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A reduced-energy intake, well-balanced diet improves weight control in children with Prader-Willi syndrome

J. L. Miller,* C. H. Lynn,* J. Shuster,† & D. J. Driscoll*‡

*University of Florida, Department of Pediatrics, Gainesville, FL, USA
†Department of Health Outcomes and Policy, University of Florida, Gainesville, FL, USA
‡Center for Epigenetics, University of Florida, College of Medicine, Gainesville, FL, USA

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Correspondence
Jennifer L Miller, Department of Pediatrics, Division of Endocrinology, University of Florida, Gainesville, FL 32608, USA.
Tel.: +1 352 334 1390
Fax: +1 352 334 1325
E-mail: millejl@peds.ufl.edu

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Abstract

Background: Children with Prader-Willi syndrome (PWS) have a predictable pattern of weight gain, with obesity beginning in early childhood and worsening as they get older and hyperphagia increases. Data on the most effective dietary modifications are scant and primarily anecdotal. As part of a longitudinal study investigating the natural history of PWS, we evaluated the effect of a well-balanced, energy-restricted diet on body composition and weight in young children with PWS.
Methods: Sixty-three children, aged 2–10 years, with genetically proven PWS participated in the present study. These children had measurements of body composition by dual-energy X-ray absorptiometry and resting energy expenditure (REE), as well as a 3-day diet history analysis both before and after intervention. Energy calculations were based on the individual's REE, with the recommendation that the macronutrients of the diet consist of 30% fat, 45% carbohydrates and 25% protein, with at least 20 g of fibre per day.
Results: Thirty-three families adhered to our dietary recommendations for both energy intake and macronutrient distribution. Those 33 children had lower body fat (19.8% versus 41.9%; $P < 0.001$) and weight management (body mass index SD score 0.3 versus 2.23; $P < 0.001$) than those whose parents followed the energy intake recommendations but did not alter the macronutrient composition of the diet. Those who followed our recommendations also had a lower respiratory quotient (0.84 versus 0.95; $P = 0.002$).
Conclusions: Our recommendation for an energy-restricted diet with a well-balanced macronutrient composition and fibre intake improves both weight and body composition in children with PWS compared to a simple energy-restricted diet.

Introduction

Prader-Willi syndrome (PWS) is a complex neurobehavioural disorder which is a result of the absence of normally active paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with approximately 70% of the cases being a result of a *de novo* deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15, and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (i.e. imprinting defects) (Butler *et al.*, 2008; Cassidy & Driscoll, 2009). Clinical features of PWS include hypotonia, poor feeding in infancy often associated with failure to thrive, with obesity beginning at approximately age 2 years, hyperphagia that worsens the obesity, developmental and cognitive delay, behavioural problems, central and/or obstructive sleep apnoea, and neuroendocrine abnormalities.

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Although the specific cause of the hyperphagia in PWS is unknown, the increased appetite and decreased satiety are typically ascribed to hypothalamic dysfunction, which is part of the syndrome (Goldstone, 2006; Davies *et al.*, 2008). In addition to abnormalities in the hypothalamus, individuals with PWS have evidence of increased neuronal reward circuitry activation in response to food, especially high-energy foods, both pre- and post-meal (Holsen *et al.*, 2006, 2009; Miller *et al.*, 2007). They also have differences in various gut hormones, including high levels of ghrelin (an orexogenic hormone) and lower levels of insulin (an anorexogenic hormone), which are considered to contribute to their appetite abnormalities (Haqq *et al.*, 2007; Cassidy & Driscoll, 2009; Bizzarri *et al.*, 2010). Adipokines produced by the excess adipose tissue in individuals with PWS are also assumed to play a role in regulating food intake in this syndrome (Kennedy *et al.*, 2006; Lindmark *et al.*, 2010).

