


5-2010

An assessment of obesity and hyperphagia in individuals with Smith-Magenis syndrome

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BACKGROUND

Introduction

Smith-Magenis syndrome (SMS; OMIM# 182290) is a genetic disorder characterized by multiple congenital anomalies and mental retardation most commonly caused by a 3.7- Mb deletion on human chromosome 17p11.2. In addition, mutations in the *RAI1* gene have also been described as a cause of SMS (Greenberg et al., 1996, Slager et al., 2003). Smith-Magenis syndrome was first described in 1982 and has an estimated prevalence of 1/25,000 births (Greenberg et al., 1991). Since its first description in 1982 and the publication of the spectrum of clinical features by Smith et al. in 1986, the more subtle features of this syndrome have been delineated. Individuals with SMS encompass a phenotypic spectrum that includes congenital anomalies, characteristic craniofacial features, growth abnormalities, mental retardation and a distinctive neurobehavioral profile.

History of Smith-Magenis syndrome

The first official account of what is now known as Smith-Magenis syndrome was published in the American Journal of Human Genetics in 1982. Smith et al. reported two unrelated males with facial clefts and congenital heart disease. The first individual carried a diagnosis of Pierre Robin sequence, a ventricular septal defect (VSD), congenital heart block, skeletal abnormalities and hearing loss (Smith et al., 1986). Individual number one died at six months of age from complications related to surgical repair of his VSD (Smith et al., 1986). The second individual had bilateral cleft lip and palate and VSD. Both of the individuals were diagnosed with failure to thrive (FTT) and were less than the 3rd percentile

for their growth parameters. Cytogenetic analysis revealed that both of these individuals had an interstitial deletion of the p11 band on chromosome 17 (Smith et al., 1982).

A follow-up article published in 1986 by Smith et al. provided detailed case reports of seven newly identified and two previously identified individuals with congenital heart defects and facial clefts. Cytogenetic analysis of these nine cases revealed, all had at a minimum, a small interstitial deletion in 17p11.2 and individual 1, the most severely affected of the cases reported, was deleted for the entire 17p11.2 band (Smith et al., 1986). The phenotypes of the individuals were compared and the majority of individuals had the following: brachycephaly, midface hypoplasia, broad nasal bridge, prognathism, short stature, scoliosis, speech delay, behavior problems and mental retardation (Smith et al., 1986).

Smith et al. 1986 were the first to report that the prognathism present in SMS individuals is “age dependent.” They observed the two youngest patients in their cohort had micrognathia, where as prognathism was present in the older patients. The most commonly described features included: speech delay, which was present in seven of eight (87.5%) living patients, a hoarse deep voice was identified in four of eight (50%) individuals and hearing loss was present in six of nine (66.67 %) individuals. They also found that seven of eight (87.5%) living individuals had similar behavioral problems that began in early childhood including hyperactivity and self-destructive behaviors (Smith et al., 1986).

At the time of the Smith et al. publication in 1986, there were seven additional individuals with 17p11.2 deletions with similar phenotypes to those described by Smith et al. reported in the medical literature (Patil and Bartley, 1984; Stratton et al., 1986.) Since

the initial publications by Smith et al., several different groups of researchers have contributed invaluable information to the field of SMS research. One of these such groups was lead by Doctors Greenberg and Lupski at Baylor College of Medicine and Texas Children's Hospital through a multidisciplinary clinical study of individuals with SMS. The results of this study, published by Greenberg et al. in 1991 and 1996, provided phenotypic information on a cohort of individuals with SMS. Their examination of individuals with SMS confirmed the common clinical features and provided information on features that had never been reported in individuals with Smith-Magenis syndrome.

Since 1997 another group of researchers at the NIH/NHGRI have been conducting a study of the natural history of SMS with the goals of further characterizing the phenotype to ensure increased recognition of the syndrome and earlier diagnosis. They have also been working to develop therapies and interventions to treat the developmental delays and behavioral abnormalities seen in individuals with SMS. The 2006 publication by Gropman et al. provided a comprehensive review of the SMS phenotype using data collected from the NIH natural history study.

Clinical Findings

Congenital Anomalies

Although congenital anomalies are not present in all individuals with SMS, the most common congenital anomalies are cleft lip with or without cleft palate, renal/urinary tract abnormalities and cardiac defects. Renal abnormalities were present in two of nine (22 %) of individuals studied by Smith et al. 1986. One individual was found to have bilateral ureterovesicular obstruction and a second individual was found to have a single hypertrophic

right kidney with malposition of the ureterovesicular junction. The prevalence of renal and urinary tract abnormalities in the Greenberg SMS cohort was 34.6% and included the following abnormalities: duplication of the collecting system, unilateral renal agenesis and ectopic kidney (Greenberg et al., 1996). Due to the high prevalence of renal and urinary tract abnormalities, renal ultrasounds should be performed following a diagnosis of SMS to ensure appropriate treatment and surgical correction if necessary.

Five out of twelve (43%) individuals studied by echocardiography by Greenberg et al., 1996 were found to have cardiac anomalies that included: mild tricuspid regurgitation, mild mitral regurgitation, subvalvular aortic stenosis, VSD and supra-ventricular pulmonic stenosis. Four individuals had been diagnosed with a cardiac abnormality previously and these abnormalities included pulmonic stenosis, VSD, mitral valve prolapse and an ASD. Ten of twenty-seven (37%) individuals evaluated in the Greenberg SMS cohort were found to have cardiac anomalies. Due to the high prevalence of congenital heart defects in individuals with SMS, echocardiogram should be performed following the initial diagnosis and if a heart defect is identified, surgical repair is indicated.

Craniofacial

The facial appearance of individuals with SMS, though distinct, can vary between infancy and adulthood. Infants with SMS may only display subtle dysmorphic facial features including a broad, square shaped face with mid-face hypoplasia, while adolescents and adults with SMS show more pronounced dysmorphic facial features (Gropman et al., 2006). In addition to the broad, square-shaped face, adults with SMS can have brachycephaly, midface hypoplasia, tented upper lip, up-slanting palpebral fissures, deep-set

eyes, short full-tipped nose and prognathism (Greenberg et al., 1991). The facial features present in adults with SMS have also been described as coarse with deep-set eyes, relative prognathism, heavy brows and synophrys (Allanson, Greenberg, & Smith, 1999)

Growth and Development

To assess the SMS phenotype during infancy Gropman, Duncan & Smith (2006) performed medical histories and physical exams, and analyzed parent questionnaires and medical records of patients 24 months or older. They found that the weight, length and FOC of infants with SMS are within normal limits at birth. However, at approximately 12 months of life, infants with SMS begin to show features of failure to thrive (FTT) including poor weight gain and poor linear growth (Gropman, Duncan, & Smith, 2006; Greenberg et al., 1991). The FTT was thought to be related to the oral motor dysfunction present in all infants studied as well as hypotonia, lethargy, increased sleepiness and daytime napping (Gropman, Smith, Allanson, & Greenberg, 1998). It was also reported that all infants studied showed some degree of oral motor dysfunction, with poor feeding being present in some (Gropman, Duncan, & Smith, 2006).

All infants studied by Gropman, Duncan & Smith., in their 2006 publication also had motor delays and decreased crying and babbling but were within normal limits, or only slightly delayed for their social-emotional function.

Sleep Disturbances

Prior to childhood, the sleep patterns of infants with SMS are not characterized as problematic or troublesome. In fact, many parents of SMS infants describe them as “perfect babies” (Gropman et al., 2006). It is during childhood that characteristic sleep disturbances

of SMS become evident. However, retrospective analysis has found sleep abnormalities are present in infants with SMS (Greenberg et al, 1991). Infants with SMS have “excessive daytime sleepiness” and decreased 24-hour sleep (Greenberg et al., 1991). In the Greenberg et al. 1991 cohort, 62% of individuals showed signs of a sleep disorder that included difficulty falling asleep, staying asleep, and frequent awaking during the night. They also reported that REM sleep was absent in two individuals studied by polysomnography. In 1996, Greenberg et al., reported of the 24 individuals who underwent sleep studies, 29% patients had decreased sleep time due to frequent night-time awakening. Decreased rapid eye movement (REM) sleep was found in 12 of 24 (50%) individuals, normal REM sleep was found in 11 of 24 (45.8%) individuals and one patient (4 %) had increased REM sleep. Greenberg et al. reported all individuals studied had problems falling and staying asleep throughout the night. They concluded that there was a defect in REM sleep but were unsure of the underlying mechanism.

DeLeersnyder et al., in 2001 measured the plasma concentrations of melatonin over a 24-hour period in 20 subjects with SMS as well as their age matched controls. Their results showed individuals with SMS had different melatonin cycling when compared to their age matched controls. Typically the circadian rhythm functions such that melatonin is low during the day light hours, however as darkness sets, the pineal gland begins to produce melatonin indicating to the body that it is time to sleep. In individuals with SMS, their melatonin secretion began at 6 AM \pm 2 hours, their levels peaked at 12 PM \pm 1 hour and their offset occurred at 8 PM \pm 1 hour (DeLeersnyder et al., in 2001). This is in contrast to the melatonin cycling seen in their age matched controls who experienced onset of secretion at 9 PM \pm 2 hours, peak of secretion at 3:30 AM \pm 1.30 hours and offset of melatonin at 6

AM \pm 1 hour. DeLeersnyder et al., also found a positive correlation between the frequency of a SMS child's tantrums and increasing daytime melatonin levels. As the amount of melatonin increased during the day, the frequency of tantrums in individuals with SMS increased as well. DeLeersnyder et al. hypothesized the behavioral problems could be aggravated by the fact that children with SMS have elevated melatonin levels during the daytime and that their daytime sleepiness could be causing or contributing to their behavioral problems.

Since these abnormalities in melatonin cycling have been discovered, researchers have attempted to treat the sleep disturbances by using melatonin and acebutolol an oral beta-1-adrenergic antagonist. A trial conducted by De Leersnyder et al. in 2003 studied the daytime usage of acebutolol and an evening dose of 6 mg of melatonin. This dosage pattern was able to increase the nocturnal melatonin levels, improve nighttime sleep and decrease daytime sleepiness and improve overall daytime behavior (Leersnyder et al. in 2003).

The sleep disturbances present in children with SMS present a management challenge. No well controlled treatment trials have been conducted. There is currently no standard of care or management protocol to control the sleep disturbances in children with SMS.

Neurobehavioral

The neurobehavioral abnormalities present in SMS are a distinctive component of its clinical phenotype. Self-destructive behavior was present in 67% of individuals described by Greenberg et al. in 1991. The neurobehavioral profile of 29 individuals with SMS was studied and self-injurious behaviors were present in 96.6% of individuals (Finucane, Dirrigi,

& Simon, 2001). Individuals with SMS exhibit the following: hyperactivity, sleep disturbances, temper tantrums, attention seeking, self-hitting, self-biting, self-hugging, polyembolokoilomania (inserting foreign bodies into body orifices) and onychotillomania (pulling out one's fingernails) (Greenberg et al., 1991). Greenberg et al. also reported self-destructive behaviors such as head banging and wrist biting are present as early as 2 years of age; but, more severe behavior such as onychotillomania does not present until 5-6 years of age. The stereotypic and self-injurious behaviors present in SMS are so unique that they are a major clue for diagnosis as they are distinguishable from other genetic syndromes associated with mental retardation. There is a direct correlation between the severity of self-injurious behaviors and the level of intellectual functioning in individuals with SMS (Finucane, Dirrigi, & Simon, 2001).

SMS shares common features with those seen in Prader-Willi syndrome (PWS; OMIM 176270) and before much was known about SMS, some individuals with SMS were misdiagnosed as having PWS (Dykens & Smith, 1998). As first published by Greenberg et al., the overlapping features of PWS and SMS include the following: infantile hypotonia, short stature, skin picking, sleep disturbances and behavioral abnormalities. Greenberg et al., 1996 also noted that individuals with SMS also have hyperphagia (Greenberg et al., 1996b). Although there continues to be overlap of the PWS and SMS phenotypes, there are certain features now known to be unique to each of these syndromes (Dykens & Smith, 1998). In a study comparing the neurobehavioral abnormalities of PWS and SMS, individuals with PWS were found to have higher levels of obsessive food related thoughts (Dykens & Smith, 1998). SMS individuals were also found to show obsessive thinking but

these thoughts were not necessarily always related to food and were more often related to “specific topics or events” (Dykens & Smith, 1998).

Cognitive

Although varying degrees of mental capacity are seen, adolescents and adults with SMS continue to experience cognitive delays and the majority of individuals have moderate mental retardation (Greenberg et al. 1991). Behavioral abnormalities continue to become more pronounced during adolescence and remain constant throughout adulthood. Adolescents with SMS experience aggressive and explosive outbursts, attention seeking behaviors and impulsive, disobedient actions. They continue to engage in the self-injurious behaviors that began in childhood (Dykens & Smith, 1998).

Most individuals with SMS are not able to live on their own as adults and require supervision from caregivers to ensure that their daily needs are met. Lifespan is not thought to be different than other individuals with mental retardation and there is no decline in cognitive abilities (Dykens and Smith 1998). The oldest individual known to have SMS died at the age of 88 from a stroke (<http://www.ncbi.nlm.nih.gov/sites/GeneTests>; 04/09/10).

As part of the multidisciplinary study conducted by Greenberg et al., imaging studies were performed on individuals with SMS to determine whether or not brain malformations contributed to their neurobehavioral phenotype and mental retardation. Brain MRI showed abnormalities in 13 individuals that included findings of ventriculomegaly and enlarged cisterna magna; both of which were considered clinically insignificant (Greenberg et al., 1991, Greenberg et al., 1996a). Based on these insignificant findings, researchers

were able to conclude the cognitive impairments and behavioral abnormalities in individuals with SMS were not attributed to brain malformations.

Other Phenotypic Findings

The following describes abnormalities that are occasionally seen in individuals with SMS and warrant evaluation during annual physical examination. Ophthalmologic abnormalities were seen in 23 out of 27 individuals studied by Greenberg et al in 1991. These abnormalities included strabismus, myopia, microcornea, iris dysplasia, nasal corectopia and iris coloboma. Hearing loss has also been described in individuals with SMS, therefore periodic audiologic evaluation is recommended. Of twenty-five patients who underwent audiologic evaluations 10 individuals were found to have conductive hearing loss, 5 were found to have sensorineural hearing loss and 2 had mixed hearing loss; giving a combined prevalence of hearing impairment of 68% (Greenberg et al., 1991; Potocki, Shaw, Stankiewicz, & Lupski, 2003). Hearing loss was also present in the two individuals first described with SMS (Smith et al., 1982). Individuals with SMS can also develop scoliosis. Mild to moderate thoracic scoliosis was present in 13 of 20 or 65% of patients greater than 4 years of age (Greenberg et al., 1991; Potocki, Shaw, Stankiewicz, & Lupski, 2003). More recent data suggests that vertebral anomalies and scoliosis are present in approximately 60% of SMS individuals and thus spine radiographs are needed to evaluate for these conditions.

Diagnosis

The diagnosis of SMS was first made using routine G banded cytogenetic techniques. However this method missed a large number of deletions that were not visible

using standard cytogenetic technology. Fluorescence in-situ hybridization (FISH) was able to identify smaller deletions in 17p11.2. With the development of array comparative genomic hybridization (array CGH), many individuals with smaller deletions in 17p11.2 that would have been missed using FISH technologies have been identified on array CGH. Array CGH, also known as chromosomal microarray or whole genome array has now become the primary method of diagnosis of SMS. Even with the advances that have been made in array CGH technologies, there remains a subset of patients who meet SMS clinical criteria who do not have identifiable deletions of 17p11.2. In individuals with the clinical phenotype of SMS without identifiable deletions in 17p11.2, mutation analysis of the *RAI1* gene should be performed.

Genetics of Smith Magenis syndrome

Smith-Magenis syndrome (SMS; OMIM# 182290) is a genetic disorder that is caused by a deletion on human chromosome 17p11.2 or a mutation in the *RAI1* gene (Greenberg et al., 1996, Slager et al., 2003). SMS is thought to be contiguous-gene deletion syndrome (CGS). Contiguous-gene deletion syndromes can cause both microduplications and microdeletions due to misalignment of homologous chromosomes. Although both small (approximately 1.5 Mb) and large (approximately 9 Mb) deletions of 17p11.2 have been reported in SMS patients, 75% of individuals have a common 3.5 Mb deletion in this region (Trask et al., 1996). The minimum deletion region is approximately 700 kB in size (Girirajan et al., 2005). In addition, it is also known that mutations in the *RAI1* gene result in an SMS phenotype (Slager et al., 2003.)

Low Copy repeats

In 1997 Chen et al., discovered homologous recombination between flanking SMS-REP repeat-gene clusters was the molecular basis for the SMS common deletion. Low copy repeats have been implicated in the molecular basis of several genetic conditions including DiGeorge/velo-cardiofacial syndrome, Prader-Willi/Angelman syndrome and Williams syndrome. Genetic diseases, caused by microdeletions or microduplications occur when there is nonallelic homologous recombination (NAHR) between the low-copy repeats (LCR) gene clusters during maternal and paternal gametogenesis (Erdogan, Chen, Kirchhoff et al., 2006).

Discovery of *RAII*

Girirajan et al., (2005) were able to define the critical region of SMS to a ~700 kb region that was commonly deleted in all SMS patients with deletions in 17p11.2. Further study of this region led researchers to discover that there were small deletions present within the *RAII* gene in patients who did not have deletions in 17p11.2 detectable by FISH (Slager et al 2003). In 2003 it was discovered that dominant frameshift mutations in the *retinoic acid inducible 1 (RAII)* gene were present in three individuals who had clinical features of SMS but did not have 17p11.2 deletions present (Slager et al., 2003). Further studies have identified additional individuals with the “hallmark” clinical features of SMS including developmental delay, sleep disturbances and self injurious behavior with deletions in *RAII*. In 2005, Girirajan et al. summarized the findings of all of the individuals found to have mutations in *RAII* and found that none of these individuals with *RAII* mutations had the less common features seen in individuals with SMS including heart defects, urinary system

malformations or other birth defects. These data lead researchers to postulate that haploinsufficiency of *RAII* is responsible for the behavioral, neurological, otolaryngological and craniofacial features of SMS and more variable features including congenital defects are caused by hemizyosity of other genes in the 17p11.2 region (Slager et al., 2003).

