Understanding the causes of obesity in children with Trisomy 21: hyperphagia versus physical activity

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Background

Individuals with intellectual disabilities are at increased risk of becoming overweight or obese. This is particularly evident in people with Trisomy 21 and Prader-Willi syndrome (PWS). Although metabolic factors are known to contribute to obesity in Trisomy 21 and hyperphagia plays a primary role in PWS, hyperphagia has not yet been investigated as a possible contributing factor to obesity in Trisomy 21.

Methods

Participants comprised three diagnostic groups: Trisomy 21 (T21 group), PWS (PWS group) and lifestyle-related obesity (LRO group). They were required to be aged 6-18 years and have a BMI over the 85th percentile for age and gender. A parent of each participant completed the Hyperphagia Questionnaire and the Children's Leisure Activity Study Survey. Mean scores for each domain and across all domains of the Hyperphagia Questionnaire and the Children's Leisure Activity Study Survey were compared between diagnostic groups using linear regression analysis.

Results

The study group consisted of 52 young people (23 males, 29 females) aged 6 to 18 years (mean 12.5 years; T21 group n=17, PWS group n=16, LRO group n=19). As hypothesised, the PWS group had the highest mean scores across all domains of the Hyperphagia Questionnaire, and the LRO group had the lowest. Food-seeking behaviour was more pronounced in the PWS group than the T21 group (mean score 13.2 vs 8.6, $p=0.008$). The LRO group spent more hours per week engaged in physical activity (14.7) in comparison to the other groups (9.6 and 9.7), whereas between group differences in time spent in sedentary activities were less pronounced.

Conclusions

Preoccupation with food and low levels of physical activity may contribute to the development of overweight and obesity in some individuals with Trisomy 21. These factors warrant consideration in the clinical context.

Keywords: Trisomy 21, Down syndrome, Prader-Willi syndrome, weight, hyperphagia, physical activity

Background

Globally ten percent of school-aged children are classified as overweight or obese (Lobstein et al., 2004) and the combined rate of overweight and obesity for Australian children has been reported to be as high as 19 to 24%. (Booth et al., 2001, O'Dea, 2003) Children and adolescents with intellectual disability are at increased risk of overweight and obesity, (De et al., 2008) with reports of the frequency of overweight and obesity for individuals with intellectual disability varying from 31% (Lionti et al., 2013) to almost 40%. (De et al., 2008, Rimmer et al., 2010) Syndromes associated with intellectual disability, where the predisposition to weight gain is well-known, include Prader-Willi syndrome (Holland and Wong, 1999) and Trisomy 21 (Down syndrome). (Rubin et al., 1998, Hawn et al., 2009, van Gameren-Oosterom et al., 2012)

Trisomy 21 has a birth prevalence of 1:1,100 live births in Australia. (Riley and Halliday, 2008) Reports of the prevalence of overweight and obesity in individuals with Trisomy 21 have varied internationally. In a Dutch study of 1,596 individuals with Trisomy 21 aged 0-26 years, the prevalence of overweight and obesity was reported as 25.5% and 4.2% for males and 32% and 5.1% for females respectively. (van Gameren-Oosterom et al., 2012) In the United States of America, Rimmer et al. reported a prevalence of 55% overweight and 31.2% obese, for a sample of 81 adolescents (aged 12-18 years) with Trisomy 21. (Rimmer et al., 2010) A retrospective study from the United States of America of 283 adolescents and adults with Trisomy 21 reported a 56% prevalence

of overweight for females and 45% for males. This study demonstrated an environmental influence on weight, showing that those who lived in the family home had a tendency toward overweight in comparison to those living in group homes.(Rubin et al., 1998)

