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Increase in colonic propionate as a method of preventing weight gain in adults aged 20–40 years: iPREVENT, a multicentre, double-blind, randomised, parallel-group trial

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Scientific summary

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Scientific summary

Background

Obesity is a major global health concern and over 60% of UK adults are obese or overweight. Most research focuses on obesity treatment rather than the prevention of initial weight gain and fat deposition. Young people aged between 20 and 35 years have the fastest rates of weight gain at an average of approximately 1 kg/year. Weight gain during early adulthood increases the likelihood of poor metabolic health outcomes like elevated fasting glucose or hypertension, which contribute to chronic metabolic disease risk. Epidemiological and intervention studies have shown that dietary fibre is associated with lower body weight and better metabolic outcomes. Dietary fibre has a range of impacts on the gastrointestinal tract and gut microbiota. The fermentation of fibre by bacteria in the colon produces short-chain fatty acids (SCFAs) which may have beneficial effects on appetite and substrate metabolism. A collaboration between Scottish Universities Environmental Research Centre and Imperial College London led to the creation of inulin-propionate ester (IPE), a compound consisting of inulin (fibre) and propionate (SCFA) to specifically increase the production of propionate in the colon. This facilitates a more targeted investigation of the role of individual SCFAs on weight gain compared with general fibre supplementation. In previous work, IPE has prevented weight gain, lowered visceral fat mass (FM) and improved insulin sensitivity in middle-aged cohorts. However, the effect of increasing colonic propionate production using IPE in younger adults at risk of weight gain has not been explored. Therefore, this multicentre, randomised, placebo-controlled, double-blind trial was designed to investigate the effect of IPE on body weight in younger adults (20–40 years) with self-reported behaviours linked with phenotypic susceptibility to weight gain (e.g. low physical activity).

Main study objectives

The primary objective was to investigate whether IPE has a superior effect on preventing body weight gain, compared with inulin, in younger adults over 12 months.

The secondary objectives were to:

- Assess the effect of IPE compared to inulin on blood pressure, fasting biochemistry, and body composition.
- Determine the safety profile of IPE via adverse events (AEs), compliance and withdrawal reporting.

The substudy objectives were to assess the mechanisms by which IPE affects:

- Energy balance by measuring whole-body energy expenditure, hepatic lipid metabolism and whole-body lipid oxidation.
- Appetite by measuring peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) concentrations, subjective appetite ratings and ad libitum energy intake.
- The colonic environment via 16S ribosomal ribonucleic acid (rRNA) and metabolite analysis.
- The urinary, faecal and serum metabolite profile using nuclear magnetic resonance (NMR) spectroscopic analyses.
- Breath hydrogen as a surrogate measure of colonic bacteria fermentation.

Methods

Trial design

iPREVENT was a randomised, placebo-controlled, double-blind trial to investigate the efficacy of IPE versus inulin control upon weight gain prevention and to determine the safety profile of IPE. Participants were randomised to take 10 g/day of either IPE or inulin control daily for 12 months, with study visits at baseline, and 2, 6 and 12 months after

randomisation. A subset of participants consented, before study randomisation, to participate in further assessments of mechanistic measures in a substudy.

Study settings

The trial was performed at two UK sites: National Institute for Health and Care Research Imperial Clinical Research Facility (CRF) in London, Imperial College Healthcare NHS Trust, and University of Glasgow CRF (NHS Research Scotland).

Participants

A total of 270 participants were enrolled and randomised using Sealed Envelope software (open-source software, www.sealedenvelope.com), of whom 52 also took part in the mechanistic substudy.

The study recruited participants who were males and females aged 20–40 years with a body mass index (BMI) of 24.0–27.0 kg/m^2 if of South Asian ethnicity or 25.0–30.0 kg/m^2 if non-South Asian. Potential participants had to meet at least one of the following criteria at screening:

- a self-reported weight gain of 2 kg or more over the last 12 months
- low self-reported physical activity
- low self-reported fruit and vegetable intake (< 2 servings per day)
- high self-reported intake of sugar-sweetened beverages (> 1 serving per day).

Participants were excluded if they:

- were diagnosed with chronic disease; type 2 and type 2 diabetes, cancer, renal failure, heart disease, organic acidaemia (propionic acidaemia, methylmalonic acidaemia)
- were diagnosed with gastrointestinal conditions including coeliac disease, inflammatory bowel disease and irritable bowel syndrome
- had previous bowel reconstruction surgery
- were pregnant or lactating
- had used antibiotics at any time in the past 3 months
- had untreated vitamin B_{12} deficiency (< 160 ng/l)
- were taking part in a weight loss programme or consuming a weight loss product
- had lost 3 kg or more in the last 3 months (self-reported)
- had diarrhoea, constipation, bloating or abdominal cramping in the last 2 weeks (self-reported).

Substudy exclusion criteria included:

- anaemia or as per screening haemoglobin levels of < 130 g/l for males and < 110 g/l for females
- allergies or intolerances to any of the ingredients in the set substudy meals.