RAII

At the time of its discovery in 2003, researchers were uncertain of the clinical roles of *RAII*. Since 2003, researchers have discovered the RNA product of *RAII* is expressed in all tissues studied and was present in high levels in the heart and neuronal structures (Slager et al., 2003; Toulouse, Rochefort, Roussel, Joober, & Rouleau, 2003). The *RAII* gene is highly conserved throughout mammalian evolution. The current hypothesis regarding the function of the *RAII* gene is that *RAII* is a transcriptional regulator involved in the development of neurons but its exact function is unknown (Girirajan et al., 2005).

SMS Mouse Models

Mouse models of SMS, del(17)(p11.2p11.2) and the Potocki-Lupski syndrome, dup(17)(p11.2p11.2) (PTLS; OMIM#610883) the recombination reciprocal of the SMS deletion, have been created to further understand the phenotypes of the two syndromes. Human chromosome 17p11.2 is syntenic to a 32-to-34 cM region on mouse chromosome 11. The critical interval for SMS is a ~1-Mb region that includes 19 genes that are conserved in the same order and orientation in mice (Bi et al., 2002). Studies performed in the SMS mice, *Df(11)17/+* and the PTLS mice, *Dp(11)17/+* have demonstrated differences in the growth patterns consistent with what is reported in humans with SMS and PTLS.

An important finding of studies of mice with SMS and PTLs are the differences in body weight first reported by Walz et al., in 2003. During the first month of life the *Dp(11)17/+* and *Df(11)17/+* mice were both significantly lower in weight when compared to their wild-type litter mates. The PTLs mice, *Dp(11)17/+*, remained underweight throughout their lives and the homozygous duplication mice *Dp(11)17/Dp(11)17* were significantly underweight, even compared to the heterozygous duplication mice, *Dp(11)17/+*. Starting at 4 months of age, the SMS mice *Df(11)17/+*, were significantly overweight when compared to the wild-type mice. By 8 months of age the *Df(11)17/+* mice weighed more than 60g, whereas the wild-type mice weighed approximately 30g. The abdominal fat contents were also compared between the different genotypes. The *Df(11)17/+* mice had an average abdominal fat content of 1.93 ± 0.20 g. The *Dp(11)17/+* mice had an average abdominal fat content of 0.30 ± 0.06 g and the wild-type mice had an average abdominal fat content of 0.56 ± 0.05 g. The amount of abdominal fat made up 4.5% of the total body weight in *Df(11)17/+* mice, 1.2 % of the total body weight of the *Dp(11)17/+* mice and 2.0% of the total body weight of the wild-type mice. When the *Df(11)17/Dp(11)17* mice were studied they were found to have weights similar to that of the wild-type mice. This finding suggests that the presence of the wild-type number of genes can rescue the overweight phenotype of the *Df(11)17/+* mice and the underweight phenotype of the *Dp(11)17/+* mice (Walz et al., 2003).

In addition to describing the weight differences between the deletion and duplication mice, there is also data available about other phenotypic characteristics. It is known that the craniofacial features of SMS become more pronounced as an affected individual ages. The craniofacial features of the *Df(11)17/+* mice have been documented throughout the life span

of the mouse. No craniofacial abnormalities were appreciated during the newborn period of *Df(11)17/+* mice when compared to wild-type mice. All of the adult *Df(11)17/+* mice were found to have craniofacial abnormalities including shorter skull lengths, broader and shorter snouts and distinctive nasal bone shape. Congenital heart defects, urinary tract defects and seizures have been reported in 35%, 29% and 19% of individuals with SMS respectively (Chen et al., 1997 and Greenberg et al., 1996). No defects were found in the heart or urinary system of *Df(11)17/+* or *Dp(11)17/+* mice. Seizures and abnormal EEGs were present in *Df(11)17/+* mice. This finding led researchers to postulate that there was a direct effect of the deletion on neuronal excitability (Walz et al., 2003). Seizures were not present in the *Dp(11)17/+* mice.

Before haploinsufficiency of *RAI1* was determined to be responsible for major features of SMS, a mouse model with a null mutation in *RAI1* was created to study the relationship between the *RAI1* copy number and the *Df(11)17/+* and *Dp(11)17/+* phenotypes. The weights of the *Rai1*^{+/-} mice were measured from 3 weeks to 7 months. At 4-7 weeks of age the *Rai1*^{+/-} mice were underweight when compared to their wild-type litter mates. However, by 23 weeks of age both male and female *Rai1*^{+/-} mice were overweight when compared to their wild-type littermates. Researchers were able to conclude that haploinsufficiency of *Rai1* was a major factor in the obesity that is present in SMS individuals (Bi et al., 2005).

Obesity

In the General Population

The negative health, economic, and social consequences of obesity are well documented. The American Medical Association considers obesity the fastest growing health problem in the United States. Obesity kills more than 300,000 Americans per year, which is more than AIDS, all cancers and all accidents combined. More than 66% of the adult population in the United States is overweight or obese (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal, 2006). More frightening than the facts about obesity in US adults, are the statistics about overweight and obese children. The prevalence of overweight and obesity in US children has tripled over the past two decades (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal, 2006)

Overweight and obesity have been shown to increase morbidity/mortality and decrease life expectancy. The health risks associated with obesity include: insulin resistance, type 2 diabetes, hyperlipidemia, hypertension, coronary heart disease, congestive heart failure and gastrointestinal complications including gastroesophageal reflux, gallstones and gallbladder disease, gout and non-alcoholic fatty liver disease (Pi-Sunyer, 1991). Overweight and obese individuals are at increased risks for developing certain types of cancer including: endometrial, colon, kidney, gallbladder and postmenopausal breast cancer (Krebs et al., 2007). In addition to the physical risks associated with overweight and obesity, there are also emotional and psychosocial risks that are often under appreciated. Overweight and obese individuals have increased risks for depression, low self-esteem, poor self-image and social isolation (Krebs et al., 2007).

As with most health conditions, family history is important in determining a child's risk to develop obesity and the strongest predictor of childhood obesity is the weight status of the parents. If one parent is obese, the odds ratio that a child will be obese as an adult is 3:1. This odds ratio jumps to 10:1 if both parents are obese (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). It is thought that the relationship between parental and childhood obesity is multi-factorial in etiology, with multiple genes and environmental factors playing a role. Genome wide association studies have been performed to gain more information about genes that are associated with obesity. The results of these studies showed that obesity is polygenic, with more than 300 genes and genetic loci associated with obesity (Chagnon, Rankinen, Snyder, Weisnagel, Perusse, & Bouchard, 2003). Additionally, there are 50 loci related to Mendelian syndromes associated with obesity that have been mapped (Rankinen, et al., 2006).

In Genetic Conditions

It is well documented that obesity and food seeking behaviors are present in certain genetic conditions associated with cognitive impairment. Prader- Willi syndrome (PWS; OMIM 176270) is an example of a genetic condition that is primarily associated with obesity, cognitive impairments, maladaptive behaviors and hyperphagia, an abnormally increased appetite for and consumption of food (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007).

Although the negative effects of obesity in the general population are well known, little is known about the prevalence or cause of any obesity that is present in the SMS population. In more recent studies of SMS individuals, a new concern for the involvement

of obesity has been raised. Of those studies that have been published, information obtained was often incomplete and small in number. Because so little is available, it is not clearly defined how obesity is involved in the natural history of this condition.

An abstract presented by Smith et al. in 2004 provided an overview of parametric measurements of growth and body mass index (BMI) of 54 individuals with SMS. BMI is a measurement of weight in relation to height that is used to determine if an individual is overweight or obese. BMI is calculated in the following manner: $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$. In adults, normal weight is defined as a BMI between 18.5- 24.9, underweight is classified as a BMI less than 18.5, overweight is defined as a BMI of 25-29.9 and obesity is defined as a BMI of 30 or greater. In the abstract presented by Smith et al., the mean birth weight was between the 5th -25th percentile and birth length was between the 25th - 50th percentiles. They reported that poor growth, as defined by <5th percentile, was noted within the first six months of age and that it may persist into early childhood. The abstract also reported that on average, males with SMS were at the 25th percentile for weight at age 6 years and grew to the 90th percentile by 14 years. Females with SMS were reported to be between the 25-50th percentile for weight between the ages of 1- 7 years and increased to >90th percentile by age 12 (Smith, Leonard, Gropman, & Krashewich, 2004). Another study investigating hypercholesterolemia in 49 individuals with SMS reported the mean BMI in individuals with SMS was 18.43 with a range of 14.08- 31.67 (Smith, et al., 2002). A meta-analysis of 105 individuals with SMS published in 2007 provided valuable information about genotype-phenotype information in individuals with SMS (Edelman, et al., 2007). However information regarding growth and BMI was unavailable for over 60% of the cases

examined. Because of these conflicting findings, further studies regarding the role of obesity in the Smith-Magenis population are needed.

The severe neurobehavioral abnormalities present in individuals with SMS make this facet of the phenotype an interesting avenue to explore in an attempt to provide an explanation of the obesity seen in individuals with SMS. Therefore the specific aims of this study are to:

- 1.) Characterize the growth (height, weight and BMI) of a cohort of individuals with Smith-Magenis syndrome to determine if obesity is a component of SMS in our patient population.
- 2.) Assess if hyperphagia or food seeking behaviors are present in individuals with Smith-Magenis syndrome.

Determining whether or not neurobehavioral abnormalities such as food seeking behaviors and hyperphagia are present in individuals with SMS would aid in further characterizing the natural history of this genetic syndrome. In addition, if obesity and behavioral components can be characterized, targeted and age appropriate therapies can be developed in order to better manage individuals with SMS.

MATERIALS & METHODS

This study used two methods of data collection in order to address the two specific aims. Part I of the study aims to characterize the growth (height, weight and BMI) of a cohort of individual with Smith-Magenis syndrome to determine the prevalence of obesity through the use of a retrospective chart review. Part II of this study aims to assess if hyperphagia or related behaviors are present in individuals with SMS through the use of a parent questionnaire which includes a validated instrument, the Hyperphagia Questionnaire (Dykens et al., 2007). This study was approved by the University of Texas Health Science Center Committee for the Protection of the Human Subjects (HSC-GEN-09-0393) and the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (H-25766). A consent form was required and was mailed to participants along with the study questionnaire.

Participants

There were essentially two different sets of participants in this study. For Part I of the study, the retrospective chart review, participants were individuals with a confirmed medical diagnosis of Smith-Magenis syndrome by chromosome analysis, fluorescence in situ hybridization (FISH) or array CGH (aCGH). For Part II of the study, the assessment of hyperphagia and related food seeking behaviors, all participants were parents or caregivers of individuals with a confirmed medical diagnosis of Smith-Magenis syndrome. Participants were ascertained through a database of SMS patients maintained by Baylor College of Medicine (BCM) at Texas Children's Hospital (TCH). All participants whose child carried a confirmed medical diagnosis of SMS had either:

1.) Participated in or contacted researchers regarding participation in clinical research at BCM/TCH, or:

2.) Have been, or are, currently followed in the genetics clinic at Texas Children's Hospital

Individuals without a confirmed medical diagnosis of SMS were not included in the retrospective chart review, nor were their parents mailed a study questionnaire.

Procedure

In Part I of this study, a retrospective chart review was conducted of participant's medical records. Sources of available information included: electronic medical record, paper charts and research charts. All documented height and weight measurements were abstracted for each individual. This data was collected by hand, matched with the individual's unique study ID and entered into an Excel database.

For Part II of this study, a questionnaire was mailed to the corresponding parents of individuals in Part I of the study. Each household was limited to one questionnaire and the questionnaire was to be filled out by only one parent/caregiver. A total of eighty-nine questionnaires were mailed; twenty-two questionnaires were returned without a forwarding address for a total of seventy-seven potential participants. Twenty-five completed questionnaires were returned, corresponding to a response rate of 28% (25 out of 89). Questionnaires were initially mailed in October 2009 and data was collected through March 2010.

The questionnaire consisted of 51 questions subdivided into five sections. Section 1, a set of 10 demographic questions, provided demographic information regarding the parent

completing the questionnaire. The remaining four sections of the questionnaire provided information regarding the individual with SMS. Section 2 consisted of 15 medical and social history questions, Section 3 consisted of 3 exercise history questions and Section 4 consisted of 10 diet history questions. The final 13 questions were taken from a validated hyperphagia questionnaire (HQ), developed by Elizabeth Dykens, PhD.

The HQ was initially developed to assess hyperphagia in individuals with Prader-Willi syndrome (PWS) (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007). This questionnaire has been validated in the Prader-Willi population and has also been used in individuals with Down syndrome and undiagnosed intellectual disabilities who show food seeking behaviors or “Prader-Willi-like” preoccupations with food. Dr. Dykens has given permission via email for the use of the hyperphagia questionnaire in this research project. The HQ was created to measure hyperphagia in individuals with PWS by looking at the following: specific food related behaviors, preoccupations and thoughts about food and the severity of the symptoms. Responses on the HQ are rated on a 5 point scale (1 = not a problem to 5 = severe and/or frequent problem.) In their initial publication describing the use of the HQ in 153 individuals with PWS, Dykens et al. conducted a factor analysis and found three factors emerged which accounted for 58.93% of the variance seen in hyperphagia (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007). These factors were labeled, Hyperphagic Behavior, which accounted for 34.47% of the variance (eigenvalue = 3.79, Cronbach’s alpha = 0.76), Hyperphagic Drive, which accounted for 15.28% of the variance (eigenvalue = 1.68, Cronbach’s alpha of 0.80) and Hyperphagic Severity which accounted for 9.17% of the variance (eigenvalue = 1.01, Cronbach’s alpha = 0.60). There were two questions on the questionnaire that did not load onto any factor and these items

were: age of onset of hyperphagia and variability in the drive for food. As these items did not specifically correlate with factor, they were dropped from further analysis (Dykens et al., 2007).

Individuals who completed and returned the questionnaire were eligible to receive a \$15 gift certificate to Target®. The financial support for this project (including postage, the printing of study related materials and incentive) was provided by a donation received by Dr. Potocki to investigate obesity in individuals with SMS.

Analysis:

Part I- Retrospective Chart Review

Based on their age at their last recorded measurement, individuals were categorized into age groups using the classifications provided by the CDC. Table 1 provides an overview of the age classification system used in this study.

Table. 1 Age Classifications	
Age Group	Corresponding Age
1	0-23 months
2	2-5 years
3	6-11 years
4	12-19 years
5	≥ 20 years

Z-scores

For all growth measurements, including those obtained from the parent questionnaire and chart review, Z-scores (SD units) for height-for-age, length-for-age and BMI-for-age were calculated using the reference growth standards provided by National Center for Health statistics and the Centers for Disease Control and Prevention (Statistics, N.C.f.H., 2000). The calculation of Z-scores allowed for comparison between the SMS patient population and the reference standard as defined by the CDC. For individuals less than 20 years of age, the Z-scores were calculated using the values provided by the CDC corresponding to their given age and gender. For individuals greater than or equal to 20 years of age, Z-scores were calculated using the values provided by the CDC corresponding to that of a nineteen year old of their respective gender. One sample t-tests were run to assess for differences in the weight-for age, height for age and BMI-for age Z-scores between our SMS cohort and reference standards.

BMI

BMI was calculated for all individuals ≥ 24 months of age using the following formula: $BMI = \text{weight (kg)} / [\text{height(m)}^2]$. For individuals < 20 years of age (age 24 months through 19 years of age) BMI and BMI percentile were calculated. It was necessary to calculate BMI percent in order to interpret the BMI of individuals less than 20 years of age, as the interpretation of BMI during childhood and adolescence is different than the interpretation of BMI in adulthood. The interpretation of BMI in childhood is dependent on age and gender. For individuals greater than 20 years of age, BMI was calculated and interpreted using the CDC's recommendation for the interpretation of BMI in adults.

Through the use of BMI, individuals were classified as underweight, healthy weight, overweight or obese. Table 2 provides an explanation of the interpretations of BMI in individuals' ≥ 2 and < 19 years of age. Table 3 provides an explanation of the interpretations of BMI in individuals' ≥ 20 years of age.

Table 2. BMI-for-Age Individuals age ≥ 2 years & < 20 years of age	
Weight Status Category	Percentile Range
Underweight	$< 5^{\text{th}}$ percentile
Healthy weight	5^{th} percentile through $< 85^{\text{th}}$ percentile
Overweight	85^{th} percentile to less than 95^{th} percentile
Obese	$\geq 95^{\text{th}}$ percentile

Table 3. BMI in Adults Individuals ≥ 20 years of age	
Weight Status Category	BMI
Underweight	< 18.5
Healthy weight	18.5-24.9
Overweight	25.0-29.9
Obese	30.0 and above

Part II- Parent Questionnaire

The data obtained from the non-validated portion of the questionnaire was entered into an Excel database and descriptive statistics were performed for the following: participant demographics (parents of children with SMS), affected child's medical, social, exercise and diet history.

Hyperphagia Questionnaire

The hyperphagia questionnaire used in Part II of the study was scored according to the validated parameters. As the HQ is scored on a Likert scale, mean scores were calculated for each question in the HQ. Individuals were also given a mean score for the three factors

present in the HQ: hyperphagic behavior, hyperphagic drive and hyperphagic severity. The mean scores for the three factors were compared using the following variables: age, gender and BMI. Two sample t-tests were calculated to assess for differences between the mean HQ scores between individuals who were healthy weight and obese weight, overweight and obese, healthy weight and overweight, obese and non-obese. An ANOVA was performed to assess for differences in the mean behavior, drive and severity scores between all BMI classifications. Two sample t-tests were performed to assess for differences in mean behavior, drive and severity scores between males and females. Individuals were also categorized by age group and an ANOVA was performed to assess for differences in mean scores according to age group. Comparisons were made between responses from the non-validated portions of the questionnaire to responses from the validated portion of the questionnaire.

Fisher's exact test allowed for the examination of the relationship between reported amount of food eaten and BMI classification and the relationship between reported increased interest in food and BMI classification.