There are several interrelated factors, common in individuals with Trisomy 21, which are known to contribute to the development of obesity within this group. Metabolic factors are well-known such as hypothyroidism, decreased basal metabolic rate and increased leptin levels.(Murray and Ryan-Krause, 2010) In addition to this metabolic predisposition to weight gain, children and adolescents with Trisomy 21 have been shown to participate in less high-intensity physical activity than their siblings,(Whitt-Glover et al., 2006) and do not meet the recommended daily requirements of moderate to vigorous physical activity.(Esposito et al., 2012, Nordstrom et al., 2013) Although there are valid medical reasons for the lower level of exercise, such as the risk of atlantoaxial subluxation or dislocation,(Au-Yong et al., 2008, Semine et al., 1978) unfortunately environmental factors may also play a role in preventing regular participation in physical activity for individuals with intellectual disability. Heller *et al* reported that many adults with Trisomy 21 are unaware of opportunities for engagement in team sports or gym programs within the community,(Heller et al., 2002) or may have difficulty with independent exercise and require the support, or participation, of family and friends.

In addition to environmental and metabolic factors, abnormally increased appetite, or hyperphagia, plays a role in the development of obesity in some conditions associated with intellectual disability, such as Prader-Willi syndrome.(Holland et al., 1995) Prader-Willi syndrome is a genetic condition with a prevalence of approximately 1: 15, 000(Lionti et al., 2015) to 1: 25, 000 live births in Australia.(Smith et al., 2003) Features of Prader-Willi syndrome include low muscle tone, characteristic facial features, short stature, autistic traits, global developmental delay and intellectual disability.(Cassidy et al., 2012) Hyperphagia is a prominent characteristic of this condition, beginning in early childhood and persisting throughout the adult years. The presence and severity of hyperphagia in Prader-Willi syndrome have been the focus of many research studies.(Dykens et al., 2007, Fieldstone et al., 1998) Although the mechanisms which cause hyperphagia in this population are not yet completely understood, abnormal changes in hunger and satiety signals in the brain are evident,(Hinton et al., 2006, Shapira et al., 2005, Holsen et al., 2012) as are metabolic abnormalities.(Haqq et al., 2007, Holland et al., 1993) People with Prader-Willi syndrome are subsequently at risk of morbid obesity and early death,(Lionti et al., 2012, Einfeld et al., 2006) if the hyperphagia is not controlled by calorie restriction, meticulous food supervision and regular physical activity. The propensity toward obesity in Prader-Willi syndrome is further complicated by a low muscle mass, which means that persons with this condition expend less energy when they exercise.(Butler et al., 2007). Like individuals with Trisomy 21, they have also been shown to do minimal regular vigorous exercise.(Nordstrom et al., 2013)

Although the presence of eating disorders in intellectual disability is acknowledged in the literature,(Gravestock, 2000) there is little in the published literature that casts light on the contribution of hyperphagia to the development of obesity in this population, and specifically about hyperphagia in people with Trisomy 21.

Aim

To further our understanding of pathways to obesity in individuals with Trisomy 21, we aimed to investigate the presence of hyperphagia and levels of physical and sedentary activity in children and adolescents with Trisomy 21 compared to individuals with lifestyle-related obesity and individuals with Prader-Willi syndrome.

Based on the known association between hyperphagia and Prader-Willi syndrome, we hypothesised that the children and adolescents with Trisomy 21 would have less hyperphagia than those with

Prader-Willi syndrome but more than children and adolescents with lifestyle-related obesity. Furthermore, based on the recognised barriers to physical activity in individuals with intellectual disability, we hypothesised that individuals with lifestyle-related obesity would have higher levels of physical activity than individuals with either Trisomy 21 or Prader-Willi syndrome.

Methods

Setting, participants and recruitment procedure

This study was undertaken at The Royal Children's Hospital, Melbourne, Australia. Ethics approval was obtained from the host institution's Human Research Ethics Committee.

Inclusion criteria required participants to have a body mass index (BMI) denoting the presence of overweight or obesity, as defined by internationally published cut-points.(Cole et al., 2000) Each individual's BMI standard deviation score (BMI SDS) was also calculated. Adjusted for age and gender, overweight was defined as a BMI SDS between the 85th and 95th percentile and obesity was defined as a BMI SDS over the 95th percentile. All individuals with a BMI SDS under the 85th percentile were excluded from the study, as were any individuals with physical disabilities that limited their ability to ambulate and exercise.