Recruitment

Study recruitment ran from July 2019 to October 2021 and was paused from March to September 2020 due to coronavirus disease 2019 (COVID-19). Trial participants were recruited from the following sources which are ranked from most to least productive:

- contacting NHS trusts
- contacting local general practices
- social media adverts
- posters
- newspaper adverts
- pop-up events.

Interventions

Participants received unlabelled, identical-looking trial interventions of IPE and inulin in 10 g pre-packed, foil-backed sachets, and they were instructed to take one sachet per day, mixed in a cold drink/water, at any time with their normal diet.

Study procedures

At the screening visit, the study rationale and protocol were explained. Participants were then asked to provide informed consent. Body weight and body composition (body water, FM, lean mass) were measured. A blood sample was taken for a full blood count to rule out the risk of B_{12} deficiency or anaemia. Participants were asked about their medical history, current medications, physical activity, alcohol intake, smoking or vaping, and recreational drug use. Blood pressure and waist and hip circumference were also measured.

Participants who were asked to attend their baseline (randomisation) study visit fasted for 12 hours and had abstained from intense physical activity and alcohol the day before. A blood sample was taken for fasting glucose, insulin, cholesterol and lipids. The participants were randomised via Sealed Envelope software and provided with IPE or inulin sachets lasting them for 2 months.

The same measurements were taken at the 2-, 6- and 12-month visits. No blood samples were taken at the 2-month visit. Compliance was measured by counting used and unused inulin/IPE sachets and the occurrence of AE or serious adverse events (SAEs) was documented.

Outcomes

Primary outcome:

Weight gain from baseline to 12 months

Secondary outcomes:

- Occurrence of AEs and SAEs over the duration of the study.
- Changes in fasting biochemistry from baseline to 6 and 12 months:
    - Glucose.
    - Insulin.
    - Triglycerides.
    - Total cholesterol.
    - Low-density lipoprotein cholesterol.
    - High-density lipoprotein cholesterol.
- Changes in blood pressure from baseline to 2, 6 and 12 months.
- Changes in body weight from baseline to 2 and 6 months.
- Changes in waist/hip/BMI/body composition measurements – FM, fat mass index (FMI), per cent body fat (fat%), fat-free mass (FFM) and FM/FFM ratio, from baseline to 2, 6 and 12 months.
- Changes in compliance (sachet count) from baseline to 2, 6 and 12 months.

Exploratory/mechanistic study outcomes

- Gut microbiota: 16S rRNA profiles from stool sample.
- Impact on neuroendocrine cell number: Proliferation in intestinal organoids using the level of SCFA and other metabolites identified from NMR spectroscopic analyses of stool.
- Appetite regulation: Measured by visual analogue scales, food diaries, ad libitum intake, and appetite-regulating gut hormones PYY, GLP-1, gastrin and cholecystokinin.
- Energy expenditure: Open-loop indirect calorimetry.
- Hepatic lipid metabolism: Stable isotope tracers of fat oxidation (^{13}C palmitate) and de novo lipogenesis.
- Total body water through dilution analysis of deuterated water.

Other data observations:

- Changes in physical activity from baseline to 2, 6 and 12 months.
- Changes in other lifestyle factors (drinking, smoking, recreational drugs) from baseline to 2, 6 and 12 months.
- Changes in diet from baseline to 2, 6 and 12 months (via food diaries).

Statistical analysis

The sample size for this study was 270 participants, based on the randomised proof-of-concept trial, the difference between arms in the change in body weight over 24 weeks was 1.4 kg [95% confidence interval (CI) −0.3 to 3.1], $p = 0.099$. A 2 kg between-arm 12-month effect size was therefore chosen. This agreed with a weight gain prevention trial over 9 months in young adults which aimed to detect a 2 kg effect and achieved 4.3 kg, with a pooled standard deviation (SD) for body weight change of 4.35 kg, and 81% retention.

The analysis of the primary end point incorporates the earlier correlated interim measurements of body weight in a linear mixed-effects (LME) model and is adjusted for baseline continuous body weight and other categorical randomisation stratifiers with further specification of the role of time point, and correlation structure, detailed in the statistical analysis plan. The implicit 'missing at random' assumption has been challenged through a set of sensitivity analyses. As these involve all randomised participants, the LME model and the sensitivity analyses taken together therefore constitute an intention-to-treat strategy.

Where possible, continuous secondary end points have been adjusted for their baseline to improve the precision of estimated intervention effects. Repeated measures have been analysed using LME models adjusting also for randomisation stratifiers. Comparisons between arms for binary outcomes are summarised as differences in proportions. Ninety-five per cent CIs have been used to make inferences from estimated effect sizes.

Results

Participants were recruited for the study from July 2019 and the target sample size was reached in October 2021 with 135 participants randomly allocated into 2 arms. Recruitment was paused from March 2020 to September 2020 during COVID-19. Participant retention was in line with estimates, with 16% (42/270) participants completely withdrawing from trial interventions. At 12 months, a compliance threshold of ≥ 50% was reached by 53% (72/135) of the inulin control arm and 63% (85/135) of the IPE arm. A high threshold of ≥ 80% was reached by 32% (43/135) of the inulin control arm and 48% (65/135) of the IPE arm, resulting in a total of 40% (108/270) of participants. Participant baseline characteristics were similar between trial arms. Primary outcome was provided for 84% (227/270) of participants.