Individuals with PWS are known to have decreased resting energy expenditure (REE), a lower lean muscle mass and an increased fat mass compared to weight and body mass index (BMI)-matched peers. Current dietary modifications for individuals with PWS include simple energy restriction to 25.1–29.3 J cm^{-1} (6–7 calories cm^{-1}) of height per day; the 'red, yellow, green' diet that limits foods with higher energy density, sugar or fat; and fat restriction in the diet (Schmidt *et al.*, 2008; Bonfig *et al.*, 2009). All of these diets have proven to be successful in individuals with PWS at reducing BMI and weight-for-height, although none have been shown to be effective at reducing the proportion of adipose tissue to lean muscle mass, which is important for metabolism. Additionally, none of these diets have been studied in young children with PWS.

Children with PWS typically begin to experience weight gain, which usually precedes an increase in appetite between 18 and 36 months of age. This weight gain is hypothesised to be a result of decreased REE and possibly abnormalities in carbohydrate metabolism (Gunay-Aygun *et al.*, 2001; McCune & Driscoll, 2005; Goldstone *et al.*, 2008). However, to date, the aetiology of the weight gain before a change in appetite remains unknown. Having followed the natural history of individuals with PWS over the past 10 years at the University of Florida, we noted the increased weight preceded an increase in appetite and that the respiratory quotient (RQ) increased significantly at this time, indicating that excess carbohydrates were being stored as adipose tissue (Miller *et al.*, 2011a,b). Knowing that excess carbohydrates were likely responsible for increased adiposity and assuming a decline in the energy expenditure must be responsible for the weight gain, in the present study, we advised the parents of these children to decrease energy intake at the same time as placing the children on a healthy, well-balanced diet of approximately 30% fat, 45% carbohydrates and 25% protein, with the carbohydrates given as complex carbohydrates to provide a goal of 20 g of fibre per day. We implemented this diet to determine whether we could slow down the rate of weight gain in these young children, and possibly prevent the obesity associated with this syndrome.

Materials and methods

The participants in the present study comprised 63 individuals, aged 2–10 years, with genetically confirmed PWS. Fifty-one percent were female and 90% were white (5% black, 5% Hispanic). Demographic data on the population are provided in Table 1. Sixty-one of the children were being treated with growth hormone therapy. These individuals came from 12 different states and Canada. The study was approved by the University of Florida Institutional Review Board, and all guardians provided their written informed consent and, where appropriate, participants provided their assent. Children were seen annually before the age of 4 years, and every other year if they were >4 years of age. Children in the present study were followed for a minimum of 5 years and a maximum of 7 years. The study was conducted at the University of Florida Clinical Research Center.

Table 1 Characteristics of participants

	Age Range (mean)	Sex	BMI SD score*	% Body fat by DEXA*	RQ†	REE [kJ kg^{-1} (kcal kg^{-1}) per day]	REE [kJ kg^{-1} (kcal cm^{-1}) per day]
Energy restriction with 30% fat, 45% carbohydrate, 25% protein, 20 g of fibre diet	3–13 years (6)	17 F/16 M	0.3 (0.95)	19.8% (5.7%)	0.84 (0.14)	3935.05 (4790.68) [940.5 (1145)]	27.196 (6.5)
Energy restriction only	3–15 years (6.5)	20 F/10 M	2.23 (0.77)	41.9% (9.05%)	0.95 (0.13)	4668.92 (6221.60) [1115.9 (1487)]	27.196 (6.5)

*$P < 0.001$. †$P = 0.002$.

BMI, body mass index; RQ, respiratory quotient; REE, resting energy expenditure; M. male; F, female; DEXA, dual-energy X-ray absorptiometry.

