Dose-Dependent Associations of Dietary Glycemic Index, Glycemic Load, and Fiber With 3-Year Weight Loss Maintenance and Glycemic Status in a High-Risk Population: A Secondary Analysis of the Diabetes Prevention Study PREVIEW

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OBJECTIVE

To examine longitudinal and dose-dependent associations of dietary glycemic index (GI), glycemic load (GL), and fiber with body weight and glycemic status during 3-year weight loss maintenance (WLM) in adults at high risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this secondary analysis we used pooled data from the PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World (PREVIEW) randomized controlled trial, which was designed to test the effects of four diet and physical activity interventions. A total of 1,279 participants with overweight or obesity (age 25–70 years and BMI $\geq$25 kg · m^{-2}) and prediabetes at baseline were included. We used multiadjusted linear mixed models with repeated measurements to assess longitudinal and dose-dependent associations by merging the participants into one group and dividing them into GI, GL, and fiber tertiles, respectively.

RESULTS

In the available-case analysis, each 10-unit increment in GI was associated with a greater regain of weight (0.46 kg · year^{-1}; 95% CI 0.23, 0.68; $P < 0.001$) and increase in HbA_{1c}. Each 20-unit increment in GL was associated with a greater regain of weight (0.49 kg · year^{-1}; 0.24, 0.75; $P < 0.001$) and increase in HbA_{1c}. The associations of GI and GL with HbA_{1c} were independent of weight change. Compared with those in the lowest tertiles, participants in the highest GI and GL tertiles had significantly greater weight regain and increases in HbA_{1c}. Fiber was inversely associated with increases in waist circumference, but the associations with weight regain and glycemic status did not remain robust in different analyses.

CONCLUSIONS

Dietary GI and GL were positively associated with weight regain and deteriorating glycemic status. Stronger evidence on the role of fiber is needed.

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Type 2 diabetes is a global health problem and is related to multiple comorbidities such as cardiovascular disease (CVD) (1). Substantial evidence supports that type 2 diabetes may be largely prevented by management of body weight (BW) and improvement in glucose homeostasis with lifestyle modification (2). Studies have shown effectiveness of various dietary interventions on weight loss (WL) and diabetes prevention (3,4). In particular, low-energy diets (LED) based on total or partial meal replacements have been found to result in rapid WL, exemplified by the findings in PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World (PREVIEW) (5,6). However, weight regain is a common problem after rapid WL, and maintaining WL is a considerable challenge (7).

Diet composition, including the relative contribution of the different macronutrients to total energy intake, may play a role in weight loss maintenance (WLM) and diabetes prevention (8,9). In addition to carbohydrate quantity, carbohydrate quality is of interest (10), but the effect of glycemic index (GI), a marker of carbohydrate glycemic effect (11), and glycemic load (GL), a marker of carbohydrate quality and quantity combined (12), remains controversial. A recent meta-analysis of four randomized controlled trials (RCTs) suggested that there was no difference between low- and high-GI diets in prevention of weight regain, but this result had high heterogeneity (13). For glucose regulation and diabetes incidence, a recent meta-analysis of prospective cohort studies indicated that dietary GI and GL were important predictors of type 2 diabetes development worldwide (14). Nonetheless, most previous clinical trials reporting the effect of GI and GL on WLM and glycemic status did not exceed 1 year (15–17) and, hence, were potentially too short given the longer time frame over which the disease manifests itself. Moreover, few observational studies focused on long-term WLM and glycemic status, especially after diet-induced WL.

A recent meta-analysis of prospective and clinical studies suggested that dietary fiber could be a better marker than GI and GL of potential weight control efficacy and risk of noncommunicable diseases including diabetes (10). Unfortunately, evidence based on large-scale observational studies regarding long-term effects of fiber on WLM is scarce. Only one secondary analysis of a long-term RCT explored the association of fiber with 30-month WLM (18), but as with most previous studies on GI and GL, it was conducted in individuals who had excessive BW but were otherwise healthy. It is unclear whether an association would be observed in adults with higher risk of developing type 2 diabetes.

Therefore, the aim of the current study was to investigate longitudinal and dose-dependent associations of GI, GL, and fiber with 3-year WLM and glycemic status after rapid diet-induced WL in adults at high risk of type 2 diabetes in PREVIEW, a randomized controlled trial designed to examine the effects of four diet and physical activity (PA) interventions on diabetes prevention.

