I, Janet S Basil, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Retrospective Study of Obesity in Children with Down Syndrome

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Retrospective Study of Obesity in Children with Down Syndrome

A thesis submitted to the
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Master of Science

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Abstract

**Background:** Down syndrome is the most common live-born chromosome aneuploidy condition, and many features associated with this syndrome increase the risk for obesity. Few studies have conducted an in-depth review of children with Down syndrome with regard to obesity prevalence and co-occurrence of health risk factors that may be associated with obesity.

**Objectives:** To characterize the obesity burden in children with Down syndrome by determining the obesity and obstructive sleep apnea (OSA) prevalence, developing a trajectory of obesity from childhood to young adulthood, and comparing the prevalence of obesity in our study population with the general pediatric population. We hypothesized that children with Down syndrome would have a higher prevalence of obesity, which would increase through childhood, and those who are obese would have a higher co-occurrence of OSA.

**Methods:** This study was a retrospective chart review that included children between the ages of 2 and 18 who have a diagnosis of Down syndrome. All children had been seen at Cincinnati Children’s Hospital Medical Center with at least three height and weight measurements. To determine obesity burden, the rate of obesity was compared to a local control cohort using 2x2 contingency tables. Change in obesity rate through time was determined with mixed models. Impact of obesity on OSA risk was determined with 2x2 contingency tables.

**Results:** We evaluated data from 303 individuals, 47.8% of whom were obese (BMI $\geq 95^{th}$ percentile for age and sex). This was significantly higher than the general pediatric population, which had a 12.1% obesity rate ($p<0.0001$). BMI z-scores did not change markedly over time, indicating that those who were obese at young ages tended to remain obese and those who were not obese at young ages tended to not become obese. Of note, the majority of children with Down syndrome also had OSA (71.6%). However, OSA risk was further increased in obese children ($RR=2.5$, $p=0.0005$).

**Conclusions:** Our data indicate that children with Down syndrome are at a substantial risk for obesity and OSA. These findings support the need for more aggressive weight management in early childhood and throughout the lifespan. It will be important to design further studies of metabolism and growth to determine the actual caloric requirements for children with Down syndrome.

*Key Words: Down syndrome, obesity, obstructive sleep apnea*
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Acknowledgements

I would like to acknowledge my Research Advisors, Dr. Howard Saal and Dr. Stephanie Santoro, and Research Committee, Dr. Lisa Martin and Katie Wusik, for all of their assistance and hard work throughout this process. I would also like to acknowledge the Cincinnati Children’s Research Foundation and its Cincinnati Genomic Control Cohort for providing data from the Cincinnati Genomic Control Cohort to serve as a referent population.
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Introduction

Down syndrome is a chromosomal anomaly caused by the presence of three copies of chromosome 21. With an incidence of 1 in 691 live births in the United States, it is the most common live born trisomy, the most common birth anomaly and the most common cause of intellectual disability (Canfield et al., 2006). Health complications that are frequently seen in patients with Down syndrome include heart malformations, seen in 40-50%; autoimmune thyroid disease including hypothyroidism in 60% by adulthood; and hematologic issues such as transient myeloproliferative disorder in 10% of newborns (Hobson-Rohrer & Samson-Fang, 2013). Although the spectrum of medical complications that individuals with Down syndrome exhibit is wide, certain common features may increase susceptibility to weight gain. A few of these common features include hypotonia (Dey et al., 2013), lower respiratory capacity due to cardiovascular anomalies, pulmonary hypoplasia, and smaller nasal passages (Fernhall et al., 1996), and lack of adherence to weight management plans due to cognitive impairment (Lytle, 2012). Due to the many health risks that children with Down syndrome may have, it is important for early establishment of appropriate medical management and meticulous monitoring throughout their lives to provide optimal care.

Obesity, defined as greater than 30 kg/m² in adults or greater than the 95th percentile for age and sex in children, increases the risks for early morbidity, mortality, and other serious health complications. Alarming, the number of individuals who are obese is reaching epidemic levels globally (Verhulst, Van Gaal, De Backer, & Desager, 2008). In 2012, 16.9% of children ages 2-19 and 34.9% of adults were obese in the United States (Ogden, 2014). Obesity increases the risk for diabetes mellitus type 2, coronary heart disease, sleep apnea and pulmonary dysfunction, stroke, liver disease, and many other life-limiting conditions (Mokdad et al., 2003).
While overweight is a trend noted in many reports, a detailed description of obesity in children with Down syndrome in the United States is not available.