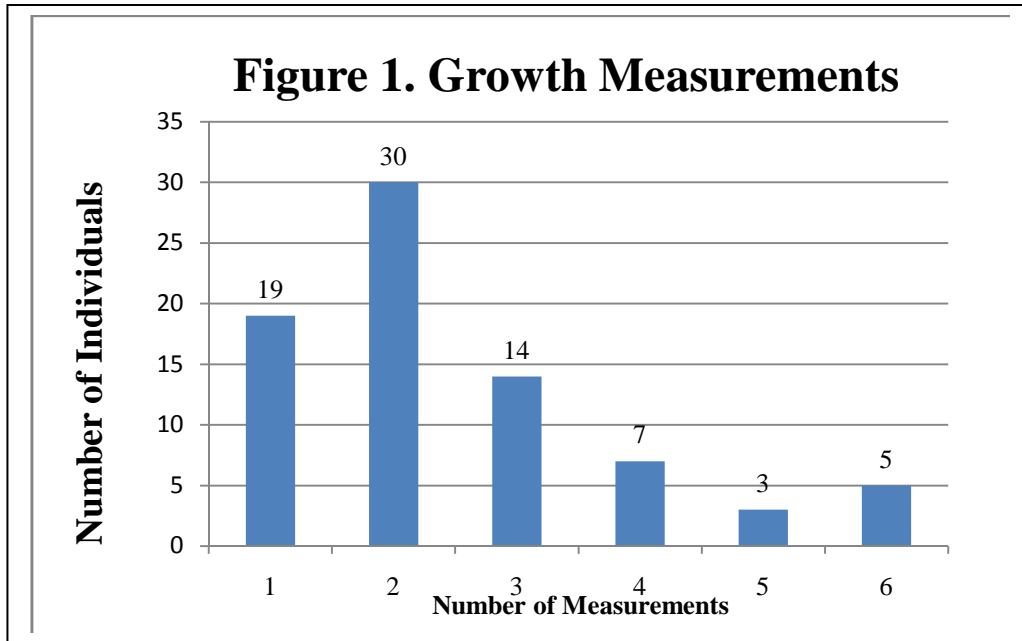
As the true prevalence of hyperphagia in individuals with SMS is currently unknown there were no definitive guidelines as to what defines hyperphagia in the SMS population.

RESULTS

Part I-Characterization of Growth Patterns

In order to characterize the growth (height, weight and BMI) of a cohort of individuals with Smith-Magenis syndrome, a retrospective chart review was conducted. In addition to the data collected using the retrospective chart review, the data presented in Part I also includes the height, weight and corresponding BMI measurements of 25 individuals with SMS whose parent's recorded their child's height and weight on the parent questionnaire.

When the data obtained from the chart review and questionnaire was combined, at least one set of growth measurements (both height and weight ascertained at the same time) was available for all 78 individuals with SMS. Of the 78 total individuals, 35 were male (45%) and 43 were female (55%). The number of growth measurements available for each individual varied from one to six sets of measurements. The majority of individuals, 51 (61.5%), had only one or two growth measurements available. Figure 1 provides a graphical representation of available growth measurements.



A total of 194 weight measurements were analyzed of which, 169 were obtained from the chart review and 25 were obtained from the questionnaire. A total of 167 height measurements were analyzed, of which, 142 were obtained from the chart review and 25 were obtained from the questionnaire. There were 167 sets of measurements that included both weight and height measurements.

Age

The mean and median age was calculated using the individual's age at the last recorded measurement. The mean age at the final measurement was 13.7 years and the median age was 11.1 years for all 78 individuals. The youngest age recorded was a birth measurement (age=0) and the oldest age recorded was 51 years. Based on their age at their last recorded measurement, individuals were coded into age groups using the classifications provided by the CDC. Table 4 provides a detailed overview of the age distribution in our SMS cohort.

Table. 4 Age Distribution, Overall Population n=78			
Age Group	Corresponding Age	# of individuals	%
1	0-23 months	4	5%
2	2-5 years	16	21%
3	6-11 years	22	28%
4	12-19 years	22	28%
5	≥20years	14	18%
Total		78	100%

Growth Measurements

The mean height and weight were calculated for the combined cohort, as well as separately for males and females after stratification by age group. Table 5 summarizes the mean height and weight for the combined cohort. The mean age for each age group is also provided.

Table 5. Growth Measurements, Combined Males & Females								
Age Group	Age	Mean Age (years)	Mean height (cm)			Mean weight (kg)		
			n	μ	SD	n	μ	SD
1	0 -23 m	0.34	24	61.5	13.3	49	4.93	2.76
2	24 m - 5yrs	4.09	50	94.4	9.09	51	15.25	3.65
3	6 - 11 yrs	8.60	42	120.99	14.09	42	28.47	15.06
4	12- 19 yrs	15.79	32	151.78	11.14	33	60.75	20.77
5	\geq 20 yrs	30.88	19	162.21	11.17	19	73.73	15.22
<u>Total</u>			167			194		

Both weight and its corresponding height measurement were obtained for 96 females in the cohort. There were 19 females who had weight measurements but were missing the corresponding height measurement. Table 6 summarizes the mean height and weight for the females in the cohort. The mean age for each age group and the number of measurements are also provided.

Table 6. Growth Measurements, Females Total Number of Female Growth Measurements									
Age Group	Age	n	Mean Age (years)	Mean height (cm)			Mean weight (kg)		
				n	μ	SD	n	μ	SD
1	0 -23 m	24	0.36	15	58.8	12.05	24	4.9	2.8
2	24 m - 5yrs	28	4.12	28	92.94	8.91	28	14.9	3.84
3	6 - 11 yrs	27	8.59	27	119.34	12.77	27	25.9	12.1
4	12- 19 yrs	19	15.99	19	148.93	10.92	19	57.9	21.07
5	\geq 20 yrs	7	32.3	7	153.14	7.17	7	68.8	14.67
<u>Total</u>		105		96			105		

Both height and weight measurements were obtained at the same time for 71 males in the cohort. There were 18 males who had a weight measurement but they were missing the corresponding height measurement. Table 7 summarizes the mean height and weight for males in the cohort. The mean age for each age group is also provided.

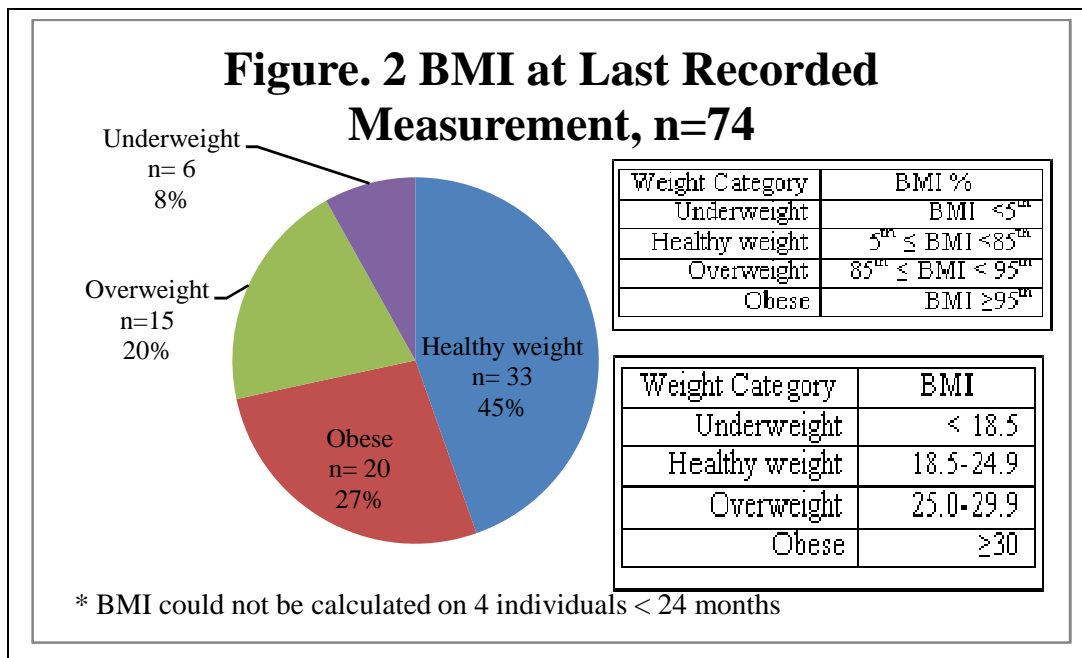
Table 7. Growth Measurements, Males									
Total Number of Male Growth Measurements									
Age Group	Age	n	Mean Age (years)	Mean height (cm)			Mean weight (kg)		
				n	μ	SD	n	μ	SD
1	0 -23 m	25	0.33	9	66.01	14.05	25	4.95	2.79
2	24 m - 5yrs	23	4.06	22	96.25	9.18	23	15.68	3.43
3	6 - 11 yrs	15	8.63	15	123.98	16.24	15	33.0	18.89
4	12- 19 yrs	14	15.5	13	155.93	10.5	14	64.58	20.47
5	\geq 20 yrs	12	30.1	12	167.5	9.66	12	76.13	15.5
<u>Total</u>		89		71			89		

Body Mass Index (BMI)

Body Mass Index (BMI) was calculated for all individuals greater than 24 months of age. There were four individuals who were less than 24 months of age at their last recorded measurement; therefore BMI could not be calculated for these individuals. For individuals less than 20 years of age, BMI and BMI percentile for age were calculated. The interpretation of BMI during childhood and adolescence is different than the interpretation of BMI in adulthood, thus it was necessary to calculate BMI percentile in order to interpret the BMI of individuals less than 20 years of age. For individuals greater than 20 years of

age, BMI was calculated and interpreted using the CDC's recommendation for the interpretation of BMI in adults (Statistics, N.C.f.H., 2000.).

Figure 2 provides a graphical representation of BMI distribution of SMS individuals at the last recorded measurement for 74 individuals.



Weight-for-age, Height-for-age and BMI-for-age Z-score calculations

In order to interpret the meaning of the height, weight and BMI values of individuals with SMS, height-for-age, weight-for-age and BMI-for-age Z-scores were calculated. The z-score is defined as: “the deviation of a given variable, x, from the mean divided by the standard deviation” (Dawson & Trapp, 2004,2001) and it indicates how different a raw value is from a population mean. A negative z-score corresponds to a value less than the population mean and a positive z-score corresponds to a z-score greater than the mean. For our analysis the population mean and standard deviation used in the calculation were based on the normally distributed reference standard as defined by the CDC (Statistics, N.C.f.H., 2000). Therefore, the calculation of z-scores is able to provide information on how the growth parameters of individuals with SMS compare to that of the general US population.

For males and females age 24 months – 19 years of age the height-for-age, weight-for age and BMI-for-age Z scores were calculated using the reference standard values corresponding to their given age and gender. For males and females ≥ 20 years of age their height-for-age, weight-for age and BMI-for-age Z-scores were calculated using the reference standard for a 19-year-old of their given gender.

One sample t-tests were run using the calculated Z-scores for the following: height-for-age, weight-for-age and BMI-for-age. Table 8 provides detailed information regarding the mean Z-scores for males and Table 9 provides detailed information regarding the mean Z-scores for females, reported by age category.

Males-height-for age Z-scores

For males in all age categories, the difference in height-for-age mean Z-scores between males at the previously described age groups and what is expected for their age was statistically significant ($p = 0.01, <0.001, 0.03, 0.02$ and 0.0065 , respectively) demonstrating the male SMS individuals in all age categories in this cohort are shorter than the reference age-specific standards for the general population. Table 8 provides detailed information regarding the height-for-age Z-scores for males.

Males-weight-for age Z-scores

For males in all age categories, the weight-for-age Z score p-values were not statistically significant demonstrating the weight of males in our SMS cohort did not differ (either higher/larger or lower/smaller) from what is expected in the general population based on age ($p = 0.12, 0.10, 0.68, 0.22$ and 0.35 respectively.)

Males-BMI-for age Z-scores

For all males in all age categories, the calculated mean BMI-for-age Z-scores were positive, demonstrating that the mean-BMI-for-age was greater than the 50th percentile. At age groups 6-11 years, 12-19 years and ≥ 20 years, the difference in BMI-for-age mean Z-scores between males of these age groups and what is expected in the similar age-specific general population was statistically significant ($p = 0.023, 0.0023$ and 0.0018 , respectively) demonstrating that the male SMS individuals in this cohort have a higher BMI than what is expected for their age.

Females-height-for age Z-scores

For females of all age groups, all of the mean z-scores for height were negative which correspond to raw values below the age-specific 50th percentile. This difference in height-for-age mean Z-scores and what is expected for their age was statistically significant ($p= 0.0016, <0.001, < 0.001, 0.001$ and 0.009 , respectively) demonstrating the female SMS individuals in this cohort in all age groups are significantly shorter than expected based on their age.

Females-weight-for age Z-scores

The calculated weight-for-age mean z-scores were negative for females 0-23 months, 24 months- 5 years and 6-11 years. These negative z-score for females correspond to values less than the 50th percentile. The difference in mean-weight-for-age Z-scores and what is expected based on their age was statistically significant ($p= 0.0035, 0.0122$ and 0.008 , respectively.), demonstrating the female SMS individuals in this cohort from the ages of 0-23 months, 24 months -5 years and 6-11 years, weigh less than what is expected for their age. It is only in the age category of 12-19 years and ≥ 20 years that the mean weight-for-age Z-scores are positive. In other words, prior to age 12, female SMS individuals in this cohort had weight-for-age mean z-scores less than the 50th percentile and at age 12 years and older, female individuals with SMS in this cohort had weight-for-age mean z-score greater than the 50th percentile. Although the weight-for-age mean z-scores for females crossed from less than the 50th percentile to greater than the 50th percentile as they aged, statistical significance was not achieved ($p= 0.50$ at 12-19 years and $p= 0.192$ at ≥ 20 years.)

Females BMI-for-age Z-score

For females of all age groups, the calculated mean BMI-for-age Z-scores are positive, thus corresponding to BMI's greater than the 50th percentile. In the following age groups: 24 months -5 years, 12- 19 yrs and ≥ 20 years, the difference in BMI for age mean Z-scores and what is expected for their age was statistically significant ($p = <0.001, 0.013$ and 0.0039 , respectively) demonstrating that the female SMS individuals in these age groups have higher BMI than what is expected for their age.

In summary, it appears that both males and females with SMS are shorter than their peers, but have average weight, thus corresponding to higher BMI's. Figures 3-5 provide a graphical representation of the mean height-for-age, weight-for age and BMI-for-age Z-scores for males and Figures 6-8 provide a graphical representation of the mean height-for-age, weight-for-age and BMI-for-age Z-scores for females.

Table 8. Z-score for Males, by age group												
	Z score height				Z score weight				Z score BMI			
	N	μ	SD	p	n	μ	SD	p	n	μ	SD	p
0 -23 m	9	-1.19	1.08	0.01	25	-0.33	1.03	0.12				
24 m - 5 yrs	22	-1.43	1.49	< 0.001	23	-0.52	1.45	0.10	22	0.59	1.48	0.074
6 - 11 yrs	15	-1.31	2.11	0.0304	15	0.288	2.65	0.68	15	1.63	2.47	0.023
12- 19 yrs	13	-1.50	1.39	0.0022	14	0.575	1.67	0.22	13	1.45	1.36	0.0023
\geq 20 yrs	12	-1.40	1.43	0.0065	12	0.351	1.25	0.35	12	1.10	0.93	0.0018
Total	69				89				62			

Table 9. Z-score for Females, by age group												
	Z score height				Z score weight				Z score BMI			
	n	μ	SD	p	n	μ	SD	p	n	μ	SD	p
0 -23 m	15	-1.46	1.45	0.0016	24	-0.813	1.223	0.0035				
24 m - 5 yrs	28	-2.13	1.05	<0.001	28	-0.719	1.42	0.0122	28	1.09	1.19	<0.001
6 - 11 yrs	27	-1.99	1.12	<0.001	27	-0.842	1.51	0.008	27	0.43	1.52	0.16
12- 19 yrs	19	-1.89	1.51	<0.001	19	0.294	1.884	0.5041	19	1.29	2.04	0.013
\geq 20 yrs	7	-1.65	1.17	0.009	7	0.717	1.29	0.192	7	1.84	1.07	0.0039
Total	96				105				89			