There were three groups of overweight and obese participants in this study. A group of young people with lifestyle-related obesity and no known physical or intellectual disabilities (LRO group), was recruited from the Weight Management clinic at The Royal Children's Hospital, a group of individuals with Trisomy 21 (T21 group) was recruited from the Down Syndrome Association of Victoria, and the third group comprised children and adolescents with Prader-Willi syndrome (PWS group) who were recruited from both the Prader-Willi syndrome clinic at The Royal Children's Hospital and the Victorian Prader-Willi Syndrome Register (VPWSR).

At both the Weight Management and Prader-Willi syndrome clinics, the treating clinician approached eligible participants at the time of their consultation to introduce the study. If the family agreed to participate, weight and height were collected in order to calculate BMI and BMI SDS.

Families who had consented to be contacted for research by the VPWSR were approached by the Register manager either at the Prader-Willi syndrome clinic or by telephone if they did not have an appointment. If consent was obtained via telephone, the parent/ carer was asked to collect the young person's weight and height in the family home.

The Down Syndrome Association of Victoria contacted, by mail, families of individuals with Trisomy 21 who were in the correct age bracket. The letter included a reply-slip (to be returned to the research assistant) to indicate whether they would like to participate. If so, the research assistant telephoned the family to further explain the project and offer participation.

In all cases where consent was obtained, a research assistant provided the family with a questionnaire booklet, comprising two parent-report questionnaires about hyperphagia and engagement in both physical and sedentary activities, as well as demographic questions and questions on food restriction and supervision in the family home.

Outcome measures

The primary outcome measure was the Hyperphagia Questionnaire.(Dyken et al., 2007) This 13-item multiple choice questionnaire was designed for carers of people with Prader-Willi syndrome to measure the presence of hyperphagia. The questions are divided into three domains that assess the range and severity of food-related issues: hyperphagic behaviour, drive and severity. Although developed specifically for PWS, the authors have also used the Hyperphagia Questionnaire for

persons with Trisomy 21 or undiagnosed intellectual disabilities who show unusual food seeking behaviors.(State et al., 1999)

The Children's Leisure Activities Study Survey (CLASS) was used as a secondary outcome to determine how much time each participant spent engaged in both physical and sedentary activities in a typical week, including during school hours.(Salmon et al., 2004) Physical and sedentary activities were analysed and reported individually, including separate scores for team sports and other physical activities, and separate scores for television viewing, computer time, and other sedentary activities.

Statistical analysis

Sample size calculations were performed using published means and standard deviations (SD) for each domain on the Hyperphagia Questionnaire in a PWS sample.(Dykens et al., 2007) Using a power of 0.8, and a two-sided level of statistical significance of 0.05, a sample size of 16 per group was calculated to be sufficient to find a 1 SD difference in each of the domains of the Hyperphagia Questionnaire. In the absence of any relevant data, this difference was deemed to represent a clinically meaningful difference.

Univariable linear regression analysis and chi-squared tests were used, for **interval** and categorical variables respectively, to compare demographic and clinical variables across the three diagnostic groups. Linear regression was also performed to compare mean total and domain scores from the Hyperphagia Questionnaire and the CLASS between diagnostic groups, with and without adjustment for potential confounders. For all analyses, a p-value of ≤ 0.05 was used to denote statistical evidence of difference, representing **no more than a** 5% likelihood of the difference being attributable to chance alone. Analysis was performed in Stata 13.1 (StataCorp 2013, College Station, Texas, USA).

