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Resting energy expenditure and adiposity accretion among children with Down syndrome: a three year prospective study

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Abstract

Background—Children with Down syndrome (DS) have a higher prevalence of obesity than other children. Whether this increased risk for obesity is due to a lower resting energy expenditure (REE) is controversial. Our study assessed whether 1) the REE of children with DS adjusted for fat free mass (FFM) was lower than that of sibling controls and 2) the changes in fat mass (FM) over three years were associated with FFM-adjusted baseline REE.

Methods—This study used cross-sectional and prospective cohort designs. Four annual measurement visits were conducted with 28 children with DS and 35 sibling controls aged 3–10y. REE and serum thyroxine (T4) were measured at baseline. Anthropometry, skinfold thicknesses

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CONFLICT OF INTEREST

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measures, and, in a subsample, dual energy x-ray absorptiometry (DXA) were used at each visit to calculate FM.

Results—Children with DS had significantly lower REE adjusted for FFM (−78 kcal/day, 95% CI: −133 to −27, $p=0.003$). The difference remained significant after adjustment for FM, sex, and African ancestry (−49 kcal/day, 95% CI: −94 to −4, $p=0.03$). In the longitudinal analysis, the baseline REE adjusted for baseline FFM was not predictive of FM accretion over time ($p=0.8$).

Conclusion—Children with DS have lower REE than sibling controls, but REE was not associated with changes in FM over time. The results suggest that the lower REE of children with DS does not explain their increased risk for obesity.

Keywords

obesity; fat free mass; fat mass

Down syndrome (DS), or trisomy 21, is associated with intellectual disability, and many medical conditions^{1–3}. Up to 30% of children with DS are obese (BMI-for-age 95th percentile)^{4, 5}, representing a higher prevalence than children without DS (17%)⁶ and children with other intellectual disabilities (12 – 30%)^{4, 7}. One recent population based study in the Netherlands found that children with DS were twice as likely to be obese as children who did not have DS (4.2% vs 1.8% for boys; 5.1% vs 2.2% for girls)⁸. Anecdotal studies provide estimates of obesity among children with DS ranging from 18.8 to 31%^{9, 10}. As life expectancy has increased for individuals with DS over the past decades, the health complications associated with excess adiposity such as type 2 diabetes and cardiovascular disease are becoming more significant concerns^{11, 12}. Furthermore, individuals with disabilities, in general, suffer from significant disparities in obesity burden and medical management, and there is less research conducted with this population¹³. Therefore, it is important to understand the factors that lead to obesity among people with DS.

Lower resting energy expenditure (REE) relative to body size and composition is one mechanism that may predispose individuals to excessive weight gain. Small differences in REE could potentially accumulate over time and contribute to significant excessive weight gain, but previous studies of REE and weight gain for children have yielded mixed results^{9, 14–22}.

Previous studies suggesting lower REE in children with DS^{23–25} had some limitations, such as small sample size, lack of a control group, not controlling for other family factors related to obesity, possible recruitment bias of control families without DS (control families with no children with DS may participate for different reasons than families of a child with DS), and technical difficulties in REE measurements (excess movement during measurement procedure). Furthermore, with the exception of one study with a one year follow-up²⁴, these studies were cross-sectional and did not investigate whether lower REE was predictive of weight and adiposity gain over time.

The primary aim of this study was to examine whether children with DS showed differences in baseline REE that contributed to changes in fat mass (FM) over a three-year follow up. We hypothesized that: 1) REE, adjusted for FFM, would be lower in children with DS than

in sibling controls, 2) changes in FM over the three year period would be associated with baseline REE, adjusted for baseline FFM, baseline FM, sex, and age. A secondary aim was to explore potential mechanisms that could explain why children with DS have a lower REE such as higher FM and lower thyroid function that are typical of children with DS compared with children without DS^{1, 2, 4, 7, 26}. While FFM is the primary contributor to REE, FM does explain some additional variance in REE, especially in obese subjects²⁷⁻²⁹.