Figure 3, Two way scatter plot, Males, height-for-age Z-scores by age group

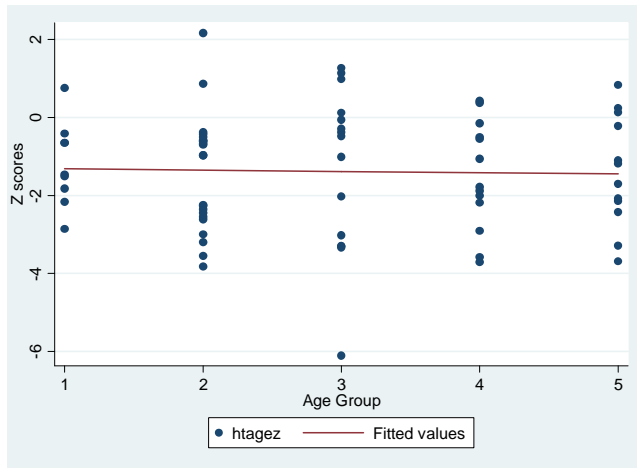


Figure 4, Two way scatter plot, Males, weight-for-age Z-scores by age group

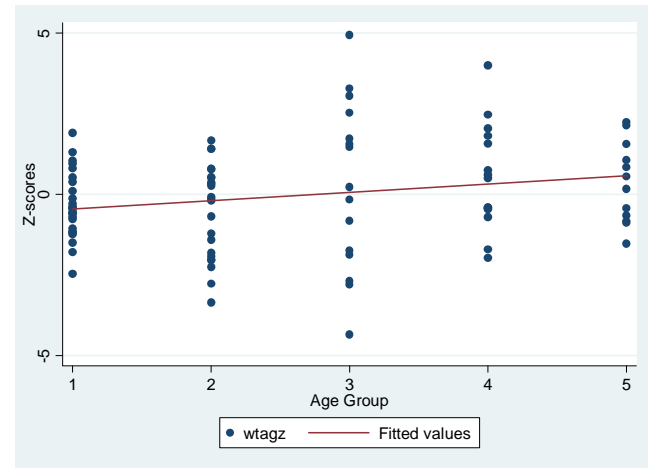


Figure 5. Two way scatter plot, Males, BMI-for-age Z-scores by age group

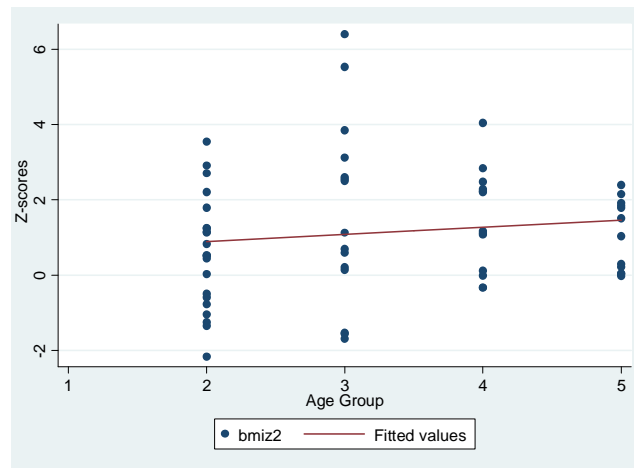


Figure 6. Two way scatter plot, Females, height-for-age Z-scores by age group

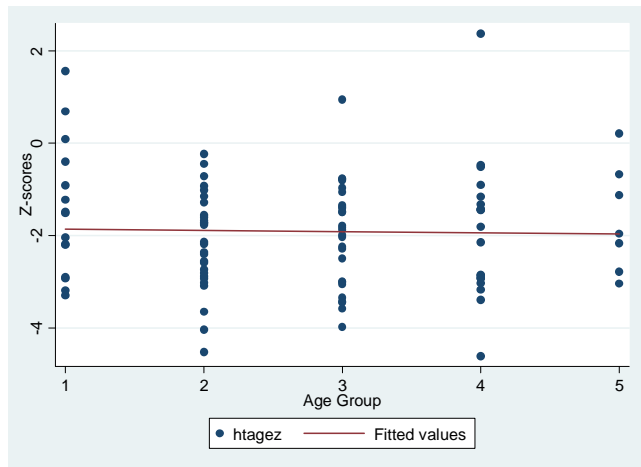


Figure 7. Two way scatter plot, Females, weight-for-age Z-scores by age group

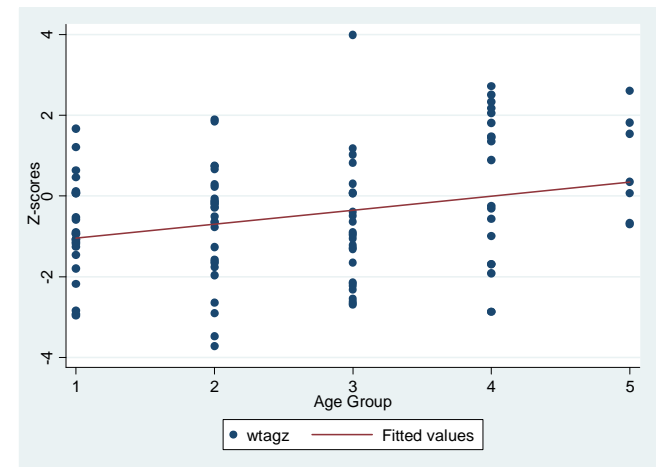
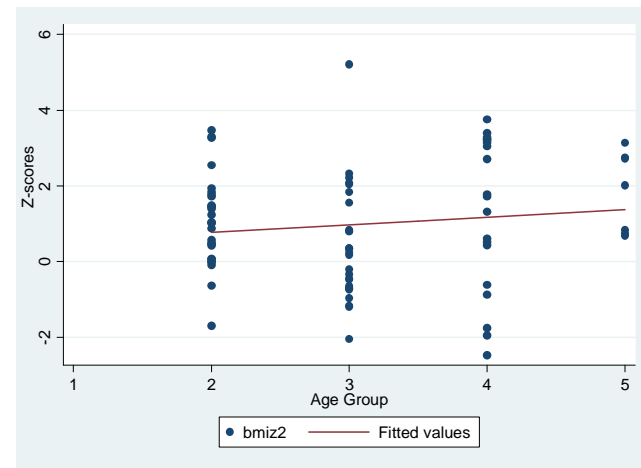


Figure 8. Two way scatter plot, Females, weight-for-age Z-scores by age group



Part 2- Parent Questionnaire

Part II of this study involved the use of a parent questionnaire to assess hyperphagia or related abnormal food behaviors in individuals with SMS. The parent questionnaire was used to provide information on the food related behaviors that may be related to overweight and obesity among individuals with SMS.

Demographics

A total of 25 questionnaires were completed by parents of children and adults with Smith-Magenis syndrome. All of the participants who completed the questionnaire were ascertained through a database of SMS patients maintained by Baylor College of Medicine (BCM) at Texas Children's Hospital. Twenty-five completed questionnaires were received out of the 89 total questionnaires mailed, corresponding to a response rate of 28.1%.

Demographic information was available for 24 of 25 questionnaires as one individual did not complete the demographic portion of the questionnaire. Not all participants answered all questions within the demographic portion of the questionnaire.

Twenty out of twenty five participants correctly reported their age on the questionnaire. There was one individual who did not respond to any question on the demographic section of the questionnaire, and four individuals who listed their child's age and not their own age. Of the twenty participants who correctly indicated their age on the questionnaire, the average age of the participants was 50.3 years with a range of 34 years to 75 years. The majority of the participants were Caucasian (n=19; 79.17%) with English being the primary language (n=21; 87.50%). Other languages included Spanish (n=2; 8.33%) and Chinese (n=1; 4.17%). The majority of participants reported they were married or living as married (n=21; 87.5%). One participant (4.17%) indicated they were separated

and two individuals (8.33%) indicated they were divorced. None of the participants identified themselves as single. The majority of participants (n=13; 54.16%) indicated they had a Bachelor's degree or an advanced education degree. The lowest level of education was 9th to 11th grade in one individual (4.17%). Seventy nine percent (n=19) of the questionnaires were filled out by mothers, with fathers completing 16.67% (n=4). One questionnaire was completed by an adoptive parent. The majority of participants (n=15; 62.5%) were employed. The average yearly income ranged from less than \$25,000 (n=1; 4.35%) to greater than \$100,000 (n=10; 43.48%). There were two individuals who preferred not to provide their average income and either indicated "prefer not to answer" or left the question blank. Table 10 provides detailed information on the demographics of the participants (parents/caregivers).

**Table 10. Demographics of Participants(Parents)
Completed Questionnaire**

	Number	%			Number	%
Total Participants (N)	25	28.1%		Marital Status		
				Married/Living as married	21	87.5%
Age				Separated	1	4.17%
34-44	6	30%		Divorced	2	8.33%
45-54	9	45%			24	
55+	5	25%		Employment Status		
	20			Yes, Employed	15	62.5%
Ethnicity				No, Not Employed	9	37.5%
White	19	79.2%			24	
Hispanic	4	16.7%		Annual Income		
Asian	1	4.17%		Less than \$25,000	1	4.2 %
	24			\$25-50,999	6	25%
Primary Language				\$21-74,999	2	8.15%
English	21	87.5%		\$75-99,999	3	12.5%
Spanish	2	8.33%		\$100,000 or more	10	42%
Other (Chinese)	1	4.17%		Prefer not to answer/left blank	2	8.15%
	24				24	
Relationship to child with SMS				Highest Education Level		
Mother	19	79.2%		9 th to 11 th grade	1	4.17%
Father	4	16.7%		High School or GED	3	12.5%
Other (adoptive mother)	1	4.2%		Some college	6	25.0%
	24			Associates Degree	1	4.17%
				Bachelor's Degree	5	20.8%
				Advanced Degree	8	33.3%
					24	

Demographics of SMS individuals

Demographic information was available for 25 individuals with SMS. Nine individuals (36%) were male and 16 individuals (64%) were female. The median age of individuals with SMS in this study was 20 years with a range of 8 years of age to 51 years of age. Thirteen individuals (52%) were greater than 20 years of age. Individuals were categorized by age using the classifications provided by the CDC. Table 11 provides information on the age distribution of SMS individuals.

Age Group	Corresponding Age	#	%
1	0-23 months	0	0
2	2-5 years	0	0
3	6-11 years	3	12%
4	12-19 years	9	36%
5	≥20years	13	52%
		25	100%

Child's Medical History

The average age at diagnosis was 8.65 years of age with a range of 1 month of age to 30 years of age, with most individuals (n=12; 48%) diagnosed prior to five years of age. The majority of parent's (n=17; 68%) reported their child was diagnosed by a geneticist and most had a 17p11.2 deletion (n=22; 88%). One parent reported their child had a *RAII* mutation, while two parents reported they were unsure of the genetic etiology of SMS in their child. Seven out of twenty four parents (28%) reported their child had been diagnosed

with failure to thrive (FTT). Two parents (8%) reported their child needed a feeding tube; neither reporting surgical placement of the feeding tube.

Regarding congenital anomalies, the most common congenital anomaly reported by parents was heart defect; eight parents (32%) reported their child had been diagnosed with a heart defect. One parent reported their child was diagnosed with a cleft lip (4%), four parents reported their child was diagnosed with a cleft palate (16%), two parents reported their child was diagnosed with a kidney defect (8%), four parents reported their child was diagnosed with a urinary tract defect (16%) and five parents reported their child was diagnosed with low thyroid function (20%). Table 12 provides a detailed overview of the medical history data as reported by parents completing the questionnaire.

Table. 12 Medical History of SMS Individuals (as reported by parent on questionnaire)					
	#	%		#	%
Age Diagnosed			Diagnosed Cleft Lip		
Birth- 5 years	12	48%	Yes	1	4%
6-10 years	6	24%	No	24	96%
11-20 years	4	16%			
21+ years	3	12%	Diagnosed Cleft Palate		
			Yes	4	16%
Diagnosis Made By			No	21	84%
Pediatrician	1	4%			
Geneticist	17	68%	Diagnosed Heart Defect		
Neurologist	1	4%	Yes	8	32%
Developmental Specialist	4	16%	No	17	68%
Other	2	8%			
			Diagnosed Kidney Defect		
Genetic Etiology			Yes	2	8%
17p11.2 deletion	22	88%	No	23	92%
<i>RAI1</i> mutation	1	4%			
Don't know	2	8%	Diagnosed Urinary Tract Defect		
			Yes	4	16%
Diagnosis of Failure to Thrive (FTT)			No	21	84%
Yes	17	68%			
No	7	28%	Diagnosed Low Thyroid Function		
Don't know	1	4%	Yes	5	20%
			No	20	80%
Feeding Tube Placed					
Yes	2	8%			
No	23	92%			

Child's Medication History

Parents were asked if their children had ever taken medication for any of the following: heart defects, seizures, diabetes, high cholesterol, high blood pressure, thyroid problems, kidney problems, acid reflux, kidney reflux, anxiety, depression, hyperactivity/ADD, sleep disturbances, self-injurious behavior, aggression or obsessive compulsive behaviors. Twenty respondents, (83.33%), reported their child had been prescribed medication for sleep disturbances. Sixteen parents (69%) reported their children had been prescribed medication for anxiety and fourteen, (58.33%) reported their children had been prescribed medication for hyperactivity/ADD. Table 13 provides a detailed overview of the medication history reported by the participants regarding their children with SMS.

Table 13. Medication History of Individuals with SMS as Reported by Participating Parent					
	Number	%		Number	%
Heart Defect			Acid Reflux		
Yes	1	4.55%	Yes	8	65.22%
No	21	95.45%	No	15	34.78%
Seizures			Anxiety		
Yes	5	21.74%	Yes	16	69.57%
No	18	21.74%	No	7	30.43%
Diabetes			Depression		
Yes	3	13.64%	Yes	6	26.09%
No	19	86.36%	No	17	73.91%
High Cholesterol			Hyperactivity/ADD		
Yes	4	18.18%	Yes	14	58.33%
No	18	81.82%	No	10	41.67%
High Blood Pressure			Sleep Disturbances		
Yes	1	4.55%	Yes	20	83.33%
No	21	95.45%	No	4	16.67%
Abnormal Thyroid			Self Injurious Behavior		
Yes	4	18.18%	Yes	11	50%
No	18	81.82%	No	11	50%
Abnormal Kidney Function			Obsessive Compulsive Behaviors		
Yes	1	4.55%	Yes	11	50%
No	21	95.45%	No	11	50%
Kidney Reflux			Aggression		
Yes	2	9.09%	Yes	11	47.83%
No	20	90.91%	No	12	47.83%

Parents were also asked if any of the medications taken by their child had affected their appetite, weight or activity level. Nine parents listed at one least medication; however only seven parents indicated the name of the medication as well as effect of the drug. Among the nine parents who reported any medication use in their child, the most commonly reported medication was Risperdal (n=5). Of interest is that the most commonly used drug (Risperdal), as well as other drugs (Thorazine, Serequel, Fluoxetine), were reported to result in increased weight and/or increased appetite. Table 14 summarizes the limited information obtained regarding medication history and effect of appetite, weight or activity level.

Table 14. Medications Prescribed		
Rx Name	#	Possible Effects
Risperdal	5	INCREASED(NOTHING SPECIFIED); INCREASE WEIGHT; INCREASE WEIGHT, INCREASE APPETITE
Topamax	1	
Ritalin	3	DECREASE (NOTHING SPECIFIED); DECREASE WEIGHT, DECREASE APPETITE, INCREASE PHYSICAL ACTIVITY
Thorazine	1	INCREASE WEIGHT, INCREASE APPETITE, DECREASE PHYSICAL ACTIVITY
Serequel	1	INCREASE WEIGHT, INCREASE APPETITE
Fluoxetine	1	INCREASE WEIGHT, INCREASE APPETITE
Adderall	1	
Abilify	1	
Inprimine	1	

To further investigate if a medication may have caused a change in behavior or weight in a child, the corresponding BMI of the child was examined. Of those who reported that a medication increased their child's weight or appetite levels (n= 6), one individual had a BMI in the healthy range, 2 had an overweight BMI and three had an obese BMI. Of those who listed a medication but did not report the effect (n=2), both individuals had a healthy BMI. Of those individuals who did not respond to the question, eight were classified as

healthy BMI, four were classified as overweight BMI and four were classified as obese BMI. One parent reported a medication (Ritalin) decreased her child’s weight; this individual had an obese BMI.

Family History Information

To assess for additional factors that could affect a child’s weight, and in turn BMI and overall health status, parents were asked whether or not there was a family history of any of the following: overweight, obesity, hypertension, diabetes, pre-diabetes, high cholesterol and heart disease. Table 15 provides family history information.

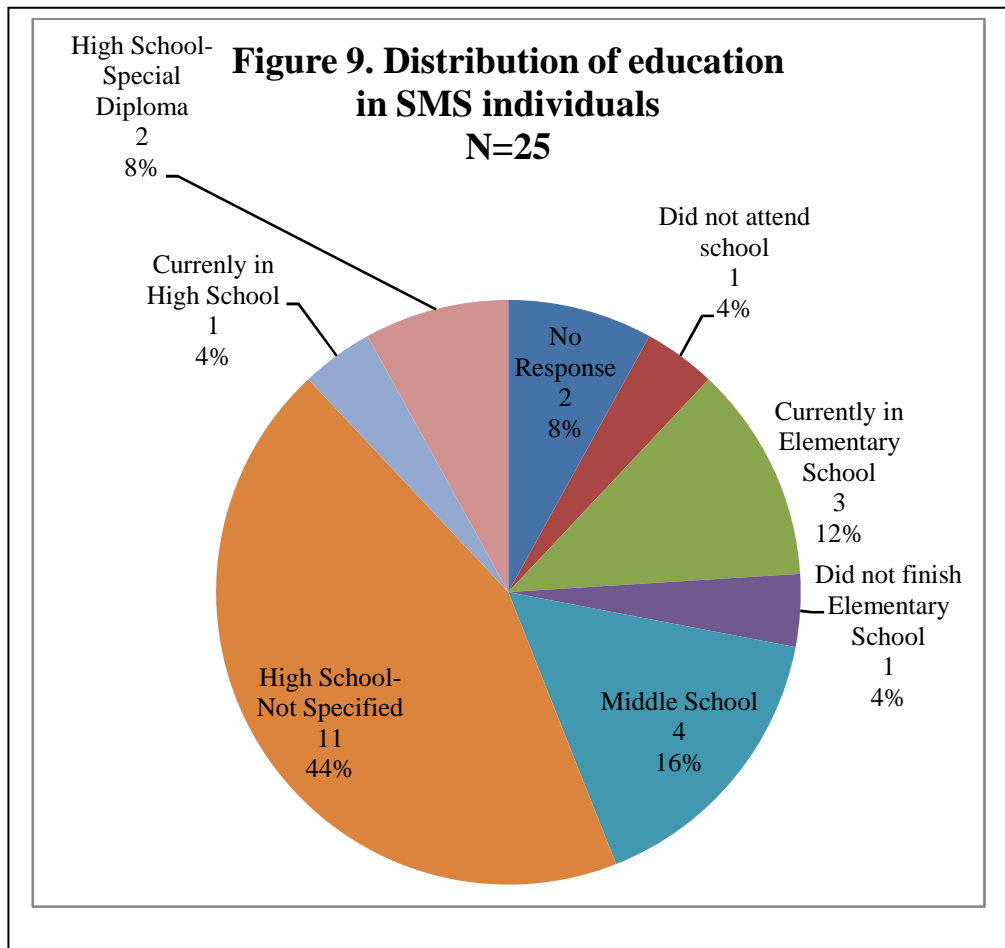
Table 15. Family History		
	Number	%
Overweight		
Yes	9	36%
Missing	16	64%
Obesity		
Yes	7	28%
Missing	18	72%
Hypertension		
Yes	11	44%
Missing	14	56%
Diabetes		
Yes	10	40%
Missing	15	60%
Pre-Diabetes		
Yes	5	20%
Missing	20	80%
High-Cholesterol		
Yes	12	48%
Missing	13	52%
Heart Disease		
Yes	5	20%
Missing	20	80%

Child's Social and Education History

Sixteen out of twenty-four (66.67%) of parent's indicated their children lived at home, with seven (29.17%) parents indicating their child lived in a group home/assisted living facility. One parent (4.16%) indicated her child lived in her own home with 24-hour support staff.

Parents were also asked "what was the highest level of schooling your child has completed?"

Figure 9 summarizes the responses regarding the child's education.



Child's Exercise History

Twelve parents, 48%, reported their child had a regular exercise program. Of those parent's who reported their child was able to exercise but that their child did not have a routine, the most common response provided as to why those children did not exercise was "will not participate in physical activity."