Results

Characteristics of the study group (Table 1)

The study group consisted of 52 children and adolescents (23 males, 29 females) aged 6 to 18 years (mean 12.5 years). It included 17 individuals with Trisomy 21 (T21 group), 19 with lifestyle-related obesity (LRO group) and 16 with Prader-Willi syndrome (PWS group); all participants were living in the family home. Participants with Prader-Willi syndrome all had molecular confirmation of the diagnosis. Across the entire study group, 42 of the 52 individuals (81%) **were** classified as obese and 10 of 52 (19%) as overweight. The mean BMI SDS for the entire group was 2.1 (range 1.1 to 3.4).

There were some relevant sampling differences between the three diagnostic groups. The LRO group included a similar proportion of males and females, whereas the T21 and PWS groups comprised relatively more females (65% and 56%, respectively). The LRO group had the highest mean BMI SDS (2.4 vs 2.1 and 1.7 for the PWS and T21 groups, respectively) and the highest proportion of persons classified as obese (95% vs 81% and 65% for the PWS and T21 groups, respectively). Indicative of differences in the frequency of intellectual disability, members of the LRO group were all educated at mainstream schools, whereas the majority of participants with non-missing data from the other two groups attended special schools. Compared to both the T21 and LRO groups, parents of the PWS group were more likely to lock fridges and cupboards in the family home for additional food restriction, and were more likely to require children to ask for permission before having a snack. Despite differences between the groups in food availability, a similar proportion of individuals in each group was permitted to get their own snacks.

Potential confounding

We found no strong statistical evidence of association between total hyperphagia scores, total physical activity scores or total sedentary activity scores and age, gender or BMI SDS in this cohort

(all $p>0.05$). However, this did not rule them out as potential confounders in the association between diagnostic groups and study outcomes. Type of schooling was not considered as a potential confounder as it is indicative of intellectual status, a defining characteristic of the diagnostic groups.

Hyperphagia (Table 2)

The mean hyperphagia scores for the T21 group fell between the mean scores for the LRO and PWS groups for each domain of the Hyperphagia Questionnaire and for total hyperphagia scores.

When the mean total and domain scores for the T21 and LRO groups were compared statistically, we observed no differences between the two groups that could not be attributable to chance. The results were similar when statistical adjustment was made for age, BMI SDS and gender.

When the unadjusted mean scores for the T21 and PWS groups were compared, there were no differences between the groups in hyperphagic drive and severity that could not be attributable to chance. There was strong evidence, however, that hyperphagic behaviours such as food foraging and stealing were more prevalent in the PWS group. After statistical adjustment was made for age, BMI SDS and gender, there was strong evidence for a real difference between the two groups in hyperphagic behaviours, severity of hyperphagia, and mean total scores.

Physical and sedentary activities (Table 3)

Data on physical and sedentary activities were available for 48 individuals (four parents of individuals with PWS did not complete the CLASS questionnaire).

On average, the T21 group spent fewer total hours each week engaged in physical activity compared to the LRO group (10 vs 15 hours) but a comparable amount of time to the PWS group (10 hours). This trend was seen for participation in team sports as well as for engagement in other forms of physical activity. We found no strong statistical evidence in support of a difference between either the T21 and LRO groups or the T21 and PWS groups in mean hours spent engaged in physical activities on either unadjusted or adjusted analysis.

With respect to sedentary activities, variation was seen between diagnostic groups according to the type of activity. Of the three groups, the LRO group spent the most overall time engaged in sedentary activity (mean 44 vs 35 and 31 hours/week for the T21 and PWS groups) and the most time playing computer games or surfing the internet (mean 11 vs 2 and 4 hours/week for the T21 and PWS groups). On the other hand, the T21 group spent the most time watching television (mean 13 vs 12 and 11 hours/week for the LRO and PWS groups).

There was statistical evidence of difference between the T21 and LRO groups in their mean computer times (2 vs 11 hours/week; $p=0.03$), but we observed a slightly higher likelihood that this difference could be attributable to chance when adjustment was made for gender, age and BMI SDS ($p=0.09$).