RESEARCH DESIGN AND METHODS

Study Design

PREVIEW was a long-term, large-scale RCT conducted at eight intervention centers in Denmark, Finland, the Netherlands, the U.K., Spain, Bulgaria, Australia, and New Zealand (19). The study was initially performed to examine the effects and interactions of two diets and two PA programs on the prevention of type 2 diabetes. There were two phases in this study: an 8-week WL phase with a formula LED containing 810 kcal · day^{-1} consumed by all participants (6) and a 148-week WLM intervention phase. The four intervention groups were high-protein, low-GI (HP-LGI) diet (25% of energy [25 E%] from protein, GI $<$50) or moderate protein, moderate GI diet (15 E% protein, GI $>$56) combined with either high- or moderate-intensity PA. The study was approved by the human ethics committees at all intervention centers and was conducted in accord with the latest revision of the Declaration of Helsinki.

The current study is a secondary observational analysis based on the data on WLM (8–156 weeks) of PREVIEW, irrespective of original randomization. The start of WLM (at 8 weeks) was considered the baseline for this analysis. Main outcomes were BW and glycosylated hemoglobin A_{1c} (HbA_{1c}). Other outcomes of interest were fat mass (FM), waist circumference (WC), fasting plasma glucose (FPG), fasting insulin, HOMA of insulin resistance (HOMA-IR), and type 2 diabetes events, information regarding which was collected at 8, 26, 52, 104, and 156 weeks relative to the pre-WL baseline and cardiovascular events self-reported by participants over the course of the study. Self-reported dietary intakes, 24-h urinary nitrogen or urea level, and information regarding PA were collected at 26, 52, 104, and 156 weeks.

Study Population

Participants were recruited from June 2013 to April 2015. The main inclusion criteria were age 25–70 years, overweight or obesity, and prediabetes (19). Overweight and obesity were defined as BMI 25–29.9 kg · m^{-2} and $\geq$30 kg · m^{-2}, respectively. Prediabetes was evaluated in accordance with American Diabetes Association criteria (20). Eligible

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participants provided written informed consent and were enrolled into the study. Those who lost ≥8% of initial BW and were not diagnosed with diabetes after WL were allowed to enter the WLM phase. Both complete-case and available-case analyses were conducted in this study. The complete-case and available-case analyses involved participants who finished all phases and those who commenced the WLM phase, respectively. Participants with unavailable dietary GI and fiber data at 26 weeks and/or implausible energy intake data (<600 or >3,500 kcal · day^{-1} for women and <800 or >4,200 kcal · day^{-1} for men) (21) were excluded.

Dietary Assessment

Dietary intake was assessed by food diaries on four consecutive days including one weekend day. Participants were instructed how to use scales and conventional household measurements and to record the foods consumed in detail. Food diaries were collected and in the case of lack of clarity were discussed and, when possible, checked with the participant to clarify any ambiguities. All data from food diaries were entered into national nutrient analysis software (Supplementary Material). The GI of each food was obtained with use of GI databases (Supplementary Table 1). Regarding mixed meals and some recipes, the weighted mean GI of the components was used (22). Total GI and GL were calculated according to the formula of van Woudenbergh et al. (23):

$$\text{Dietary GI} = \frac{\sum_{i=1}^{n}(\text{GI}_i \times \text{carbohydrates}_i)}{\sum_{i=1}^{n}(\text{carbohydrates}_i)}$$

$$\text{Dietary GL} = \frac{\sum_{i=1}^{n}(\text{GI}_i \times \text{carbohydrates}_i)}{100}$$

Protein intake was also objectively assessed by 24-h urine collection (nitrogen or urea) with the following formula: dietary protein (g · day^{-1}) = [24-h urinary nitrogen (g) / 0.81] × 6.25, and conversion factor urea × 0.4664 = nitrogen (24,25).

Assessment of Anthropometric Outcomes and Body Composition

BW was measured when participants were in a fasting state with an empty bladder and wearing light clothing or underwear. FM was measured by DEXA, bioelectrical impedance, or BOD POD at different intervention centers. WC was measured when participants were at the end of breath expiration, at the midway point between the bottom of the rib cage and the top of the iliac crest.