One health complication more frequently seen in patients with Down syndrome is obstructive sleep apnea (OSA) (Marcus, Keens, Bautista, von Pechmann, & Ward, 1991). Sleep apnea refers to periods during sleep where breathing is shallow or stops due to partial or complete airway obstruction, and is particularly dangerous because it has been associated with metabolic and cardiovascular morbidities (Tauman & Gozal, 2006). Signs of OSA include noisy breathing, snoring, abnormal chest and abdominal movements, difficulty breathing, cyanosis, sweating, and restlessness during sleep. OSA has been associated with pulmonary and systemic hypertension, developmental delay, failure to thrive, and sudden death (Tauman & Gozal, 2006). Several studies of individuals who do not have Down syndrome have shown that OSA is more frequent in obese individuals than non-obese individuals (Amin & Daniels, 2002; Beebe et al., 2007). Since OSA is more common for individuals with Down syndrome, and is thought to be impacted by obesity, it is an important health factor to consider when studying obesity in children with Down syndrome.

While significant effort has been made by The American Academy of Pediatrics to develop guidelines for appropriate health management for children with Down syndrome, the recommendations for weight management are minimal (Bull et al., 2011). Current guidelines recommend that physicians monitor growth using standard growth charts at every health maintenance visit and counsel regarding healthy diet and exercise, but the tendency of children with Down syndrome to become obese is not greatly emphasized (Bull et al., 2011). However, the guidelines do stress that more population-based research is needed to direct optimal care for individuals with Down syndrome (Bull et al., 2011). Therefore, the aims of this study were to
better characterize a population of children with Down syndrome with regard to obesity prevalence, trajectory of obesity from early childhood to young adulthood, prevalence of OSA, and associations between obesity and OSA. We also compared the prevalence of obesity in our study population with the general pediatric population of Cincinnati to determine if obesity is more or less common for children with Down syndrome than the general pediatric population. Ultimately, a better understanding of obesity prevalence and age of onset may encourage more directive weight management recommendations, which may in turn lead to a decreased rate of morbidity and mortality caused by obesity among patients with Down syndrome.
Methods

Study Population

Approval from the Cincinnati Children’s Hospital Medical Center Institutional Review Board was obtained to access patient electronic medical records. We requested a patient list from our institutional data warehouse, i2b2® (Informatics for Integrating Biology and the Bedside, NIH-funded National Center for Biomedical Computing), of those who met our inclusion criteria. The inclusion criteria were: a clinical diagnosis of Down syndrome (ICD-9 code 758.0), seen at CCHMC between January 1, 2008 and December 31, 2013 and age 2-18 at the time heights and weights were obtained. Of the list generated by i2b2®, we extracted 645 potential subjects who had 3 or more growth measurements in 3 separate years within the given timeframe. We excluded subjects who had fewer than 3 growth measurements to demonstrate longitudinal modeling within each individual. Measurements more than 4 standard deviations from the mean were not deemed accurate and were also excluded. Records of subjects with chromosome abnormalities other than Down syndrome were excluded.

We were granted permission by investigators on the Genomic Control Cohort (GCC) study to use aggregate data (sex, BMI, and age data) of children in the region as a referent population. The GCC is a representative sample of over 1,000 children between the ages of 3 and 18 who live in the Greater Cincinnati region. The sample is representative of the region with respect to socioeconomic status, race, and sex. Using these data we were able to compare prevalence of obesity in children with Down syndrome to the general pediatric population of the Greater Cincinnati region.

Procedures
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, Vanderbilt University), a secure online application for collection and storing data (Appendix A). Race, sleep study records, obstructive index values, and OSA diagnosis determined by a pulmonologist were collected by manually reviewing the medical charts of each subject.

**Derived Variables**

We calculated the BMI (height (m²)/weight (kg)) at each time point. Height and weight percentiles and z-scores for each subject were calculated using the Center for Disease Control SAS macros. An individual was classified as obese if he/she was greater than or equal to the 95th BMI percentile.

**Obstructive Sleep Apnea**

Polysomnogram reports and/or notes written by a pulmonologist in the electronic medical record were reviewed to establish a diagnosis of sleep apnea. If an individual had an obstructive index greater than or equal to 2 or had been described as having moderate to severe sleep apnea by a pulmonologist, we reported that the individual had OSA. Occurrence of OSA was a categorical variable and was reported as either present or absent (0=absent, 1=present) for each subject.

