Retrospective Study of Obesity in Children with Down Syndrome

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Objectives To assess whether children with Down syndrome in the US are at an increased risk for obesity, we determined the obesity prevalence and analyzed obesity development throughout childhood in a cohort of children with Down syndrome. In addition, we analyzed a comorbidity that is associated with Down syndrome and obesity, obstructive sleep apnea syndrome (OSAS).

Study design This study was a retrospective chart review that evaluated 303 children ages 2 through 18 years with a diagnosis of Down syndrome. All children were patients at Cincinnati Children's Hospital Medical Center with multiple height and weight measurements. To determine obesity burden, the rate of obesity was compared with a local control cohort using contingency tables. Change in obesity rate through time was determined with mixed models. Association of obesity with OSAS was determined with contingency tables.

Results We evaluated 303 individuals, 47.8% of whom were obese (body mass index ≥95th percentile for age and sex). This was significantly higher than the general pediatric population, which had a 12.1% obesity rate ($P < .0001$). Body mass index z-scores did not change markedly over time ($P = .40$). The majority of children with Down syndrome also had OSAS (74.0% of the 177 children who had polysomnography studies). However, OSAS risk was elevated in obese children (risk ratio = 2.4, $P = .0015$).

Conclusions Our results indicate that children with Down syndrome are at a substantial risk for obesity and OSAS. These findings support the need for more aggressive weight management in early childhood and throughout the lifespan. *(J Pediatr 2016;173:143-8)*.

With a live birth prevalence of 1 in 792 births in the US, Down syndrome is the most common live born trisomy, birth anomaly, and cause of intellectual disability.[1,2] Although there is a wide spectrum of medical complications among individuals with Down syndrome, some associated features increase susceptibility to weight gain. These features include hypotonia[3]; lower respiratory capacity attributable to cardiovascular anomalies, pulmonary hypoplasia, and smaller nasal passages[4]; and lack of adherence to weight management plans because of cognitive impairment.[5] One health complication frequently seen in patients with Down syndrome that is greatly influenced by obesity is obstructive sleep apnea syndrome (OSAS).[6,7] OSAS has been associated with pulmonary and systemic hypertension; developmental delay; mood, attention, and learning problems; and sudden death attributable to cardiovascular complications.[7] Because of the many health risks that children with Down syndrome may have, including OSAS, it is important to establish appropriate medical management at a young age for optimal care.

Although the American Academy of Pediatrics (AAP) has developed guidelines for appropriate health management of children with Down syndrome, weight management recommendations are limited.[8] Current guidelines recommend monitoring growth using standard growth charts at health maintenance visits and counseling about healthy diet and exercise, but the tendency for children with Down syndrome to become overweight is not greatly emphasized.[8] Importantly, the guidelines stress that more population-based research is needed to direct optimal care for individuals with Down syndrome.[8] Previous studies have significant limitations including small sample size, limited age groups studied, or outdated results.[9-12] Therefore, we sought to characterize better a sample of children with Down syndrome in regard to obesity prevalence, trajectory of obesity from early childhood to young adulthood, prevalence of OSAS, and associations between obesity and OSAS. We also compared the prevalence of obesity in our study sample with a sample reflecting the populace of Cincinnati to determine how children with Down syndrome compare with the general pediatric population. Ultimately, a better understanding of obesity prevalence and age of onset may encourage more directed weight management recommendations, leading to

AAP	American Academy of Pediatrics
AHI	Apnea hypopnea index
BMI	Body mass index
CCHMC	Cincinnati Children's Hospital Medical Center
GCC	Genomic Control Cohort
OSAS	Obstructive sleep apnea syndrome
PWS	Prader-Willi syndrome

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Supported by the Cincinnati Children's Hospital Medical Center Research Foundation through use of the Cincinnati Genomic Control Cohort. The use of RedCap was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (8UL1 TR000077). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.02.046

decreased rates of obesity and comorbid medical issues[13] in patients with Down syndrome.

Methods

Approval from the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board was obtained to access patient electronic medical records. We requested a patient list from our institutional data repository, i2b2 (Informatics for Integrating Biology and the Bedside, NIH-funded National Center for Biomedical Computing, Boston, Massachusetts). The inclusion criteria were a clinical diagnosis of Down syndrome (*International Classification of Diseases, Ninth Revision* code 758.0), seen at CCHMC between January 1, 2008 and December 31, 2013, and age 2-18 years when heights and weights were obtained. Of the list generated by i2b2, we extracted 303 subjects who had growth measurements in 3 separate years within the given time frame to allow longitudinal modeling. Measurements more than 4 SDs from an individual's mean were not deemed accurate and were excluded. At that point, if more than 1 measure was available per year, the first measure in a calendar year was selected. For the longitudinal analyses 15 individuals had 2 years of data, 142 had 3 years of data, 93 had 4 years of data, 36 had 5 years of data, and 17 had 6 years of data.