Assessment of Markers of Glycemic Status

Fasting (>10 h) blood samples were drawn from an antecubital vein and, after processing, were frozen at −80°C and transported to the Finnish Institute for Health and Welfare for determination of FPG, HbA_{1c}, and fasting insulin. HOMA-IR was calculated with the following formula: HOMA-IR = (fasting insulin in mU · L^{-1} × FPG in mmol · L^{-1})/22.5. The diagnosis of type 2 diabetes and CVD incidence is described in Supplementary Material.

Covariates Assessment

Information on age, sex, and ethnicity was collected with self-administered questionnaires at week 0. Stature was measured at week 0. BMI was calculated as BW in kilograms divided by the square of height in meters. PA was assessed by 7-day accelerometry (ActiSleep+, ActiGraph, LLC, Pensacola, FL) in order to obtain mean activity counts, expressed in counts · min^{-1} over valid wear time.

Statistical Analysis

Descriptive statistics were used to summarize characteristics for participants. Further information is described in Supplementary Material.

Participants were merged into one group for assessment of longitudinal associations among GI, GL, fiber, and yearly changes in BW, body composition, and markers of glycemic status during WLM. Yearly changes were calculated as changes in outcomes from 8 to 26, 52, 104, and 156 weeks divided by corresponding changes in years. For best representation of the long-term dietary and PA patterns of participants during WLM, a cumulative average method (21) based on all available measurements of self-reported dietary intake, protein intake from urinary nitrogen, and accelerometry-measured PA was used in all analyses. Cumulative average GI, GL, fiber, and other dietary components and PA from 8 to 26, 52, 104, and 156 weeks were calculated. PA and 26-week diet were used to estimate the average PA and dietary intake from 8 to 26 weeks (Supplementary Material and Supplementary Table 2).

Linear mixed models with repeated measurements were used, assuming that missing data occurred at random. Model 1 was adjusted for age (continuous), sex (categorical), ethnicity (categorical [Caucasian, Asian, Black, Arabic, Hispanic, or other]), weight-related or glycemic outcomes at 8 weeks (continuous), BMI at 8 weeks (continuous), and time (categorical) as fixed effects and intervention center (categorical) and participant identifier as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured PA (continuous) and self-reported energy intake (kcal · day^{-1}) and dietary components (continuous) including percentage of energy from fat, protein, fiber or carbohydrate, and alcohol (continuous, all in E%) as fixed effects. Model 3 was additionally adjusted for time-varying yearly weight change. A stratified analysis was conducted to examine potential effect modification by sex, age, ethnicity, BMI at 8 weeks, PA, and dietary components.

All participants with available dietary data, irrespective of whether they completed the study, were divided into tertiles by cumulative average GI, GL, and fiber at each interval from 26 weeks (Supplementary Table 2). Dose-dependent associations of GI, GL, and fiber with BW and HbA_{1c} were assessed with use of linear mixed models with repeated measurements adjusted for the covariates in model 2 or 3. For markers of glycemic status, the models were additionally adjusted for time-varying weight change. Differences among three tertiles or between the highest and lowest tertiles in changes in BW and HbA_{1c} were examined. Post hoc analyses with multiple comparisons with Bonferroni adjustment or pairwise comparisons were performed to compare tertiles at each time point where appropriate.

Assessment of the association of GI, GL, and fiber with type 2 diabetes or CVD incidence is described in Supplementary Material.

We performed sensitivity analyses by *1*) replacing self-reported protein intake

(E%) with protein intake from urinary nitrogen (g · day^{-1}), *2*) further adjusting for intervention group as fixed effect, and *3*) assuming that data were not missing at random (26) (results were reported if they were modified). All data analyses were performed by IBM SPSS, version 26.0 (SPSS, Chicago, IL). Statistical significance was set at a two-tailed *P* value of <0.05.