SUBJECTS AND METHODS

Design and Participants

The design of the study was cross-sectional followed by a prospective cohort design. Thirty-six families were recruited through referring physicians, parent support groups, and word of mouth. Inclusion criteria were: 1) at least two prepubertal children, ages 3 to 10 years, per family, one child with DS and one child without DS (siblings without DS were used as a control group to minimize the variability in other potential family contributors to REE or obesity and to avoid recruitment bias of healthy controls); and 2) a body mass index (BMI) below the 95th percentile range for age and sex³⁰, on the basis of reported weight and height during a screening telephone interview. However, the final sample included some children with a BMI-for-age >95th percentile, on the basis of the measured height and weight at baseline. Exclusion criteria were: 1) cancer, including leukemia; 2) congenital heart disease necessitating open heart surgery; 3) intestinal resection; 4) hypothyroidism requiring thyroid hormone replacement therapy; or 5) other significant chronic conditions affecting growth or energy balance. For two families where more than one control sibling was eligible, the caregiver decided which child would participate based on the child's interest.

Of the 72 eligible participants, one subject with DS was excluded for hypothyroidism. Eight participants were excluded for missing data critical to this analysis because the participant did not cooperate or because of technical problems (four participants with DS and one control participant were missing REE, three participants with DS were missing baseline skinfold data), leaving a final sample of 63 participants (28 DS and 35 controls) with complete baseline data and 212 visits. 41 participants (16 DS and 25 control) had complete data for all four visits. 53 participants (19 DS and 34 control siblings) had dual energy x-ray absorptiometry (DXA) data for at least one visit. The other participants did not cooperate or technical problems occurred. Written consent and assent were obtained from all subjects before participation, and the study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia.

Procedure and Measurements

For the baseline visit, families were admitted to the Clinical Translational Research Center (CTRC) of Children's Hospital of Philadelphia in late afternoon for an overnight stay. Families returned to the CTRC for three brief annual outpatient follow-up visits.

REE was measured for 60 min at baseline only after a 12-hour supervised overnight fast prior to breakfast or any physical activity in a humidity and temperature controlled room using open-circuit indirect calorimetry (Vmax 29 metabolic cart, SensorMedics, Yorba

Linda, CA). Children rested quietly under a clear, plastic ventilated hood while watching a video of their choice during the test. Sampled ambient and expiratory gases were analyzed every second, and one minute averages were used. The first 10 minutes of the REE test were eliminated to allow for equilibration of the technique. For the remaining 50 minutes, subjects were carefully monitored for motion (including coughing), and corresponding data points were excluded from the calculation of average REE. The REE was calculated from the oxygen consumption and carbon dioxide production by equations described by Weir³¹.

To assess thyroid function, a blood sample was drawn at baseline for serum T4 (thyroxine, reference range: 5.53–11.0 ug/dL) using immunoassays with chemoluminescence (Ortho Vitros ECi, Ortho-Clinical Diagnostics, Johnson & Johnson, Rochester, NY). Prepubertal status was confirmed at baseline using a validated self-assessment questionnaire (assisted by parent if needed)³². Anthropometric measurements were collected by trained research anthropometrists at each visit. Weight (0.1 kg) was measured with the subject wearing a light gown and no shoes using a digital scale (Scaletronix, White Plains, NY). Height (0.1 cm) was measured with a wall-mounted stadiometer (Holtain Ltd., Crymych, UK). BMI (weight/height²) was calculated and transformed into BMI z-scores using sex and age-specific reference data³⁰. Triceps, biceps, subscapular, and suprailiac skinfolds were measured with standard techniques using Holtain skinfold calipers³³. All anthropometric measurements were obtained in triplicate and the average used in analyses. Sex and age-specific equations^{34, 35} were used to calculate FM and FFM based on anthropometric measurements. While these equations were developed before the dramatic increase in childhood adiposity, they likely are still appropriate for a sample where children were ineligible if their reported weight and height for age were >95th percentile.

FFM and FM were also assessed at each visit by DXA in a subsample of cooperative subjects using a Hologic Delphi densitometer (Bedford, MA) with a fan beam in the array mode (software version 12.4) following standard positioning techniques^{10, 36}. In our laboratory the long-term in vitro coefficient of variation (CV) for bone mineral density is <0.6% and the in vivo coefficient of variation is <1%.⁸ The CV for FFM, FM and percent body fat were 0.4%, 1.27% and 1.26% respectively. The instrument was calibrated daily using a hydroxyapatite phantom and weekly with a whole-body phantom. One investigator (B.S.Z.) reviewed all scans to determine acceptability.