**Analysis**

Demographic data were described using frequencies and means ± standard deviations (SD). To characterize the prevalence of obesity and OSA, frequencies were used. To test whether the prevalence of obesity is enriched in children with Down syndrome, we used goodness of fit tests with the GCC as a referent group. To provide an estimate of enrichment, the risk ratio was
also calculated with 95% confidence intervals (CI). In addition, we compared the percentiles of BMI, weight, and height between the children with Down syndrome 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. The fixed effect was age to test for linear effects with age, and a categorical age grouping to account for non-linear effects. The age grouping was 2-7, 7-10, 10-12, and greater than 12, and was selected to account for timing of growth spurts. 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 OSA in individuals who were obese, we compared the rates of OSA in children with Down syndrome who were obese to those who were not using goodness of fit tests. To provide an estimate of enrichment, the risk ratio was also calculated with 95% confidence intervals (CI).
Results

**Down Syndrome Cohort**

Our study cohort included 303 patients with a clinical diagnosis of Down syndrome. The study cohort was primarily of Caucasian race (83.1%), balanced by sex, was an average age of 10.6 years, and ranged in age from 2.14-19.1 years (Table 1). Of note, those who were 19 years old during the study period had at least two growth measurements prior to age 18 and only 1 growth measurement after age 18, and thus were included in the study cohort.

**Obesity is Enriched in Down Syndrome**

We compared our study cohort to the GCC and found that the children with Down syndrome were significantly more likely to be obese than their age matched controls (p<0.0001, Risk Ratio=3.5, confidence interval 2.8-4.36). The obesity prevalence for our study cohort was 47.8%, while the obesity prevalence for the GCC was 12.1% (Figure 1). Additionally, we found that males and females were equally at risk for being obese as there was no statistically significant difference in BMI based on sex (p=0.892) (Figure 1). Because BMI is a ratio of weight and height, we also investigated the relationships between weight and height z-scores and percentiles between the Down syndrome and control populations. Our Down syndrome cohort had significantly lower weight (Chi square=57.2, p<0.0001) and height (Chi square=545.6, p=0.0008) percentiles than the controls even though BMI was higher. The inverse relationship between BMI percentile and height-weight percentiles can be explained by the fact that the height percentiles are markedly lower than the weight percentiles (Figure 2). This indicates that those with Down syndrome are proportionally heavier given their shorter stature, but when compared to their age and sex matched peers do not weigh more (Figure 2).
To assess how BMI changed over time, we tested for longitudinal changes in BMI-z-scores. When considering age as a linear effect, we failed to identify any significant change over time ($\beta = 0.008 \pm 0.009$ per year, $p = 0.40$). However, when we allowed for differential linear effects based on timing of growth spurts in children who do not have Down syndrome (2-7, 7-10, 10-12, and 12+ years) we identified a significant interaction effect ($p=0.0095$)(Figure 3). We then performed stratified analyses by age class. We found a significant increase in BMI-z with age in those over 12 years ($\beta = 0.046 \pm 0.014$, $p = 0.0014$). While not significant, we found a negative relationship between age and BMI-z for children aged 10-12 ($\beta = -0.085 \pm 0.047$, $p = 0.079$). For children ages 2-7 ($\beta = -0.039 \pm 0.051$, $p = 0.44$) and 7-10 ($\beta = 0.00065 \pm 0.030$, $p = 0.83$), there was not a significant association between age and BMI-z. This indicates that while BMI does increase slightly after puberty, BMI is fairly consistent throughout childhood and adolescence.

In contrast, there was a significant linear age effect with height-z-scores ($\beta = -0.052 \pm 0.009$ per year, $p < 0.0001$). However, there was also a significant interaction between height and age group ($p<0.0001$) indicating the changes with height are not linear through childhood (Figure 4). Between ages 7-10, there was a statistically significant increase in height z with age ($\beta = 0.11 \pm 0.03$, $p = 0.0008$). However, after age 12, there was a statistically significant decrease in height z with age ($\beta = -0.18 \pm 0.02$, $p < 0.0001$). Neither age 2-7 nor age 10-12 exhibited significant changes in height z with age ($\beta = -0.03 \pm 0.03$, $p = 0.42$ and $\beta = 0.04 \pm 0.08$, $p = 0.59$, respectively).

**OSA is Correlated with Down Syndrome**

We analyzed the relationship between OSA and obesity and found a significant correlation between obesity and OSA (Risk Ratio=2.5 (1.4-4.4), $p=0.0005$). We found that
84.34% of the study subjects who were obese had OSA, while 60.82% of those who were not obese had OSA (Figure 5). There was a significant risk for OSA for all children with Down syndrome as 71.6% of all children with Down syndrome were diagnosed with OSA; however, the risk was further increased for those who were obese.
Discussion

This study provides a detailed characterization of children with Down syndrome in the Cincinnati area with regard to BMI, height, weight, changes in these parameters over time, and incidence of obstructive sleep apnea. In comparing our study cohort with a referent population we were able to determine that obesity is more prevalent in children with Down syndrome than those who do not have Down syndrome, and therefore propagates additional health risks for these children. This study provides novel findings with multiple growth points of each individual, demonstrating that obesity onset occurs early in life and remains fairly stable through development. This study also supports previous findings that OSA is more common for individuals who are obese than those who are non-obese, although the risk for OSA is substantial for all children with Down syndrome. We demonstrate that obesity is a significant problem for children with Down syndrome and needs to be addressed in their clinical management.

