

# Effects of polydextrose with breakfast or with a midmorning preload on food intake and other appetite-related parameters in healthy normal-weight and overweight females: An acute, randomized, double-blind, placebo-controlled, and crossover study



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## ABSTRACT

Polydextrose (PDX) reduces subsequent energy intake (EI) when administered at midmorning in single-blind trials of primarily normal-weight men. However, it is unclear if this effect also occurs when PDX is given at breakfast time. Furthermore, for ecological validity, it is desirable to study a female population, including those at risk for obesity. We studied the effects of PDX, served as part of a breakfast or midmorning preload, on subsequent EI and other appetite-related parameters in healthy normal-weight and overweight females. Per earlier studies, the primary outcome was defined as the difference in subsequent EI when PDX was consumed at midmorning versus placebo. Thirty-two volunteers were enrolled in this acute, double-blind, placebo-controlled, randomized, and crossover trial to examine the effects of 12.5 g of PDX, administered as part of a breakfast or midmorning preload, on subsequent EI, subjective feelings of appetite, well-being, and mood. Gastric emptying rates and the blood concentrations of glucose, insulin, cholecystokinin, ghrelin, glucagon-like peptide 1 (GLP-1), and peptide tyrosine-tyrosine were measured in the group that received PDX as part of their breakfast. There were no differences in EI between volunteers who were fed PDX and placebo. PDX intake with breakfast tended to elevate blood glucose ( $P = 0.06$ ) during the postabsorptive phase, significantly lowered insulin by 15.7% ( $P = 0.04$ ), and increased GLP-1 by 39.9% ( $P = 0.02$ ); no other effects on blood parameters or gastric emptying rates were observed. PDX intake at midmorning reduced hunger by 31.4% during the satiation period ( $P = 0.02$ ); all other subjective feelings of appetite were unaffected. Volunteers had a uniform mood profile during the study. PDX was well tolerated, causing one mild adverse event throughout the trial.

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**Abbreviations:** CCK, cholecystokinin; CON-B, placebo at breakfast; CON-M, placebo at midmorning; EI, energy intake; GLP-1, glucagon-like peptide 1; PDX, polydextrose; PDX-B, verum (12.5 g of PDX) at breakfast; PDX-M, verum (12.5 g of PDX) at midmorning; PYY, peptide tyrosine-tyrosine; T2D, type 2 diabetes; VAS, visual analogue scale.

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## 1. Introduction

The prevalence of obesity and type 2 diabetes (T2D) continues to rise worldwide (Chen, Magliano, & Zimmet, 2012; NCD-RisC, 2016). It is estimated that by 2025, the global incidence of obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) in women will reach 21% and 9% of all women will have severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) (NCD-RisC, 2016). Epidemiological evidence indicates that dietary fibers can prevent the development of obesity and T2D (Clark & Slavin, 2013; Liu et al.,

2003). Several types of dietary fiber control appetite and subsequent energy intake; however, the effects tend to be small, and the dose-response relationships are not always apparent (Clark & Slavin, 2013; Wanders et al., 2011). The capacity of dietary fibers to affect appetite is linked to their physicochemical properties (Wanders et al., 2011). In general, fibers that are more viscous reduce appetite and control energy intake more extensively than those with less viscosity (Wanders et al., 2011). However, this generalization does not apply universally (Clark & Slavin, 2013).

Polydextrose (PDX) is a soluble fiber with low viscosity that provides one-fourth of the energy that is supplied by glucose (Auerbach, Craig, Howlett, & Hayes, 2007), thus lowering glycemic and insulinemic responses (Canfora & Blaak, 2015; Shimomura et al., 2004). Recent studies suggest that its consumption governs appetite. In a meta-analysis, we found that PDX reduces subsequent energy intake (EI) dose-dependently (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2015) and alters subjective feelings of appetite (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2016). Most studies have measured the effects of administering PDX as a mid-morning preload, with which its reduction of subsequent EI is better observed (Astbury, Taylor, & Macdonald, 2013; Astbury, Taylor, French, & Macdonald, 2014; Hull, Re, Tiihonen, Viscione, & Wickham, 2012; Ranawana, Muller, & Henry, 2013). However, these studies are considered to be susceptible to a high risk of bias, based on their single-blinded design—primarily due to the complexity of the setup of acute appetite studies (Ibarra et al., 2015); thus, double-blind designs are needed to strengthen the existing scientific evidence in this regard.

Many studies on EI have enrolled normal-weight populations of males only (Astbury, Taylor, & Macdonald, 2008; Ranawana et al., 2013; Soong et al., 2016) or mixed-sex cohorts (Astbury et al., 2014; Astbury et al., 2013; Hull et al., 2012; King, Craig, Pepper, & Blundell, 2005), and although our meta-analysis concluded that the effects of PDX on appetite are similar in both sexes (Ibarra et al., 2015, 2016), no study has been conducted solely in females. This sex category is of ecological interest as they represent the majority of consumers of weight-loss dietary supplements (Pillitteri et al., 2008). Thus, we are particularly interested in assessing the appetite suppression effect of PDX in a female population, including those at risk for obesity, to confirm the results for this sex category.

Observational studies in children and adults suggest an inverse (protective) association between the frequency of eating breakfast and the risk of obesity and chronic diseases, such as T2D (Pereira et al., 2011). Thus, the administration of dietary supplements at breakfast is usually preferred to the consumption of snacks between meals. When consumed with breakfast, PDX regulates glucagon-like peptide 1 (GLP-1), a potential biomarker for appetite control, in obese persons (Olli et al., 2015). However, previous studies that aimed to determine whether PDX reduces subsequent EI when given with breakfast failed to show such an effect (Monsivais, Carter, Christiansen, Perrigue, & Drewnowski, 2011; Timm, 2012). Also, little is known about the influence of PDX on other mechanisms of appetite control, such as gastric emptying and mood. Thus, the effects of PDX when administered with breakfast or with a midmorning preload should be compared in the same trial, which should include other appetite-related parameters.

We conducted a double-blind intervention to study the effects of 12.5 g of PDX—an effective and safe dose that reduces subsequent EI (Ibarra et al., 2015)—served as part of a breakfast or midmorning preload. Per earlier studies (Astbury et al., 2014; Astbury et al., 2013; Hull et al., 2012; Ibarra et al., 2015; King et al., 2005; Ranawana et al., 2013), the primary outcome was defined as the difference in subsequent EI when PDX was consumed midmorning versus a placebo. Further, other appetite-related parameters that are associated with food intake, such as

subjective feelings of appetite (Blundell et al., 2010; Flint, Raben, Blundell, & Astrup, 2000), glycemia and insulinemia (Benelam, 2009), gastrointestinal peptides (Benelam, 2009; Blundell et al., 2010), and gastric emptying (Jackson et al., 2004), were assessed as secondary outcomes. Well-being and mood (Hetherington et al., 2013) were also evaluated, because they may influence appetite.