RESULTS

The flow of participants is shown in Supplementary Fig. 1. A total of 1,857 participants entered the WLM phase. Of these, 1,279 (4,033–4,130 observations of main outcomes) had available dietary GI and fiber data and plausible energy intake data and were included in the available-case analysis. Of these, 43 and 22 developed type 2 diabetes and CVD, respectively. A total of 847 (3,268–3,344 observations) were included in the complete-case analysis. The median age of the 1,279 participants (66.5% women) was 56 years (range 25–70) (Table 1) and the median values for BW and BMI were 83.0 kg (25th, 75th percentiles 74.1, 94.4) and 29.2 kg · m^{-2} (26.6, 32.8), respectively, at 8 weeks. Mean ± SD HbA_{1c} was 5.3% ± 0.3% (34.6 ± 3.1 mmol · mol^{-1}) at 8 weeks and GI 53.5 ± 8.2, GL 90.5 ± 35.6, and fiber intake 22.6 ± 8.2 g · day^{-1} at 26 weeks. On average, compared with noncompleters, completers were older and had lower BW, BMI, FM, WC, FPG, fasting insulin, and HOMA-IR and higher energy intake, GI, GL, and fiber intake at 8 or 26 weeks.

Figure 1 shows the associations of cumulative average GI with yearly weight regain and changes in markers of glycemic status during WLM. In model 2, GI was positively associated with regains in BW and FM and increases in HbA_{1c}, fasting insulin, and HOMA-IR in both the complete-case and available-case analyses. Only the association with HbA_{1c} remained significant after adjustment for weight change. Some of the associations were weaker in older participants and those with greater PA volume and alcohol intake, whereas there were no differences in sex (Supplementary Fig. 2). In the available-case analysis, there were significant changes in BW and HbA_{1c} at multiple time points among the GI tertiles (Fig. 2*A* and *B*). Specifically, compared with those in the lowest

Table 1—Characteristics of participants at the start of WLM (8 weeks) or at 26 weeks (diet and lifestyle outcomes)

	All participants‡	Completers	Noncompleters	*P*
N	1,279	847	432	—
Sociodemographics*				
Women, *n* (%)	851 (66.5)	550 (64.9)	301 (69.7)	0.089
Age (years)	56 (45, 63)	57 (48, 63)	53 (43, 61)	<0.001
Height (m)	1.68 ± 0.09	1.68 ± 0.09	1.67 ± 0.09	0.057
Ethnicity, *n* (%)				0.016
Caucasian	1,158 (90.5)	780 (92.1)	378 (87.5)	—
Asian	29 (2.3)	19 (2.2)	10 (2.3)	—
Black	19 (1.5)	13 (1.5)	6 (1.4)	—
Arabic	4 (0.3)	3 (0.4)	1 (0.2)	—
Hispanic	22 (1.7)	12 (1.4)	10 (2.3)	—
Other	47 (3.7)	20 (2.4)	27 (6.3)	—
Anthropometric outcomes and body composition*				
BW (kg)	83.0 (74.1, 94.4)	81.3 (72.8, 90.7)	86.3 (76.5, 99.7)	<0.001
BMI (kg · m^{-2})	29.2 (26.6, 32.8)	28.4 (26.0, 31.7)	30.8 (28.2, 34.6)	<0.001
FM (kg)	31.1 (24.5, 39.8)	29.6 (23.1, 37.0)	35.2 (28.0, 42.5)	<0.001
WC (cm)	98.7 ± 12.4	97.4 ± 11.9	101.2 ± 13.1	<0.001
Glucose tolerance and blood biochemistry*				
FPG (mmol · L^{-1})	5.7 ± 0.5	5.6 ± 0.5	5.7 ± 0.6	<0.014
HbA_{1c} (%)	5.3 ± 0.3	5.3 ± 0.3	5.3 ± 0.3	0.825
HbA_{1c} (mmol · mol^{-1})	34.6 ± 3.1	34.5 ± 3.1	34.8 ± 3.2	0.893
Fasting insulin (mU · L^{-1})	6.8 (5.1, 9.5)	6.5 (4.9, 8.9)	7.6 (5.6, 10.4)	<0.001
HOMA-IR	1.7 (1.3, 2.4)	1.6 (1.2, 2.3)	1.9 (1.4, 2.8)	<0.001
Diet and lifestyle outcomes†				
Energy intake from food diary (kcal)	1,648.9 ± 447.6	1,674.1 ± 431.9	1,599.7 ± 473.4	0.005
GI from food diary	53.5 ± 8.2	53.9 ± 8.0	52.8 ± 8.5	0.028
GL from food diary	90.5 ± 35.6	92.5 ± 35.6	86.5 ± 35.5	0.005
Dietary fiber from food diary (g · day^{-1})	22.6 ± 8.2	23.4 ± 8.1	21.2 ± 8.1	<0.001
Dietary fiber from food diary (E%)	2.7 ± 0.8	2.7 ± 0.8	2.6 ± 0.8	0.001
Protein intake from food diary (E%)	21.0 ± 4.6	21.0 ± 4.6	21.1 ± 4.5	0.688
Protein intake from urinary nitrogen (g · day^{-1})	88.9 ± 35.6	89.4 ± 34.8	88.0 ± 37.3	0.518
Carbohydrate intake from food diary (E%)	41.0 ± 8.2	41.1 ± 8.4	40.8 ± 7.9	0.527
Fat intake from food diary (E%)	32.8 ± 6.9	32.5 ± 7.0	33.4 ± 6.7	0.022
PA (counts · min^{-1})	311.6 (248.2, 396.9)	315.1 (255.2, 404.1)	305.2 (228.0, 382.0)	0.022