Although there was no evidence of difference between the T21 and PWS groups for any of the sedentary behaviour scores on unadjusted analysis (all $p>0.05$), after adjustment for gender, age and BMI SDS, we found a higher likelihood beyond chance that the T21 group spent more hours each week watching television ($p<0.01$) and engaging in other non-computer related sedentary activities ($p<0.01$).

Discussion

Overweight and obesity are significant problems not only in the general Australian population, but also place significant burden on individuals with intellectual disability, where opportunities for a

physically active lifestyle may be limited. There are many factors that contribute to the development of obesity in this population, both metabolic and environmental. Hyperphagia is a well-known characteristic of Prader-Willi syndrome that has been extensively researched for its contribution to life threatening obesity if left uncontrolled. To our knowledge; this is the first research paper to investigate hyperphagia in individuals with Trisomy 21.

Consistent with our a priori hypotheses, our research shows that individuals with Trisomy 21 who are overweight or obese may display some characteristics of hyperphagia that are often present in individuals with Prader-Willi syndrome, although to a lesser degree. For all domains of the Hyperphagia Questionnaire, the mean scores for the T21 group fell between the mean scores for the LRO and PWS groups. Statistical evidence of difference in food-seeking behaviours between the T21 and PWS groups was evident, supporting the idea that the T21 group was less likely than the PWS group to practise pathological food-seeking behaviours.

Lack of physical activity continues to be a major contributor to the development of obesity within the Australian population. Ten percent of Australian children aged 5-14 years reportedly play video games 20 hours or more per fortnight or 2 hours per day.(Australian Bureau of Statistics, 2006) In our study, all groups exhibited high levels of sedentary activity, with an average of 6.3 hours per week spent playing video games or surfing the internet.

Despite the high levels of sedentary activity, the Australian Bureau of Statistics has also reported that Australian children aged 5-14 years participate in organised team sports for an average of 3 hours per week.(Australian Bureau of Statistics, 2006) In our study, the average time spent participating in team sports for the LRO group (2.8 hours per week) was similar to the general population. This was not the case for the PWS and T21 groups where, on average, only 1.7 hours per week was spent participating in team sports. This may be an indication of the barriers faced by persons with intellectual disability in trying to access organised team sports or gym programs, particularly once they reach adolescence.(Heller et al., 2002) It is possible that group differences may reflect variation in educational settings, in particular there may be differences in physical education programs between primary and secondary school settings and between special and mainstream schools.

The authors acknowledge that this study had some limitations. Firstly, the measure used for the investigation of hyperphagia was developed for people with PWS and not for Trisomy 21 or lifestyle-related obesity. Despite this, the authors of the questionnaire report that they have found the measure useful in other populations such as Trisomy 21.(State et al., 1999) Secondly, although we met our sample size requirements for finding a 1 SD difference between groups in hyperphagia scores, larger numbers may have produced more generalisable results. Thirdly, the CLASS relies upon parent recollection of physical and sedentary activities that their child engages in each week and this may have resulted in some measurement error around the amount of time their child spent engaged in each type of activity. Furthermore, parents may not be aware of the time spent in particular kinds of activity at school or in other settings outside the home.

In conclusion, this research suggests that a preoccupation with food may play a role in the development of obesity in some individuals with Trisomy 21, however differences between this group and the LRO group were not definitive. In the clinical setting, it may be worthwhile for families of individuals with intellectual disability to be provided with more information about the risks of over-eating for their child and to be linked in with local dieticians, exercise programs and support networks.

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Conflict of interest

None of the authors have conflicts of interest to declare.