Statistical analysis

Comparison of skinfold and DXA measures—Analyses were implemented using Stata/SE software version 10.1 (Statacorp, College Station, Tx). Pearson correlational analysis was conducted to assess the relationship between skinfold measures of FFM and FM and DXA measures of FFM and FM across all visits where both measures were completed.

Cross-sectional study—The primary outcome of the cross-sectional analysis was REE, the primary exposure was DS status, and a priori selected confounding factors were FFM, sex, age, and African ancestry. REE was normally distributed and therefore did not require

transformation for analyses. African ancestry was included in the model because of previous findings of lower REE among African-Americans^{16, 37}.

Generalized estimating equations (GEE) were used in the analysis (including tests for differences in background characteristics) to account for the lack of independence between siblings. A simple paired analysis was inappropriate, as the differences between siblings (sex and FFM) are likely to outweigh similarities. The following models were conducted using the skinfold measures of FFM and FM, and then repeated with the DXA measures of FFM and FM, limited to participants with both body composition methods completed, in order to compare the two methods.

Model 1 included DS status and FFM only (the main determinant of REE). Model 2 additionally included potential confounders: sex, age, and African ancestry. Model 2 was the primary model to test hypothesis 1 of this study. The additional models were exploratory, and were performed to investigate possible mechanisms in the association between DS and REE. Model 3 included the variables in model 2 and one of the potential pathway variables: FM. Model 4 included the variables in model 2 and the other potential pathway variable: T4. Model 5 included all potential confounders and pathway variables. The sample size calculation for hypothesis 1 was informed by the variability of 8.5% in REE (adjusted for FFM, bone, age, race, and gender) that was previously observed in our laboratory for 37 non-obese healthy children in the age range of 3 to 10 years. In order to detect a clinically significant difference in REE between groups of greater than 5% (hypothesis 1 of the study), with a power of 80% (type II error $\beta = 0.2$) and an α value of 0.05 (type I error), correlation within pairs of 0.60, and to account for protocol failure and dropouts (up to 20%), the necessary sample size was calculated as 36 families. The sample size calculation was based on a comparison of means, adjusted for the correlation within pairs.³⁸

Prospective cohort study—The outcome variable for the prospective cohort analysis was FM over time. Because FFM is a critical determinant of REE and FFM is highly collinear with REE^{16, 39}, baseline REE was expressed as the standardized residual of REE as follows: a linear regression analysis was conducted with baseline REE as the outcome and baseline FFM the predictor. The standardized residual REE (REE-SR) was then calculated for all participants and used to predict changes in FM over time. In the main model, the predictor of interest was the interaction of REE-SR with time (e.g. does REE adjusted for baseline FFM predict change in FM over time). GEE were also used to account for the lack of independence between siblings and within subjects over time and to include participants with missing follow-up visit data. Participants were included in the analysis if they had complete data on variables relevant to the analysis for the baseline visit and at least one follow-up visit. Although GEE does not assume normality, FM was transformed to a normally distributed variable using a zero skewness log transformation. As in the cross sectional study, the analyses were first conducted using the skinfold measures of FFM and FM, and then repeated with the DXA measures of FFM and FM limited to the sample with both body composition methods completed in order to compare the two methods. Model 1 included baseline FM, time, baseline REE-SR, and baseline REE-SR X time interaction. Model 2 included the variables of Model 1 plus the following a-priori selected confounders: DS status, sex, African ancestry, age, and baseline T4.

The sample size calculation for hypothesis 2 was informed by the variability in FM change over three years of 83% that was observed in previous studies of 22 healthy controls ages 3 to 10 years followed for three years⁴⁰. With a sample size of 36 families and a power of 80%, we would be able to detect a difference of 40% in FM gain between a group of children with FM increasing from 10 to 15 kg (difference 5 kg) and a group of children with a FM increasing from 10 to 17 kg (difference 7kg) over three years; this calculation is based on an assumed correlation of 0.40 within pairs. Additional post-hoc analyses were conducted limited to the DS participants to explore whether REE-SR predicted FM over time among children with DS.

RESULTS

Body Composition

In the subsample that completed both skinfold and DXA measures, FFM (mean±sd) was similar for both children with DS (21.2±6.0 kg; 20.4±6.8 kg, respectively) and controls (23.8±7.7 kg; 23.3±8.3 kg, respectively), and the measures were highly correlated ($r=0.99$, $p<0.001$, Figure 1). FM results for skinfold and DXA measures were also similar for children with DS (7.3±3.7 kg; 8.6±3.7 kg, respectively) and controls (7.0±5.3 kg; 8.0±4.9 kg, respectively), and highly correlated ($r=0.97$, $p<0.001$, Figure 2).