Dietary History

On the questionnaire that was created for use this study, there were ten questions targeted to assess the dietary history of SMS individuals. Parents were asked if they felt their child had daily eating patterns similar to other children his or her age. Fifteen parents answered Yes (60%) and 10 parents answered No (40%). All parents (N=25; 100%) indicated their children ate breakfast, lunch, dinner and snacks each day. Fifty-two percent of parents (n=13) indicated their child snacked prior to bed time.

Parents were asked to list their child's top three favorite snacks. Because of the variable responses provided, categorizations of snacks were created for better analysis. After all of the questionnaires were received, the responses to this question were looked at as a whole and categorizations were created for the snack items listed. The snack categories were: "healthy", which included items such as fruits and vegetables; "non-healthy", which included items such as cookies, chips and cakes and a third "other" category which included foods such as pretzels, popcorn and pudding. Based on these snack classifications, 18 out of 25 parents (72%) indicated their child's favorite snack was an item classified under the "non-healthy" item, 2 out 25 (8%) indicated their child's favorite snack was in the "other" category and 5 out of 25 parents indicated their child's favorite snack was an item classified as "healthy."

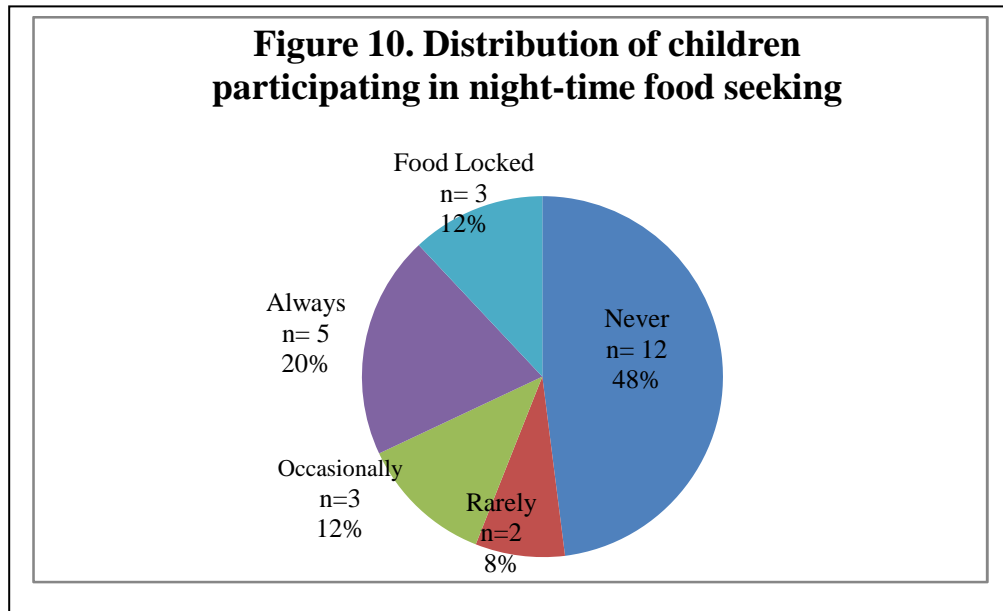
Parents were also asked to categorize the amount of food their child ate. Six parents (25%) indicated they felt their child ate less than normal amounts of food, eight parents (33.33%) indicated

they felt their child ate normal amounts of food and ten parents (41.67%) indicated they felt their child ate greater than normal amounts of food. Parents were asked if their child binge ate; 50% indicated Yes and 50% indicated No.

As individuals with SMS have disruptive sleep patterns, it was important to assess the presence of this finding within our questionnaire as well as to investigate whether individuals with SMS were also participating in night-time food seeking which may be considered an abnormal food seeking behavior. The majority of parents (n=12;48%) indicated their child woke up 2-3 times per night, with 13.64% (n=3) of parent's indicating their child woke up greater than or equal to four times each night.

Parents also reported, of the times their child woke per night, how often they ate. Twelve parents (48%) indicated never, two (8%) indicated rarely, three (12%) indicated occasionally and five (20%) indicated always (Figure 10). Three parents hand wrote on their questionnaire that their child does not participate in night-time food seeking because the food is now locked. This response was interpreted to mean night-time food seeking is currently not a problem for these three SMS individuals because the food is now locked and they are unable to access it. A separate category was created for those individuals(12%) who indicated their child no longer participated in night-time food seeking, as the food is now locked.

Figure 10. Distribution of children participating in night-time food seeking



The majority of parents, (nineteen; 76%) indicated they have to lock food away from their child. Of those six parents who indicated they did not lock food from their child, one parent reported they try not to have tempting food in the house, but they don't lock the food.

Growth Measurements of individuals with SMS as reported by their Parents

In order to obtain the most recent growth parameters for the SMS individuals whose parents completed the mail out questionnaire, parents were asked to provide their child's current height and weight. Growth parameters were reported by parents in all 25 responses. The average height for the cohort was 153.6 cm and the average weight was 65.2 kg. For males, (n=9) the average height was 167.67 cm, the average weight was 73.9 kg and the average BMI was 26.2. For females, (n=16) the average height was 145.71 cm the average weight was 60.4 kg and the average BMI was 27.73. Tables 16-18 provide an overview of growth parameters in the cohort.

**Table 16. Growth Measurements, All individuals,
N=25**

	Height (cm)				Weight (kg)				BMI				
	N	μ	SD	Min	Max	μ	SD	Min	Max	μ	SD	Min	Max
	25	153.6	18.64	91.4	183	65.2	20.32	23	100	27.17	5.55	16.89	38.95

**Table 17. Growth Measurements, Males
n=9**

	Height (cm)				Weight (kg)				BMI				
	n	μ	SD	Min	Max	μ	SD	Min	Max	μ	SD	Min	Max
6-11yrs	0												
12-19yrs	1	163	----	----	----	55	----	----	----	20.7	----	----	----
\geq 20yrs	8	168.13	9.46	155	183	76.2	14.62	60	100	26.8	3.52	22.6	30.78
Total	9	167.6	9.011	155	183	73.9	15.4	55	100	26.2	3.88	20.7	30.78

**Table 18. Growth Measurements, Females
n=16**

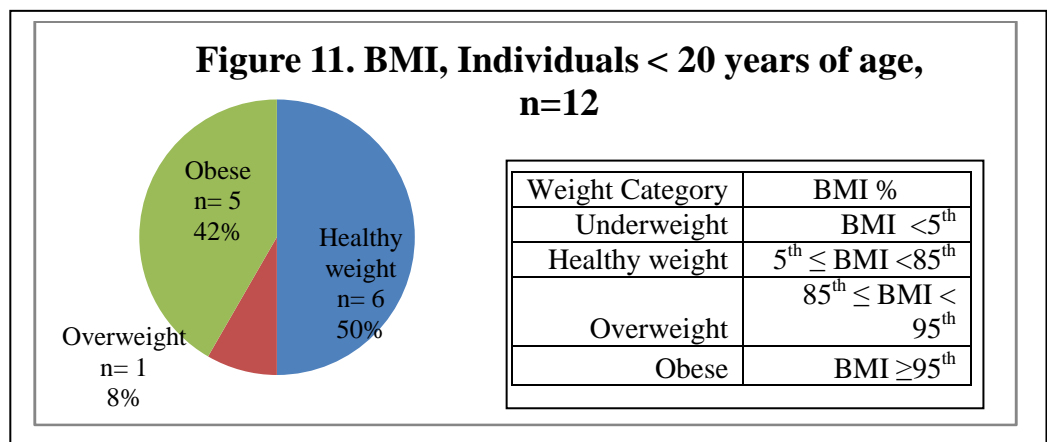
	Height (cm)				Weight (kg)				BMI				
	n	μ	SD	Min	Max	μ	SD	Min	Max	μ	SD	Min	Max
6-11yrs	3	115.5	21.13	91.4	131	28.3	5.03	23	33	21.82	5.1	16.9	27.1
12-19yrs	8	152.9	8.76	135	163	67.6	19.14	39	90	28.9	6.9	21.4	38.9
\geq 20yrs	5	152.4	5.77	145	160	68	11.78	52	79	29.3	4.8	24.2	35.1
Total	16	145.71	18.15	91.4	163	60.4	21.55	23	90	27.73	6.35	16.9	39

BMI and BMI percentile in individuals < 20 years

For individuals less than 20 years of age BMI and BMI percentile were calculated. BMI percentile provides information regarding a given child’s BMI in comparison to that of other children his or her own age and gender. There were eleven females and one male less than 20 years of age, to give a total of twelve individuals for which the BMI percent was calculated. As there was only one male, limited statistically analysis could be performed regarding BMI in males less than 20 years of age. For females less than 20 years of age, the average BMI was 27.04 and the average BMI percent was 78.1, which is considered “healthy”. Table 19 provides detailed information on the BMI of individuals less than 20 years of age.

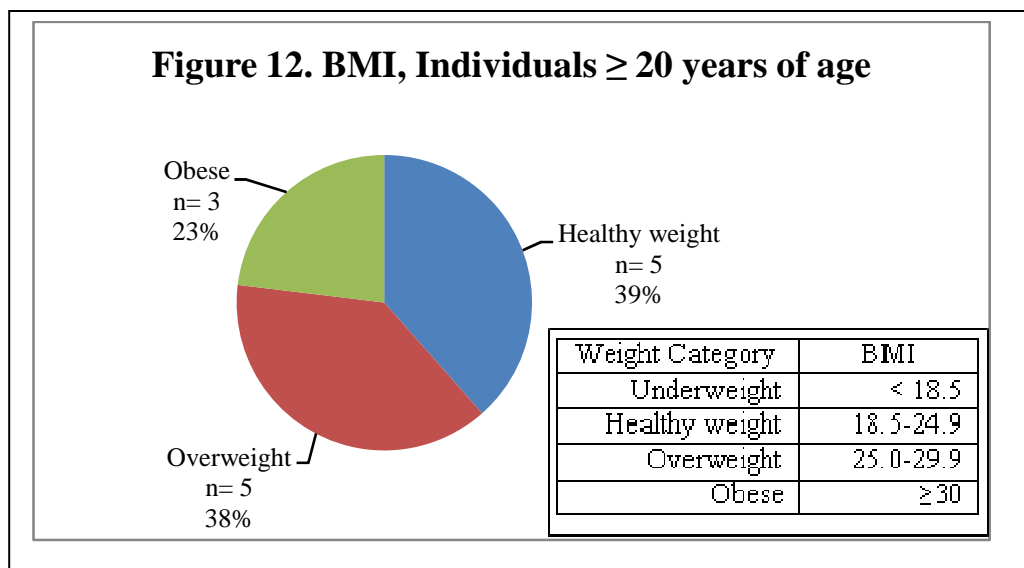
Table 19. BMI and BMI% in individuals < 20 years of age n=12										
	BMI					BMI percentile				
	n	μ	SD	Min	Max	n	μ	SD	Min	Max
Males	1	20.7	-	-	-	1	29	-	-	-
Females	11	27.04	7.03	16.9	39	11	78.1	25.6	23.1	98
All	12	26.5	6.9	16.9	39	12	74.0	28.2	23.1	98

Figure 11 illustrates the distribution of BMI classifications in individuals less than 20 years of age, based off BMI%.



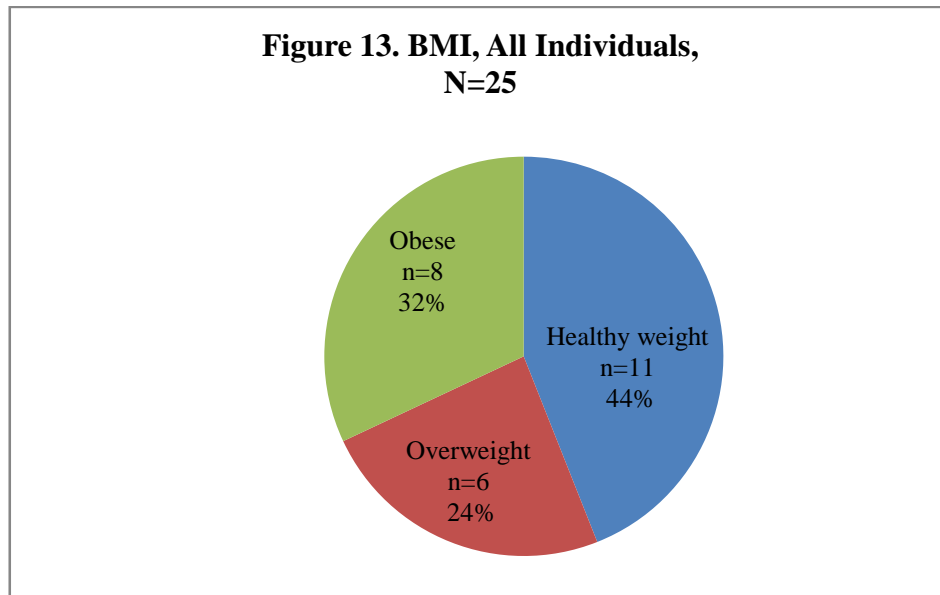
BMI in individuals ≥ 20 years

There were 13 individuals greater than 20 years of age, for which BMI was calculated and interpreted using the CDC's recommendation for the interpretation of BMI in adults. The average BMI for individuals ≥ 20 years of age was 27.8. Based on these classifications, 5 individuals (38.46%) were classified as healthy weight, 5 individuals (38.46%) were classified as overweight and 3 individuals (23.08%) were classified as obese, corresponding to 61.54% of all individuals greater than 20 years of age being either overweight or obese. There were no individuals classified as underweight. Figure 12 illustrates the BMI classifications in individuals greater than 20 years of age.



Calculation of BMI% in individuals < 20 years of age and BMI in individuals greater than 20 years of age allowed for the examination of BMI in all individuals combined. When analyzing BMI classifications for all individuals (N=25), 11 (44%) were classified as healthy weight, 6 (24%) were classified as overweight and 8 (32%) were classified as obese. Thus 56% of individuals in the

combined cohort have an overweight or obese BMI. There were no individuals classified as underweight. Figure 13 provides an illustration of BMI classifications in all individuals.



Z-scores

It was necessary to calculate the Z-score for height-for-age, weight-for-age and BMI-for-age to allow for comparison between the reference standard as defined by the CDC and the SMS cohorts. One sample t-tests were run using the calculated Z-scores for the following: height-for-age, weight-for-age and BMI-for-age. The negative mean Z-score for height ($\mu = -1.72$) demonstrates this cohort of SMS individuals were significantly shorter for their age ($p = 0.001$). The mean weight-for-age Z-scores for the combined cohort, were not statistically significant ($p\text{-value} = 0.062$), demonstrating the weight for age Z-scores in the SMS individuals were not statistically different (either higher/larger or lower/smaller) from age matched standardized controls in the general population. Despite non-significant weight-for-age mean Z-scores, the positive mean Z-score for BMI for age ($\mu = 1.59$) demonstrates the SMS individuals have significantly higher BMI's for age ($p < 0.001$). Table 20 provides detailed information regarding the mean Z-scores for all individuals for height, weight and BMI.

Table 20. Z-scores for All individuals								
N=25								
Z score height			Z score weight			Z score BMI		
μ	SD	p	μ	SD	p	μ	SD	p
-1.72	1.8	0.0001	0.513	1.3	0.062	1.59	1.24	<0.001

Z-score comparisons by Gender

The height-for-age Z scores, weight-for-age Z scores BMI-for-age Z-scores were examined separately for males and females. One sample t-tests were also run separately for males and females and by age groups to assess for differences within these categories. For males, (n=9), their height-for-age Z score and weight-for-age Z score were not statistically significant demonstrating the height and weight in the male SMS cohort did not differ (either higher/larger or lower/smaller) from what is expected for their age (p=0.052 and p=0.21 respectively). However, the difference in BMI for age mean Z-scores between SMS males and age appropriate controls was statistically significant, demonstrating male SMS individuals have higher average BMI for age. (p=0.01) Table 21 provides a detailed overview of Z-score values in males.

Table 21. Z-score for Males,								
n=9								
Z score height			Z score weight			Z score BMI		
μ	SD	p	μ	SD	p	μ	SD	p
-1.02	1.34	0.052	0.46	1.02	0.21	1.06	0.95	0.01

For females, n=16, their weight for age mean Z-score was not statistically significant demonstrating the mean weight-for-age in the female SMS cohort did not differ from what is seen in the general population (p=0.16). The mean Z-score for height (μ= -2.12) demonstrated the females in our population were significantly shorter for their age (p= 0.006). The difference in BMI-for-age

mean Z-scores between all females and what is expected for their age was statistically significant ($p < 0.001$) demonstrating female SMS individuals have higher BMI for age than what is expected.

Table 22 provides a detail overview of Z-score values in females.

Z score height			Z score weight			Z score BMI		
μ	SD	p	μ	SD	p	μ	SD	p
-2.12	1.94	0.006	0.54	1.48	0.16	1.89	1.31	< 0.001

Z-score comparisons by Age & Gender

We also examined the Z-scores for height-for-age, weight-for-age and BMI-for-age by first subdividing by gender and then by age. For males, the only Z-score p-value that reached statistical significance was the BMI-for-age Z-score for males ≥ 20 years of age, demonstrating that males ≥ 20 years of age had larger BMI's than what was expected for their age ($p = 0.005$). Table 23 provides a detailed overview of Z-scores for males, by age group.

	n	Z score height			Z score weight			Z score BMI		
		μ	SD	p	μ	SD	p	μ	SD	p
6 - 11 yrs	0	0	0	0	0	0	0	0	0	0
12- 19 yrs	1	-0.15	-	-	-0.407	-	-	-0.34	-	-
≥ 20 yrs	8	-1.12	1.39	0.055	0.57	1.034	0.163	1.23	0.8514	0.005
Total, All Males	9	-1.02	1.34	0.052	0.46	1.02	0.21	1.06	0.95	0.01

For females, $n=16$, there were several Z-score p-values that reached statistical significance. For females 12-19 years of age, their height-for-age Z score and BMI-for-age Z score p-values were both statistically significant ($p = 0.007$ and $p=0.01$ respectively), demonstrating females age 12-19

years of age were significantly shorter and had larger BMI's than what was expected based on their age. For females ≥ 20 years of age their height-for-age Z score and BMI-for-age Z score p-values were both statistically significant ($p= 0.01$ and $p=0.019$ respectively), demonstrating females ≥ 20 years of age were significantly shorter and had larger BMI's than what was expected based on their age. Table 24 provides a detailed overview of Z-scores for females, by age group.

