Associations of changes in reported and estimated protein and energy intake with changes in insulin resistance, glycated hemoglobin, and BMI during the PREVIEW lifestyle intervention study

Mathijs Drummen,[1] Tanja C Adam,[1] Ian A Macdonald,[2] Elli Jalo,[3] Thomas M Larssen,[4] J Alfredo Martinez,[5,6,7,8]
Teodora Handjiev-Darlenska,[9] Jennie Brand-Miller,[10,11] Sally D Poppitt,[12] Gareth Stratton,[13] Kirsi H Pietiläinen,[14,15]
Moira A Taylor,[2] Santiago Navas-Carretero,[6,7,16] Svetoslav Handjiev,[9] Roslyn Muirhead,[10,11] Marta P Silvestre,[12,17]
Nils Swindell,[13] Maija Huttunen-Lenz,[18,19] Wolfgang Schlicht,[18] Tony Lam,[20] Jouko Sundvall,[21] Laura Raman,[21]
Edith Feskens,[22] Angelo Tremblay,[23] Anne Raben,[4,24] and Margriet S Westerterp-Plantenga[1]

[1]Department of Nutrition and Movement Sciences, NUTRIM—School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands; [2]MRC/Arthritis Research UK (ARUK) Centre for Musculoskeletal Ageing Research, ARUK Centre for Sport, Exercise, and Osteoarthritis, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Division of Physiology, Pharmacology, and Neuroscience, School of Life Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, United Kingdom; [3]Department of Food and Nutrition, University of Helsinki, Helsinki, Finland; [4]Department of Nutrition, Exercise, and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark; [5]Department of Physiology and Nutrition, University of Navarra, Pamplona, Spain; [6]Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBEROBN), Madrid, Spain; [7]IdisNA Institute for Health Research, Pamplona, Spain; [8]Precision Nutrition and Cardiometabolic Health Program, IMDEA-Food Institute (Madrid Institute for Advanced Studies), Campus of International Excellence (CEI) UAM + CSIC, Madrid, Spain; [9]Department of Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria; [10]School of Life and Environmental Sciences, The University of Sydney, Sydney, New South Wales, Australia; [11]Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia; [12]Human Nutrition Unit, School of Biological Sciences, Department of Medicine, University of Auckland, Auckland, New Zealand; [13]Applied Sports Technology, Exercise, and Medicine (A-STEM), College of Engineering Research Centre, Swansea University, Swansea, United Kingdom; [14]Obesity Research Unit, Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland; [15]Obesity Center, Abdominal Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [16]Centre for Nutrition Research, University of Navarra, Pamplona, Spain; [17]Center for Research in Health Technologies and Services (CINTESIS), NOVA Medical School, NOVA University of Lisbon, Lisbon, Portugal; [18]Exercise and Health Sciences, University of Stuttgart, Stuttgart, Germany; [19]Institute of Nursing Science, Schwäbisch Gmünd University of Education, Schwäbisch Gmünd, Germany; [20]NetUnion sarl, Lausanne, Switzerland; [21]Biochemistry Laboratory, Forensic Toxicology Unit, Department of Government Services, National Institute for Health and Welfare, Helsinki, Finland; [22]Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, Netherlands; [23]Department of Kinesiology, Laval University, Quebec City, Quebec, Canada; and [24]Steno Diabetes Center, Copenhagen, Denmark

ABSTRACT

Background: Observed associations of high-protein diets with changes in insulin resistance are inconclusive.

Objectives: We aimed to assess associations of changes in both reported and estimated protein (P_{Rep}; P_{Est}) and energy intake (EI_{Rep}; EI_{Est}) with changes in HOMA-IR, glycated hemoglobin (HbA1c), and BMI (in kg/m^2), in 1822 decreasing to 833 adults (week 156) with overweight and prediabetes, during the 3-y PREVIEW (PREVention of diabetes through lifestyle intervention and population studies In Europe and around the World) study on weight-loss maintenance. Eating behavior and measurement errors (MEs) of dietary intake were assessed. Thus, observational post hoc analyses were applied.

Methods: Associations of changes in EI_{Est}, EI_{Rep}, P_{Est}, and P_{Rep} with changes in HOMA-IR, HbA1c, and BMI were determined by linear mixed-model analysis in 2 arms [high-protein-low-glycemic-index (GI) diet and moderate-protein-moderate-GI diet] of the PREVIEW study. EI_{Est} was derived from energy requirement: total energy expenditure = basal metabolic rate × physical activity level; P_{Est} from urinary nitrogen, and urea. MEs were calculated as

$[(EI_{Est} - EI_{Rep})/EI_{Est}] \times 100\%$ and $[(P_{Rep} - P_{Est})/P_{Est}] \times 100\%$. Eating behavior was determined using the Three Factor Eating Questionnaire, examining cognitive dietary restraint, disinhibition, and hunger.

Results: Increases in P_{Est} and P_{Rep} and decreases in EI_{Est} and EI_{Rep} were associated with decreases in BMI, but not independently with decreases in HOMA-IR. Increases in P_{Est} and P_{Rep} were associated with decreases in HbA1c. P_{Rep} and EI_{Rep} showed larger changes and stronger associations than P_{Est} and EI_{Est}. Mean ± SD MEs of EI_{Rep} and P_{Rep} were 38% ± 9% and 14% ± 4%, respectively; ME changes in EI_{Rep} and En% P_{Rep} were positively associated with changes in BMI and cognitive dietary restraint and inversely with disinhibition and hunger.

Conclusions: During weight-loss maintenance in adults with prediabetes, increase in protein intake and decrease in energy intake were not associated with decrease in HOMA-IR beyond associations with decrease in BMI. Increases in P_{Est} and P_{Rep} were associated with decrease in HbA1c. This trial was registered at clinicaltrials.gov as NCT01777893. *Am J Clin Nutr* 2021;114:1847–1858.

Introduction

The global increase in the rate of type 2 diabetes (T2D), mainly due to overweight and obesity, calls for prevention of T2D in predisposed individuals (1). The primary factor in remission and prevention is body-weight loss, as was shown by the DiRECT (Diabetes Remission Clinical Trial) study (2, 3). In addition, the 3-y PREVIEW (PREVention of diabetes through lifestyle intervention and population studies In Europe and around the world) study showed that reduction in insulin resistance, expressed as HOMA-IR, was associated with weight-loss maintenance (4). Previous diabetes prevention lifestyle intervention studies including energy-restriction diets for weight-loss maintenance, possibly together with physical activity (PA) programs, have found reductions in the incidence of T2D

using low-fat, high-carbohydrate (CHO), high-fiber energy-restricted diets (5–7). The PREVIEW study hypothesized that a relatively high-protein, low-glycemic-index (GI) diet (hereafter HP) would support weight-loss maintenance to a greater extent and concurrently reduce insulin resistance. This study compared HP with a moderate-protein, moderate-GI diet (hereafter MP) for body-weight reduction and concurrent prevention of T2D (4, 8–15). However, despite the differences in dietary instructions, both the HP and MP groups achieved considerable and similar weight-loss maintenance, reduced HOMA-IR, and reduced glycated hemoglobin (HbA1c), a measure of average blood glucose concentration (4). None of the aforementioned lifestyle intervention studies analyzed the independent effects of the diets on HOMA-IR and HbA1c, independently of their effects on weight-loss maintenance (4–8). The present study addresses the question of whether an increase in protein (P) intake and decrease in energy intake (EI) may independently be associated with a decrease in HOMA-IR and HbA1c, as a post hoc analysis of the PREVIEW study. Previous reports on this topic are inconclusive (15–20). In the Lifelines study, a P score indicating total energy percentage (En%) P, plus the ratio of plant to animal P, was independently inversely associated with HbA1c (16). Moreover, plant and egg P seemed to decrease (17), whereas reported animal P seemed to increase, T2D risk (18, 19). However, the self-reported diets carry the risk of measurement error (ME), as shown by a concordance of self-reported P with a urinary biomarker of only 48% (16). MEs may be due to error in reporting, the measurement tool, or the nutrient database, which may lead to incorrect conclusions (21–29). However, total EI and P intake can be estimated based upon measured parameters such as those collected during the PREVIEW study (8, 26–32). In the current post hoc analysis, we investigated associations of changes in reported and estimated P (P_{Rep}; P_{Est}) and EI (EI_{Rep}; EI_{Est}) with changes in HOMA-IR, HbA1c, and BMI (in kg/m^2) during weight-loss maintenance after 8 wk weight loss. MEs were determined, and possible associations of changes in MEs with changes in HOMA-IR, HbA1c, and BMI investigated. Because weight-loss maintenance has also been shown to be associated with changes in cognitive dietary restraint, disinhibition, and hunger (10, 11, 33–35), these factors were included in the present analysis.