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Metabolic rate and body fat measurements

REE and RQ were measured on all participants after an overnight fast in the General Clinical Research Center at the University of Florida using a metabolic cart (ParvoMedics, Sandy, UT, USA). Humidity was controlled by having the metabolic cart acclimated to the patient room for 2 h before testing. The room door was kept closed to ensure ambient temperature and humidity stability. Gas calibration was performed by the TrueMax2400 system (ParvoMedics), which was provided with the metabolic cart. REE expenditure is a calculation of the basal metabolism of an individual, whereas RQ is a measure of the ratio of the volume of carbon dioxide (V_c) produced by an organism to the volume of oxygen consumed (V_o). Measurement of RQ provides information about which foods are being used as an energy source. Individuals eating a 'standard American diet' have an average RQ of 0.85, indicating that they are utilising the fat, protein and carbohydrates they are consuming for energy production. When an individual is being underfed, which promotes use of endogenous fat stores for energy, the RQ is low and is typically closer to 0.7 (Gropper *et al.*, 2009). Overfeeding, however, which results in lipogenesis, increases the RQ typically to >0.95, indicating that the excess carbohydrates and fats being eaten are being converted into adipose tissue (Gropper *et al.*, 2009). Only those data points obtained during a steady-state (i.e. when oxygen consumption and carbon dioxide excretion were stable) were used for data analysis. Body fat was measured using a dual-energy X-ray absorptiometry (DEXA; General Electric, Fairfield, CT, USA) scanner at the University of Florida.

Dietary compliance

To reflect the marketplace throughout the study, dietary intake data were collected using Nutrition Data System for Research (NDSR) software, versions 2007–2009, developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN, USA. Final calculations were completed using NDSR, version 2009. The NDSR time-related database updates analytic data at the same time as maintaining nutrient profiles true to the version used for data collection.

We obtained an NDSR 3-day diet history report from the parents at least every 6 months, as well as when the families were admitted to the General Clinical Research Center at the University of Florida. NDSR provides a complete nutrient profile for all foods in the database. If an analytic value is not available for a nutrient in a food, the NCC calculates the value based on the nutrient content of other nutrients in the same food or on a product ingredient list, or estimates the value based on the nutrient content of similar foods. A missing value is allowed only if: (i) the value is considered to be negligible; (ii) the food is usually eaten in very small amounts; (iii) it is unknown if the nutrient exists in the food at all; or (iv) there is no way to estimate the value because the food is unlike any other. The NDSR software utilises the multiple-pass system of the interview methodology. The primary caregiver for the child typically provided the report, although a review of portion sizes and food types was carried out with both parents separately to ascertain, as much as possible, that the information we received was accurate and complete. Feedback was consistently given to the parents by our dietician after we received the dietary logs for each child. For comparison, the dietary records for the siblings of the affected children were also obtained and analysed at each visit. The dietician would review the dietary analysis in the context of the results of the DEXA scan, REE and RQ values, and the child's weight and height parameters and trajectory. She would then provide recommendations for any alterations to the diet, including macronutrient composition, vitamin and mineral supplementation, and energy intake for all participants. Daily, moderate exercise was recommended for all participants. Families were provided with a handout detailing the amounts of macronutrients recommended, which was broken down into the percentage of total energy for each macronutrient, grams of each, and also serving sizes for each. The families could then choose which method of maintaining the dietary recommendations was the easiest for them to follow.

Dietary recall included at least one school day, and one weekend day to account for variation in diet depending on environment. Although the majority of children in the present study had not yet reached the nutritional phase associated with hyperphagia because the average age of onset of that phase is 8 years, (Miller *et al.*, 2011a,b), we requested that food be inaccessible to children in their homes, either by food being locked up or placed where the child could not reach it, to ensure that the dietary recall was as accurate as possible. All parents completed a questionnaire about food behaviours at each visit and, if the child was food-seeking or stealing, we did not include their results in the study.

Medications

Twenty-one individuals were taking carnitine supplementation throughout the time of the study (15 in dietary compliant group, six in restricted-energy group), 14 were on coenzyme Q10 (12 in dietary compliant group) and 61 were on growth hormone supplementation throughout the study (two in the dietary restriction group were not taking growth hormone). All individuals had serum insulin-like growth factor (IGF)-1 levels and growth velocity

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measured at each research study visit, and those on growth hormone had serum IGF-1 levels measured by their local endocrinologists during the interim between visits as well. All participants were on fish oil (docosahexaenoic acid and arachidonic acid) supplementation because this is a standard of care after age 12 months in our institution.