Data are mean ± SD, median (25th, 75th percentiles), or the number of participants (%). *Data were collected at 8 weeks. †Data were collected at 26 weeks. ‡Participants who entered the WLM phase. Difference between completers and noncompleters in characteristics was examined by *t* test, Wilcoxon nonparametric test, and χ^2 test. *t* test was used for approximately, normally distributed variables; Wilcoxon nonparametric test was used for non–normally distributed variables; and χ^2 test was used for categorical variables.

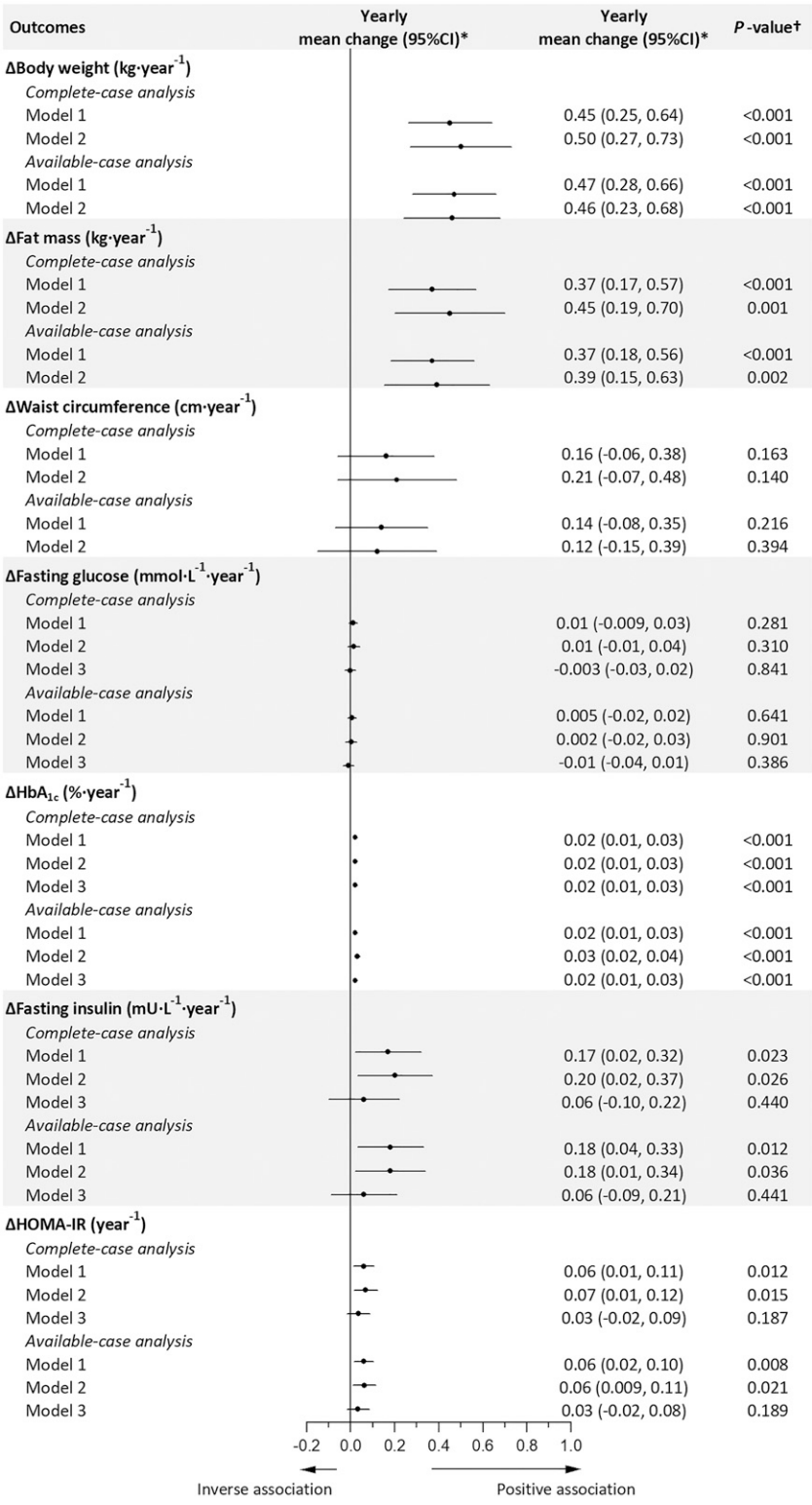

Figure 1—Longitudinal associations of cumulative average GI (each 10 unit) with yearly weight regain and changes in markers of glycemic status during WLM. Model 1 was adjusted for age, sex, ethnicity, anthropometric outcomes or body composition, and markers of glycemic status at 8 weeks, BMI at the start of WLM (8 weeks), and time as fixed effects and intervention center and participant identifier as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured PA and time-varying self-reported energy intake (kcal · day^{-1}) and dietary components including percentage of energy from fat, protein, fiber, and alcohol (all in E%). Model 3 was additionally adjusted for time-varying yearly changes in BW. *Yearly mean change and 95% CI of main effects indicating the increase in anthropometric outcomes or body composition or markers of glycemic status increased per year by 10-unit increment in GI. †*P* values for main effects.

tertile (GI ∼45 [∼52% of participants from the HP-LGI group]), participants in the highest GI tertile (GI ∼61 [∼48% from HP-LGI]) had greater weight regain and increases in HbA_{1c} (Supplementary Fig. 3*A* and *B*).