Methods

PREVIEW lifestyle intervention study protocol

The design (8) and main results (4) of the PREVIEW study (NCT01777893) have been published previously. In short, the PREVIEW lifestyle intervention study was a multicenter randomized controlled trial (RCT) aimed at finding an effective lifestyle intervention to prevent the development of T2D in 2326 individuals with prediabetes as defined by the American Diabetes Association criteria (8): fasting plasma glucose 5.6–6.9 mmol/L and/or 7.8–11.0 mmol/L at 2 h after an oral-glucose-tolerance test of 75 g glucose, with a fasting plasma glucose concentration <7.0 mmol/L. Inclusion and exclusion criteria have been described before (8). The study consisted of 2 phases: an 8-wk weight loss period using a low-energy diet, i.e., the Cambridge Weight Plan© Ltd., 3.4 MJ/d (8), followed
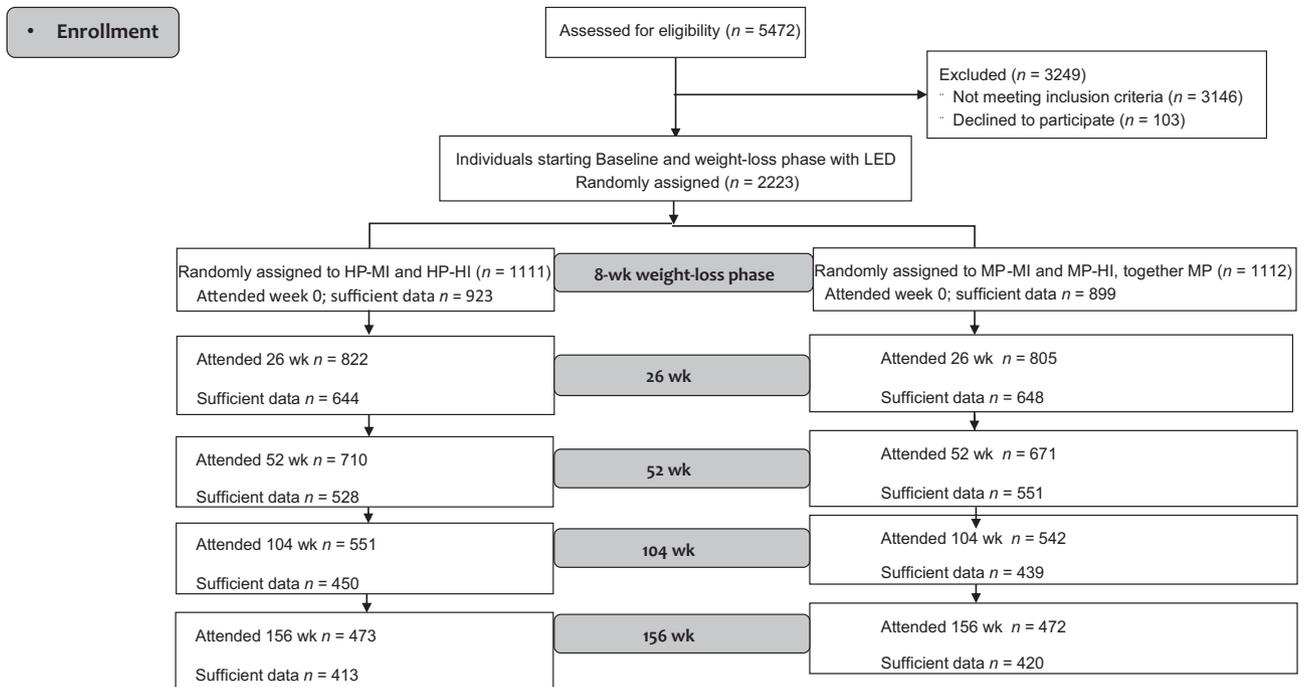
FIGURE 1 Participant flowchart. Numbers of participants in the HP and MP groups. Data used for the present analysis are indicated by "sufficient data," including complete data on BMI, body composition, HOMA-IR, glycated hemoglobin, 4-d food diaries, urinary nitrogen, and accelerometry. HI, high-intensity; HP, high-protein, low-glycemic-index diet; LED, low-energy diet; MI, moderate-intensity; MP, moderate-protein, moderate-glycemic-index diet.

by a 148-wk weight-maintenance period with instructions to follow the guidelines of 1 of the 4 intervention groups: MP or HP, combined with either moderate- or high-intensity PA (8). The primary endpoint was 3-y incidence of T2D analyzed by diet treatment. Secondary outcomes included HOMA-IR, HbA1c, and body weight (8). In the main study, a conservative estimate of sample size was 649/group or 1298 participants in total (2-sided comparison, power $= 80\%$, $\alpha = 0.05$), based upon a risk reduction of 50% in the HP and 25% in the MP group. With 30% dropout, 1854 subjects should have started the weight-maintenance phase (4). A secondary power calculation for HbA1c anticipated a difference between the 2 diet groups of 0.2% points (SD $= 0.6\%$ points). Using an 80% power and α of 0.05, the estimated sample size for each group was 142. Allowing for 30% dropout, the sample size required was 205/group (4). The study protocol and amendments were reviewed and approved by the local Human Ethics Committee at each of the 8 intervention centers. The work of the PREVIEW study was carried out in full compliance with the relevant requirements of the latest version of the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, Republic of Korea, October 2008) and The International Conference on Harmonisation for Good Clinical Practice, to the extent possible and relevant. All participants provided written informed consent before any screening procedures. All information obtained during the trial was handled according to the local regulations and European Directive 95/46/CE (the directive on protection of individuals with regard to the processing of personal data and on the free movement of such data). Recruitment of participants for the 3-y study started in 2013; the first clinical investigation day (week 0) was in 2014; the last participants had their final clinical investigation days (week 156) in 2018.

The methods used to measure body weight, height, and body composition, blood sampling, and analyses have been described previously (4, 8).

HOMA-IR appeared to be significantly reduced by 38% after weight loss, and by 16% after weight maintenance, in the completers (4). The primary outcome, i.e., total number of T2D cases, was 62 and the cumulative incidence rate was 3.1%, with no significant differences between the 2 diets, PA, or their combination (4). T2D incidence was similar across intervention centers, irrespective of attrition. There were no group differences in body weight change (-11% after 8 wk weight reduction; -5% after 3 y weight maintenance) or in other secondary outcomes (4). It was concluded that the 3-y incidence of T2D was much lower than predicted and did not differ between diets, PA, or their combination. The overall protocol combining weight loss, healthy eating, and PA was successful in markedly reducing the risk of T2D (4).

The 1822 PREVIEW study participants included in the present post hoc analyses were those with completed 4-d food intake diaries, urine collection, and accelerometry at the clinical investigation days at baseline (week 0), and throughout the weight-maintenance phase at 26, 52, 104, and 156 wk (**Figure 1**, **Table 1**).