We were able to compare our study cohort to their typically-developing normal controls in the region and found that the incidence of obesity was alarmingly higher for children with Down syndrome than their typical peers. Our study supports the findings of van Gameren-Oosterom et al. (2012), who found that Dutch children with Down syndrome were more often overweight or obese than their typical peers. However, our rates of obesity were substantially higher with 47.8% of our cohort of children with Down syndrome being obese compared to 12.1% obesity rate of Dutch children with Down syndrome. The differences between our study and the previous study could be a result of cultural differences with regard to diet and exercise habits as well as other social and environmental factors.

Additionally, it is well-recognized that adults with Down syndrome tend to be overweight or obese (Asua et al, 2014, Melville et al., 2005), but obesity has not been adequately studied in
children in the United States. This study is a powerful addition to the current literature and has identified that obesity is a health risk not only in adults with Down syndrome, but children with Down syndrome as well. Our data demonstrate the discordance between weight-height percentiles and BMI percentiles of those with Down syndrome and their age matched controls. These data highlight that while individuals with Down syndrome may not appear heavier than their typically-developing peers by weight measurements, due to their height measurements being substantially lower than their typically-developing peers they are proportionally heavier, which is evident by BMI measurements. Therefore, it is important to calculate BMI rather than depend on weight measurements when assessing healthy weight. Importantly, while obesity was more prevalent in our cohort of children with Down syndrome than the control cohort, a majority of children were not obese in either population, indicating that having a diagnosis of Down syndrome does not automatically determine that an individual will be obese.

Our study contributes novel findings to the current literature in examining multiple growth points for each subject and examining an age range of 2-18 years in order to determine when obesity typically develops in children with Down syndrome. We stratified by age class in order to account for growth spurts that typically occur during childhood and adolescence. We found a significant increase in BMI for those over 12 years old and a slight decrease (though insignificant) in BMI for children ages 10-12. There was no significant association between age and BMI for ages 2-7 and 7-10. Taken together, these data indicate that BMI is fairly consistent throughout childhood and adolescence with a slight increase after puberty. In contrast, there was a significant increase in height between ages 7 and 10, and after age 12 there was a statistically significant decrease in height. This indicates that while height z-scores when compared to controls did fluctuate a bit to reflect growth spurts, BMI measurements in our study cohort were
consistently above that of their typically developing peers. Interestingly, we found that children who were deemed obese prior to age 2 tended to remain obese, while children who were not obese at age 2 tended to not become obese by age 18. There are no other studies in the literature which report findings of multiple BMI measurements for children with Down syndrome over a range of 2-18 years. These longitudinal data indicate that it is vital to identify overweight based on BMI early in childhood and take proactive management steps before the child becomes obese. Early counseling of parents of infants with Down syndrome should include information regarding the high risk for their child to be overweight or obese and appropriate anticipatory management of diet and related issues should be provided.

Our data indicate that children who are obese are more likely to have obstructive sleep apnea than those who are not obese. These data are in concurrence with Berger et al. (2009) who found in individuals who do not have Down syndrome that those who have a higher BMI demonstrated higher sleep disordered events than those who have a lower BMI. Our results support the study by Dyken et al. (2003) who noted in a cohort of 19 children with Down syndrome, those with a higher BMI had more severe OSA. Our study strengthens these assertions with a larger sample population of 303 children with Down syndrome. Therefore, it is essential to evaluate for and treat sleep-disordered breathing for children who have Down syndrome, especially those who are obese.

Detailed guidelines for health management of children with Down syndrome have been painstakingly developed and adapted over time (Bull, 2011). However, our data clearly demonstrate obesity is a major health risk for children with Down syndrome, and therefore more structured weight management guidelines are needed and need to take effect in early childhood. The Health Supervision Guidelines for Children with Prader-Willi Syndrome are very specific
and directive with weight management guidelines due to hyperphagia behaviors and high obesity incidence seen in children with this condition (McCandless, 2011). While children with Down syndrome do not demonstrate the extreme hyperphagia that is seen in children with Prader-Willi syndrome, perhaps the Prader-Willi health management guidelines could be used as a model for the level of detail necessary for optimal lifelong weight management for children with Down syndrome.