Statistical analysis

The two groups were compared using one-way analysis of variance. Each visit for every individual was dealt with as an independent data point. Two-sample, two-sided *t*-tests are only reported if the three-way comparisons were significant. $P < 0.05$ was considered statistically significant for all measures. The dependent variables utilised were: BMI *Z*-score, mean RQ, mean REE, and percentage of body fat by DEXA scan. Type III sum of square analysis was used to adjust for variables of carnitine, coenzyme Q10 and growth hormone use in the two groups.

Results

Of the 63 children who participated in the present study, 33 complied with our recommendations to restrict the energy intake to approximate the REE and to provide the children with a well-balanced diet consisting of approximately 30% fat, 45% carbohydrates and 25% protein, with a goal of at least 20 g of fibre per day. The other thirty families did restrict the energy intake of their children to approximate the REE but did not alter the dietary composition to meet our recommendations. There were no significant differences between these two groups in age, genetic subtype of PWS or socioeconomic status (Table 1).

The dietary macronutrient composition for those who did not adhere to our recommendations was found to be 10–23% fat, 50–70% carbohydrates and 15–20% protein, with 12 g or less of fibre per day (Fig. 1). The families who did not follow our recommendations consistently reported that the easiest way to restrict energy intake for the children with PWS was by decreasing the fat in the diet. Those who did provide their children with the dietary composition that we recommended were feeding the children a diet composed of, 25–30% fat, 40–50% carbohydrates and 20–30% protein, with 14–26 g of fibre per day (Fig. 1). By analysing the dietary composition for the siblings, we found that the typical diet for unaffected children ages 2–10 years is composed of 70% carbohydrates, and was identical in macronutrient composition to that being given by the families who were compliant only with the reduction of energy intake for the child with PWS.

All of the families attempted to comply with energy restriction for the child with PWS to prevent obesity. The energy intake for all children was 125.5–251 kJ kg^{-1} (30–60 kcal kg^{-1}) and 29.3–46 kJ kg^{-1} (7–11 kcal kg^{-1}) per day, which is 60–80% of the recommended daily allowance for the general population of children in the age-matched range in the USA (Table 2).

Despite a reduction in energy intake in both groups, there were differences between those who adhered to the macronutrient recommendations and those who did not. The 33 individuals who adhered to our dietary recommendations were, on average, able to consume slightly