Reported dietary intake

Dietary intake was reported using 4-d dietary intake diaries including weekdays and weekend days, at baseline (week 0), and during the weight-maintenance phase at 26, 52, 104, and 156 wk. Consumption of all foods and drinks on those 4 d had to be recorded both quantitatively (the amount) and qualitatively (the type of food or drink). The diaries were returned at the

TABLE 1 Participant characteristics at baseline (week 0) and during the intervention in the HP and MP groups[1]

Characteristic	Group	Week 0	Week 26	Week 52	Week 104	Week 156
n (female/male)	HP	923 (618/305)	644 (429/215)	528 (352/176)	450 (288/162)	413[§] (271/142)
	MP	899 (594/305)	648 (428/220)	551 (354/197)	439 (273/166)	420[§] (271/149)
Age	HP	51.7 ± 11.6	—	—	—	—
	MP	51.4 ± 11.5	—	—	—	—
BMI, kg/m^2	HP	35.4 ± 6.6	30.8 ± 5.5[§]	31.1 ± 5.5[§]	31.3 ± 5.4[§]	31.6 ± 5.3[§]
	MP	35.5 ± 6.6	30.6 ± 5.5[§]	31.1 ± 5.9[§]	31.6 ± 5.7[§]	32.0 ± 6.0[§]
Body fat, %	HP	43.2 ± 7.5	37.2 ± 8.9[§]	37.7 ± 8.9[§]	38.6 ± 8.8[§]	39.6 ± 8.6[§]
	MP	43.4 ± 7.6	37.5 ± 8.8[§]	38.3 ± 9.1[§]	39.2 ± 9.0[§]	40.5 ± 8.9[§]
BMR, MJ/d	HP	7.6 ± 1.4	7.2 ± 1.2[§]	7.2 ± 1.2[§]	7.2 ± 1.2[§]	7.2 ± 1.2[§]
	MP	7.7 ± 1.4	7.2 ± 1.2[§]	7.2 ± 1.3[§]	7.3 ± 1.3[§]	7.3 ± 1.3[§]
PAL	HP	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
	MP	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
HOMA-IR	HP	3.8 ± 2.6	2.3 ± 1.3[§]	2.5 ± 1.4[§]	2.7 ± 1.7[§]	2.8 ± 1.8[§]
	MP	3.7 ± 2.4	2.2 ± 1.3[§]	2.4 ± 1.6[§]	2.6 ± 1.5[§]	2.8 ± 1.9[§]
HbA1c, mmol/mol	HP	36.7 ± 3.9	34.9 ± 3.0[§]	35.4 ± 3.1[§]	36.4 ± 3.6	36.3 ± 3.4
	MP	36.7 ± 4.1	34.8 ± 3.2[§]	35.5 ± 3.6[§]	36.0 ± 3.8	36.5 ± 3.8
HbA1c, %	HP	5.5 ± 0.4	5.3 ± 0.3[§]	5.4 ± 0.3	5.5 ± 0.3	5.5 ± 0.3
	MP	5.5 ± 0.4	5.3 ± 0.3[§]	5.4 ± 0.3	5.4 ± 0.3	5.5 ± 0.3
TFEQ F1	HP	7.9 ± 4.0	13.6 ± 3.6[§]	13.2 ± 3.7[§]	12.5 ± 4.1[§]	12.3 ± 4.0[§]
	MP	8.0 ± 4.3	13.6 ± 3.8[§]	13.2 ± 4.0[§]	12.7 ± 4.2[§]	12.3 ± 4.3[§]
TFEQ F2	HP	9.2 ± 3.5	7.3 ± 3.5[§]	7.6 ± 3.6[§]	7.8 ± 3.6[§]	7.7 ± 3.6[§]
	MP	9.0 ± 3.5	7.4 ± 3.4[§]	7.7 ± 3.6[§]	7.8 ± 3.7[§]	7.9 ± 3.8[§]
TFEQ F3	HP	7.0 ± 3.6	4.9 ± 3.5[§]	5.3 ± 3.7[§]	5.5 ± 3.7[§]	5.5 ± 3.8[§]
	MP	7.0 ± 3.5	5.1 ± 3.5[§]	5.4 ± 3.6[§]	5.4 ± 3.7[§]	5.4 ± 3.8[§]

[1]Values are means ± SDs. Linear mixed-model analyses adjusting for age, sex, study center, and BMI were used to assess differences between the intervention groups. None were observed. BMR, basal metabolic rate; F1, cognitive dietary restraint; F2, disinhibition; F3, hunger; HbA1c, glycated hemoglobin; HP, high-protein, low-GI diet; MP, moderate-protein, moderate-GI diet; PAL, Physical Activity Level; TFEQ, Three Factor Eating Questionnaire.

[§]Statistically significant difference from week 0 ($P < 0.01$).

clinical investigation days at baseline and 26, 52, 104, and 156 wk, and were checked by the researcher together with the participant. Reported dietary intake data were analyzed using national food tables for each country. If available, national GI data for the GIs of food items were used; if not, the Australian GI data were used (36). Analyses of reported dietary intake provided total EI (EI_{Rep}), macronutrient composition, GI, and glycemic load (GL) (4, 10). The means of these data over 4 d were calculated and reported for the 1822 participants in the present study (**Table 2**). These reports of EI and P intake were used in the present analyses.

Estimated dietary intake

At 0, 26, 52, 104, and 156 wk EI was estimated (EI_{Est}), based upon energy requirement determined by total energy expenditure (TEE): TEE = basal metabolic rate (BMR) × Physical Activity Level (PAL) (26–29, 32). During diet- and PA-induced weight loss and subsequent weight maintenance, body mass, fat mass (FM), fat-free mass (FFM), and PA will change. Consequently TEE, including BMR, changes during that period of time. Therefore, we applied a model using existing knowledge on the relation between EI, FFM, and FM, and EE in energy balance as well as at changing energy balance (32). The adaptation of BMR to a changing diet, a changing activity budget, and to resulting changes in FM and FFM was included (32). Under these dynamic conditions, BMR was calculated based upon measured FFM and FM at each time point, i.e., on the clinical investigation days in weeks 0, 26, 52, 104, and 156. Body composition was determined using DXA, BodPod, or bioimpedance, yielding FFM and FM (4,

8). Thus BMR was calculated as BMR (MJ/d) = 0.102FFM (kg) + 0.024FM (kg) + 0.85 (32). Also, at each of these time points, PAL was calculated based upon the accelerometer outputs (4, 8, 37–40). For activity-induced energy expenditure, the ActiSleep+ (ActiGraph LLC) accelerometer was worn. It was attached to an elastic waist belt worn over the right mid-axillary line 24 h/d for 7 consecutive days before the clinical investigation day, and removed only for water-based activities. Counts per minute were derived and used to estimate PA (4, 8). The ActiSleep+ has previously been validated with doubly labeled water–assessed TEE (36–39). PAL was estimated using accelerometer counts, with the following equation: PAL = 0.0005882 counts/min daily + 1.45 (39, 40). EI_{Rep} was compared with EI_{Est}, yielding the relative ME of EI_{Rep}, calculated as [($EI_{Est} - EI_{Rep}$)/EI_{Est}] × 100%.