Figure 3 shows the associations of cumulative average GL with yearly weight regain and changes in markers of glycemic status during WLM. In model 2, GL was positively associated with regains in BW and FM and increase in HbA_{1c} and fasting insulin in the complete-case and available-case analyses. Only the association with HbA_{1c} remained significant to adjustment for weight change. After addition of protein intake from urinary nitrogen as a covariate, WC showed significant association with GL, and the associations of fasting insulin and HbA_{1c} with GL were independent of weight change (data not shown). Some of the associations were modified by age, ethnicity, BMI at 8 weeks, PA, and fat and protein intake, whereas there was no difference in sex (Supplementary Fig. 2). In the available-case analysis, there were significant differences in changes in BW and HbA_{1c} at multiple time points among the GL tertiles (Fig. 2*C* and *D*). Specifically, compared with those in the lowest tertile (GL ∼58), participants in the highest GL tertile (GL ∼125) had greater weight regain and increases in HbA_{1c} (Supplementary Fig. 3*A* and *B*).

Supplementary Fig. 4 shows the associations of cumulative average fiber intake with yearly weight regain and changes in markers of glycemic status during WLM. In model 2, fiber was inversely associated with regains of FM and increases in WC, HbA_{1c}, and fasting insulin in the available-case analysis. Only the association with HbA_{1c} remained significant to adjustment for weight change. After adjustment for protein intake from urinary nitrogen, the association between FM and fiber was lost (data not shown). The associations were not modified by age and sex (Supplementary Fig. 2). There were no differences among the fiber tertiles (Fig. 2*F* and Supplementary Fig. 3*F*) or quartiles or quintiles or sextiles (data not shown) in HbA_{1c} in the available-case analysis.

After multivariable adjustment, there were no associations of GI, GL, or fiber with type 2 diabetes or CVD incidence (Supplementary Table 3).