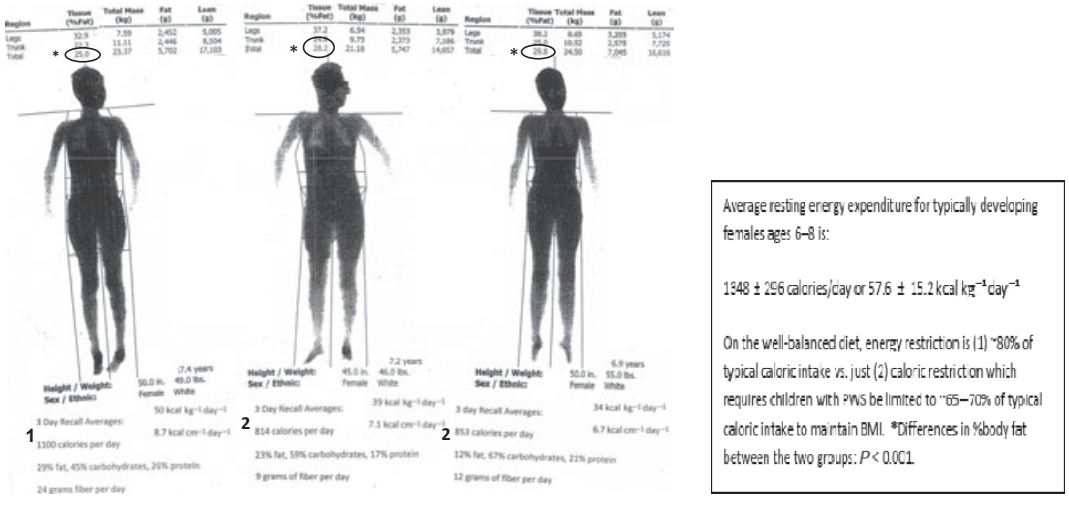

Figure 1 Average resting energy expenditure for typically developing females aged 6–8 years: 5640 ± 1238 J (1348 ± 296 calories) per day or 240.99 ± 63.59 kJ kg^{-1} (57.6 ± 15.2 kcal kg^{-1}) per day. On the well balanced diet, energy restriction is (1) approximately 80% of typical energy intake versus (2) energy restriction that requires children with Prader-Willi syndrome be limited to approximately 65–70% of typical energy intake to maintain body mass index (BMI). *Differences in percentage body fat between the two groups: $P < 0.001$.

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Table 2 Summary statistics for analysis

Variable	Mean (SD) compliers; 33 subjects	Mean (SD) noncompliers; 32 subjects	Difference (95% confidence interval)	Adjusted *P*-value*
BMI *Z*-score	0.31(0.95)	2.27(0.78)	1.96 (1.53–2.40)	<0.001
	n = 33	*n* = 31		<0.001
RQ	0.84(0.13)	0.96(0.25)	0.12 (0.003–0.24)	0.045
	n = 25	*n* = 20		0.050
IGF-1	252(119)	273(161)	21 (–56 to 97)	0.59
	n = 30	*n* = 24		0.38
% Body fat by DEXA	19.8(5.7)	41.9(9.1)	22.1 (17.8–26.5)	0.001
	n = 24	*n* = 27		0.001

**P*-values on the upper line are by Student's *t*-test (two-sided) and, on the lower line, by analysis of covariance, adjusting for carnitine, growth hormone and coenzyme Q10 use.
BMI, body mass index; RQ, respiratory quotient; IGF-1, insulin-like growth factor 1; DEXA, dual-energy X-ray absorptiometry.