Cross Sectional Study

Analyses using skinfold data—Baseline characteristics for DS and sibling controls are reported in the Table. As expected, DS participants had significantly lower weight (because of their overall smaller body size), height, FFM, and REE; significantly higher BMI, BMI z-scores, and percent fat mass; and were more likely to be obese (BMI-for-age 95th percentile).

In Model 1, DS was associated with significantly lower REE, adjusted for FFM (−79.7 kcal/day, 95% CI: −132.8 to −26.6, $p=0.003$, see Figure 3). In the main model, Model 2, this difference between DS and controls remained significant after additional adjustment for sex, age, and African ancestry (−48.7 kcal/day, 95% CI: −93.6 to −3.85, $p=0.03$). When the analysis was further adjusted for FM, a variable potentially in the pathway between DS and REE, in Model 3, the REE difference between the DS and control participants remained significant (−64.7 kcal/day, 95% CI: −113.6 to −15.8, $p=0.009$). FM (7.4 kcal/day, 95% CI: −1.8 to 16.7, $p=0.12$) was not a significant predictor of REE in this sample of children. In Model 4, which included the variables in Model 2 and the potential pathway variable T4, the difference between DS and controls remained significant (−43.1.7 kcal/day, 95% CI: −83.5 to −2.77, $p=.04$). T4 (−6.6 kcal/day, 95% CI: −23.8 to 10.5, $p=0.45$) was not a significant predictor of REE in this sample of children. The difference between DS and controls remained significant in Model 5 when all potential confounders and pathway variables were included in the model (−62.0 kcal/day, 95% CI: −105.2 to −18.7, $p=0.005$).

Analyses using DXA data—In Model 1, DS was associated with significantly lower REE, adjusted for FFM (−63.7 kcal/day, 95% CI: −120.5 to −6.9, $p=0.03$). In the main model, Model 2, this difference between DS and controls was not significant after additional

adjustment for sex, age, and African ancestry (-17.0 kcal/day, 95% CI: -66.3 to 32.4 , $p=0.50$).

Prospective cohort study

Analyses based on skinfold data—The interaction of REE-SR with time was not significant to predict FM in Model 1 ($p = 0.88$) or Model 2 ($p = 0.99$). In a post-hoc analysis limited to participants with DS, the interaction of REE-SR with time was close to statistical significance for Model 1 ($p = 0.08$) and Model 2 ($p = 0.07$).

Analyses based on DXA data—The interaction of REE-SR with time was not significant to predict FM in Model 1 ($p = 0.19$) or Model 2 ($p = 0.10$).

DISCUSSION

This study strongly supports the hypothesis that REE is lower in children with DS compared to children without DS. In this study, the difference is not explained by thyroid function or adiposity. Having a lower REE at baseline, however, was not predictive of gain in FM over time, suggesting that a lower REE is not the main reason for the increased risk for obesity among children with DS.

Although previous research has reported a lower REE among children with DS^{23–25}, REE findings for adults with DS have been less consistent, with some studies finding lower REE for adults with DS compared to healthy controls⁴¹ and others finding no differences^{42, 43}. The current study provides the strongest evidence to date that REE is lower in children with DS because it addresses some of the limitations of the previous studies (e.g. small sample size, lack of a control group, not controlling for other family factors related to obesity, and excess movement during measurement procedure). Furthermore, the current study was designed to investigate the extent to which a lower REE was predictive of increased adiposity as indicated by FM over three years. To our knowledge there has only been one study that examined the relationship between REE and changes in body composition over time among subjects with DS²⁴. While this study also found that REE did not predict FM changes over time, the follow up period was limited to one year.