P intake was estimated (P_{Est}) based upon urinary nitrogen (4, 8, 30, 31) or urea (4, 8), collected during a day just before the clinical investigation day. Urine collection was ensured by a standard operating procedure as well as an instruction material and tools for the participants. A urine collection <0.5 L/d was regarded as incomplete. The participants brought it with them to the laboratory on the clinical investigation days, at the previously indicated time points. The total volume of the 24-h urine was recorded, and aliquots were taken and frozen at −20°C until analysis. Individually estimated P intake (g/d) was calculated as 6.25 × 24-h urinary nitrogen (g/d) × 1.1, yielding P_{Est} (30, 31). Multiplication of urinary nitrogen by 1.1 was applied to correct for nitrogen loss in feces (30, 31). When urea was measured, the conversion factor urea × 0.4664 = nitrogen was used (4,

TABLE 2 EI$_{Est}$ and EI$_{Rep}$, reported macronutrient intakes, and reported GI and GL at baseline (week 0) and during the intervention in the HP and MP groups[1]

	Group	Week 0	Week 26	Week 52	Week 104	Week 156
n (female/male)	HP	923 (618/305)	644 (429/215)	528 (352/176)	450 (288/162)	413[§] (271/142)
	MP	899 (594/305)	648 (428/220)	551 (354/197)	439 (273/166)	420[§] (271/149)
EI$_{Est}$, MJ	HP	12.3 ± 2.2	11.7 ± 2.0[§]	11.7 ± 2.0[§]	11.7 ± 1.9[§]	11.6 ± 1.9[§]
	MP	12.4 ± 2.2	11.7 ± 2.0[§]	11.6 ± 2.0[§]	11.7 ± 2.1[§]	11.7 ± 2.0[§]
EI$_{Rep}$, MJ	HP	8.8 ± 2.7	7.1 ± 1.9[§,†]	7.1 ± 2.2[§,†]	6.9 ± 2.1[§]	6.8 ± 1.8[§]
	MP	8.8 ± 2.7	6.8 ± 2.0[§]	6.8 ± 2.0[§]	6.7 ± 1.9[§]	6.8 ± 2.1[§]
P$_{Est}$, g	HP	83.2 ± 33.1	92.7 ± 40.7[§,†]	97.8 ± 43.1[§,†]	88.1 ± 33.6[§]	80.3 ± 30.8
	MP	81.1 ± 33.4	83.3 ± 40.6	87.1 ± 37.1	82.5 ± 35.5	79.9 ± 31.3
P$_{Est}$, En%	HP	11.1 ± 4.1	13.0 ± 5.7[§,†]	13.5 ± 5.7[§,†]	12.0 ± 4.2[§]	11.5 ± 4.4
	MP	10.8 ± 4.2	11.5 ± 5.4	12.5 ± 5.7	11.1 ± 4.2	11.2 ± 4.3
P$_{Rep}$, g	HP	93.2 ± 30.9	92.9 ± 26.4[†]	91.9 ± 29.1[†]	88.2 ± 28.2[†]	84.8 ± 26.6
	MP	91.2 ± 30.2	76.0 ± 23.0[§]	73.9 ± 21.3[§]	74.3 ± 21.7[§]	76.0 ± 25.8[§]
En% CHO$_{Rep}$	HP	41 ± 7	38 ± 7[†]	38 ± 7[†]	38 ± 8[†]	38 ± 8[†]
En% F$_{Rep}$	HP	36 ± 7	33 ± 7	34 ± 7	34 ± 7	34 ± 7
En% P$_{Rep}$	HP	18 ± 4	23 ± 5[§,†]	22 ± 6[§,†]	22 ± 5[§,†]	22 ± 5[§,†]
En% Alc$_{Rep}$	HP	3 ± 5	3 ± 5	3 ± 4	3 ± 5	3 ± 5
En% CHO$_{Rep}$	MP	41 ± 8	44 ± 8	44 ± 8	43 ± 8	42 ± 8
En% F$_{Rep}$	MP	37 ± 7	32 ± 7[§]	33 ± 8	33 ± 7	34 ± 7
En% P$_{Rep}$	MP	18 ± 4	19 ± 4	19 ± 4	19 ± 4	19 ± 4
En% Alc$_{Rep}$	MP	3 ± 5	3 ± 4	3 ± 5	3 ± 4	3 ± 4
GI	HP	56.3 ± 6.5	51.2 ± 7.8[§,†]	51.0 ± 8.7[§,†]	51.7 ± 8.6[§,†]	51.6 ± 9.6[§,†]
	MP	56.5 ± 6.6	55.9 ± 8.0	54.8 ± 8.6	55.2 ± 8.6	54.9 ± 9.1
GL	HP	119.3 ± 45.7	82.5 ± 33.0[†,§]	82.8 ± 33.9[§,†]	81.4 ± 32.6[§,†]	79.7 ± 31.1[§,†]
	MP	119.0 ± 45.0	98.7 ± 37.7	95.5 ± 37.1	94.3 ± 36.6	93.3 ± 35.8

[1]Values are means ± SDs. Linear mixed-model analyses adjusting for age, sex, study center, and BMI were used to assess differences between the intervention groups. Alc$_{Rep}$, reported alcohol intake; CHO$_{Rep}$, reported carbohydrate intake; EI$_{Est}$, estimated energy intake; EI$_{Rep}$, reported energy intake; En%, energy percentage; F$_{Rep}$, reported fat intake; GI, glycemic index; GL, glycemic load; HP, high-protein, low-GI diet; MP, moderate-protein, moderate-GI diet; P$_{Est}$, estimated protein intake; P$_{Rep}$, reported protein intake.

[§]Statistically significant difference from week 0 ($P < 0.01$).

[†]Significant difference between the intervention groups ($P < 0.001$).

8). Because P intake is more stable than CHO and fat (F) intake between days, 24 h urinary nitrogen collection during 1 d may be reasonably representative for P intake over that particular period of time, including the days when the food intake diaries were completed (30, 31). En% P intake was determined as En% P$_{Est}$ = MJ estimated P intake/EI$_{Est}$ MJ × 100%, and similarly as En% P$_{Rep}$ = MJ reported P intake/EI$_{Rep}$ MJ × 100%.

Four-day mean P$_{Rep}$ was compared with P$_{Est}$, yielding the ME of P$_{Rep}$: $[(P_{Rep} - P_{Est})/P_{Est}] \times 100\%$. The EI from CHO, F, and alcohol together was estimated as nonprotein EI$_{Est}$ = EI$_{Est}$ − P$_{Est}$. The ME of the nonprotein EI$_{Rep}$ or (CHO$_{Rep}$ + F$_{Rep}$ + Alc$_{Rep}$) = {[nonprotein EI$_{Est}$ − (CHO$_{Rep}$ + F$_{Rep}$ + Alc$_{Rep}$)]/nonprotein EI$_{Est}$} × 100%, where Alc$_{Rep}$ is reported alcohol intake.

Eating behavior

The Three Factor Eating Questionnaire (TFEQ) by Stunkard and Messick (33) was provided to collect Factor 1 (F1) scores for cognitive dietary restraint, indicating control regarding amount of food consumed and food choice; Factor 2 (F2) scores for disinhibition and emotional eating, indicating inhibition of restraint and breaking the self-imposed diet, and eating as consolidation for emotional life events; and Factor 3 (F3) scores for general perception of hunger (33). The TFEQ consists of 51 questions, i.e., 21 questions scoring on F1, 16 on F2, and 14 on F3, and was administered at each clinical investigation day

either on paper or electronically. It has been translated into and validated in the relevant local languages, i.e., Danish, Finnish, Dutch, Spanish, and Bulgarian (8). Its validity and reliability have been reported for females and males, among weight groups, in several countries, e.g., by Bohrer et al. (34). Regarding the use of the TFEQ in studies on weight-loss maintenance, the significance of the change and magnitude of scores on the TFEQ lies in their role in explaining eating behavior in relation to weight management. In healthy individuals, increased cognitive dietary restraint (F1), together with decreased disinhibition, emotional eating (F2), and hunger (F3), were associated with more favorable weight maintenance (10–13, 34, 35).