We were granted permission by investigators on the Genomic Control Cohort (GCC) study to use aggregate data (sex, body mass index [BMI], and age data) of children in the region as a referent population. The GCC is a population representative sample of 1020 children between the ages of 3 and 18 years who live in the 7 counties that comprise the Greater Cincinnati region. This sample was drawn from community recruitment, neighborhood schools, and day care centers, and enrollment was monitored to ensure that the sample is representative of the region with respect to race, ethnicity, sex, and socioeconomic status.[14-16] Children with a major medical diagnosis such as Down syndrome were excluded from enrollment; however, cognitive delay was not an exclusion criterion. Heights and weights of all study participants were measured in duplicate using a stadiometer and calibrated scale. Of note, although our cohort of children with Down syndrome included children as young as 2 years old for the first visit, all participants were seen over the course of at least 2 years, thus, the age range of 3-18 years aligns with our cohort of children with Down syndrome.

A study subject list was compiled from i2b2, including the medical record number, date of birth, sex, height at each time point, weight at each time point, and date of encounter. This information was uploaded into REDCap (Research Electronic Data Capture).[17] Manual chart review of the medical record and polysomnography studies extracted obstructive apnea hypopnea index (AHI) values and OSAS diagnosis by a pediatric pulmonologist certified in sleep medicine. Race was extracted from the medical record and was based on parent-reported race using standard electronic medical record choices.

We calculated the BMI (weight [kg]/height^2 [m^2]) at each time point. Height and weight percentiles and z-scores for each subject were calculated using the Centers for Disease Control SAS macros (SAS Institute, Cary, North Carolina). An individual was classified as obese if BMI was ≥95th percentile for age and overweight if BMI was 85th-95th percentile for age.

Polysomnography reports and/or progress notes in the electronic medical record authored by a pediatric pulmonologist board-certified in sleep medicine were reviewed to establish a diagnosis of OSAS. We examined the AHI, which includes obstructive apneas, obstructive hypopneas, and mixed apneas. If an individual had an AHI ≥2, we reported that the individual had OSAS; otherwise, OSAS was considered absent. Degree of OSAS was categorized as mild OSAS with an obstructive AHI 2-5, moderate OSAS with an obstructive AHI >5-10, and severe OSAS with an obstructive AHI >10. Polysomnography scoring conducted at CCHMC is based upon the American Academy of Sleep Medicine scoring manual,[18] which does not define normative or severity thresholds for respiratory events. However, sleep medicine specialists have categorized obstructive AHI of ≤1.5 as normal; therefore, our lower threshold of obstructive AHI ≥2 prevented borderline cases from being categorized as having OSAS.[19-21]

Statistical Analyses

Demographic data were described using frequencies and means ± SDs. To characterize the prevalence of obesity and OSAS, frequencies were used. Goodness-of-fit tests evaluated whether the obesity prevalence was enriched in children with Down syndrome. The risk ratio was also calculated with 95% CIs to provide an estimate of enrichment. In addition, we compared the percentiles of BMI, weight, and height between the children with Down syndrome (average of available measures used) and the GCC using Wilcoxon rank sums.

To determine the change through time in z-score measure (BMI and height), we used mixed models including a random effect of individual to account for the correlation within an individual through time. Age was fixed to test for linear effects with age, and categorical age groupings were used to account for non-linear effects. The age groupings were 2-7, 7-10, 10-12, and greater than 12 years, and were selected to evaluate nonlinear growth (eg, growth spurts).[22] We included an age-by-age group interaction to test whether the rate of change in the z-score was constant through time. We then performed mixed modeling stratified by age grouping.

To test for enrichment of OSAS in individuals with Down syndrome who were obese, we compared the rates of OSAS in children with Down syndrome who were obese with children with Down syndrome who were not obese using goodness-of-fit tests. We also compared the rates of moderate to severe OSAS for individuals who were obese with those who were not obese. To provide an estimate of enrichment, the risk ratio was calculated with 95% CI. Lastly, we performed nonparametric correlation analyses between BMI percentile (highest reported value) and obstructive AHI. The