	Z score height				Z score weight			Z score BMI		
	n	μ	SD	p	μ	SD	p	μ	SD	p
6 - 11 yrs	3	-3.6	4.06	0.26	-0.59	1.54	0.58	1.89	2.05	0.251
12- 19 yrs	8	-1.7	1.3	0.007	0.92	1.64	0.16	1.89	1.35	0.0053
≥ 20 yrs	5	-1.83	0.89	0.01	0.62	1.06	0.26	1.88	1.1	0.019
Total	16	-2.12	1.94	0.006	0.54	1.48	0.16	1.89	1.31	< 0.001

Hyperphagia Questionnaire

The HQ was scored and analyzed using the methods described by Dykens et al., 2007. Through the use of the HQ in the PWS population, three factors, also known as subscales, emerged that accounted for 57% of the variance within hyperphagia. These subscales were: behavior, drive and severity. Eleven of thirteen questions on the HQ corresponded to one of these three subscales. Question 12 and question 13 did not correspond to any of the three subscales and were therefore considered separately. Means scores were calculated for each question in the HQ. Mean scores for the behavior, drive and severity subscales were also calculated. Comparisons of overall scores as well as mean scores for each subscale were made.

Questions on the HQ were scored based on a Likert scale of 1 to 5, with a score of 1= not a problem and a score of 5= a severe and/or frequent problem. The results to the questions are grouped by the corresponding subscale. Higher scores on the HQ indicate higher levels of hyperphagia. The overall behavior, overall drive and overall severity scores for each individual are the sum of the scores for each question within its given subscale. For example if everyone had answered every question within the hyperphagic behavior subscale with a 5, indicating the highest level of severity, the overall hyperphagic behavior score would be equal to 25 (there are five questions within hyperphagic behavior; 5 questions multiplied by a score of 5 would give a total score equal to 25.) In the same respect if everyone had answered every question within the hyperphagic behavior subscale with a 1 indicating the lowest level of hyperphagic severity, the mean hyperphagic behavior scale would be equal to 5. These overall subscale scores for all individuals were used to calculate the mean subscale score for our cohort. Table 25 provides the mean scores for all 25 individuals who completed the HQ.

Table 25. Hyperphagia Questionnaire Results, Mean Scores, All Individuals, N=25					
Question #	N*	Mean Score	SD	Min	Max
Behavior					
10	25	3.08	1.32	1	5
2	23	2.52	1.5	1	5
8	22	2.45	1.5	1	5
5	23	2.48	1.7	1	5
4	25	1.28	0.74	1	4
<i>Mean Behavior</i>	20	11.45	4.96	5	22
Drive					
1	25	3.04	1.17	1	5
3	25	2.8	1.04	1	5
6	25	3.12	1.09	1	5
9	24	2.38	1.05	1	5
<i>Mean Drive</i>	24	11.3	3.71	4	20
Severity					
7	24	2.54	1.32	1	5
11	25	1.96	0.68	1	4
<i>Mean Severity</i>	24	4.54	1.77	2	9
* At least one question was left unanswered within the behavior, drive and severity subscales by 5, 1 and 1 individuals, respectively. Scores from these individuals were not used in the subscale mean score calculations.					

Item 12 on the HQ asked: “at what age did you child first show an increased interest in food?” 18 out of 25 parents (72%) reported their child did have an increased interest in food. Of those 18 parents who reported their child had an increased interest in food, the mean age of onset was 8.22 years.

Comparison of HQ Scores by BMI

We also looked at the overall hyperphagia mean scores within the different BMI classifications. Table 26 summarizes the overall hyperphagia mean scores for each question on the HQ across the different BMI classifications; normal weight, overweight and obese weight. The results are grouped by factor and items 12 and 13 were the questions that did not load onto any factor and are therefore considered separately from the other three factors.

Interestingly individuals with an obese BMI tended to have higher behavior and drive scores but lower severity scores.

Table 26, Overall Mean Scores, by BMI Classification			
Question #	Healthy Weight	Overweight	Obese
Behavior	11.56	8	12.63
10	3.36	2.33	3.25
2	2.8	2.2	2.38
8	2.6	1.75	2.63
5	2.5	1.6	3
4	1.36	1	1.38
Drive	11.9	8.83	12.38
1	3	2.17	3.75
3	3	2.17	3
6	3.45	2.5	3.125
9	2.5	2	2.5
Severity	5.1	3.67	4.5
7	2.9	1.17	2.75
11	3.36	2	1.75

T-tests were performed to look for statistically significant differences between the mean HQ scores between individuals who were healthy weight and obese weight. Although the mean behavior and drive scores were higher in individuals with obese BMI than in individuals with healthy BMI, none of these values reached statistical significance (p-values = 0.68 and 0.79, respectively.) Table 27 provides detailed information regarding the mean behavior, drive and severity scores in individuals with healthy and obese weight.

Table 27. Mean Hyperphagic Behavior Drive and Severity scores, Healthy weight vs. obese weight							
Hyperphagic factors	Healthy Weight			Obese			p-value
	n	Mean	SD	n	Mean	SD	
Behavior	9	11.55	5.53	8	12.625	4.75	0.68
Drive	10	11.9	4.04	8	12.375	3.42	0.79
Severity	10	5.1	2.02	8	4.5	1.69	0.51

Furthermore, comparisons were made between the mean HQ scores of individuals who were overweight and those who were obese. Although the mean behavior, drive and severity scores were higher in individuals with obese BMI than in individuals with overweight BMI, none of these values reached statistical significance (p-values = 0.16, 0.06, and 0.33 respectively.) However, the mean drive scores were approaching statistical significance in obese individuals. Table 28 provides detailed information regarding the mean behavior, drive and severity scores in overweight and obese individuals.

Table 28. Mean Hyperphagic Behavior Drive and Severity scores, Overweight vs. Obese weight							
Hyperphagic factors	Overweight			Obese			p-value
	n	Mean	SD	n	Mean	SD	
Behavior	3	8	3	8	12.63	4.75	0.16
Drive	6	8.83	2.78	8	12.4	3.42	0.06
Severity	6	3.67	1.211	8	4.5	1.69	0.33

Two sample t-tests were also calculated to look for differences between the mean HQ scores between individuals who were healthy weight and overweight. Although the mean behavior, drive and severity scores were higher in individuals with healthy BMI than in individuals with overweight BMI, there were not statistically different, suggesting increasing BMI is not associated with higher mean scores on the HQ. Table 29 provides detailed information regarding the mean behavior, drive and severity scores in healthy and overweight individuals.

Hyperphagic factors	Healthy weight (2)			Overweight (3)			p-value
	N	Mean	SD	N	Mean	SD	
Behavior	9	11.55	5.53	3	8	3	0.32
Drive	10	11.9	4.04	6	8.83	2.79	0.13
Severity	10	5.1	2.02	6	3.67	1.21	0.14

Finally the data was reclassified and an analysis was also run comparing obese and non-obese individuals (the latter group including both health and overweight individuals). Although the mean behavior, drive and severity scores were higher in individuals with an obese BMI than in individuals with a non-obese BMI, none of these values reached statistical significance (p-values = 0.40, 0.32, and 0.94 respectively) indicating that there was no statistically significant difference between the mean behavior, drive and severity scores between individuals who are obese and those who are not obese. Table 30 provides detailed information regarding the mean behavior, drive and severity scores in healthy and overweight individuals.

Hyperphagic factors	Obese			Non-obese			p-value
	n	Mean	SD	n	Mean	SD	
Behavior	8	12.63	4.75	12	10.67	5.14	0.40
Drive	8	12.38	3.42	16	10.75	3.84	0.32
Severity	8	4.5	1.69	16	4.56	1.86	0.94

An ANOVA test was performed to assess for differences in the mean behavior, drive and severity scores between all BMI classifications. No significant differences were detected (p-values = 0.41, 0.17 and 0.30 respectively). No association between BMI and hyperphagic subscales was found in this data set. Table 31 provides detailed information regarding the mean behavior, drive and severity scores in healthy and overweight individuals.

Table 31. Comparison of Mean Hyperphagic Behavior, Drive and Severity scores, by BMI Classification					
Hyperphagic factors	BMI Classification	N	Mean	SD	p-value
Behavior	Healthy	9	11.56	5.53	0.41
	Overweight	3	8	3	
	Obese	8	12.65	4.75	
		20			
Drive	Healthy	10	11.9	4.04	0.17
	Overweight	6	8.83	2.79	
	Obese	8	12.4	3.42	
		24			
Severity	Healthy	10	5.1	2.02	0.30
	Overweight	6	3.67	1.21	
	Obese	8	4.5	1.69	
		24			

Comparison by Gender

Two sample t-tests were run to assess for differences in mean behavior, drive and severity scores between males and females. Although females had higher mean scores for all three factors, behavior, drive and severity, only the mean severity score was statistically significant (p-value= 0.038) suggesting that females with SMS may have higher levels of hyperphagic severity. Table 31 provides detailed information regarding the mean behavior, drive and severity scores in healthy and overweight individuals.

Table 32. Comparison of Mean Hyperphagic Behavior, Drive and Severity scores by Gender					
Hyperphagic factors	Gender	N	Mean	SD	p-value
Behavior	Male	6	10	3.9	0.407
	Female	14	12.07	3.4	
		20			
Drive	Male	8	9.5	3.38	0.095
	Female	16	12.19	3.63	
		24			
Severity	Male	8	3.5	1.20	0.038
	Female	16	5.06	1.80	
		24			

Comparison by Age

A series of ANOVAs were used to assess for difference in mean behavior, drive and severity scores among different age classifications of SMS individuals. Individuals were classified by age group and ANOVAs were used to assess for differences. Although not statistically significant, the mean behavior, drive and severity scores increased with increasing age, suggesting that there may be a relationship between age and hyperphagic severity. The mean behavior, drive and severity score p-values were 0.11, 0.52 and 0.71 respectively. Table 33 provides detailed information regarding the mean behavior, drive and severity scores in healthy and overweight individuals.

Table 33. Comparison of Mean Hyperphagic Behavior, Drive and Severity scores by Age Group					
Hyperphagic factors	Age Group	N	Mean	SD	p-value
Behavior	6-11yrs	3	8	1.73	0.11
	12-19yrs	9	10.2	3.83	
	≥20yrs	8	14.13	5.82	
Drive	6-11yrs	3	10	3.46	0.52
	12-19yrs	9	10.5	2.79	
	≥20yrs	12	12.16	4.39	
Severity	6-11yrs	3	4	1.73	0.71
	12-19yrs	9	4.33	1.802	
	≥20yrs	12	4.83	1.85	

Comparison by Age and Gender

Due to differences between gender and age distribution within our study population (Table 34), data for behavior, drive and severity scores were reanalyzed after adjusting age and gender for each other. Stratification by gender showed that among females, behavior scores were highest in the oldest age group ($p=0.0018$) (Table 34). In addition, among females, although there were trends of higher scores by increasing age, there were no statistically significant differences between the different age groups for drive ($p=0.063$) or severity ($p=0.115$) scores. Among males, there were no statistically significant differences in behavior ($p=0.460$), drive ($p=0.302$) or severity ($p=0.200$) scores between the different age groups.

Table 34. Distribution of Gender by Age Groups			
	Males	Females	Total
6-11yrs	0	3	3
12-19yrs	1	8	9
≥ 20 yrs	8	5	13

Comparison of scores for males and females was also performed after stratification by age group. The only statistically significant difference was in the oldest age group, where females had higher scores than males for behavior ($p=0.010$), drive ($p=0.035$) and severity ($p=0.005$) (Table 35)

Table 35. Comparison of Mean Hyperphagic Behavior, Drive and Severity scores by Age Group and Gender							
		Males			Females		
		n	Mean	SD	n	Mean	SD
6-11 yrs	Behavior				3	8.00	1.73
	Drive				3	10.00	3.46
	Severity				3	4.00	1.73
12-19 yrs	Behavior	1	7.00		8	10.63	3.89
	Drive	1	6.00		8	11.13	2.36
	Severity	1	2.00		8	4.63	1.66
≥ 20 yrs	Behavior	5	10.60	4.04	3	20	1.73
	Drive	7	10.00	3.32	5	15.2	4.09
	Severity	7	3.71	1.11	5	6.4	1.52

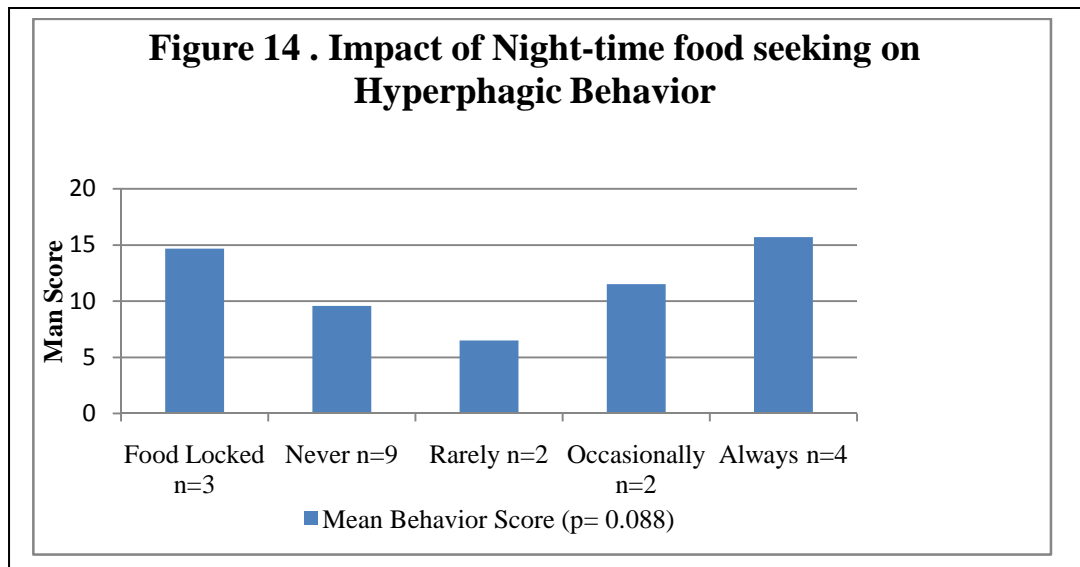
Comparisons between night-time food seeking and mean hyperphagic behavior scores

Since a portion of the questionnaire used in this study was not validated, as a measure of control, comparisons were made between validated and non-validated questions. One of the main areas of interest was to determine if there was a correlation between night-time food seeking (question 9 on the non-validated portion of the questionnaire) and an individual’s mean behavior score. The mean behavior score was chosen because question 5 on the validated HQ asked “How often does your child get up at night to food seek?” which was categorized as hyperphagic behavior.

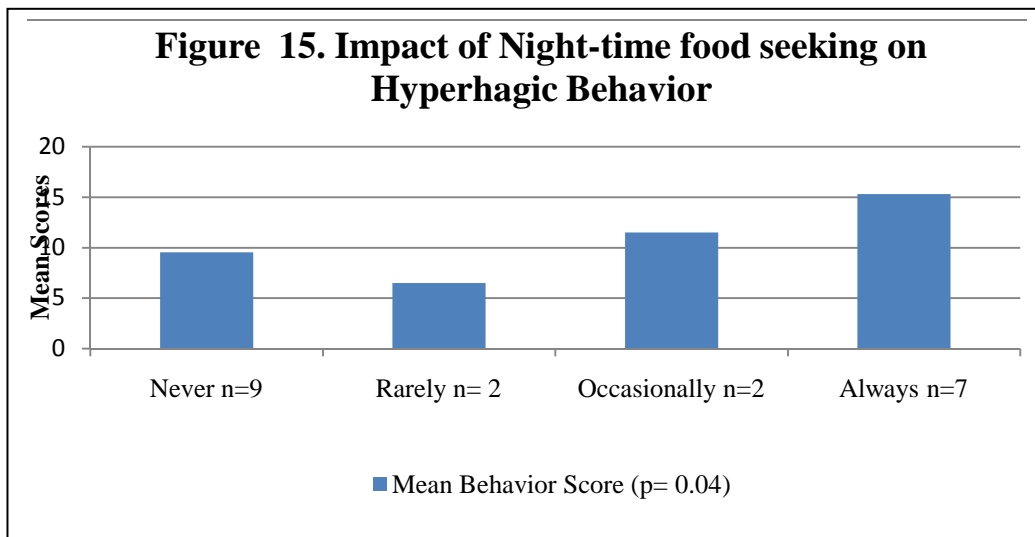
Three parents indicated their child no longer participates in night-time food seeking behavior as the food is now locked. Since these parents did not answer using the responses provided on the questionnaire, it was unclear if these individual’s night time food seeking behaviors would be classified as “never”, “rarely”, “sometimes” or “always.” Therefore, a sensitivity analysis was performed using the following two assumptions: the behavior occurred “always” and a separate analysis assuming the behavior occurred “rarely”.

When analyses were performed using only those 20 individuals who answered question 9 on the non-validated portion of the questionnaire using the responses provided and answered all other questions assessing hyperphagic behavior, no statistically significant relationship was found ($p=0.051$). However, of note, individuals in the “always” category had the highest mean behavior scores (mean =15.75).

When analyses were performed on those individuals who answered question 9 on our questionnaire and answered all questions which were classified under hyperphagic behavior, there was no statistically significant difference between the mean hyperphagic behavior score and the amount of night-time food seeking ($p=0.088$). Although there was no statistically significant relationship, those four individuals classified as “always” participating in night-time food seeking had the highest mean behavior scores (mean=15.75) and those classified as “food locked” had the second highest mean behavior scores (mean =14.667). Figure 14 provides a graphical representation of this data.



When analyses were performed grouping those three individuals who reported the food was now locked into the “always” category, a statistically significant relationship was found ($p=0.04$) demonstrating increased frequency of night-time food seeking is associated with higher mean hyperphagic behavior scores. Figure 15 provides a graphical representation of this data.



Analyses were performed grouping those three individuals who reported the food was now locked into the “rarely” category and no statistically significant relationship was found between increased night-time food seeking and mean hyperphagic behavior scores ($p= 0.24$).