Statistical analyses

For the analyses based on dietary intake during the complete study of 36 mo, the data were pooled into 2 groups, yielding the HP and the MP group, with both groups including the same 2 PA arms. Statistical analyses were performed using the Statistical Package for the Social Sciences version 23 (IBM SPSS Statistics). Regarding the data distribution, skewness and kurtosis were within acceptable ranges. Differences in BMI, body fat percentage, HOMA-IR, HbA1c, TFEQ scores, and food intake diary data between the 2 groups and changes over time were assessed with linear mixed-model analysis. To answer the main questions, associations of changes over time from baseline in

P_{Rep}, P_{Est}, EI_{Rep}, and EI_{Est} with changes in HOMA-IR, HbA1c, and BMI were assessed with linear mixed-model analyses. Possible associations of changes in MEs, [($EI_{Est} - EI_{Rep}$)/EI_{Est}] × 100% and [($P_{Rep} - P_{Est}$)/P_{Est}] × 100%, with changes in HOMA-IR, HbA1c, BMI, and TFEQ scores were also assessed with linear mixed-model analyses. Secondarily, associations with age were investigated with linear mixed-model analyses. The mixed-model analyses included the data from all participants present at the particular time point, including those who dropped out later. The linear mixed models included a participant-level random intercept, a repeated subject-by-study center component, and fixed effects for time, age, sex, and updated BMI at each of the different time points, when applicable. Interaction terms with time were removed from the model, if nonsignificant. The subject-by-study center component accounted for differences, e.g., in methods of measuring body composition. Results from the mixed modeling analyses are presented as estimates and CIs. Differences in MEs between groups and between sexes were investigated separately, each with one-factor ANOVA.

Pearson's correlation analyses were used to determine associations between EI_{Rep} and EI_{Est} or between P_{Est} and P_{Rep}.

Results

Characteristics of the participants

The present analyses included 1822 participants at week 0 which decreased to 833 at week 156, after excluding incomplete 4-d food intake diaries, urine collection, or accelerometry (Figure 1). Anthropometric characteristics, HOMA-IR, HbA1c, and TFEQ scores of the participants in the HP group and the MP group did not differ statistically significantly from each other at any time point (Table 1). Mixed-model analysis showed statistically significant decreases from baseline in BMI, body fat percentage, BMR, HOMA-IR, TFEQ-F2, and TFEQ-F3, and at some time points for HbA1c (weeks 26 and 52), and increases from baseline in TFEQ-F1 in both groups, without differences between the HP and MP groups (Table 1). Moreover, no differences were observed between study centers (data not shown).

Changes in estimated and reported dietary intakes

Overall, EI_{Est} and EI_{Rep} decreased significantly in both groups. At weeks 26 and 52 EI_{Rep} was higher in the HP than in the MP group (Table 2). Macronutrient compositions changed differentially between groups. In the HP group, P_{Est} (g or En%) increased significantly from week 0 to week 104, whereas GI and GL decreased from week 0 to week 156. Although in the HP group there were no significant differences in En% reported for F and CHO intake over time, whereas Alc_{Rep} was stable, together ($CHO_{Rep} + F_{Rep} + Alc_{Rep}$) decreased significantly over time, from 80En% to 75En% ($P < 0.01$).

In the MP group En% P_{Est}, P_{Rep}, GI, and GL did not change significantly from week 0, whereas P_{Rep} (g) decreased significantly, and En% F_{Rep} decreased significantly at week 26 (Table 2). P_{Est} (En% and g) and P_{Rep} (g) were significantly higher in the HP than in the MP group from week 26 to week 52; P_{Rep} (g) was also higher in the HP than in the MP group at week 104

(Table 2). No differences were observed between study centers (data not shown).

### Comparison of reported with estimated EI and P intake

Overall, EI_{Rep} was positively associated with EI_{Est} ($r = 0.28$; $P < 0.001$) and P_{Rep} was positively associated with P_{Est} ($r = 0.26$; $P < 0.001$). Comparison of reported with estimated figures on overall daily EI (EI_{Rep} compared with EI_{Est}) and P intake (P_{Rep} compared with P_{Est}) resulted in a lower EI_{Rep} than EI_{Est} and a higher P_{Rep} than P_{Est}. The difference between EI_{Rep} and EI_{Est} increased during the study, whereas the difference between P_{Rep} and P_{Est} was largest at weeks 0 and 156 (**Figures 2, 3**).

The mean ± SD ME of EI_{Rep} was 4.34 ± 2.54 MJ/d or 1042.3 ± 259.2 kcal/d, or 37.8% ± 9.4%, representing underreporting. The mean ± SD ME of EI_{Rep}, adjusted for the relevant confounders, was larger in the MP than in the HP group (4.49 ± 0.86 compared with 4.26 ± 0.79 MJ/d, or 1069.6 ± 204.0 compared with 1014.7 ± 187.5 kcal/d, or 38.8% ± 7.4% compared with 36.8% ± 6.8%; $P < 0.01$), and larger in males than in females (4.79 ± 1.1 compared with 4.18 ± 1.0 MJ/d or 1141.5 ± 256.4 compared with 995.4 ± 239.9 kcal/d, or 41.4% ± 9.3% compared with 36.1% ± 8.7%; $P < 0.01$). Associations of changes in the independent variables BMI, HOMA-IR, and HbA1c with changes in the dependent variable ME were expressed by an estimate that indicates the change in the dependent variable associated with a 1-unit change in the independent variable. For example: a change of 1 in BMI was associated with a change of 0.619 MJ ME in EI_{Rep} (**Table 3**).

Overall, changes in BMI and TFEQ-F1 were positively, whereas changes in TFEQ-F2 and TFEQ-F3 were inversely, associated with changes in the ME of EI_{Rep} (Table 3). No associations of changes in HOMA-IR or HbA1c with changes in ME of EI_{Rep} were observed (Table 3). Age was not significantly associated with change in ME of EI_{Rep} (estimate: 0.001; 95% CI: -0.002, 0.004; $P = 0.29$).

The mean ± SD ME of P_{Rep} (g) was 26.7 ± 6.7 kcal, or 112 ± 27.9 kJ, or 13.5% ± 3.7%, representing overreporting. The ME of P_{Rep} (g), adjusted for the relevant confounders, was larger in the HP than in the MP group (30.0 ± 6.8 compared with 17.6 ± 3.8 kcal, or 126.1 ± 28.7 compared with 74.0 ± 15.9 kJ, or 16.7% ± 3.8% compared with 9.8% ± 2.1%; $P < 0.01$), and larger in females than in males (30.2 ± 7.01 compared with 11.3 ± 2.9 kcal, or 126.9 ± 29.5 compared with 47.6 ± 12.1 kJ, or 16.8% ± 3.9% compared with 6.3% ± 1.6%; $P < 0.01$).