## 2. Methods

### 2.1. Ethics and good clinical practices

The study was performed per the Declaration of Helsinki (WMA, 2001), following Good Clinical Practice (GCP) standards (ICH, 1996), and registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT02064205). The protocol and informed consent forms were approved by the IEC “Stichting Beoordeling Ethiek Bio-Medisch Onderzoek” on March 17, 2014. The trial was conducted at QPS Netherlands B.V. (Groningen, NL) and TNO (Zeist, NL) and sponsored by DuPont Nutrition and Health (Kantvik, FI). The screening started on May 27, 2014 and the intervention took place between June 6 and October 31, 2014. The site and labs were audited by TFS A.B. (Lund, SE). The study is reported following the CONSORT statement (Schulz, Altman, & Moher, 2010).

### 2.2. Investigational products

The verum was 400 g of nonfat yogurt (Friesland Campina, NL) that contained 17.86 g of Litesse® Ultra™ (DuPont, Terre Haute, IN, US) in solution (70% solids), equivalent to 12.5 g of PDX, with a caloric content of 800 kJ. The placebo control (CON) was 400 g of yogurt that was supplemented with glucose syrup to match the energy content in the verum. The yogurt was selected as a vehicle, based on previous studies of PDX (Hull et al., 2012; King et al., 2005), which used similar nutritional compositions in their formulations. The formulations and nutritional compositions are shown in [Supplementary Table S1 and S2](#). The off-flavor from the <sup>13</sup>C-octanoate sodium salt that was added to the formulations was masked with flavorings that were developed *ad hoc* in collaboration with Firmenich Denmark ApS (Brabrand, DK). A ranking test (Watts et al., 1992) of experimental products that was conducted at DuPont Nutrition and Health (Kantvik, FI) showed no differences in overall quality, appearance, flavor, or off-flavor. There was a significant difference in texture between yogurts with or without PDX that was deemed to be irrelevant due to the 1-week washout between test days.

### 2.3. Study design

The trial was an acute, randomized, double-blind (during the entire study), placebo-controlled, and four-arm crossover (allocation ratio 1:1:1:1) study that was designed to measure the effects of 12.5 g of PDX, consumed as part of a breakfast ( $t = 0$  min) or midmorning preload ( $t = 150$  min) before an *ad libitum* lunch meal ( $t = 240$  min).

The study consisted of a screening visit, followed by four test days that were separated by a washout of at least four days. [Table S3](#) describes the assessment schedule for each visit, and [Table S4](#) and [Table S5](#) show the schedules on the test days. The four treatments that we evaluated were:

- PDX-B: Verum (12.5 g of PDX) at breakfast ( $t = 0$  min)
- CON-B: Placebo at breakfast ( $t = 0$  min)
- PDX-M: Verum (12.5 g of PDX) at midmorning ( $t = 150$  min)
- CON-M: Placebo at midmorning ( $t = 150$  min)

The primary outcome was the difference in EI between PDX-M and CON-M. Differences in EI between PDX-B and CON-B were secondary outcomes. Other secondary outcomes included differences in subjective feelings of appetite between PDX-B and CON-B and between PDX-M and CON-M; and changes in blood gastrointestinal peptides, glucose, and insulin, and gastric emptying rates between PDX-B and CON-B. Well-being, mood, and adverse events were measured and compared (if possible) between treatments with regard to compliance.

Thirty-two females were included after being informed and giving written consent. Eligible volunteers were aged between 20 and 45 years—at least 50% (16 volunteers) had to be aged over 25 years, with BMI levels between 20 and 30 kg/m<sup>2</sup>—at least 50% (16 volunteers) had to be overweight (>25 kg/m<sup>2</sup>), with all volunteers following normal Dutch eating habits (Van Strien, Frijters, Bergers, & Defares, 1986).

Volunteers were excluded if they were pregnant, were undergoing treatment for a chronic disease (eg, diabetes, hypertension, coronary heart disease, rheumatoid arthritis, Crohn's disease, eating disorders, and any other condition that could interfere with the investigational products), were menopausal, had menstruation problems, were on a special diet (eg, slimming), had an aversion toward the study product, were using any slimming preparations, were restrained eaters (Van Strien et al., 1986), consumed more than 23 g of dietary fiber per day—defined as the 75th percentile according to the Dutch National Food Consumption Survey (Ocké et al., 2005), had smoked in the past 3 months, drank more than 6 cups of coffee per day, engaged in significant physical activity (eg, more than 3 h of intense training per week, excluding cycling), consumed more than 14 units of alcohol per week, or had any dysfunction of the digestive tract, food allergy, chronic constipation, or recent or actual gastroenteritis.

#### 2.4. Procedure

On the day before the test, volunteers were asked to refrain from consuming alcohol, exercising, and ingesting any food after 11:00 PM. On test days, volunteers were advised not to drink after 6:30 AM, and they arrived at the lab at 7:15 AM in a fasting state; the breakfast was then served at 8:30 AM—the start of the experiment. A technician prepared the formulations, coded using six alpha numeric digits, then the investigator (or delegate) gave the investigational products to volunteers following a randomized and blinded list. All volunteers consumed the same 800-kJ breakfast on all 4 test days within 30 min (Table S6). On test days for PDX-B and CON-B, a nonfat yogurt that provided an additional 800 kJ with 12.5 g of PDX or placebo, respectively, was consumed with breakfast. On test days for PDX-M and CON-M, a yogurt that supplied an additional 800 kJ with 12.5 g of PDX or placebo, respectively, was consumed 150 min after breakfast. Thus, all volunteers consumed 1600 kJ before the *ad libitum* lunch. Afterward, they were given a food diary to complete throughout the remainder of the day.

#### 2.5. Energy intake

EI was measured in the 4 treatments. The EI at lunch time ( $t = 240$  min) was calculated from the amounts of food items that were consumed *ad libitum*. The lunch consisted of several food items in small portions: slices of brown bread, currant bread, and ginger bread; slices of cheese, sausage, a portion of jam, a portion of hazelnut chocolate spread, and 1 package of low-fat margarine spread as toppings; and 1 bottle of water (500 mL). These items had a caloric density of ~1260 kJ/100 g of meal. The lunch was consumed within 30 min.