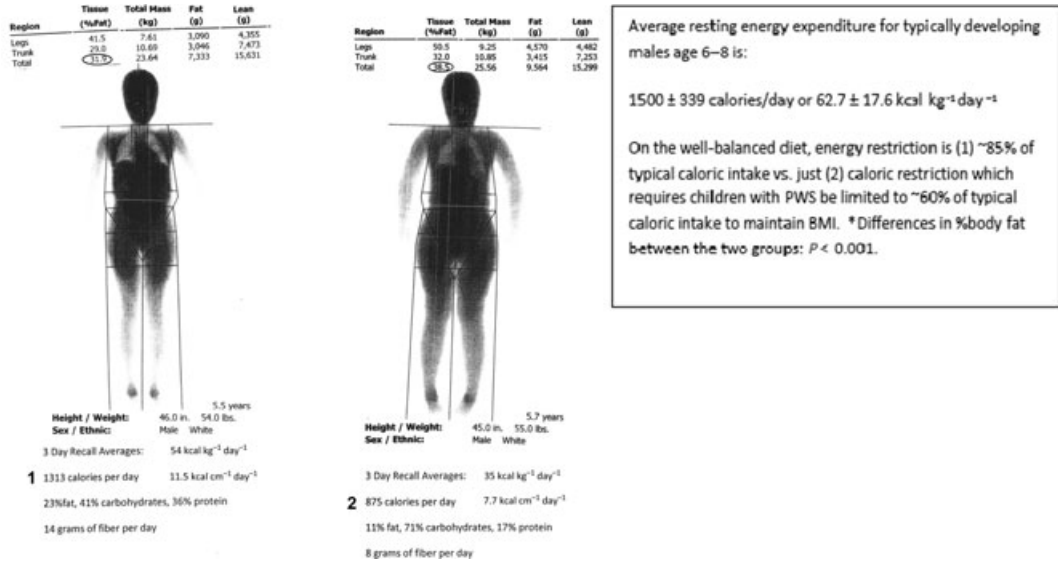

Figure 2 Average resting energy expenditure for typically developing males aged 6–8 years: 6276 ± 1418 J (1500 ± 339 calories) per day or 262.33 ± 73.63 kJ kg^{-1} (62.7 ± 17.6 kcal kg^{-1}) per day. On the well balanced diet, energy restriction is (1) approximately 85% of typical energy intake versus (2) energy restriction that requires children with Prader-Willi syndrome be limited to approximately 60% of typical energy intake to maintain body mass index (BMI). *Differences in percentage body fat between the two groups: $P < 0.001$.

more energy and had lower body fat (19.8% versus 41.9%; $P < 0.001$) than those who did not. The ratio of gynoid to android fat by DEXA scan measurements (data not shown) decreased for those who did not adhere to our recommendations, indicating that more metabolically active abdominal fat was being accumulated in these individuals. Additionally, these 33 children had better weight management (BMI SD score 0.3 versus 2.23; $P < 0.001$) than those children whose parents followed the energy intake recommendations but did not alter the macronutrient composition of the diet. The BMI SD score was highly statistically significantly different, regardless of coenzyme Q10, carnitine or growth hormone usage. The effect size for BMI SD score adjusted for supplement/growth hormone use was 1.92 (SE 0.237; $P < 0.001$) and unadjusted was –1.97 (SE 0.221; $P < 0.001$).

Those who followed our recommendations had a lower RQ (0.84 versus 0.96; $P = 0.04$), suggesting that they had a more normal energy expenditure than the other group of children. However, when carnitine and coenzyme Q10 use was accounted for, RQ differences became nonstatistically significant ($P = 0.056$). The compliant individuals had a lower REE (940.5 versus 1115.9; $P = 0.08$) which was likely driven by their lower BMI SD score because REE is determined by both body weight and body composition. The duration of treatment with growth hormone, the dosage and serum IGF-1 levels had no significant effect on the RQ or REE between the two groups.

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Discussion

A restricted-energy diet is the standard recommendation for children with PWS to achieve weight management (Bonfig *et al.*, 2009). Several types of diets have been recommended to improve the weight in these individuals, including a low-fat, energy-restricted diet, a modified food pyramid with vegetables comprising the majority of the diet, with smaller and equal serving sizes of fruits and carbohydrates, and the 'red, yellow, green' diet, which restricts high-fat, high-energy foods (Schmidt *et al.*, 2008; Bonfig *et al.*, 2009). All of these diets restrict fats and energy, although they offer no specific recommendations for amount of carbohydrates and protein, nor fibre intake. Our dietary recommendations in the present study were based on energy restriction to the amount of the REE in addition to maintaining a healthy well-balanced macronutrient composition with adequate fibre. Families were provided with sample menus and serving size recommendations, with specific macronutrient and fibre amounts to aim for in their daily diet. Our dietician was available for consultation with the families during the follow-up period after children were evaluated on the Clinical Research Unit, and she performed dietary analysis every 6 months for all of the families and continued to reinforce our dietary recommendations to everyone.

We found that, by following our recommendations, individuals with PWS had improvements in weight control, body composition and RQ compared to children who were placed on low-fat, restricted-energy diets. Although, when compared with the historic data, both groups of our patients did well with weight control and body composition, our dietary recommendations significantly improved these parameters. The fact that the majority of our patients had improved weight control and body composition compared to the historical data is likely a result of 61 of the 63 individuals in the present study being on growth hormone treatment. Growth hormone improves body composition and REE in individuals with PWS (Sipilä *et al.*, 2010; Cassidy *et al.*, 2011; Colmenares *et al.*, 2011). However, growth hormone has not been shown to have any effects on eating behaviours in PWS, and so it is unlikely that the treatment affected the amount of energy consumed by the individuals in the present study. Additionally, we found no significant effects of growth hormone dosage or serum IGF-1 levels on the RQ or REE in the individuals in the present study. All of the 61 individuals who were treated with growth hormone during the study had titration of growth hormone dose to maintain serum IGF-1 levels within 2 SDs of the normal range for sex, Tanner stage and bone age.