Finally, a t-test was performed between individuals who reported their child “never” participated in night-time food seeking or “always” participated in night-time food seeking, which demonstrated a statistically significant relationship ($p=0.029$), suggesting the true amount of night-time food seeking in our SMS individuals lies somewhere in between “never” and “always.”

Relationship between amount of food eaten and BMI

A Fisher's exact test was performed to determine if there was a relationship between the reported amount of food eaten by the SMS individual and their BMI classification. The p-value for this test was, $p= 0.397$, demonstrating there is no statistically significant relationship between the reported amount of food eaten and the BMI classification in our SMS population.

Relationship between increased interest in food and BMI

A Fisher's exact test was performed to determine if there was a relationship between increased interest in food and BMI classification. The p-value for this test was, $p= 0.529$, demonstrating there is no statistically significant relationship between increased interest in food and BMI classification in our SMS population

Relationship between hyperphagia and BMI, hyperphagia and age

Analyses were also performed comparing individuals whose parent's reported their child had an increased interest in food and those who parents reported their child did not have an increased interest in food. No statistically significant relationships were found between an increased interest in food and BMI or age group.

DISCUSSION

Through the work of numerous researchers, the Smith Magenis Syndrome (SMS) phenotype has been well described, including its unique and characteristic neurobehavioral profile. Although these publications provide invaluable information regarding the phenotype of SMS, the majority of SMS related literature is lacking detailed information regarding height, weight and BMI. Due to the lack of detailed information available, the specific aims of this project were to (1) characterize the growth of a cohort of individuals with Smith-Magenis syndrome in order to determine the prevalence of overweight and obesity and (2) investigate hyperphagia and related food-seeking behaviors as possible factors related to overweight and obesity in individuals with SMS.

Growth Patterns of Individuals with SMS

Specific aim one was addressed through detailed analyses on the growth measurements of children and adults with SMS through the use of a retrospective chart review and growth data obtained from parental questionnaires. A minimum of one growth measurement was available for 78 individuals with SMS. One of the initial concerns regarding the use of a retrospective chart review involved the possibility that the majority of the growth data obtained would be of children with SMS and would not provide information on the growth of adolescents and adults with SMS. However, the growth data available for review ranged from birth parameters to that of an individual 51 years of age. The wide age range allowed for the examination of growth patterns in young children, adolescents and adults with SMS, as well as provided information on how the growth of individuals with SMS changes over time.

Z-scores were helpful in comparing the growth parameters in the SMS population to those in the general US population. For males and females in all age categories, the difference in height-for-age mean Z-scores was statistically significant. This finding clearly demonstrates that SMS individuals in this cohort are shorter than individuals in the general population. Both males and females in this cohort of 78 SMS individuals had negative height-for-age mean z-scores indicating heights less than the 50th percentile. This finding further supports the findings in published literature regarding decreased linear growth in individuals with SMS (Smith et al., 2004).

To further characterize the significance of height in the SMS cohort, the Z-scores were converted into their corresponding growth percentile. At 0-24 months of age, males were at the 10th -25th percentile and fell to the 5th - 10th percentile at age 24 month, then remained at the 5th -10th percentile through the ≥ 20 years. These percentile changes show that although the linear growth percentile of males with SMS does fluctuate over time, after 2 years of age, the mean height for males was never greater than the 10th percentile.

The results of this study slightly contrast to the data published by Smith et al. in 2004 who found that males with SMS were at 25th percentile for height by the age of 14. In this study, the highest height percentile reached by males occurred at the age of 0-23 months.

When the height-for-age mean z-score and corresponding percentiles for females are examined, their decreased linear growth is even more striking than what was seen in males. At age 0-23 months, females were at the 10th -5th percentile. However, at age 24 months-5 years, they fall to less than the 3rd percentile and remain less than the 3rd percentile through 19 years of age. By the age of ≥ 20 years, females reach the 5th -3rd percentile. As an

individual is considered to have short stature if they are less than or equal to the 5th percentile for age (CDC age specific growth charts, 2000), females in this cohort from the age of ≥ 24 months have short stature.

The results of this study regarding height for age percentiles in females are similar to those reported by Smith et al., in 2004 in that both Smith et al., and this study found females were at the less than 3rd percentile for height by age 12 years. However, Smith et al., found that female with SMS were between the 5th -25th percentiles for height from age 3-7 years, whereas this study found that females age 24 months-19years were at less than the 3rd percentile for height.

It is possible that the highest percentile for height for both males and females occurred within 0-23 months of age because infants with SMS typically have normal growth parameters at birth (Smith & Gropman, 2005). Although males with SMS in this cohort were also at their highest height percentile at 0-24 months, they remained at the 10th -5th percentile for almost all of the age ranges examined and did not fall to less than the 3rd percentile as was seen in the females. The discrepancies in height percentile between males and females with SMS is most likely related to the fact that in the general population, males are taller than females and although both males and females with SMS are shorter than their age matched peers, it would be expected that males with SMS may be taller than females with SMS solely due to gender differences.

Both males and females with SMS had negative weight-for-age mean z-score in early in infancy. This finding could be related to the FTT reported in individuals with SMS at around 12 months of age (Gropman et al., 1999; Greenberg et al., 1991). At first glance,

the changes in weight-for-age mean Z-scores for males and females with SMS are not evident as there was no statistically significant difference between the weight-for-age Z-scores. Although statistical significance was not achieved, the mean weight-for-age Z-scores for males and females did increase with age. Interestingly, males had z-scores less than the 50th percentile until age 6-11 years and females had z-scores less than the 50th percentile until 12 years of age. By the age of ≥ 20 years males had weight-for-age mean z-scores equivalent to the 50-75th percentile and females had weight-for-age mean z-scores equivalent to the 75th-95th percentile. These results confirm those published by Smith et al., in 2004 who reported females with SMS were at that or above the 90th percentile for weight by the age of 12 years. However the results of this study did not correspond to those published by Smith et al., in 2004 who reported males were at the 90th percentile for weight by age 14.

Although the results of this study do not exactly correspond to those published by Smith et al., in 2004, the trends in height and weight are similar. Both Smith et al., 2004 and this study found that males and females with SMS are less than the 50th percentile for height in all age groups where as their weight percentiles are as high as the 90th percentile by age 12 years. These changes in percentiles from early childhood to adulthood suggest that there may be an underlying factor present in both males and females with SMS that causes their weight to increase to greater than the 50th percentile sometime during childhood and adolescence. This underlying factor may be related to hyperphagia as it was reported by 72% of parents surveyed in Part II of this study, who felt their child had an increased interest in food. The majority of parents (55%) reported their child first showed an increased interest

in food at around 5 years of age. Additional findings related to hyperphagia in this study will be discussed in detail later in this discussion.

For all males, the calculated mean BMI-for-age Z-scores were positive, demonstrating the mean-BMI-for-age was greater than the 50th % percentile in all age groups. In age groups 6-11 years, 12-19 years and ≥ 20 years, the difference in BMI for age mean Z-scores between SMS males and the general population was statistically significant ($p=0.023$, 0.0023 and 0.0018 , respectively) demonstrating male SMS individuals are more obese than what is expected for their age. Similar to weight-for-age findings, when examining the corresponding BMI-for-age percentiles in individuals <20 , an increase in percentile over time was appreciated. At age 24 months to 5 years, males are between the 50-75th percentiles, then increase to the 90-95th percentile at age 6-11 years, remain at the 90-95th through 19 years and then return to the 85- 90th percentile at age ≥ 20 years.

Similar to what was found in males, the calculated mean BMI-for-age Z-scores for females were also positive, demonstrating the mean-BMI-for-age was greater than the 50th percentile in all age groups. At age groups 24 months – 5 years, 12-19 years and ≥ 20 years, the difference in BMI for age mean Z-scores between female controls in the general population was statistically significant demonstrating female SMS individuals have higher BMIs for their age ($p= <0.001$, 0.013 and 0.0039 , respectively). Although the changes in percentiles in females with SMS are somewhat less striking than the changes seen in males, females with SMS age ≥ 20 years were at the 95th -97th BMI percentile, which is the highest mean percentile among any age group or gender in this cohort.

If abnormal weight is truly a component of the SMS phenotype, then males and females would be overweight and often have an obese BMI. The presence of elevated BMIs and obesity was a main finding in this study. The mean BMI for males' age ≥ 20 years fell within the 85th-90th percentile, corresponding to an overweight BMI. BMI for females' age ≥ 20 fell within the 95-97th percentile, corresponding to an obese BMI. A possible conclusion for this finding is that females with SMS have higher BMI percentiles than males with SMS because the prevalence of female obesity in the general population is higher than the prevalence of male obesity (Ogden et al., 2006).

The depressed linear growth of individuals with SMS in this cohort generally remains constant throughout the lifespan, as evidenced by a maximum 10th percentile adult height for SMS males and maximum 5th percentile adult height for SMS females. It appears that depressed linear growth is a universal feature of the SMS individuals studied in this cohort and has also been reported by others studying SMS (Edelman et al., 2007).

Obesity in the SMS population

As the prevalence of elevated BMI and obesity continue to increase in the general population, it is difficult to assess the significance of the obesity present in this SMS population (Ogden et al., 2006). Over the past twenty years, the prevalence of obese adults in the general population has doubled while the prevalence of obesity in children has tripled (Ogden et al., 2006). As of 2004, 32.2% of US adults were obese and 34.1% were overweight (Ogden et al., 2006). For US children, 16% were overweight and 16% were obese (Ogden et al., 2008). The data reported in this study demonstrates obesity is present in this cohort of individuals with SMS. This is evidenced by SMS individuals of all ages

having negative height-for-age mean z-scores, positive weight-for-age mean z-score thus leading to positive BMI-for-age mean z-scores.

The prevalence of elevated BMI and obesity in this study population is similar to rates in the general populations. Figure's 16 -19 provide a graphical illustration of the comparison. However, it is important to keep in mind that although the percentage of obesity in SMS adults is similar to that of the general population, the height of individuals with SMS are significantly shorter than those of males and females in the general population. The average height of an adult male is 5'9½" and the average height of an adult female is 5'4" (Ogden et al., 2004). This is in contrast to the average height of males in this study of 5'3" and the average height of females in this study of 5'0".

What is perhaps most striking about the growth data obtained from the parent questionnaire regarding growth of children and adolescents, is the prevalence of elevated BMI and frank obesity. In the data obtained from the parent questionnaire, 50% of children and adolescents were either overweight or obese, compared with 32% of US children and adolescents within the general population classified as overweight or obese (Ogden et al., 2008).

The underlying etiology leading to increased BMIs during childhood and adolescents is not known. Additionally, it is unknown whether or not hyperphagia is the cause of obesity in SMS or is simply an effect of an underlying biochemical defect that predisposes individuals with SMS to develop elevated BMIs and obesity. Although it was beyond the scope of this project, the role of biochemical markers and their association with the development of obesity should be investigated. Future studies regarding obesity and SMS

should consider the prospective measurement of biochemical markers known to be associated with obesity including the following: ghrelin, leptin, insulin, HDL and LDL. A prospective examination would aid in the determining the time at which elevated BMIs and obesity occurs in SMS.

Figure 16. Obesity in US Adults

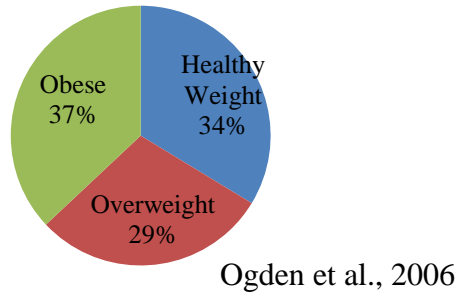


Figure 17. BMI in SMS Adults, n= 13

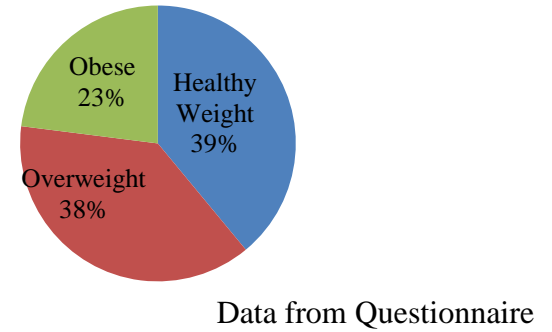


Figure 18. Obesity in US Children & Adolescents

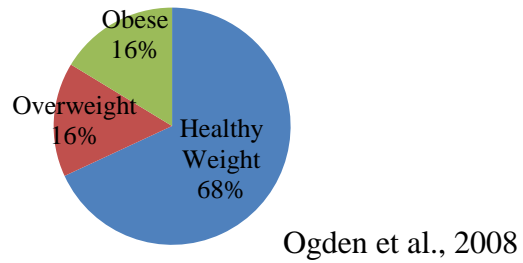
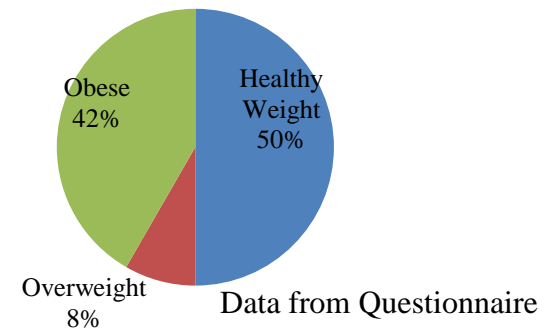


Figure 19. BMI in SMS children and adolescents, n=12



Part II-Parent Questionnaire

It has been anecdotally reported that obesity is present in individuals with SMS; however, there is little to no documented evidence of this and no possible explanation for the cause of this trend. This study hypothesized that if abnormally elevated BMIs are present in individuals with SMS, hyperphagic behaviors may be involved in this phenotype. Thus, specific aim two of this study involved the use of a parent questionnaire, including the validated Hyperphagia Questionnaire (HQ), to explore the role of hyperphagia in individuals with SMS (Dykens et al., 2007).

The results obtained from the questionnaire portion of this study indicate hyperphagia and related abnormal food behaviors may be problematic in SMS, as 72% of parents reported their child had an increased interest in food and 76 % of parents indicated they had to lock food away from their child. When asked about the frequency of their child's night-time food seeking behaviors, three parents indicated that their child no longer participated in night-time food seeking because the food is now locked and the child is no longer able to access it. One parent indicated, prior to locking the kitchen, her child's night-time food seeking was constant and her child still continues to frequently hoard food in her room.

Hyperphagia Questionnaire (HQ)

The HQ was first used to measure hyperphagia in individuals with Prader-Willi syndrome (Dykens et al., 2007). Hyperphagia is universally present in individuals with PWS and without intensive dietary monitoring; individuals with PWS will become morbidly obese (Holm, Cassidy, Butler, Hanchett, Greenswag, & Greenberg, 1993). The underlying

etiology of obesity in PWS is not definitively known, but it is thought to be caused by satiety dysfunction (Lindgren et al., 2000).

The HQ is scored on a Likert scale, ranging from 1 to 5. A score of 1 on any given question equates to the behavior as being “not a problem” and a score of 5 on any given question equates to the behavior being a “severe and/or frequent problem” (Dykens et al., 2008). When the HQ was used in the PWS population, the mean scores ranged from 1.80 on question 4, which asked: “How often does your child forage through the trash for food?” to 4.05 on question 10, which asked: “How clever or fast is your child in obtaining food?” The majority of the mean scores obtained on the HQ ranged from 2.20-2.24 to 3.06 to 3.34 (Dykens et al., 2007).

In this study, the mean scores obtained on the HQ ranged from 1.28 on question four, (“How often does your child forage through the trash for food?”) to as high as 3.12 on question six, (“ How persisent is your child in asking or looking for food when told No?”) The majority of the mean scores for the questions on the HQ ranged from 2.4 to 2.6, suggesting that, for the most part, the behaviors assessed for on the HQ were at a mininum, “somewhat of a problem” for the majority of SMS individuals whose parents’ completed the HQ.

Age and its relationship with hyperphagic tendencies were explored and found not to be significantly associated with increased hyperphagic behavior, drive or severity. The absence of a statistically significant association between age and hyperphagic tendencies in this study is in contrast to the statistically significant positive association between age and hyperphagic tendencies in the PWS patient population (Dykens et al., 2007.) Although

statistical significance between age and mean hyperphagic behavior, drive and severity scores was not reached, age does appear to influence hyperphagic tendencies in SMS. This is evidenced by individuals ≥ 20 years of age having the highest mean behavior, drive and severity scores and individuals in the youngest age category of 6-11 years having the lowest mean behavior, drive and severity scores. Evidence that supports the hypothesis that hyperphagic tendencies may increase with age come from the results obtained in Part I of this study which demonstrates as individuals with SMS age, their BMI's also increase, even into the overweight and obese ranges.

Because Dykens et al. considered gender and its relationship to mean hyperphagic behavior, drive and severity scores in individuals with PWS, the effects of gender were also examined in this cohort of SMS individuals. Surprisingly, a statistically significant relationship was found between gender and mean hyperphagic severity scores with females having higher mean scores when compared to males ($p= 0.038$). Although not statistically significant, females also had higher mean behavior and drive scores when compared to males. No statistically significant relationship was found between gender and mean hyperphagic behavior, drive or severity scores in the PWS patient population (Dykens et al., 2007).

Due to differences between gender and age distribution within our study population when the data for behavior, drive and severity scores were reanalyzed after adjusting age and gender for each other, stratification by age and gender showed the mean behavior, drive and severity scores for females were higher than males in all age groups and that females age ≥ 20 had the highest mean behavior, drive and severity scores. These data confirm similar published reports of females demonstrating more severe hyperphagic tendencies as

Edelman et al., (2007) reported “eating/appetite problems” 69.2% of females and only 21.4% of males.

The age of onset of hyperphagia was also considered. Eighteen out of twenty-five parents (72%) reported their child had an increased interest in food. As the age reported at which their child showed an increased interest in food spanned from 1 year of age to 34 years of age, it was difficult to pinpoint when exactly increased interest in food began. However upon closer examination, the majority of parents (55.5%) reported their child showed an increased interest in food between 1 and 5 years of age, suggesting there may be an underlying behavioral component involved in the age of onset of increased interest in food that becomes evident during early childhood. This increase in interest in food may be related to the fact that prior to around 5 years of age the diet of a child is primarily controlled by their parent and the increase interest in food may be related to children becoming more aware of their environment and asserting more control over their food choices.