The EI for the rest of the day was extracted from food diaries that

the volunteers filled after leaving the lab. The total daily EI was calculated by adding the caloric contributions of the breakfast, yogurt, *ad libitum* lunch, and the food that was consumed for the remainder of the day, as described (Ibarra et al., 2015).

#### 2.6. Subjective feelings of appetite

Four subjective feelings of appetite were assessed in all treatments: hunger, fullness, desire to eat, and prospective food consumption (Ibarra et al., 2016). Volunteers reported their feelings of appetite using a pencil on a 100-mm visual analogue scale (VAS). Table S4 and S5 show the schedules for the VAS assessment, and Table S7 lists the questions that were asked. The results were expressed as incremental area under the curve (iAUC) values for the satiation (pre- to postmeal) and satiety (postmeal to subsequent meal) periods, as described (Ibarra et al., 2016).

#### 2.7. Blood analyses

The concentrations of glucose, insulin, and the gastrointestinal peptides cholecystokinin (CCK), ghrelin, GLP-1, and peptide tyrosine-tyrosine (PYY) were measured for treatments PDX-B and CON-B. Table S4 shows the schedule, and Table S8 describes the procedure for the blood collection. Glucose was measured using an enzymatic method (Roche Diagnostics GmbH, Ref. Gluco-quant Glucose/HK, Mannheim, DE), and insulin was measured by electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Ref. E170 Module, Mannheim, DE) at KCL Bioanalysis B.V. (Leeuwarden, NL). CCK (Euro Diagnostica AB, Ref. E-23-0019-14, Malmö, SE) and ghrelin (EMD Millipore, Ref. GHRT-89HK, MO, US) were analyzed by radioimmunoassay, and GLP-1 (EMD Millipore, Ref. EGLP-35 K, MO, US) and PYY (EMD Millipore, Ref. EZHPYYT66K, MO, US) were determined by enzyme-linked immunosorbent assay at TNO Triskelion B.V. (Zeist, NL). All results were expressed as iAUC values.

#### 2.8. Gastric emptying

Gastric emptying was determined for treatments PDX-B and CON-B by <sup>13</sup>C-octanoid breath test, as described (Juvonen et al., 2012; Juvonen et al., 2015). <sup>13</sup>C-octanoate sodium salt (Campro Scientific GmbH, DE) was administered in the yogurt (Table S1), and breath samples were analyzed using the IRIS<sup>®</sup> <sup>13</sup>C-Breath Test System (IRIS<sup>®</sup>, nondispersive infrared spectroscopy; Wagner Analysen Technik GmbH, Bremen, DE). Table S4 shows the schedule for the breath collection. The results were expressed as  $t_{lag}$ —the time at which the gastric emptying was maximal—and  $t_{1/2}$ —the time of half gastric emptying (Ghoos et al., 1993). A pretest confirmed that the standard method with egg yolk was applicable to the yogurt in our study. The analyses were performed at the Institute of Biomedicine, University of Oulu (Oulu, FI).

#### 2.9. Well-being and mood

Well-being was assessed in the four treatments using an inventory that was adapted from Boelsma et al. (Boelsma, Brink, Stafleu, & Hendriks, 2010; Lawton et al., 2013). Mood was measured in the four treatments using a 32-item short version of the Profile of Mood States questionnaire (POMS-32), adapted from McNair (McNair, 1971) (Table S9). POMS-32 reports tension/anxiety, depression, anger/hostility, vigor/activity, fatigue, confusion/bewilderment, and total mood score. Table S4 and S5 show the schedules for the assessments of well-being and mood.

## 2.10. Adverse events

All adverse events (AEs) that occurred between the consumption of the investigational product and 24 h after the test were declared by the volunteers and recorded (if any). The principal investigator was available 24 h a day throughout the entire study to take immediate action against any emergency due to an AE or to address any questions that the volunteers might have had on the trial.

## 2.11. Statistical analysis

Due to the limited number of references in establishing mean differences in subsequent EI in normal-weight and overweight females, a well-established method for examining differences in VAS was used (Flint et al., 2000) to determine the necessary sample size—previous studies that used this method successfully detected changes in EI in normal-weight persons who consumed PDX (Ibarra et al., 2015, 2016): Assuming a between-volunteer standard deviation (SD) of 25 mm and a correlation between pairwise observations of 0.7, the required sample size for significantly establishing a mean difference of 15 mm with 80% statistical power and a two-sided significance level ( $\alpha$ ) of 5%, considering a 10% dropout rate, was 32 females (Flint et al., 2000).

The randomization list was generated at TNO using SAS, v 9.3 (SAS institute Inc., NC, US), and the codes were kept confidential by the statistician—the sole person who knew the codes—until the unblinding after the intervention. Table S10 shows the sequence of the randomization per block (eight blocks of four treatments each). The randomization numbers were allocated by the investigator to the volunteers following the blinded list generated by the statistician. The analysis was performed on the full dataset, without the removal of any data, except for missing data. All parameters were modeled using mixed models with BMI as a covariate, condition as fixed factor, and volunteer and cohort (four cohorts of eight

volunteers each) as random factors. The hypotheses were tested using model contrasts. They were computed using a general framework for multiple hypothesis testing (Hothorn, Bretz, & Westfall, 2008), which produces z scores as test statistics. Two-sided tests were applied to all parameters to achieve uniformity, and significance was established at  $P$ -value  $< 0.05$ . In addition, all pairwise correlations were assessed by Spearman's rank-order correlation. The analysis was performed using R, v 3.2.3 (R Core Team, R Foundation for Statistical Computing, Vienna, AT) (R Core Team, 2014), and multiple hypotheses were tested using the multcomp package for R (Hothorn et al., 2008).