This study has limitations that should be addressed with future studies. While we had a fairly large sample size, 303 individuals, a substantial majority was Caucasian (82.5%). It would be beneficial to see if the trends seen in this study are also found in other racial populations and of other cultural backgrounds. Additionally, we may have ascertainment bias in our sample because the patients who are seen at our institution tend to be high risk individuals with multiple complications, therefore our sample may not be truly representative of all children with Down syndrome. Also, the degree of OSA was not ascertained in this study. We categorized individuals as having OSA or not having OSA with the cutoff for having OSA being determined by an obstructive index value of 2 or greater on polysomnogram or a clinic note by a pulmonologist indicating the subject had moderate to severe OSA. Finally, while the methodology used in this study was necessary to obtain the large sample size and to conduct the study in a timely manner, the type and amount of data that is able to be obtained through a retrospective medical chart review study is limited compared to a prospective study.

Future research is needed to assist in developing guidelines that address weight management in children with Down syndrome. Previous research has indicated that children with Down syndrome exhibit lower basal metabolic rates than typical children, however, the effects of this lower metabolic rate on obesity is unclear (Hill et al., 2013). Therefore, future studies are
needed to determine the effect of metabolic rates in children with Down syndrome as well as to determine minimal caloric needs for children with Down syndrome to obtain healthy weight. Additionally, more research needs to be done to ascertain other health risk factors besides OSA in children with Down syndrome that may contribute to weight gain such as congenital heart defects, hypothyroidism, and gastrointestinal anomalies that require surgery early in life. These health factors may impact the caloric need as well as weight gain in children with Down syndrome and need to be assessed in conjunction with BMI of the child.

**Conclusions**

We propose that a child with Down syndrome needs to be assessed for being overweight or obese in early childhood and management of his/her weight needs to be undertaken early in life. Health management guidelines for children with Down syndrome need to be more specific and directive for weight management in early childhood and throughout the lifespan. Perhaps the health management guidelines for children with Prader-Willi syndrome could provide an example for the level of detail necessary in weight management. However, since children with Down syndrome do not exhibit the extreme hyperphagia that children with Prader-Willi display, the guidelines would not need to be as restrictive. This study adds valuable data to the current literature and raises the issue that overweight and obesity are a significant problem in children with Down syndrome and should be addressed in clinical management of these patients.
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*Abdom Imaging*, 37(5), 719-724.


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### Tables and Figures

#### Tables

Table 1. Demographics

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Table 1. Demographic Data of Study Participants (N=303)
Figures

Figure 1. Frequency of Obesity

Figure 1. Percentage of individuals with Down syndrome (DS) who are obese compared to the Genomic Control Cohort (GCC).
Figure 2. Average weight, height, and BMI percentiles for children with Down syndrome (DS) versus the Genomic Control Cohort (GCC).
Figure 3. BMI z-score trajectory for children with Down syndrome between ages 2 and 19.
Figure 4. Height Trajectory

Figure 4. Height z-score trajectory for children with Down syndrome between the ages of 2 and 19.
Figure 5. Obesity and Obstructive Sleep Apnea

Figure 5. Percentage of children with Down syndrome who are obese and have OSA compared to children with Down syndrome who are non-obese and have OSA.
Appendix A

Data Extraction Form

1. Subject medical record number
2. First & Last Name
3. Date of Birth
4. Sex
5. Date for each height and weight measurement
6. Height, weight, BMI at each time point
7. Zip Code
8. Race
9. Mortality (if deceased, date of death)
10. Is the subject obese?
11. If subject is obese, age he/she became obese?
12. Has subject seen a pulmonologist?
13. Has subject had a sleep study done? (If so, age?)
14. Was subject diagnosed with obstructive sleep apnea?
15. Has the subject been seen by a cardiologist?
16. Does/did the subject have a congenital heart defect (CHD)?
17. Does/did the subject have a ventricular septal defect?
18. Does/did the subject have an atrial septal defect?
19. Does/did the subject have tetralogy of fallot?
20. Does/did the subject have patent ductus arteriosus?
21. Has the subject had surgery to repair the CHD?
22. Has the subject had pulmonary hypertension?
23. Has the subject seen an endocrinologist?
24. Does the subject have hypothyroidism recorded in the medical chart (as evidence by medications levothyroxine or synthroid or diagnosis in chart)?
25. Has the subject been seen by a nutritionist?
26. Has the subject been seen by a gastroenterologist?
27. Did the subject have duodenal atresia?
28. How many specialists has the subject seen that are listed in the electronic medical record?