and HA1c in overweight and obese individuals with DS in particularly interesting in light of recent adult DS health guidelines that recommend obtaining an HA1c at age 30, and merits additional investigation to further explore the risk for diabetes in obese individuals with DS. While studies have found an increased risk for Type 1 diabetes in DS, studies have not consistently identified an increased risk of Type 2 diabetes in individuals with DS despite an increased risk for weight gain and obesity in this population (Chicoine et al., 2021). Our findings seem to confirm these findings and suggest that despite being overweight and obese, adiposity does not appear to be a driving factor in diabetes risk in individuals with DS.

Overweight and obese children with DS displayed evidence of blood lipid dysregulation, with elevated LDL-C and low HDL-C values among a sizeable portion of the population. Furthermore, adiposity seemed to predict dyslipidemia in children by lowering HDL-C and increasing LDL-C values with increased weight for height gain. Interestingly, by adult age, however, body mass index was no longer predictive of blood lipoprotein levels, but was associated with elevated triglycerides. Why adiposity predicted lipoprotein regulation in overweight and obese children but not adults with DS is unclear and merits further investigation.

Liver function was found to be associated with an increased body mass index throughout life, but with differing patterns during childhood and adulthood. Body mass index was associated with increases in GGT in children, and with increases in AST and total protein levels in adults. This study adds to prior findings of an increased risk for liver dysfunction during in children with DS (de Matteo & Vajro, 2017; Valentini et al., 2017, 2020), while our finding in adults suggest that adiposity-associated liver disease may represent a life-course process in individuals with DS.

We found that body mass index predicted hs-CRP level in overweight and obese adults with DS. Inflammatory markers including hs-CRP have been shown to be elevated in obesity in neurotypical adults, and our findings could similarly represent an association between adiposity and increased inflammation (Choi et al., 2013). Our study only included individuals with DS who were overweight and obese, and whether hs-CRP values are also elevated in individuals with DS with BMIs within a healthy range is not known. It remains unclear whether the increase in hs-CRP is related to adiposity, or represents another marker of metabolic dysregulation, consistent with other known metabolic dysregulation in this population. Elevated hs-CRP levels could also be due to infective status, which we did not assess for during enrollment. Additional studies that assess the distributive range of hs-CRP levels in adults with DS across a range of body composition categories, including underweight, healthy weight, overweight, and obesity are needed.

This study has several limitations important to note. Participants were patients followed at specialty clinics in academic medical centers which may limit generalizability of results to all patients with

DS. Having an international sample that includes subjects from multiple countries, however, makes it more likely that our findings more broadly reflect the Down syndrome population. Data included participants that were being treated for other conditions that may affect values such as hypothyroidism, hyperlipidemia, and Unexplained Regression in Down Syndrome. We were not able to calculate the Homeostatic Model Assessment, a test frequently used to assess insulin resistance, as this test requires fasting insulin and glucose values. While hs-CRP can be helpful in identifying low levels of inflammation in the body commonly occurring in metabolic dysfunction conditions including obesity, insulin resistance/pre-diabetes, and atherosclerotic cardiovascular disease, there are no standards for using this marker in patients with DS. The increased levels of hs-CRP in patients with DS could reflect other metabolic or immunologic pathways unrelated to adiposity, and the association between hs-CRP and morbidity in DS is currently not known.

This study has several implications for clinical practice and future research. Clinicians should recognize the low risk for Type II diabetes in overweight/obese adults with DS, and it may thus be reasonable to forego routine weight-based screening in this population. These data also indicate that a finding of abnormal renal function in DS should warrant further work-up. In addition to clarifying whether observed increased hs-CRP levels represent an increased risk for cardiometabolic disease or reflect an underlying metabolic, infective, or immunologic pathway intrinsic to DS, future research should also compare cardiometabolic biomarker values among individuals with DS across weight categories, including healthy BMI range, and compare blood pressure differences between individuals with healthy BMI and overweight/obese BMI to further determine the role of blood pressure on cardiometabolic risk. Additional research is needed to clarify the role of overweight/obesity on liver disease risk across the lifespan in DS. Whether the increased waist circumference we observed in individuals with DS who are overweight/obese is associated with an increased risk for cardiovascular disease, as has been found in the general population, likewise remains unclear and warrants further research.

5 | CONCLUSION

We provide distributive values for clinical cardiometabolic biomarkers across the lifespan in individuals with Down syndrome who are overweight or obese.

AUTHOR CONTRIBUTIONS

Dr. Oreskovic wrote the original draft, lead the formal data analysis, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data and contributed to the scientific writing—review and editing, and created figures and data visualization; Dr. Baumer, Dr. Di Camillo, Dr. Cornachia, Dr. Franklin, Dr. Hart, Dr. Kishnani, Dr. McCormick, Ms. Milliken, Ms. Patsiogiannis, Ms. Pawlowski, Dr. Santoro, Dr. Sargado, Dr. Scoppola, Ms. Torres, Dr. Valentini, Dr. Vellody, and Dr. Villani participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data, reviewing the formal data analysis, and contributed to the scientific writing—review and editing; Dr. Skotko supervised the overall project, participated in conceptualization, planning the methodology, project administration and conducted the investigation, collecting data and contributed to the scientific writing—review and editing; All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

SLS has received research funding from LuMind Research Down Syndrome Foundation to conduct clinical trials for people with Down syndrome within the past 2 years. She serves in a non-paid capacity on the Medical and Scientific Advisory Council of the Massachusetts Down Syndrome Congress, the Board of Directors of the Down Syndrome Medical Interest Group (DSMIG-USA), and the Executive Committee of the American Academy of Pediatrics Council on Genetics.

CF does not receive funding for this work; but does receive funding for a separate project about DS catatonia from the BICARE Foundation. Dr Franklin has a relative with Down syndrome.

BGS occasionally consults on the topic of Down syndrome through Gerson Lehrman Group. He receives remuneration from Down syndrome non-profit organizations for speaking engagements and associated travel expenses. Dr. Skotko receives annual royalties from Woodbine House, Inc., for the publication of his book, Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters. Within the past 2 years, he has received research funding from F. Hoffmann-La Roche, Inc., AC Immune, and LuMind Research Down Syndrome Foundation to conduct clinical trials for people with Down syndrome. Dr. Skotko is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. Dr. Skotko serves in a non-paid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. Dr. Skotko has a sister with Down syndrome.

The other authors do not have any conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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