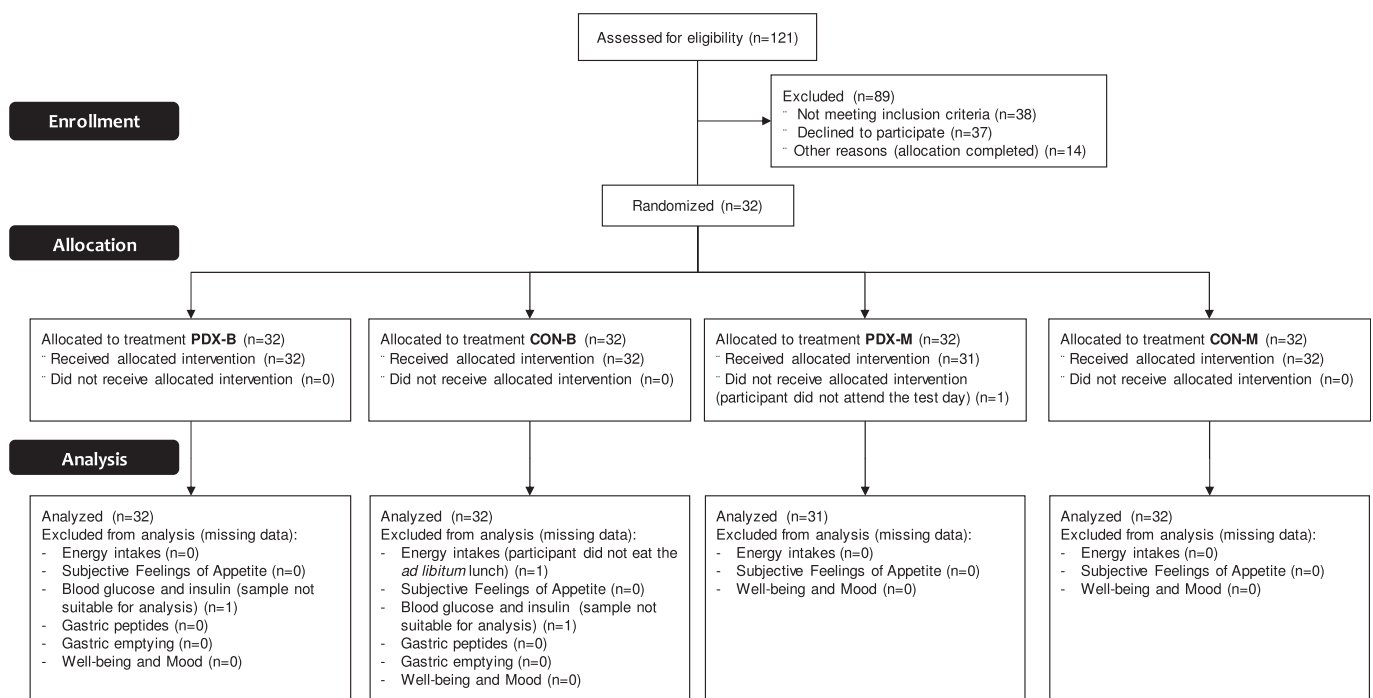
## 3. Results

### 3.1. Participants

One hundred twenty-one volunteers were screened, 46 of whom met the inclusion/exclusion criteria; the 32 volunteers who could follow the protocol per the schedule were enrolled. Fig. 1 shows the volunteers' flow diagram. Once enrolled, volunteers visited the lab in four cohorts of eight volunteers each. Thirty-one volunteers completed the trial—one volunteer discontinued for personal reasons. Table 1 lists the baseline demographics of the 32 volunteers who were enrolled. Supplementary Fig. S1 shows the distribution of BMI values by sequence of treatment.

### 3.2. Energy intake

The EI at the *ad libitum* lunch, the EI for the rest of the day, and the total daily EI values are shown in Table 2. One volunteer missed the *ad libitum* lunch in the CON-B arm. There was no significant difference in the primary outcome between the PDX-M and CON-M arms. The other levels of EI were similar between the four treatments. The EI values for individuals differed substantially between sequences, which is most likely due to the varying characteristics



**Fig. 1.** Participants' CONSORT flow diagram of the randomized, double-blind, placebo-controlled, and four-arm crossover (1:1:1:1) study. PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min); CON-B, placebo at breakfast ( $t = 0$  min); PDX-M, verum (12.5 g of polydextrose) at midmorning ( $t = 150$  min); CON-M, placebo at midmorning ( $t = 150$  min). CONSORT, consolidated standards of reporting trials;  $t$ , time of administration.

**Table 1**  
Demographics of the volunteers enrolled in the study ( $n = 32$ ).

Volunteer demographics <sup>a</sup>	Range	Mean (SD)
Age (years)	20–43	27.4 (6.6)
Body weight (kg)	58–90	74.4 (7.8)
Height (m)	1.60–1.78	1.70 (0.04)
BMI (kg/m <sup>2</sup> )	20.3–29.7	25.9 (2.7)
Dietary fiber intake (g/day)	7–23	18.0 (4)
DEBQ Score	1.5–3.1	2.4 (0.4)
Systolic blood pressure (mm Hg)	97–136	113.5 (9.9)
Diastolic blood pressure (mm Hg)	43–83	64.2 (9.0)

BMI, body mass index; DEBQ, Dutch Eating Behavior Questionnaire.

<sup>a</sup> Four volunteers were former smokers (12.5%), and 28 volunteers had never smoked (87.5%).

(eg, BMI) of the individuals in various sequences (Fig. S2.1 to S2.3).

### 3.3. Subjective feelings of appetite

The results on the subjective feelings of appetite are presented in Table 3 for the satiation and satiety periods. A significant difference was observed between PDX-M and CON-M with regard to the iAUC values for hunger during the satiation period, wherein PDX-M suppressed hunger by 31.4% ( $P = 0.02$ ) compared with placebo (Fig. 2). Full VAS curves are shown in Fig. S3.1 to S3.4. No other significant effects were noted. Subjective feelings of appetite were not compared between the four treatments, because the length of the iAUC for the breakfast (PDX-B and CON-B) and mid-morning preload (PDX-M and CON-M) groups differed.

### 3.4. Glucose and insulin

Two samples from the PDX-B and CON-B arms were not suitable

for analysis. PDX-B tended to increase the glycemic response ( $P = 0.06$ ) compared with CON-B, particularly 1 h after breakfast time. The insulinemic response decreased significantly by 15.7% ( $P = 0.04$ ) after the administration of PDX-B versus CON-B. Table 4 lists the iAUC values for glucose and insulin, and Fig. 3 shows the glycemic and insulinemic curves, adjusted to 0 at baseline. The basal values ( $t = -10$  min) for blood glucose and insulin in the entire population were 4.88 (0.47) mmol/L and 6.61 (4.14) mU/L, expressed as mean (SD), respectively.

### 3.5. Gastrointestinal peptides

The concentration of GLP-1 rose significantly by 39.9% ( $P = 0.02$ ) after the consumption of PDX-B compared with CON-B, see Table 5. PDX did not induce any significant changes in the other gastrointestinal peptides versus placebo. Fig. 4 shows the curves for the various gastrointestinal peptides, adjusted to 0 at baseline. The basal values ( $t = -10$  min) for CCK, ghrelin, GLP-1, and PYY in the entire cohort were 0.43 (0.37) pmol/L, 955.25 (276.04) pg/mL, 4.20 (2.10) pM, and 44.34 (18.33) pg/mL, expressed as mean (SD), respectively.

### 3.6. Gastric emptying

There were no significant differences in the parameters of gastric emptying (Table 6). Fig. 5 shows the curves for the percentage of the dose that was emptied from the stomach over time.