The finding that FFM-adjusted REE was lower in children with DS suggests that there are metabolic differences between DS individuals and non-DS individuals that were not explained by thyroid function (as measured by T4) or adiposity. A likely explanation may be that the composition of FFM (organs, skeletal muscle, etc) and the proportion of highly metabolically active FFM may be different in children with DS compared to siblings, as found in studies of African-Americans compared to Whites^{17, 44}. One distinctive characteristic of children with DS is short stature and short limbs which may influence the proportion of metabolic tissues. The current study was unfortunately not designed to test this hypothesis. Another possible explanation is that the metabolic activity of tissues is decreased with trisomy 21, but organ-specific energy metabolism measurements would be necessary to confirm this hypothesis. The absolute values of the REE levels for our subjects were higher than values based on the prediction equations (107% using World Health Organization prediction equations and 111% using Schofield prediction equations). It is unclear why this

is the case as the data were collected under very controlled conditions by experienced staff, and the results were edited to exclude periods of movement and environmental adjustment. It is possible that the nature of the eligibility criteria (exclusion of obese subjects) resulted in a somewhat biased sample in terms of predicted REE. The difference affects both groups equally and therefore should not alter our conclusions. Although DXA is usually considered the reference method, data analyses with the smaller sample that had DXA data produced confidence intervals that were too large to yield meaningful conclusions because of insufficient power to detect meaningful differences.

Baseline FFM-adjusted REE did not predict changes in FM over time in our sample of subjects with and without DS. In the post-hoc analysis limited to subjects with DS, the interaction was close, but not statistically significant, based on the criteria that were decided *a priori*. This finding for the DS subjects should be interpreted cautiously as this analysis was post-hoc, the study was not powered for this analysis, and the finding may represent a type 1 or type 2 error. But taken together, our results suggest that the lower REE observed in children with DS is not the main contributor to the elevated risk of obesity in DS. It is likely that other factors associated with DS play a role in excessive weight gain including differences in dietary intake patterns⁴⁵, parent feeding practices⁴⁶, leptin levels^{47, 48}, and physical activity^{49, 50}.

The strengths of this study include the measurement of FM over three years, a larger sample size than most previous studies, and the use of sibling controls to reduce recruitment bias and variability in genetic or family factors that contribute to REE or obesity. These results could also potentially be used to help determine the energy needs of children with DS. Limitations include missing data; inclusion of participants who were obese at baseline; insufficient power to account for potential effects of sex and puberty in the change in fat mass over time; primary use of skinfold measures rather than DXA to assess body composition, the use of body composition equations based on skinfolds not developed for children with DS, and not including a measure of fitness which is an important predictor of REE. As the two body composition methods were so closely related (Figures 1 and 2), we believe that the use of skinfold thickness rather than DXA did not lead to errors large enough to affect our conclusions. These results may not be generalizable to children with DS who would not meet the eligibility requirements for this study (e.g. no other major health problems, no thyroid dysfunction, sibling who does not have DS), but our focus was to understand the impact of DS, as such, on energy metabolism, not to understand the impact of the frequent co-morbidities associated with DS.

In conclusion, children with DS have lower REE than sibling controls, but REE was not associated with FM accretion over a three year follow-up, suggesting that lower REE in children with DS does not explain their increased risk for obesity.

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research. The authors' responsibilities were as follows: BSZ, JS, VAS, and NS designed the study; BSZ, VAS, and NS conducted the study; DLH, EPP, BSZ, JS, and NS analyzed the data; DLH, EPP, JS, VAS, and NS wrote the paper; NS had primary responsibility for final content.

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Abbreviations

DS	Down syndrome
REE	resting energy expenditure
FFM	fat free mass
FM	fat mass
T4	thyroxine
CTRC	Clinical Translational Research Center
DXA	dual energy x-ray absorptiometry
CV	Coefficient of variation
GEE	generalized estimating equations