As no previous studies have systematically examined the role of hyperphagia in individuals with SMS, it is unclear if data regarding age of onset of hyperphagia reported in this study is representative of age of onset of hyperphagia in the SMS population as a whole. In the use of the HQ in the PWS patient population, the reported mean age of onset of hyperphagia was 3.5 ± 1.6 years, with a range of 1.5 to 7 years (Dykens et al., 2007). Since the age of onset of hyperphagia occurs at a younger age in the PWS population, and within a better defined age range, it appears hyperphagia in SMS may be more variable in severity and age of onset than in individuals with PWS.

Another item which was examined separately was the variability in hyperphagic symptoms. The majority of parents (75%) also felt there was little to no variability in their child's interest in food suggesting any preoccupation or interest in food present in their children with SMS is not affected by outside factors such as stress or emotion. These are two factors which are well known to effect eating behavior (Geliebter & Aversa, 2003). The lack of reported variability in their child's preoccupation with food suggests hyperphagia may be an inherent component of the SMS phenotype. Similar findings of stable preoccupation with food in the PWS population also support the notion hyperphagia is an inherent aspect of the SMS phenotype (Dykens et al., 2007; Holm, Cassidy, Butler, Hanchett, Greenswag, & Greenberg, 1993).

It appears that foraging through the trash for food is present only in a small percentage (n=4;16%) of our respondents. It is most likely not present in the high frequency seen in the PWS patient population. The vast majority of parents, 88%, also felt food-related thoughts, talk or behavior had either mild to no interference with their child's normal daily routines, self-care, food or work. This suggests the possible negative effects of food-related thoughts, talk and behavior are minimal.

The results obtained from the questionnaire portion of this study indicate hyperphagia or related abnormal food behaviors may be problematic in SMS, as 72% of parent's reported their child had an increased interest in food. Perhaps more surprising was that 76 % of parent's indicated; when specifically asked, that they had to lock food away from their child. Not all parents in this study indicated their child had an increased interest in food, suggesting that although hyperphagia and related abnormal food behaviors are present in a large portion of SMS individuals examined in this study, hyperphagia may or

may not be a universal feature of SMS. It is most likely that a combination of numerous factors including environment, lifestyle as well as a hyperphagia component are involved in the development of increased BMIs overweight and obesity in individuals with SMS.

Strengths of Study

The results of Part I of this study provide detailed information on the growth of 78 individuals with SMS. As there is limited information available regarding the growth of individuals with SMS, the ability to report detailed information on the growth of 78 individuals certainly increases the knowledge of a portion of the SMS phenotype that is less well known. In comparison to the growth data reported in the medical literature, the information provided in this study is much more comprehensive and detailed. The large meta-analysis published by Edelman et al., in 2007 provided valuable information about genotype-phenotype information in individuals with SMS but was lacking comprehensive information regarding growth in individuals with SMS. In over 60% of the cases examined, information regarding growth and BMI was unavailable. An abstract presented by Smith et al. in 2004 provided an overview of parametric measurements of height and weight in 54 individuals with SMS. Detailed information regarding BMI was not provided. However, it was stated that “BMI values were variable across ages” (Smith et al., 2004). Although this abstract was able to report on how the different height and weight percentile of individuals with SMS change over time, information regarding the number of individuals in each age category was not available. This study overcame the limitations described in the two previous publications by reporting detailed information regarding the height and weight of 78 individuals with SMS. This study was also able to report on how the BMI of 74 individuals with SMS change over time, as there were only 4 individuals in this study who at last recorded measurement were less than 24 months of age.

Part II of this research project serves as a pilot study, as there is no published literature which assesses for possible causes of overweight and obesity in individuals with

SMS. Thus, one of the major strengths of this study is that it is the first to assess the role of hyperphagia in individuals with SMS as well as its relationship to the presence of elevated BMIs and obesity. An additional strength of this study is that a validated instrument, the HQ, was used to assess hyperphagia. The HQ was initially used in the PWS patient population and was able to quantify the universal aspects of the PWS phenotype related to hyperphagia. Not surprisingly, the majority of the mean scores on the HQ were lower in the SMS population compared to the PWS population. A result which was somewhat surprising was that the mean score on a few of the questions on the HQ were actually higher than the mean scores in the PWS patient population. These results demonstrate that hyperphagia is present in SMS and that the HQ was able to capture the hyperphagic characteristics of the SMS phenotype.

Limitations

The primary limitation in the chart review used in this study was that the majority of individuals (61.5%) had only one or two growth measurements available for analysis, and many were not recent measurements. The lack of multiple growth measurements at similar time points for each individual possibly limited the ability to truly assess how these individuals height, weight and BMI change over time. Another possible limitation involves the growth measurements obtained on the parent questionnaire. Although we are confident that the height and weight data abstracted from the medical record was collected using standard procedures, the same cannot be said for the information obtained from parents' self report. It is unknown how parents measured their child's height and weight, and it is possible the parent did not truly measure their child's weight, but rather estimated them.

The primary limitation related to the parent questionnaire is the small sample size. It is possible that due to the small sample size, the results regarding hyperphagia in individuals with SMS are not truly representative of the SMS population as a whole. It is perhaps difficult to assess the results of this study in terms of the implications for the SMS community as a whole, as is the first study designed to specifically assess hyperphagia in individuals with SMS. Thus, comparisons between previous studies cannot be made. In addition, the responses on the HQ are taken from parents' self report of their child's eating behaviors. It is well known that parents commonly underestimate the severity of abnormal behaviors present in their child and the same could possibly be said for the hyperphagic tendencies assessed for in this study. One potential way to overcome this limitation would be to administer the HQ to parents of children with SMS as well as other individuals involved in the child's life including, physicians, nurses or other care providers and compare

the results in hopes of obtaining results that are truly representative of the child's hyperphagic tendencies. Another potential limitation involves the fact that this questionnaire was mailed to parents and not administered in person as was the case when the HQ was used in the PWS population. It is possible parents may have been confused regarding the meaning of some of the questions on the HQ and may have left that question blank or answered the question incorrectly. Administering the HQ in person would allow for discussion regarding the questions on the HQ as well as ensure that every question on the HQ was answered.

Future Studies

The finding of females' age ≥ 20 years of age having the highest mean behavior, drive and severity scores as well as the highest BMIs, leads us to further consider the relationship between hyperphagia and elevated BMIs and obesity. An interesting future study could involve prospective examination of a cohort of males and females with SMS. The use of a prospective study would provide information on whether or not the hyperphagia developed first and thus contributed to the development of elevated BMIs and obesity. It is also possible that elevated BMIs and obesity developed for other reasons and the presence of hyperphagia in this cohort is simply an effect of the obesity. The use of a prospective study would also allow for the examination of biochemical markers associated with obesity including leptin, insulin, HDL and LDL. The prospective examination of biochemical markers would be able to provide information regarding whether or not hyperphagia or obesity develops first in SMS.

Another potential avenue to explore for future research would be to re-contact those parents who indicated their child had an increased interest in food to further investigate this response. Since there is room for interpretation of "an increased interest in food" targeted questions would be helpful. A third area for future research would be to re-contact those parents who indicated they had to lock food away from their child to learn what behaviors exhibited by their children precipitated the need to lock food away and at what age they began locking the food away. Knowledge of this information may aid in pinpointing the age of onset of hyperphagia in SMS so that measures can be taken to control hyperphagia and in turn hopefully to control elevated BMIs and obesity. It would also be interesting to look closely at those individuals who, by parent report, had an increased interest in food to see if

those individuals have higher rates of the negative health consequences known to be associated with obesity.

A potential research project unrelated to SMS, but still relevant to the topic of elevated BMIs and obesity, would be to perform a study using the HQ in the general population. It would be interesting to see how the parents of children without genetic disorders interpret their child's food related behaviors, both "normal" and "abnormal" as well as how the mean behavior, drive and severity scores are different based on weight status of individuals in the general population.

Conclusion

The results obtained in Part I of this study demonstrated short stature and a concomitant increase in weight leading to BMI percentiles in the overweight and obese range in individuals with SMS. Elevated BMIs were present in both males and females with SMS, though females tended to have higher BMIs. The results of Part II of this study, the parent questionnaire, also indicated that hyperphagia was present in individuals with SMS as evidenced by 76% of parents' reporting having to lock food away from their child.

The information gained regarding the presence of hyperphagia in individuals with SMS, as well as the propensity to develop elevated BMIs, provides healthcare professionals with valuable information regarding a component of the phenotype of SMS which has not been well described. This increase in knowledge will hopefully enable parents and caregivers of children with SMS to take preventative measures in order to control any hyperphagic tendencies present in their child and subsequently prevent the onset of obesity.

Although the severity of hyperphagia present in individuals with SMS does not reach the levels present in individuals with PWS, as individuals with PWS have died from complications related to uncontrolled hyperphagic behaviors, the negative health consequences of elevated BMIs and obesity are still a concern (Stevenson et al., 2007). There are currently no dietary or exercise guidelines in place for individuals with SMS. The results of this study indicating the presence of elevated BMIs and obesity as well as hyperphagia, may indicate the need for increased dietary monitoring in individuals with SMS.

APPENDIX 1: QUESTIONNAIRE

Please make sure to complete the form to the best of your ability. If you do not wish to answer a question or are unsure of how to answer, please leave the question blank.

A. DEMOGRAPHIC INFORMATION REGARDING INDIVIDUAL WITH SMITH-MAGENIS SYNDROME (SMS)

1.) NAME: _____
Last First

2.) Date of Birth: _____
Month Day Year

B. DEMOGRAPHIC INFORMATION, To be completed by parent/guardian of the individual with SMS named above

1.) What is your age? _____

2.) What is your gender?

Male

Female

3.) What is your ethnicity?

White

Black

Hispanic

Native American

Asian

Other, please specify _____

4.) What is your primary language?

- English
- Spanish
- Other

5.) What is your relationship to the child with Smith-Magenis syndrome?

- Mother
- Father
- Step-mother
- Step-father
- Biological grandmother
- Biological grandfather
- Other, please specify _____

6.) What is your current marital status?

- Single
- Married or living as married
- Separated
- Divorced
- Widowed

7.) What is the grade of schooling you have completed?

- 8th grade or less
- 9th to 11th grade
- High School or GED
- Some college
- Associates Degree (2 yr)
- Bachelor's Degree
- Advanced Degree
- No formal education

8.) Are you currently employed?

- Yes
- No

If yes, what is your current occupation? _____

If no, how long have you been unemployed? _____

9.) How many hours a week do you work in your current occupation?

- Fewer than 10
- 10-20 hours
- 20-40 hours
- More than 40 hours

10.) Which comes closest to the current average total annual income for your entire household before taxes. Please include the income from everyone in your household,

- Less than \$25,000
- \$25,000- \$50,999
- \$51,000-\$74,999
- \$75,000- \$99,999
- \$100,000- more
- Prefer not to answer

C. MEDICAL AND SOCIAL HISTORY REGARDING INDIVIDUAL WITH SMITH-MAGENIS SYNDROME (SMS)

1.) What is your child's current height?

_____ Ft _____ in

2.) What is your child's current weight?

_____ lbs

3.) How old was your child when he/she were diagnosed with SMS?

_____ Years _____ months

4.) Who made the initial diagnosis of SMS (choose one)?

Primary Care/Pediatrician

Geneticist

Neurologist

Developmental Specialist

Other (Please Specify): _____

5.) What were the results of the genetic testing?

17p11.2 deletion

RAI1 mutation

Don't know

6.) Was your child ever given a diagnosis of failure to thrive (FTT) during infancy?

Yes

Don't know

No

7.) Did your child ever need to have a feeding tube placed?

Yes

Don't know

No

8.) If **yes**, (that your child had a feeding tube) did he/she have a g-tube placed surgically?
 Yes Don't know
 No

9.) Was your child born with or diagnosed with any of the following?

Cleft lip	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Kidney defect	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Cleft palate	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Urinary tract defect	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Heart defect	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Low thyroid function	<input type="checkbox"/> Yes	<input type="checkbox"/> No

10.) Has your child ever taken medication for any of the following?

Heart Defects No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Anxiety	<input type="checkbox"/> Yes	<input type="checkbox"/>
Seizures No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Depression	<input type="checkbox"/> Yes	<input type="checkbox"/>
Diabetes No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Hyperactivity/ADD	<input type="checkbox"/> Yes	<input type="checkbox"/>
High cholesterol No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Sleep Disturbances	<input type="checkbox"/> Yes	<input type="checkbox"/>
High blood pressure No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Self-injurious behavior	<input type="checkbox"/> Yes	<input type="checkbox"/>
Thyroid problems No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Aggression	<input type="checkbox"/> Yes	<input type="checkbox"/>
Kidney problems No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Obsessive compulsive behaviors	<input type="checkbox"/> Yes	<input type="checkbox"/>
Acid reflux No	<input type="checkbox"/> Yes	<input type="checkbox"/> No	Kidney reflux	<input type="checkbox"/> Yes	<input type="checkbox"/>

11.) Has your child ever taken any medications that have affected his/her appetite, weight or activity level? **If yes, please list the medication and circle the appropriate effect:**

Medication Name <i>(please list)</i>	Change in Weight		Change in Appetite		Change in Level of Physical Activity	
	Increase	Decrease	Increase	Decrease	Increase	Decrease
	Increase	Decrease	Increase	Decrease	Increase	Decrease
	Increase	Decrease	Increase	Decrease	Increase	Decrease
	Increase	Decrease	Increase	Decrease	Increase	Decrease
	Increase	Decrease	Increase	Decrease	Increase	Decrease

12.) Is there a **family history** of any of the following? Please check all that apply:

- Overweight
- Obesity
- Hypertension
- Diabetes
- Pre-diabetes
- High cholesterol
- Heart disease

For questions 13-15, please check just one box for each question.

13.) Where does your child with SMS currently live?

- At home
- In a group home/assisted living facility
- Other, please specify _____

14.) What is the highest level of schooling that your child has completed?

- Elementary school
- Middle school
- High school

15.) Did your child receive assistance in school?

- Yes
- No

C. EXERCISE HISTORY:

1.) Does your child have an exercise program/physical activity program?

- Yes
- No

My child:

walks/runs ___ times per week for ___ minutes each time
swims ___ times per week for ___ minutes each time
plays outside ___ times per week for ___ minutes each time
rides bicycle ___ times per week for ___ minutes each time
other (please list below)
_____ times per week for ___ minutes each time
_____ times per week for ___ minutes each time

2.) My child is able to exercise but he/she does not have a regular routine:

- Yes
- No

3.) My child is unable to exercise due to:

Severe joint pain

Shortness of breath

Scoliosis

Muscle weakness

Will not participate in physical activity

Other, please specify _____

D. DIETARY HISTORY:

1.) Do you consider your child to have a daily eating pattern similar to other children his/her age?

Yes

No

2.) Which meals does your child eat each day? Please check all that apply

Breakfast

Lunch

Dinner

Snacks

3.) Do you feel your child eats:

Less than normal amounts of food

Normal amounts of food

Greater than normal amounts of food

4.) Does your child binge eat?

Yes

No

5.) Does your child snack?

Yes

No

6.) Does your child eat/snack just before bedtime?

Yes

No

7.) What are your child's top 3 favorite snacks?

8.) How often does your child wake up during the night?

0-1 times per night

2-3 times per night

4-5 times per night

> 5 times per night

9.) Of the times that your child wakes up during the night, how often does he or she eat?

Never

Rarely

Occasionally

Always

10.) Do you ever or have you ever had to lock food away from your child?

Yes

No

11.) How upset does your child generally become when denied a desired food?

- Not particularly upset at all
- A little upset
- Somewhat upset
- Very upset
- Extremely upset

12.) How often does your child try to bargain or manipulate to get more food at meals?

- A few times a year
- A few times a month
- A few times a week
- Several times a week
- Several times a day

13.) Once your child has food on their mind, how easy is it for you or others to re-direct your child away from food to other things?

- Extremely easy, takes minimal effort to do so
- Very easy, takes just a little effort to do so
- Somewhat hard, takes some effort to do so
- Very hard, takes a lot of work to do so
- Extremely hard, takes sustained and hard work to do so

14.) How often does your child forage (look/search) through the trash for food?

- Never
- A few times a year
- 1–2 times a month
- 1–3 times a week
- 4 to 7 times a week

15.) How often does your child get up at night to food seek?

- Never
- A few nights a year
- 1–2 nights a month
- 1–3 nights a week
- 4 to 7 nights a week

16.) How persistent is your child in asking or looking for food after being told “no” or “no more”?

- Lets go of food ideas quickly and easily
- Lets go of food ideas pretty quickly and easily
- Somewhat persistent with food ideas
- Very persistent with food ideas
- Extremely persistent with food ideas

17.) Outside of normal meal times, how much time does your child spend talking about food or engaged in food-related behaviors?

- Less than 15 minutes a day
- 15 to 30 minutes a day
- 30 minutes to an hour

- 1 to 3 hours a day
- More than 3 hours a day

18.) How often does your child try to steal (take when told not to) food (that you are aware of?)

- A few times a year
- A few times a month
- A few times a week
- Several times a week
- Several times a day

19.) When others try to stop your child from talking about food or engaging in food-related behaviors, it generally leads to:

- No distress or upset
- Mild distress or upset
- Moderate distress or upset
- Severe distress or upset
- Extreme distress, behaviors can't usually be stopped

20.) How clever or fast is your child in obtaining food?

- Not particularly clever or fast
- A little clever or fast
- Somewhat clever or fast
- Very clever or fast
- Extremely clever or fast

21.) To what extent do food-related thoughts, talk, or behavior interfere with your child's normal daily routines, self-care, school, or work?

No interference

Mild interference; occasional food-related interference in completing school, work, or hygiene tasks

Moderate interference; frequent food-related interference in completing school, work, or hygiene tasks

Severe interference; almost daily food-related interference in completing school, work, or hygiene tasks

Extreme interference, often unable to participate in hygiene tasks or to get to school or work due to food-related difficulties

22.) How old was your child when he/she first showed an increased interest in food?

___ years

My child does not have an increased interest in food

23.) How variable is your child's preoccupation or interest in food?

Hardly ever varies

Usually stays about the same

Goes up and down occasionally

Goes up and down quite a lot

Goes up and down all the time

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