### 3.7. Well-being and mood

Because volunteers had so few gastrointestinal complaints, it was not possible to analyze their well-being as planned. There were no significant differences in the results of the POMS-32 inventory

**Table 2**  
Levels of energy intake for the four treatments.

Energy intakes	PDX-B Mean (SD)	CON-B Mean (SD)	$P$ -value <sup>a</sup>	PDX-M Mean (SD)	CON-M Mean (SD)	$P$ -value <sup>b</sup>
<i>Ad libitum</i> lunch (kJ)	2694 (1028)	2537 (933)	0.43	2317 (940)	2335 (1051)	0.59
Rest of the day (kJ)	5354 (2679)	5543 (2438)	0.62	5334 (1948)	5517 (2591)	0.83
Total daily (kJ)	9647 (3127)	9681 (2514)	0.73	9251 (2357)	9452 (3138)	0.92

PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min,  $n = 32$ ); CON-B, placebo at breakfast ( $t = 0$  min,  $n = 31$ ); PDX-M, verum (12.5 g of polydextrose) at midmorning ( $t = 150$  min,  $n = 31$ ); CON-M, placebo at midmorning ( $t = 150$  min,  $n = 32$ );  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

<sup>a</sup> For PDX-B versus CON-B. Two-way ANOVA using BMI as covariate.

<sup>b</sup> For PDX-M versus CON-M. Two-way ANOVA using BMI as covariate.

**Table 3**  
Incremental area under the curve values for subjective feelings of appetite during the satiation and satiety periods for the four treatments.

Subjective Feelings of Appetite	PDX-B Mean (SD)	CON-B Mean (SD)	$P$ -value <sup>a</sup>	PDX-M Mean (SD)	CON-M Mean (SD)	$P$ -value <sup>b</sup>
<i>Satiation</i> <sup>c</sup>		<i>mm x 35 min</i>		<i>mm x 15 min</i>		
Hunger	-836 (428)	-786 (371)	0.49	-357 (169)	-280 (167)	0.02
Fullness	991 (449)	1034 (445)	0.63	327 (208)	308 (156)	0.52
Desire to Eat	-859 (425)	-846 (426)	0.86	-301 (178)	-261 (193)	0.15
Prospective Food Consumption	-712 (383)	-689 (324)	0.67	-270 (152)	-232 (186)	0.15
<i>Satiety</i> <sup>d</sup>		<i>mm x 225 min</i>		<i>mm x 75 min</i>		
Hunger	4899 (3424)	4135 (2963)	0.28	963 (1232)	593 (987)	0.18
Fullness	-6010 (3671)	-5048 (4088)	0.25	-735 (1264)	-1077 (1118)	0.16
Desire to Eat	4922 (2892)	4774 (3409)	0.82	804 (1103)	816 (981)	0.92
Prospective Food Consumption	4451 (2783)	4474 (3032)	0.97	812 (913)	757 (795)	0.69

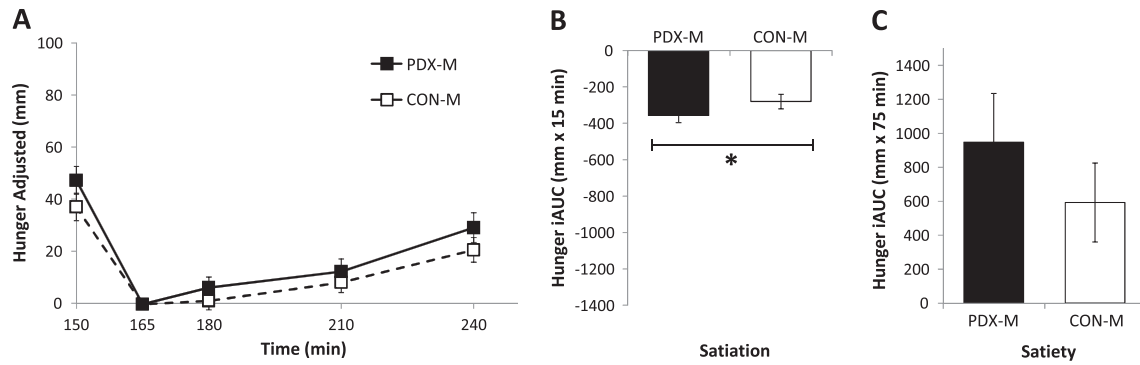
PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min,  $n = 32$ ); CON-B, placebo at breakfast ( $t = 0$  min,  $n = 32$ ); PDX-M, verum (12.5 g of polydextrose) at midmorning ( $t = 150$  min,  $n = 31$ ); CON-M, placebo at midmorning ( $t = 150$  min,  $n = 32$ );  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

<sup>a</sup> For PDX-B versus CON-B. Two-way ANOVA using BMI as covariate.

<sup>b</sup> For PDX-M versus CON-M. Two-way ANOVA using BMI as covariate.

<sup>c</sup> Satiation: Pre-to postmeal. Predose ( $-20$  min) to 15 min for PDX-B and CON-B and 150–165 min for PDX-M and CON-M.

<sup>d</sup> Satiety: Postmeal until the next meal: 15–240 min for PDX-B and CON-B and 165–240 min for PDX-M and CON-M.



**Fig. 2.** VAS results for subjective feelings of hunger for PDX-M (verum [12.5 g of polydextrose] at midmorning,  $t = 150$  min,  $n = 31$ ) and CON-M (placebo at midmorning,  $t = 150$  min,  $n = 32$ ). **(A)** VAS curves for PDX-M and CON-M, adjusted to 0 intensity, at 165 min (after intake of yogurt). **(B)** iAUC values for PDX-M and CON-M during the satiation period—*ie*, between 150 min and 165 min ( $*P < 0.05$ ). **(C)** iAUC values for PDX-M and CON-M during the satiety period—*ie*, between 165 min and 240 min. Values are expressed as means  $\pm$  SEMs. iAUC, incremental area under the curve;  $n$ , number of volunteers included in the analysis;  $t$ , time of administration; VAS, visual analogue scale.

**Table 4**  
Incremental area under the curve values for glucose and insulin for PDX-B and CON-B.

Parameters	PDX-B Mean (SD)	CON-B Mean (SD)	$P$ -value <sup>a</sup>
Glucose (mmol/L x 250 min)	99 (140)	41 (122)	0.06
Insulin (mU/L x 250 min)	4851 (3185)	5756 (3622)	0.04

PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min,  $n = 31$ ); CON-B, placebo at breakfast ( $t = 0$  min,  $n = 31$ );  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

<sup>a</sup> For PDX-B versus CON-B. Two-way ANOVA using BMI as covariate.