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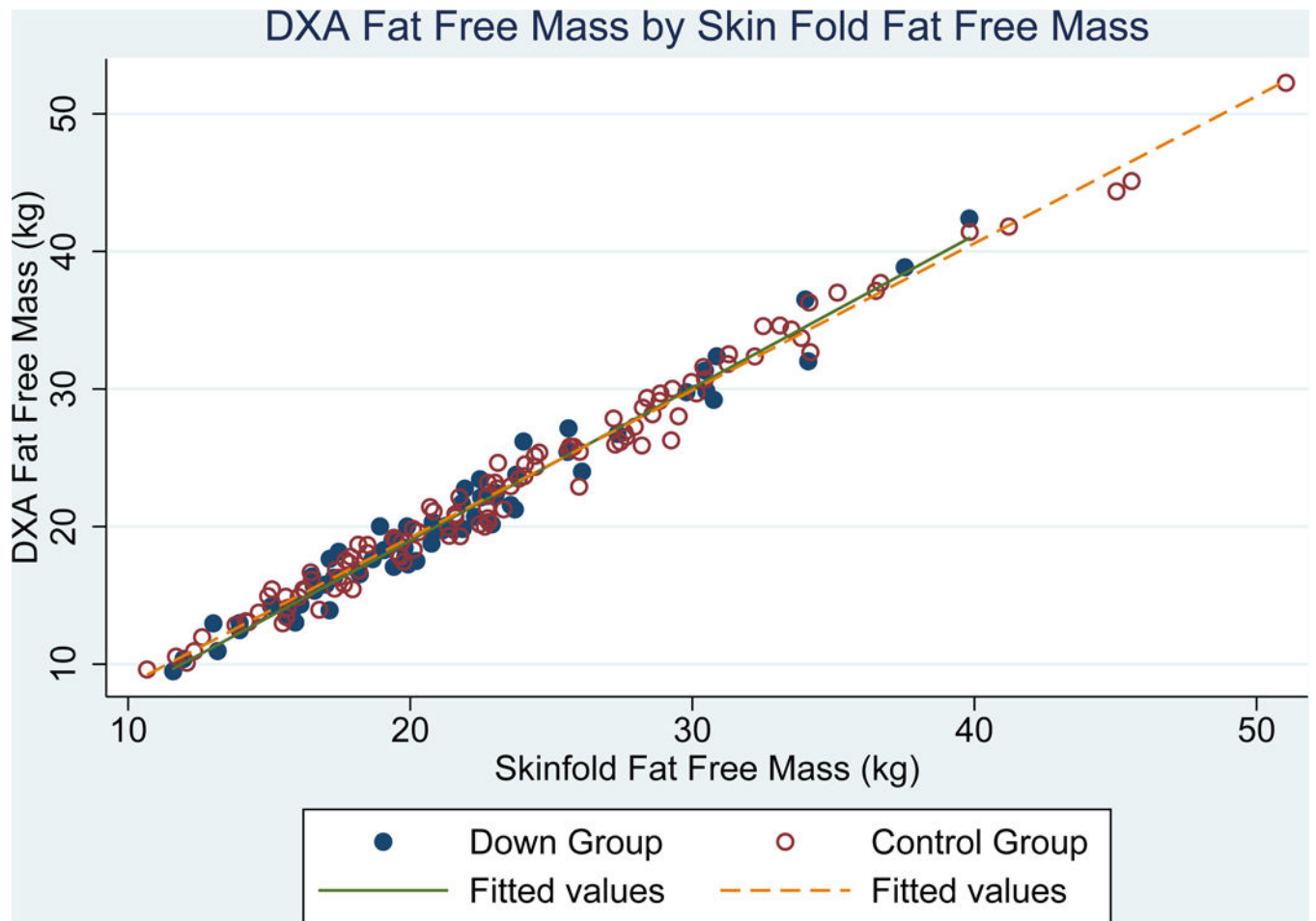


Figure 1.
Relationship between skinfold and DXA measures of fat free mass.