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	T21 group N=17	LRO group N=19	PWS group N=16	Total group N=52	P-value for group difference
Gender					0.578
Male, n (%)	6 (35.3)	10 (52.6)	7 (43.7)	23 (44.3)	
Female, n (%)	11 (64.7)	9 (47.4)	9 (56.3)	29 (55.7)	
Age (years), mean (SD)	13.8 (2.6)	11.7 (2.9)	12.1 (4.1)	12.5 (3.3)	0.119
BMI SDS, mean (SD)	1.74 (0.34)	2.44 (0.4)	2.09 (0.5)	2.10 (0.5)	<0.001
BMI category					0.074
Overweight, n (%)	6 (35.3)	1 (5.3)	3 (18.7)	10 (19.3)	
Obese, n (%)	11 (64.7)	18 (94.7)	13 (81.3)	42 (80.7)	
School type					<0.001
Mainstream, n (%)	0 (0.0)	19 (100.0)	3 (33.3)	22 (64.7)	
Special, n (%)	6 (100.0)	0 (0.0)	6 (66.7)	12 (35.3)	
Locks on fridge					<0.001
Yes, n (%)	2 (11.7)	1 (5.3)	9 (56.3)	12 (23.8)	
No, n (%)	15 (88.3)	18 (94.7)	7 (43.7)	41 (76.9)	
Permission to eat					0.121
Yes, n (%)	10 (58.8)	9 (47.4)	13 (81.3)	32 (61.5)	
No, n (%)	7 (41.2)	10 (52.6)	3 (18.7)	20 (38.5)	
Gets own snacks					0.875
Yes, n (%)	11 (64.7)	12 (63.2)	9 (56.3)	32 (61.5)	
No, n (%)	6 (35.3)	7 (36.8)	7 (43.7)	20 (38.5)	

Table 1. *Characteristics of the study group.* BMI 'Body Mass Index'; SD 'Standard Deviation'; CI 'Confidence Interval'; T21 'Trisomy 21', PWS 'Prader-Willi syndrome', LRO 'Life-style related obesity'

	LRO group N=19	T21 group N=17	PWS group N=16	T21 vs LRO group		T21 vs PWS group	
Hyperphagia score	Mean (SD)	Mean (SD)	Mean (SD)	Unadjusted p-value	Adjusted* p-value	Unadjusted p-value	Adjusted* p-value
Behaviour	7.0 (4.1)	8.6 (2.7)	13.2 (6.2)	0.186	0.466	0.008	0.010
Drive	7.7 (3.4)	9.9 (3.3)	11.1 (4.3)	0.057	0.318	0.378	0.144
Severity	2.7 (1.5)	3.3 (1.3)	4.1 (2.3)	0.257	0.410	0.239	0.005
Total score	17.5 (8.5)	21.8 (6.1)	28.4 (11.6)	0.090	0.365	0.050	0.020

*Adjusted for age, body mass index standard deviation score and gender.

Table 2: Comparison of mean domain and total scores on the Hyperphagia Questionnaire between diagnostic groups.

	LRO group N=19	T21 group N=17	PWS group N=16	T21 vs LRO group		T21 vs PWS group	
	Mean (SD)	Mean (SD)	Mean (SD)	Unadjusted p-value	Adjusted* p-value	Unadjusted p-value	Adjusted* p-value
Physical							
Team sports	2.8 (3.1)	1.7 (1.3)	1.7 (3.0)	0.176	0.230	0.980	0.296
Other	11.9 (6.9)	8.0 (6.0)	8.2 (5.6)	0.079	0.318	0.935	0.270
Total score	14.8 (8.4)	9.7 (6.1)	9.6 (5.3)	0.050	0.223	0.948	0.308
Sedentary							
Television	11.8 (9.4)	12.8 (7.6)	10.6 (10.3)	0.710	0.743	0.518	0.002
Computer	11.3 (16.7)	2.2 (3.5)	3.9 (4.7)	0.034	0.093	0.279	0.653
Other	21.0 (20.1)	21.3 (11.6)	16.6 (6.4)	0.970	0.308	0.215	<0.001
Total score	44.3 (32.8)	35.2 (11.3)	30.6 (12.9)	0.284	0.488	0.325	0.098

*Adjusted for age, body mass index standard deviation score and gender.

Table 3. Comparison of mean CLASS scores by activity type between diagnostic groups.

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