(Table S11).

### 3.8. Correlations and statistics

Correlations are presented in Fig. S4.1 and S4.2. As expected, EI parameters correlated well as codependent variables, as was observed for the gastric emptying parameters. Also, subjective feelings of appetite and mood parameters correlated well within each respective category. Among gastrointestinal peptides, GLP-1 correlated directly with PYY.

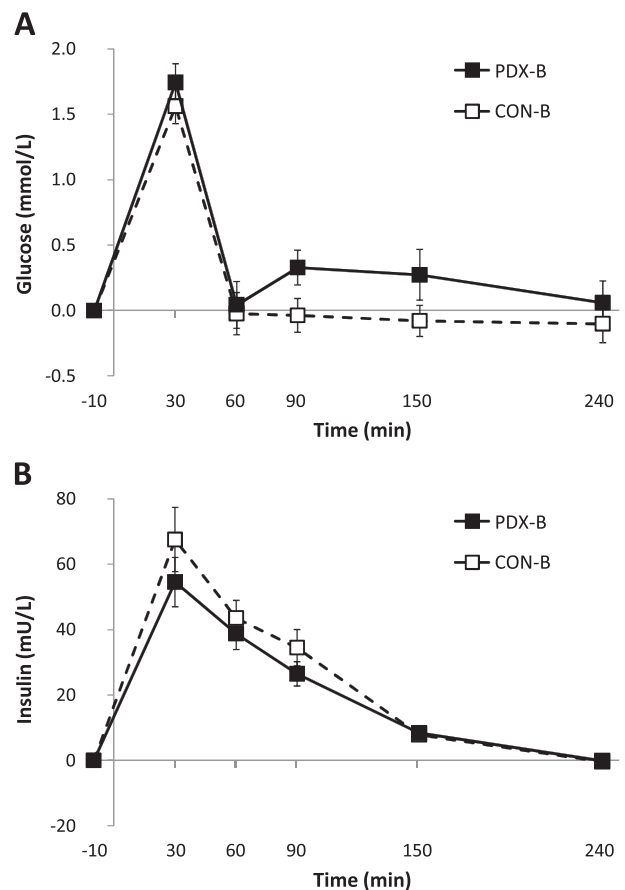
Linear model  $P$ -values and  $z$  scores are summarized in Table S13.

### 3.9. Adverse events

There were no serious adverse events (SAEs). Fourteen (43.8%) volunteers reported at least one mild AE, two of whom (6.3%) declared an AE that might have been related to the investigational products (Tables S12.1 and S12.2.). One AE—transient dizziness—could have been related to the consumption of PDX at breakfast (Table S12.3.). No volunteers discontinued the study due to AEs.

## 4. Discussion

Our study is the first double-blind trial, following strict GCP standards, conducted in normal-weight and overweight females to assess the effects of PDX given with breakfast or with a midmorning preload on subsequent EI and other appetite-related parameters. Our group concluded in a previous meta-analysis that PDX lowers EI at a subsequent meal when served as part of a midmorning preload (Ibarra et al., 2015), but other individual interventions have not had the same effect when PDX is given at breakfast time (Monsivais et al., 2011; Timm, 2012). In this trial, there were no differences in EI when PDX was served as part of a breakfast or



**Fig. 3.** Glycemia and insulinemia results for PDX-B (verum [12.5 g of polydextrose] at breakfast,  $t = 0$  min,  $n = 31$ ) and CON-B (placebo at breakfast,  $t = 0$  min,  $n = 31$ ). **(A)** Glycemia results. **(B)** Insulinemia results. The curves are adjusted to 0 at baseline. Values are expressed as means  $\pm$  SEMs.  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

midmorning preload. The EIs at *ad libitum* lunch were lower as compared to previous studies (Ibarra et al., 2015). Past interventions reporting significant differences for this parameter had EIs above 4000 kJ (Astbury et al., 2013, 2008;; Ranawana et al., 2013). Therefore, the caloric density of the subsequent *ad libitum* meal could play a role in detecting statistical differences; *ie*, if the caloric load is too low then differences may be difficult to detect. The EIs measured during the rest of the day and the total daily EI

**Table 5**

Incremental area under the curve values for gastrointestinal peptides for PDX-B and CON-B.

Parameters	PDX-B Mean (SD)	CON-B Mean (SD)	P-value <sup>a</sup>
CCK (pmol/L x 250 min)	245 (116)	270 (114)	0.21
Ghrelin (pg/mL x 250 min)	-24093 (33939)	-21487 (21574)	0.64
GLP-1 (pM x 250 min)	463 (306)	331 (254)	0.02
PYY (pg/mL x 250 min)	1808 (2896)	1260 (2882)	0.39

PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min,  $n = 32$ ); CON-B, placebo at breakfast ( $t = 0$  min,  $n = 32$ );  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide tyrosine-tyrosine.

<sup>a</sup> For PDX-B versus CON-B. Two-way ANOVA using BMI as covariate.

were in the same magnitude as previous interventions (Ibarra et al., 2015).

The lack of differences in EI between PDX and placebo could also be due to the large variability in volunteers' BMI. Our inclusion criteria allowed normal-weight and overweight females to be enrolled. The sample size that we used has been sufficient to observe differences in subsequent EI in many studies that have included normal-weight persons (Ibarra et al., 2015)—a more homogeneous population—and although overweight and obese subjects experience poorer suppression of appetite with dietary interventions (Bryant, King, & Blundell, 2008), we could not predict the variability that was induced by overweight persons in an acute design, which might have contributed to a false negative in our study.

In our trial, we provided an isocaloric breakfast to all volunteers, independent of their BMI, which also might have increased the variability. Earlier studies have reduced the variability in EI by

**Table 6**

Parameters of gastric emptying for PDX-B and CON-B.