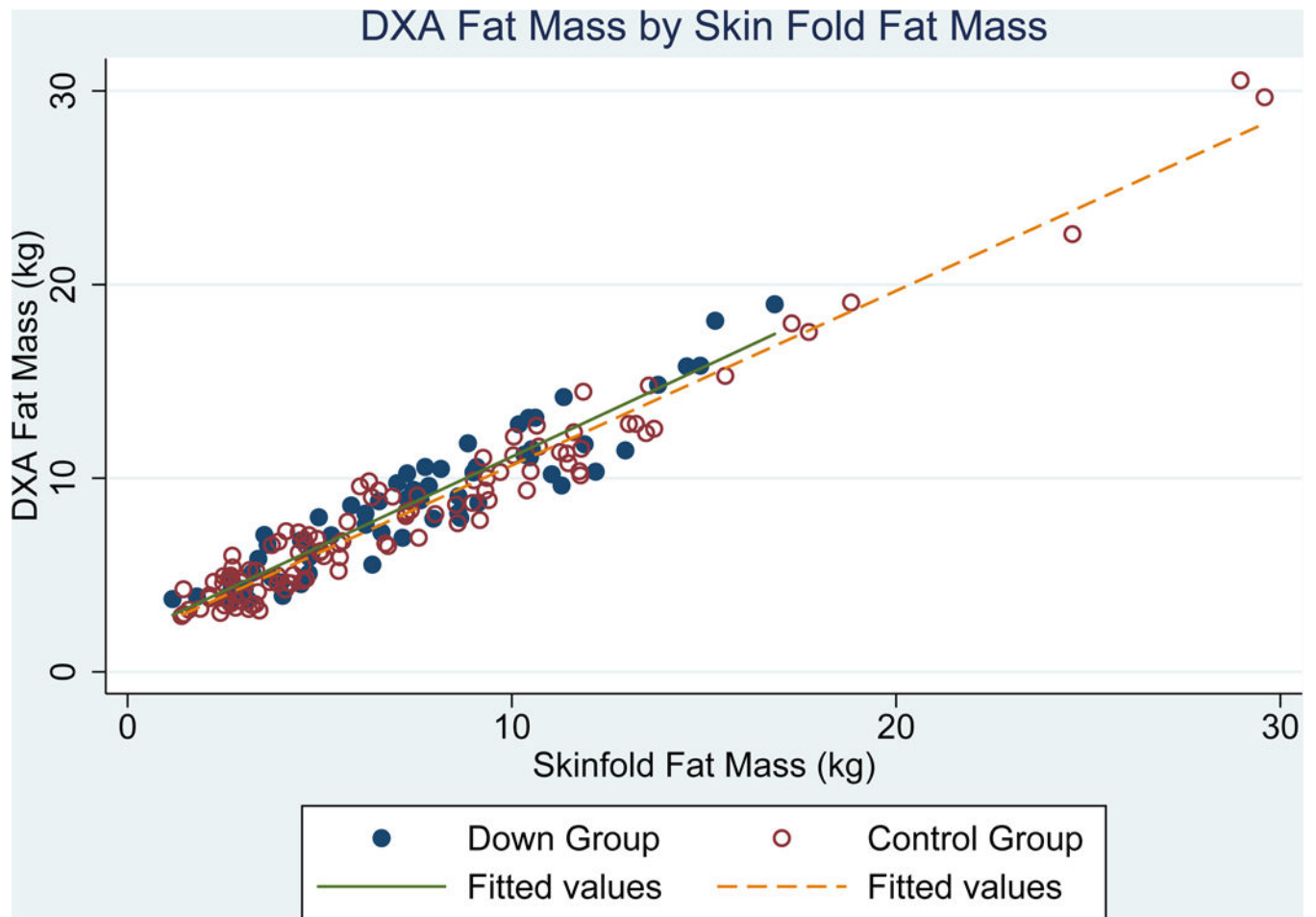


Figure 2.
Relationship between skinfold and DXA measures of fat mass.