Age was significantly associated with a change in ME of P_{Rep} (g/kg) (estimate: -0.190; 95% CI -0.368, -0.011; $P = 0.026$) and with a change in ME of En% P_{Rep} (estimate: -0.394; 95% CI: -0.786, -0.001; $P = 0.026$), indicating a smaller change in ME with increasing age. Overall, change in BMI was inversely associated with change in ME of P_{Rep} (g/kg). Changes in HOMA-IR, HbA1c, or TFEQ-scores were not associated with changes in ME of P_{Rep} (g/kg) (Table 3). Changes in BMI and in TFEQ-F1 were positively, and changes in TFEQ-F2 and TFEQ-F3 were inversely, associated with a change in ME of En% P_{Rep} (Table 3). The ME of the remaining nonprotein reported dietary intake, namely ($CHO_{Rep} + F_{Rep} + Alc_{Rep}$), was 1118.4 ± 372.8 kcal/d, or 4.66 ± 1.55 MJ/d, or 44.4% ± 14.8%. No differences in underreporting EI and overreporting P intake were observed between study centers (data not shown).
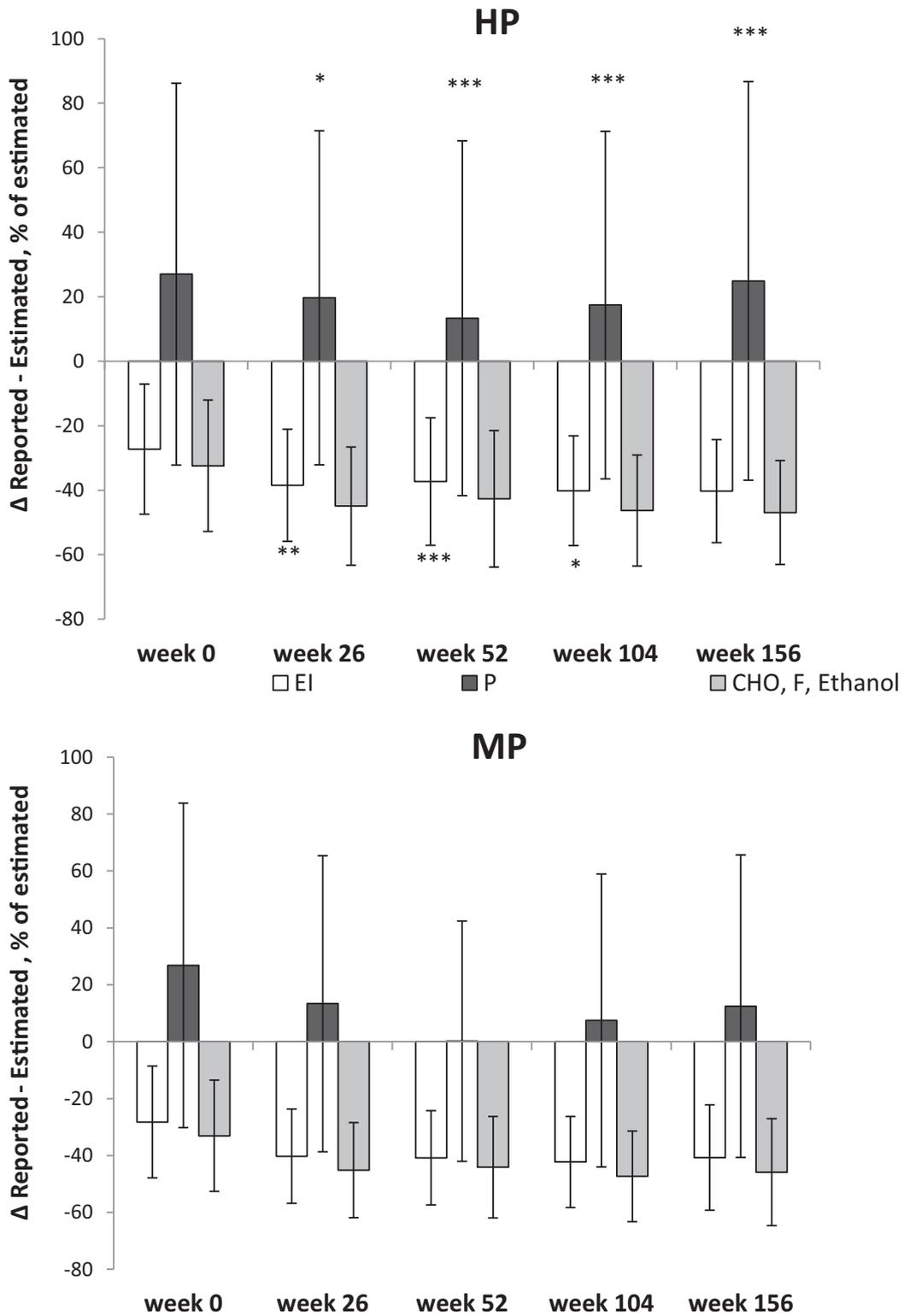
FIGURE 2 Mean reported minus estimated EI, P intake, and intake of CHO, F, and ethanol combined, as a percentage of estimated intake in the HP and MP groups. Data are presented as means ± SDs. Linear mixed-model analyses adjusting for age, sex, study center, and BMI were used to assess differences between the intervention groups. Significance levels of pairwise comparisons are indicated if the overall group effect was significant. *Significantly different from MP group: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. n (female/male), weeks 0, 26, 52, 104, and 156: HP: 923 (618/305); 644 (429/215); 528 (352/176); 450 (288/162); and 413 (271/142), respectively; MP: 899 (594/305); 648 (428/220); 551 (354/197); 439 (273/166); and 420 (271/149), respectively. CHO, carbohydrate; EI, energy intake; F, fat; HP, high-protein, low-glycemic-index diet; MP, moderate-protein, moderate-glycemic-index diet; P, protein.
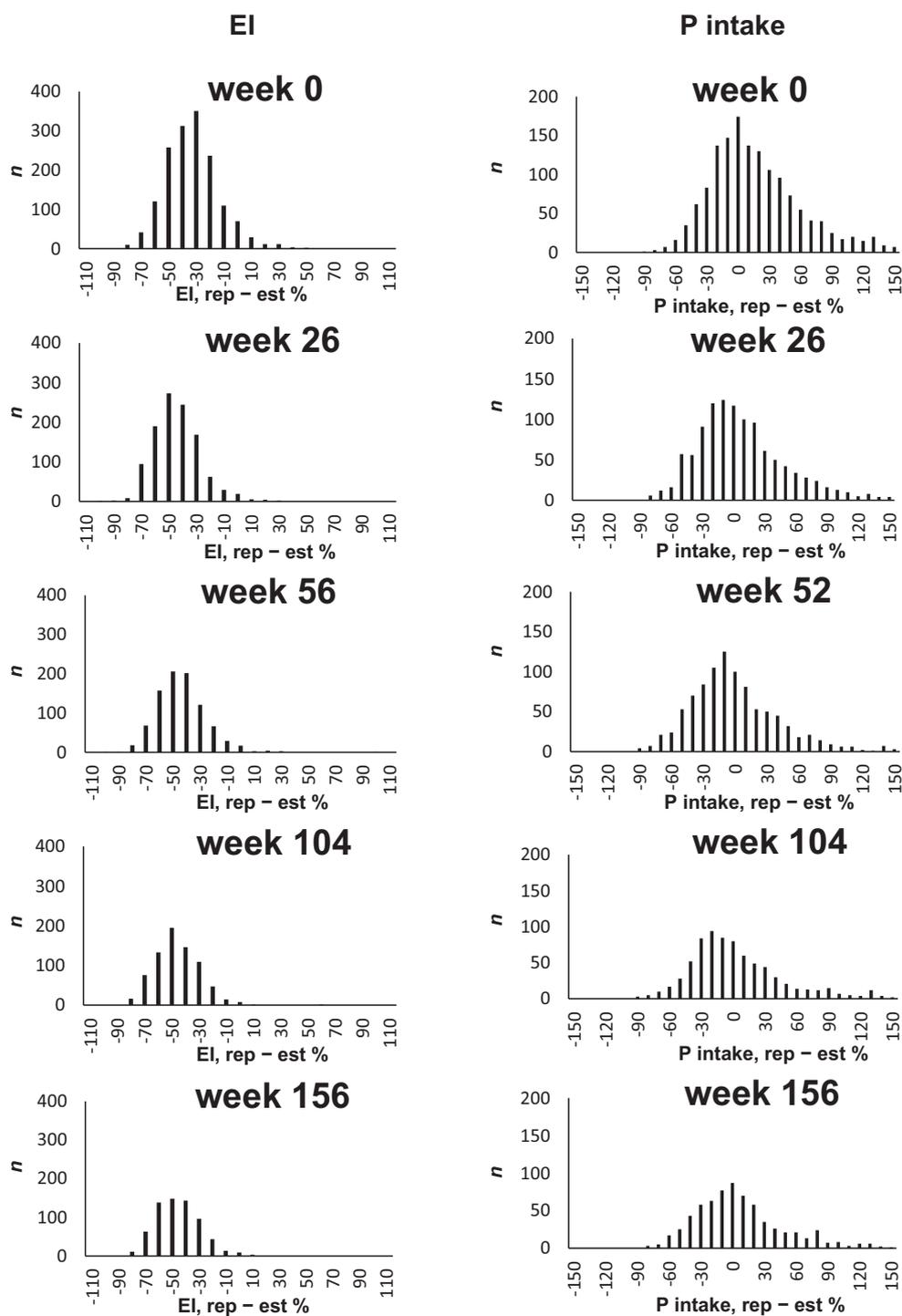
FIGURE 3 Frequency distributions of reported minus estimated EI and P intake as percentages of estimated EI and P intake in both groups together, at the different time points. *n* (female/male), weeks 0, 26, 52, 104, and 156: HP: 923 (618/305); 644 (429/215); 528 (352/176); 450 (288/162); and 413 (271/142), respectively; MP: 899 (594/305); 648 (428/220); 551 (354/197); 439 (273/166); and 420 (271/149), respectively. EI, energy intake; P, protein.