Primary outcome

Mean (± SD) body weight at baseline was 79.1 kg ± 10.6 ($n = 135$) for inulin and 79.6 kg ± 10.9 ($n = 135$) for IPE. At 12 months, body weight was 78.9 kg ± 11.8 ($n = 114$) and 81.4 kg ± 11.9 ($n = 112$), for inulin and IPE, respectively. The baseline-adjusted difference was 1.02 (95% CI −0.37 to 2.41) kg ($p = 0.15$), between the groups.

Secondary outcomes

Lifestyle factors were comparable by study arm. There were no significant differences in measures of fasting biochemistry outcomes, except for glucose: 0.11 (0.01 to 0.21). There was a difference between arms for body water of 0.72 (0.17 to 1.28) and FFM of 1.08 (0.29 to 1.86). No changes in FM, FMI, fat%, FFM and FM/FFM ratio were detected after 12 months of IPE intake.

The AE and SAE reporting was similar between the two arms. There were a greater number of moderate-severity gastrointestinal-related AEs in the inulin control arm than in the IPE arm.

The effect of COVID-19

During the COVID-19 lockdowns, researchers pivoted to collecting participants' self-reported body weight at home. Participants were encouraged to attend the clinic for their next visit, so a clinic-reported weight could be taken.

Researchers also attempted to take clinic weights when participants had self-reported their 12-month weight but could attend the clinic within the 1-month measurement window. However, we cannot discount our results were affected by the pandemic given several studies reported increased weight gain occurred during the COVID-19 lockdowns.

Conclusions

This was the first long-term study to investigate the efficacy of increasing colonic propionate production using IPE on weight gain prevention in younger adults recruited specifically due to their risk of further weight gain. IPE did not significantly alter weight gain trajectory compared with inulin. This contrasts with previous findings demonstrating that IPE prevented weight gain, lowered body fat mass and improved insulin sensitivity in middle-aged participants who were overweight or obese. Notably, despite this population being at increased risk of weight gain, neither group exhibited significant increases in body weight nor reached the predicted 2 kg weight gain. These results are encouraging given that the study was conducted during the COVID-19 pandemic, and a recent systematic review reported that the average adult gained 1.57 kg weight from March to May 2020. The role of dietary fibre in preventing weight gain warrants further investigation.

The outcomes of this trial were not influenced by unaccounted confounding variables, such as compliance rates. High compliance at 12 months was seen in 40% of participants. The safety profile of both the intervention and control appears comparable. There were no unexpected AEs or SAEs, and complete withdrawal rates were similar for both study arms. Supplement cessation was less balanced, 42 participants and 61 participants stopped intake of IPE and inulin, respectively. The study was not confounded by high rates of gastrointestinal disturbance from IPE or inulin.

The results differ from our previous observations that IPE prevented weight gain in middle-aged people with a BMI ≥ 25 kg/m^2. At present, it is not possible to understand this difference, but we could hypothesise that young adults may be less sensitive to increased propionate production and may require a larger dose of IPE for an effect to be seen. In our previous work, 10 g was determined to be the minimally effective dose of IPE to promote weight maintenance in middle-aged participants. On the other hand, it is possible that young adults are more responsive to the effects of microbial fermentation of inulin on appetite regulation, as indicated by the lack of weight gain in the inulin control group.

Discrepancies in results between older and younger adults could partially be attributed to differences in diet and lifestyle. Younger adults have a greater tendency to eat sporadically or snack throughout the day, whereas older people tend to have more regular meal patterns and settled routines. Previous studies using stable isotopes indicate that IPE releases propionate 3–4 hours post ingestion. As propionate is a short-term signalling molecule, it may have no effect on appetite and energy intake in individuals with less consistent meal patterns. Further, evidence indicates that circulating concentrations of satiety hormones, including PYY, are lower in younger adults. These habits, powerful external cues and lower baseline concentrations of satiety hormones could overcome any satiety signal driven by IPE.

Consistent intake of IPE may have resulted in adaptations to the colonic environment and reduced sensitivity to propionate. Chronic IPE intake may have contributed to the desensitisation of free fatty acid receptors 2 and 3 located on enteroendocrine cells in the gastrointestinal tract, diminishing secretion of GLP-1 and PYY and a reducing satiety response. Further investigation is required to determine whether receptor desensitisation or alterations to certain associated proteins (e.g. those involved in gut hormone degradation) contribute to the diminished impact.

This clinical trial has some limitations. Due to the COVID-19 lockdowns and pivot to collection of self-reported weight data, the 'Principal weight' measurement for the primary outcome consists of 38% self-reported weight data. Self-reported data introduce inherent bias. Additionally, discrepancies in calibration between home weight scales and those used in the CRF may introduce further variability in the measurements. There was no plan to follow up with the participants after their final visit at the 12-month point to identify changes in their weight gain trajectory after stopping the supplement.

Future studies should aim to understand the differential effects of IPE and inulin between population groups and explore drivers of appetite regulation in younger adults.

Trial registration

This trial is registered as ISRCTN16299902.

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