Parameters	PDX-B Mean (SD)	CON-B Mean (SD)	P-value <sup>a</sup>
$t_{lag}$ (min)	127 (25)	131 (32)	0.52
$t_{1/2}$ (min)	162 (39)	181 (52)	0.11

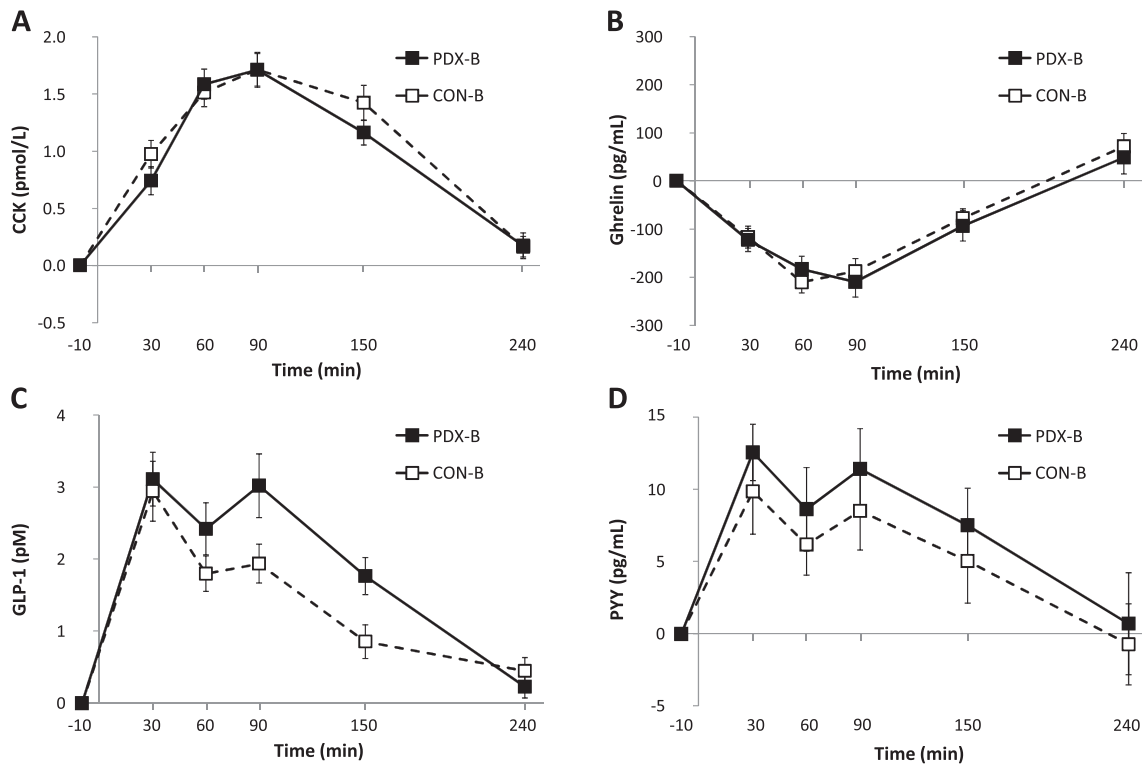
PDX-B, verum (12.5 g of polydextrose) at breakfast ( $t = 0$  min,  $n = 32$ ); CON-B, placebo at breakfast ( $t = 0$  min,  $n = 32$ );  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

$t_{lag}$ , time of fastest gastric emptying;  $t_{1/2}$ , half gastric emptying time.

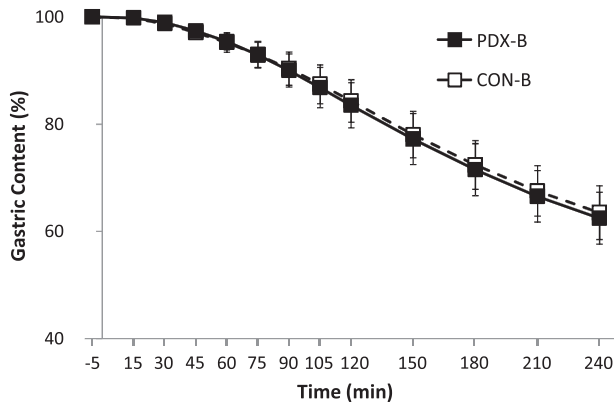
<sup>a</sup> For PDX-B versus CON-B.

standardizing the caloric content of the dinner before the test days (Astbury et al., 2013; Hull et al., 2012) and adjusting the number of calories at breakfast on test days (Astbury et al., 2013; Hull et al., 2012; King et al., 2005; Ranawana et al., 2013), based on the metabolic rate of each volunteer.

Measuring subjective feelings is a reliable method of analyzing the effects of soluble fibers on appetite (Howarth, Saltzman, & Roberts, 2001; Ibarra et al., 2016). We used an approach that allowed us to determine the levels of subjective feelings of appetite during the satiation (pre-to postmeal) and satiety (postmeal until subsequent meal) periods and to make meaningful comparisons with previous studies on PDX (Ibarra et al., 2016; Olli et al., 2015). In this trial, we found that PDX, given as part of a midmorning preload, significantly reduced hunger during the satiation period in females. This is the first study to report significant results on PDX with regard to this parameter using this method. Our meta-analysis (Ibarra et al., 2016) showed that only two studies had similar, albeit not significant, results for this parameter: Ranawana et al. (Ranawana et al., 2013), and King et al. on Day 1 (King et al., 2005). Our meta-analysis also found that preloads that contain PDX limit the



**Fig. 4.** Gastrointestinal peptide concentrations in blood for PDX-B (verum [12.5 g of polydextrose] at breakfast,  $t = 0$  min,  $n = 32$ ) and CON-B (placebo at breakfast,  $t = 0$  min,  $n = 32$ ). (A) Cholecystokinin, CCK. (B) Ghrelin. (C) Glucagon-like peptide 1, GLP-1. (D) Peptide tyrosine-tyrosine, PYY. The curves are adjusted to 0 at baseline. Values are expressed as means  $\pm$  SEMs.  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.



**Fig. 5.** Gastric emptying curves for PDX-B (verum [12.5 g of polydextrose] at breakfast,  $t = 0$  min,  $n = 32$ ) and CON-B (placebo at breakfast,  $t = 0$  min,  $n = 32$ ). Values are expressed as means  $\pm$  SDs.  $n$ , number of volunteers included in the analysis;  $t$ , time of administration.

desire to eat during the satiation period (Ibarra et al., 2016), which is consistent with our findings, wherein we observed a trend that did not reach statistical significance.

Reductions in hunger and the desire to eat during the satiation period could influence subsequent EI if the recovery during the satiety period is similar to the control (Ibarra et al., 2016). In our study, we did not find significant differences in hunger or the desire to eat during the satiety period, but again, the variability was high, preventing us from concluding that the effects during the satiation period affected the subsequent EI.

No other significant effects were observed on subjective feelings of appetite, but there was a good correlation between all of these parameters, demonstrating the consistency of the method. Differences with placebo were less clear when PDX was administered with breakfast. Similarly, other studies have failed to observe any differences in VAS scores when PDX is given at breakfast time (Monsivais et al., 2011; Timm, 2012). Interference with other nutrients and the length of the test (4 h) might have obscured the effects of PDX on appetite when combined with breakfast.