Associations of changes in reported and estimated EI and P intake with changes in HOMA-IR, HbA1c, and BMI

Because neither the changes in HOMA-IR, HbA1c, and BMI, nor the associations of changes in EI or P intakes with changes in HOMA-IR, HbA1c, and BMI differed between the groups, both dietary groups were analyzed together. Because also PA or PA intensity did not differ between the groups (4), all PREVIEW study participants were analyzed together.

The magnitudes of possible associations, analyzed by mixed modeling analyses, were expressed by an estimate indicating the change in the dependent variable associated with a 1-unit change of the independent variable. For example: 1 MJ/d

TABLE 3 Associations of the dependent variables MEs of EI_{Rep} and P_{Rep} with the independent variables BMI, HOMA-IR, HbA1c, and TFEQ in the whole group of participants[1]

Variables (dependent, independent)	Overall estimates		
	Estimate	95% CI (Low, High)	P
ME EI_{Rep}, MJ			
BMI, kg/m^2	0.619	0.493, 0.744	<0.001
HOMA-IR	0.001	−0.001, 0.003	0.14
HbA1c, mmol/mol	0.000	−0.001, 0.001	0.89
TFEQ F1	0.961	0.727, 1.196	<0.001
TFEQ F2	−0.559	−0.731, −0.387	<0.001
TFEQ F3	−0.733	−0.897, −0.569	<0.001
ME P_{Rep}, g/kg			
BMI, kg/m^2	−0.220	−0.256, −0.185	0.03
HOMA-IR	−0.001	−0.002, 0.001	0.09
HbA1c, mmol/mol	0.001	−0.002, 0.003	0.66
TFEQ F1	−0.651	−1.347, 0.045	0.06
TFEQ F2	0.000	−0.002, 0.003	0.71
TFEQ F3	0.002	−0.001, 0.005	0.20
ME P_{Rep}, En%			
BMI, kg/m^2	2.177	1.458, 2.896	<0.001
HOMA-IR	0.503	−2.049, 3.055	0.20
HbA1c, mmol/mol	0.002	−0.002, 0.006	0.32
TFEQ F1	1.642	0.074, 2.548	<0.001
TFEQ F2	−3.550	−4.604, −2.496	<0.001
TFEQ F3	−2.942	−3.861, −2.024	<0.001

[1]Linear mixed models including a participant-level random intercept, a repeated subject-by-study center component, and fixed effects for time, age, sex, and BMI when applicable were used to assess associations of MEs of EI_{Rep} and P_{Rep} with BMI, HOMA-IR, and HbA1c. ME of EI_{Rep}: (EI_{Est} − EI_{Rep})/EI_{Est} × 100%; ME of P_{Rep}: (P_{Rep} − P_{Est})/P_{Est} × 100%. Interaction terms with time were removed from the model, if nonsignificant. $P < 0.05$ indicates statistical significance. The estimates indicate the changes in the dependent variable associated with a 1-unit change of the independent variables. Example: a change of 1 kg/m^2 in BMI is associated with a change of 0.619 MJ ME in EI_{Rep}. EI_{Est}, estimated energy intake; EI_{Rep}, reported energy intake; En%, energy percentage; F1, Factor 1 (cognitive dietary restraint); F2, Factor 2 (disinhibition); F3, Factor 3 (hunger); HbA1c, glycated hemoglobin; ME, measurement error; P_{Est}, estimated protein intake; P_{Rep}, reported protein intake; TFEQ, Three Factor Eating Questionnaire.

change in EI_{Est} was associated with a change of 1.15 in BMI (**Table 4**).

Overall, changes in EI_{Est} and EI_{Rep} were positively associated with changes in BMI corrected for age, sex, and study center (Table 4). Changes in EI_{Est} and EI_{Rep} were not independently associated with changes in HOMA-IR or HbA1c, corrected for age, sex, study center, and BMI (Table 4). Change in En% P_{Est} was not independently associated with changes in HOMA-IR or HbA1c, whereas a trend appeared for the association with change in BMI ($P = 0.05$). Change in En% P_{Rep} was not associated with changes in HOMA-IR and HbA1c, yet it was inversely associated with change in BMI (Table 4).

Discussion

The present study investigated if changes in P_{Est}, P_{Rep} EI_{Est}, and EI_{Rep}, during a 3-y lifestyle intervention focused on weight-loss maintenance and reduction of HOMA-IR, were associated with changes in HOMA-IR, HbA1c, and BMI, in a pooled post hoc analysis of all eligible participants.

Overall, increases in P_{Est} and P_{Rep} (g/kg) were associated with decreases in HbA1c and BMI, but not with a decrease in HOMA-IR. Increases in En% P_{Est} and En% P_{Rep} were not associated with decreases in HOMA-IR and HbA1c. The increase in En% P_{Est} was only a trend, but the increase in En% P_{Rep} was associated with a decrease in BMI. Decreases in EI_{Est} and EI_{Rep} were

not independently associated with decreases in HOMA-IR and HbA1c. Self-evidently, decreases in EI_{Est} and EI_{Rep} were associated with a decrease in BMI (4, 32). Although the PREVIEW study showed that the decrease in HOMA-IR was associated with the decrease in BMI (4), the decrease in EI_{Est} and increase in P_{Est} were not independently associated with the decrease in HOMA-IR.

Associations of increase in P intake with decreases in HOMA-IR and HbA1c are inconclusive in the literature. This may depend on the P range and source (plant or meat) and the body-weight status of the participant (15–20, 41). The presently observed association with a decrease in HbA1c is in line with the Lifelines study (16) considering the increase in P intake, but we did not distinguish plant and animal P. The food tables we used did not enable us to discriminate between P sources, which is a limitation to the present analyses. An inverse association between HOMA-IR and P intake usually is explained by the glycemia-lowering effect of P intake, or by reduced insulinotropic properties, or by weight loss in participants with overweight (17–20). In the latter, HOMA-IR is associated with elevated plasma branched-chain amino acids that decrease during weight loss (20), which may explain the weight loss–induced increase in insulin sensitivity. In healthy subjects, a high-protein diet appeared to increase HOMA-IR in part through elevated plasma amino acid concentrations, inhibiting muscle glucose transport and/or glucose phosphorylation resulting in reduced glycogen synthesis (20).