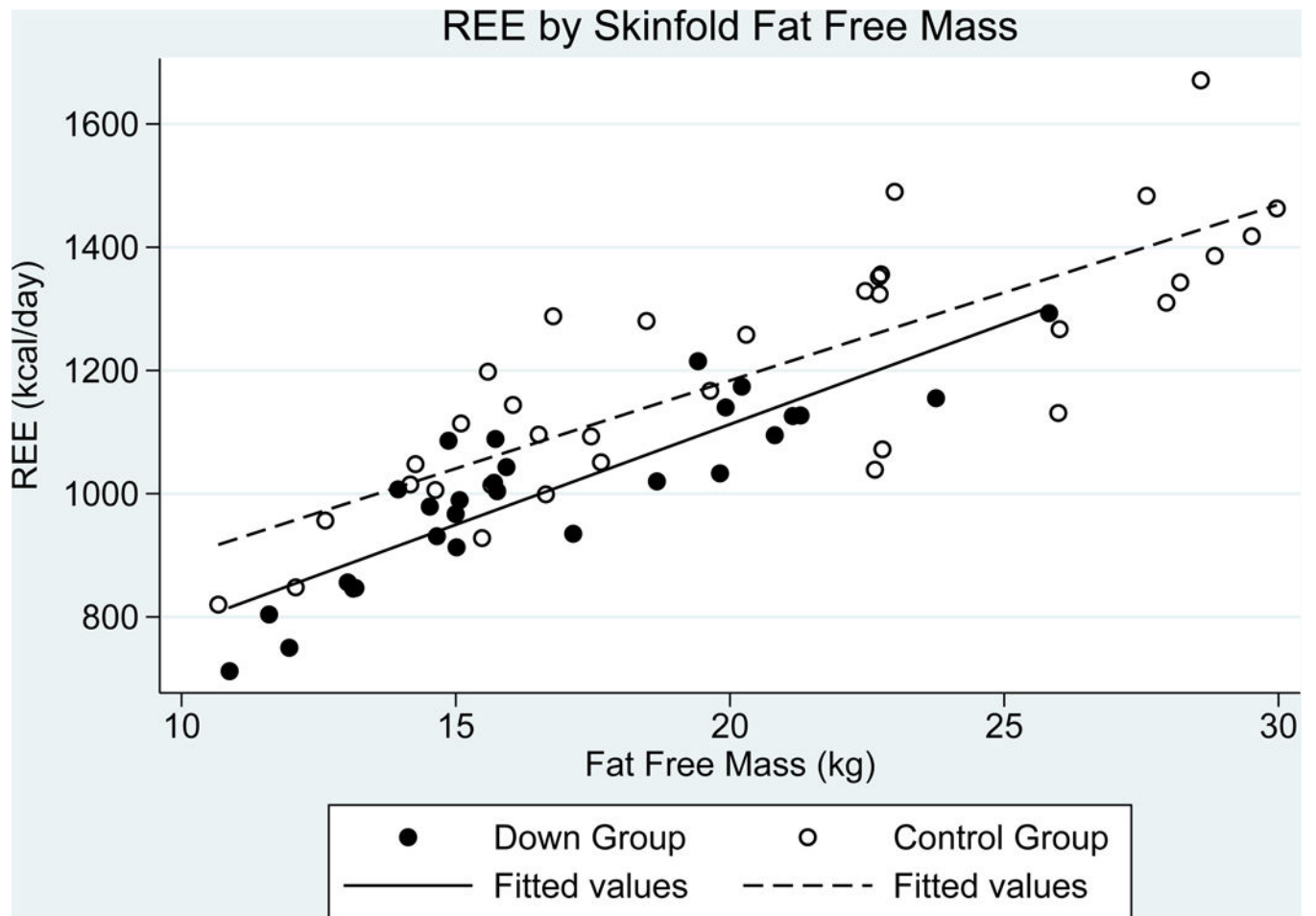


Figure 3. Resting energy expenditure (REE) predicted by fat free mass for children with Down syndrome and their sibling controls.

Table

Baseline Characteristics of Children with Down Syndrome and their Sibling Controls

	Down (n=28) Median, (IQR) or %	Control (n=35) Median, (IQR) or %	p value
Age, years	6.1 (4.8, 8.0) Range: 3.4, 10.4	6.9 (5.3, 9.0) Range: 3.4, 10.8	0.26
Sex, % female	53.6	48.6	0.70
African descent, %	7.1	8.6	0.85
Weight, kg	20.4 (17.5, 26.4)	25.3 (18.4, 31.6)	0.03*
Weight z-score	-0.6 (-1.1, 0.6)	0.0 (-0.7, 0.9)	0.05*
Height, cm	107.2 (101.3, 116.9)	122.2 (110.9, 134.4)	<0.01*
Height z-score	-1.7 (-2.5, -1.2)	0.1 (-0.4, 0.8)	<0.01*
BMI, (weight/height ²)	17.4 (16.1, 19.7)	15.8 (14.7, 17.7)	<0.01*
BMI z-score	1.2 (0.4, 1.6) Range: -0.8, 2.6	-0.1 (-0.7, 0.9) Range: -1.7, 2.3	<0.01*
Obese (BMI-for-age 95 th percentile), %	25.0	5.7	0.01*
REE, kcal/day	1012 (922, 1110)	1167 (1039, 1343)	<0.01*
Fat free mass ^I , kg	15.7 (14.2, 19.9)	19.6 (15.6, 26.0)	<0.01*
Fat mass ^I , kg	3.9 (2.7, 7.2)	4.1 (2.7, 6.4)	0.82
Fat mass ^I , %	20.7 (16.9, 26.4)	17.1 (14.7, 21.4)	0.01*
Thyroxine (T4), ug/dL	8.4 (6.9, 8.9)	8.3(7.5, 8.9)	0.52

^IBased on skinfold thickness, * p < .05