Although both groups of children in the present study had a RQ that suggests that excess carbohydrates are being converted into adipose tissue, those who were eating a smaller proportion of carbohydrates had a more normal RQ than those who were eating a typical restricted-energy diet. In our experience, we have found that, in an attempt to control energy intake for the child with PWS, many families try to decrease fat intake and substitute lower-energy options, which are often carbohydrates. We presume that this was the motivation behind the higher-carbohydrate consumption of those who did not comply with our recommendations.

Given that the standard American child does not consume nearly as much fibre as we recommended for children in the present study, we were concerned about achieving our fibre recommendations. However, those families who were committed to following our recommendations changed to all whole wheat/whole grain products, provided high fibre fruits and vegetables, and were able to achieve higher fibre intake per day, in contrast to those who attempted to just reduce energy intake. Fibre supplements were not given to the children to realise this intake.

Children in the present study were followed for 5–7 years, which allowed us to analyse their dietary compliance over time and to observe changes in body composition, RQ, REE and weight control when they chose not to follow our dietary recommendations.

Although, with enough energy restriction, other types of diets can be successful in weight reduction/maintenance for children with PWS, the well-balanced diet that we recommend for these children not only provides weight control, but also improvements in body composition (Fig. 1). With most diets, individuals with PWS remain excessively hungry and continue to actively food seek that makes weight maintenance difficult. Our dietary recommendations were designed for the children to consume 'breakfast, snack, lunch, snack, dinner, snack' each day, which may have resulted in improved food security, thus limiting food-seeking behaviours and helping with weight control.

Unfortunately, a limitation of the present study is that we did not assess the effect of the diet on appetite control because most of the children in the present study had not yet entered the 'insatiable' appetite phase when these data were analysed. However, the question of whether our diet recommendations, which are higher in fat and protein than most other diets used for individuals with PWS, help to decrease appetite drive needs to be answered and will require a longer follow-up. Additional limitations of the present study include the fact that diets were assessed only once every 6 months, which can be considered an excessive amount of time between assessments for growing children, although weights and heights were being closely monitored by their local physicians, so that we

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would hopefully have been notified if there were any significant changes or concerns.

Another possible confounder in the present study is the supplements that individuals were taking, which could have altered their body composition and energy expenditure. Within the group who were compliant with the dietary modifications, 12 individuals were taking coenzyme Q10 supplementation, whereas only two in the energy-restricted group were on this supplement. Additionally, there were more individuals in the dietary compliant group who were taking carnitine supplementation than in the energy-restricted group (15 in dietary compliant group, six in restricted-energy group). Both carnitine and coenzyme Q10 improve fat oxidation, especially during exercise (Zheng & Moritani, 2008). Carnitine and coenzyme Q10 can therefore potentially decrease fat mass secondary to improved muscle mass (Miller *et al.*, 2011a,b; Orellana-Gavaldà *et al.*, 2011). Given that we did not obtain standardised assessments of the amount of exercise the children were carrying out during the study, it is possible that these supplements had a beneficial effect on body composition in the individuals who were taking them.

The results obtained in the present study suggest that a well-balanced diet can help reduce weight gain and fat mass in individuals with PWS. Therefore, we suggest that, before these children begin to develop excessive weight gain, which typically occurs at approximately age 2 years, they be proactively started on a diet that is energy-restricted and well-balanced, with approximately 30% fat, 45% carbohydrates and 25% protein, and a goal of at least 20 g of fibre per day. All children could likely benefit from this type of well-balanced diet, given the prevalence of childhood obesity and the high carbohydrate, low fibre diet of most children this age.

Conflict of interests, sources of funding and authorship

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All authors made significant contributions to the preparation of the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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