In our trial, the blood glucose response that was induced by PDX when administered with breakfast was similar to that by placebo during the first hour—*ie*, the absorptive phase—and subsequently increased until the end of the experiment—*ie*, during the post-absorptive phase, between 60 and 240 min. However, the overall increase in the iAUC value for the glucose response that was induced by PDX did not differ significantly from that by the placebo. This finding is the first observation of this effect being induced by the consumption of PDX at breakfast time, which was unexpected, because PDX reduces the glycemic response when acting as a replacement for sugars in glucose tolerance tests (Jie et al., 2000; Shimomura et al., 2004). Unfortunately, the information that was collected in our double-blind trial did not provide the elements to explain this observation. Future studies that combine PDX with breakfast might confirm our results. In our trial, PDX with breakfast significantly decreased the levels of insulin, as reported (Konings, Schoffelen, Stegen, & Blaak, 2014; Shimomura et al., 2004).

We found that PDX, given at breakfast time, increased GLP-1 in females. Similar effects have been reported in earlier clinical interventions in lean and obese subjects using comparable doses of PDX (Astbury et al., 2014; Olli et al., 2015; Soong et al., 2016). A previous experiment, in which GLP-1, an incretin hormone that lowers blood glucose and insulin, was infused intravenously, has shown that it suppresses appetite and reduces EI in humans (Flint, Raben, Astrup, & Holst, 1998). Thus, the confirmation that PDX increases GLP-1 (markedly between 60 and 150 min) may explain,

at least in part, the declines in EI in studies in which PDX was administered within this window before a subsequent *ad libitum* meal was served (Astbury et al., 2014; Astbury et al., 2013; Hull et al., 2012; Ibarra et al., 2015; King et al., 2005; Ranawana et al., 2013). PYY also rose but not significantly, and we observed a moderate correlation between GLP-1 and PYY. These gastrointestinal peptides are released postprandially, and the combined administration of PYY<sub>3-36</sub> and GLP-1<sub>7-36</sub> amide to fasted human subjects leads to similar reductions in subsequent EI, as observed physiologically following feeding (De Silva et al., 2011). In our study, CCK increased and ghrelin decreased postprandially in both treatment groups, but there were no significant differences between PDX and the placebo.

It has been demonstrated that estradiol increases the activity of the CCK-appetite signaling pathway cyclically in animals, decreasing food intake during the ovulatory phase (Geary, 2001). Thus, to some extent, the menstrual cycle might influence the physiology of eating as shown in animal and human experiments (Asarian & Geary, 2013). In our study, we recorded menstrual cycles but did not adjust the experiments according to the phase of the participants' menstrual cycle. Astbury et al. (Astbury et al., 2013), noted a clear effect of PDX, administered at midmorning in humans, in reducing EI at a subsequent meal when females were surveyed only on Days 6–12 of their menstrual cycle to minimize hormonal fluctuations, a strategy that merits consideration in future studies. However, the lack of menstrual cycle adjustment alone in our design fails to explain the absence of an effect on subsequent EIs, because our recent meta-analysis showed that EI levels for individual sexes were comparable with those of mixed groups, regardless of whether the studies adjusted for menstrual cycles (Ibarra et al., 2015). In the present study, volunteers were administered various treatments randomly, which minimized the effects of confounders and allowed us to examine the net effect of the treatments. Further, for ecological validity, the real-life effectiveness of PDX, irrespective of hormonal responses, has greater importance with regard to actual use by consumers.

In our study, we did not observe any changes in gastric emptying due to PDX. Overall, our results on gastric emptying parameters were in the range of previous observations for solid foods (Hellmig et al., 2006). The only notable observation was a nonsignificant decrease in gastric half-emptying time ( $t_{1/2}$ ) that was induced by PDX. In general, overweight and obese females experience a prolonged lag phase and delayed gastric emptying compared with lean (Jackson et al., 2004); thus, the lack of differences in gastric emptying might be attributed to the wide range of BMI values in our study.

Stress and mood states can induce changes in appetite in females (Epel, Lapidus, McEwen, & Brownell, 2001). In our study, the inclusion and exclusion criteria and the strict adherence to laboratory procedures allowed us to examine a population with uniform mood profiles.

We conducted *post hoc* analyses by subgroup—*ie*, normal-weight versus overweight and younger versus older when applicable (data not shown)—but in most cases, the differences were not meaningful, most likely due to the lower number of volunteers in the subgroups. Subsequent EI was the only relevant parameter that could be compared between the four treatments, but it did not yield significant differences, either.

Overall, PDX was well tolerated. With regard to the AEs due to PDX, the mild-intensity dizziness was short-lived and resolved during the test session. The dose of PDX in our study (12.5 g) was under the limits of tolerability that have been established for adults (90 g/day or 50 g as a single dose) (Flood, Auerbach, & Craig, 2004). Thus, our findings do not raise any concerns over its safety.

Among the limitations we found in our study, there are design



considerations that might help future similar interventions to detect differences in EI and other appetite-related parameters, such as: powering the sample size to the variability of a mixed population of normal-weight and overweight females—Table S14 suggests a power calculation, based on the results of the present study—, standardizing the caloric content of the dinner before the test days, adjusting the number of calories at breakfast to the metabolic rate of each volunteer on test days, and providing a high caloric density meal at the *ad libitum* lunch. Also, future studies that include females might benefit from adjusting menstrual cycles to avoid hormonal fluctuations.

## 5. Conclusions

This report is the first study to determine the effects of PDX on appetite exclusively in females using a double-blind design when administered with breakfast or with a midmorning preload. There were no differences in subsequent EIs, possibly due to the high variation in BMI. PDX, consumed at breakfast time, induced a greater glucose response than placebo during the postabsorptive phase, although not significantly. The ingestion of PDX at breakfast time significantly reduced insulin levels and increased GLP-1 compared with placebo. PDX did not induce any changes in gastric emptying. Further, the administration of PDX at midmorning reduced hunger during the satiation period. The volunteers had uniform mood profiles during the trial, and the investigational products were well tolerated.

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The trial was fully sponsored by DuPont Nutrition and Health

## Authors' contributions

Ibarra, Olli, Pasman, Hendriks, Herzig, and Tiihonen designed the study. Raza analyzed the breath samples. Alhoniemi analyzed the data. All authors participated in the preparation and revision of the manuscript.

## Disclaimers and conflicts of interest

DuPont commercializes Litesse® polydextrose. Pasman, Hendriks, Alhoniemi, Raza, and Herzig were paid by DuPont to conduct the trial. Ibarra, Olli, and Tiihonen were employees of DuPont Nutrition and Health during the study.

## Clinical trial registry

ClinicalTrials.gov: NCT02064205

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.appet.2016.12.002>.

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