TABLE 4 Associations of changes in the independent variables EI_{Est}, EI_{Rep}, P_{Est}, and P_{Rep} with changes in the dependent variables BMI, HOMA-IR, and HbA1c in the whole group of participants[1]

Variables (independent, dependent)	Overall estimates		
	Estimate	95% CI (Low, High)	*P*
EI_{Est}, MJ/d			
BMI, kg/m^2	1.150	1.088, 1.227	<0.001
HOMA-IR	0.197	−0.002, 3.967	0.15
HbA1c, mmol/mol	−0.051	−0.109, 0.010	0.07
EI_{Rep}, MJ/d			
BMI, kg/m^2	0.114	0.074, 0.153	<0.001
HOMA-IR	0.010	−0.005, 0.026	0.09
HbA1c, mmol/mol	−0.012	−0.038, 0.014	0.17
P_{Est}, g/kg			
BMI, kg/m^2	−0.930	−1.230, −0.630	<0.001
HOMA-IR	0.002	−0.005, 0.080	0.80
HbA1c, mmol/mol	−0.400	−0.730, −0.080	0.02
P_{Rep}, g/kg			
BMI, kg/m^2	−1.300	−1.660, −0.950	<0.001
HOMA-IR	0.029	−0.080, 0.138	0.23
HbA1c, mmol/mol	−0.410	−0.770, −0.090	0.01
P_{Est}, En%			
BMI, kg/m^2	−0.002	−0.009, 0.005	0.05
HOMA-IR	−0.006	−0.015, 0.003	0.16
HbA1c, mmol/mol	−0.012	−0.038, 0.014	0.26
P_{Rep}, En%			
BMI, kg/m^2	−0.011	−0.020, −0.002	0.02
HOMA-IR	−0.007	−0.014, 0.001	0.07
HbA1c, mmol/mol	−0.016	−0.024, 0.001	0.06

[1]Linear mixed models including a participant-level random intercept, a repeated subject-by-study center component, and fixed effects for time, age, sex, and BMI when applicable were used to assess associations of changes in EI_{Rep} and EI_{Est}, P_{Rep} and P_{Est} (g/kg), and P_{Rep} and P_{Est} (En%) with changes in BMI, HOMA-IR, and HbA1c. Interaction terms with time were removed from the model, if nonsignificant. $P < 0.05$ indicates statistical significance. Estimates indicate the change in the dependent variable with a 1-unit change in the independent variable. For example: 1 MJ/d change in EI_{Est} is associated with a change of 1.15 kg/m^2 in BMI. EI_{Est}, estimated energy intake; EI_{Rep}, reported energy intake; En%, energy percentage; HbA1c, glycated hemoglobin; P_{Est}, estimated protein intake; P_{Rep}, reported protein intake.

The observation of increases in P_{Est} and P_{Rep} (g/kg and En%) being associated with a decrease in BMI is in line with previous observations, and has been explained by dietary P inducing sustained satiety, energy expenditure, and sparing body FFM despite weight reduction, thus preventing weight cycling (10–15). However, the decrease in BMI may be associated with not only the observed increases in P_{Est} and P_{Rep}, but also the decrease in nonprotein intake. Owing to the lack of biomarkers, we were not able to distinguish the individual contributions of the other macronutrients (21, 42). A previous study, uncoupling high P and low CHO intake, showed that weight-loss maintenance was primarily due to an increase in dietary P, and not to a reduction of CHO intake (12).

The observed lack of significant independent associations of increases in En% P_{Est} and En% P_{Rep}, and decreases in EI_{Est} and EI_{Rep}, with decreases in HOMA-IR and HbA1c may partly be due to taking changes in BMI into account, by including updated BMI at each time point as a fixed-effect level in the mixed-model analyses. In addition, En% P_{Est} and En% P_{Rep} were corrected for EI_{Est} and EI_{Rep}, showing that associations with changes in En% P were largely affected by changes in EI. The association of an increase in En% P_{Rep} but only an increase in En% P_{Est} as a trend with a decrease in BMI may be due to the ME of En% P_{Rep} being affected by the ME of EI_{Rep}.

The observed ME of EI_{Rep} and its association with BMI, and of P_{Rep} (g/kg), mainly at the start and at the end of the study, confirm earlier observations (21–29, 42), yet now they have been observed over a longer period of time. The ME of the nonprotein intake is in line with a previous study that reported that especially underreported F intake contributes to underreported EI_{Rep}. Reported dietary intakes in the HP and MP groups were in line with the dietary instructions. The lower ME of EI in the HP than in the MP group may be explained by the higher P_{Rep} in the HP group. As observed previously, TFEQ-F1 was increased whereas TFEQ-F2 and TFEQ-F3 were decreased during weight-loss maintenance, indicating a positive attitude toward dieting (10–14, 34, 35). Changes in BMI and TFEQ-F1 were positively associated with a change in ME of EI, whereas changes in TFEQ-F2 and TFEQ-F3 were inversely associated with a change in ME of EI, implying that a positive attitude toward dieting is associated with an increase in ME.

The clinical relevance of the present study lies in showing that a moderate increase in P intake and decrease in EI were independently associated with moderate decreases in HbA1c and BMI over 36 mo, whereas the main PREVIEW study showed that a reduction in BMI was associated with a reduction in HOMA-IR (4). This may contribute to reducing the incidence of T2D in people with overweight or obesity and prediabetes, by informing

on potential dietary strategies for T2D prevention. However, the larger En% P_{Rep} than P_{Est}, the association between P_{Rep} and P_{Est}, and the larger estimate with P_{Rep} than with P_{Est} of associations with changes in BMI suggest that higher En% P_{Est} would be necessary, achieved by a higher P_{Est} (g/kg) and a considerably lower EI_{Est}, in order to establish stronger associations with reductions in BMI (10, 13–15) and concurrently in HOMA-IR.

Given the range in characteristics of the participants regarding age, sex, and environment including geography, the outcomes are generalizable for individuals with overweight, obesity, postobesity, and with present or previous prediabetes.

Our estimates of EIs have strengths and limitations. Doubly labeled water–measured energy expenditure at each time point is the gold standard for estimating EI when participants are in energy balance and weight stable (42). However, this approach was not applied in the present study. Instead, we actually measured changes in body composition at each time point in order to calculate BMR, as well as changes in PA at each time point to calculate PAL, which is a strength of the present approach (29, 32, 42). The estimated BMR was in line with the observed BMR during a respiratory chamber study in a representative sample of the participants by the end of the intervention (43). The translation of counts to PAL was based upon the studies by Ekelund et al. (39) and Freedson et al. (40) yielding similar outcomes. The outcome of a PAL of ∼1.6 is in line with our previous studies on weight maintenance after weight loss in participants with overweight or obesity (10, 11). The estimate of EI being equal to EE is based upon the assumption of energy balance at the time points of measuring. However, the participants were regaining body weight from week 26 onwards (4). Their 6% weight regain (∼6.1 kg) over 130 wk after 11% weight loss (∼11.2 kg at week 26) (4) was equivalent to a positive energy balance of 6.1 kg × 30 MJ/kg = 183 MJ over 130 wk or 910 d (32), resulting in 183/910 = 201.10 kJ/d. This is within the margin of error of energy balance estimation (32). Further strengths of this study are the longitudinal design, encompassing a large number of participants from 8 different study centers; comprehensive measures of anthropometry, insulin resistance, dietary intake, and PA; and use of biomarkers, not only to confirm differences but mainly to calculate relevant results. A limitation of the present study is that it was designed as an RCT but analyzed as an observational study. A successful RCT design with full compliance would have allowed us to attribute any observed effects to the treatments being compared. The present observational analyses imply that outcomes may be caused by differences between the participants, as is indicated by, e.g., the scores on the TFEQ.

In conclusion, during weight-loss maintenance in adults with prediabetes, an increase in P intake and decrease in EI were not associated with a decrease in HOMA-IR beyond their associations with a decrease in BMI; increases in P_{Est} and P_{Rep} (g/kg) were associated with a decrease in HbA1c. P_{Rep} and EI_{Rep} showed larger changes and stronger associations than P_{Est} and EI_{Est}.

Data availability

Data described in the article, code book, and analytic code will be made available upon request.

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