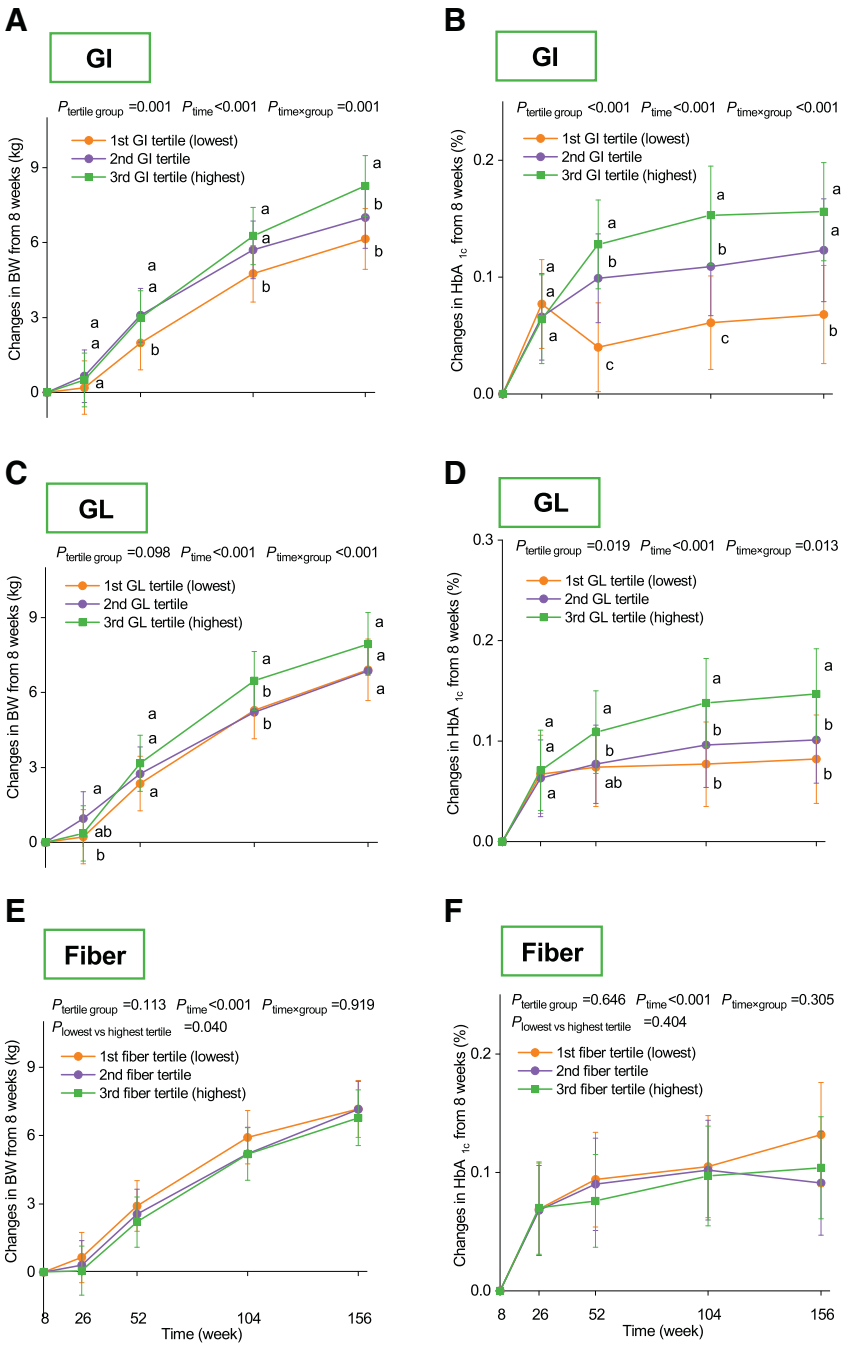

Figure 2—Changes in BW and markers of glycemic status over time during WLM by tertiles of cumulative average GI, GL, and fiber. Values are estimated marginal mean and 95% CI in changes in BW (kg) (*A*) and HbA_{1c} (%) (*B*) by GI tertiles, changes in BW (kg) (*C*) and HbA_{1c} (%) (*D*) by GL tertiles, and changes in BW (kg) (*E*) and HbA_{1c} (%) (*F*) by fiber tertiles. We performed analyses using a linear mixed model with repeated measurements with adjustment for age, sex, ethnicity, anthropometric outcomes or body composition, and markers of glycemic status at the start of WLM (8 weeks); BMI at 8 weeks; and time, time-varying accelerometry-measured PA, and self-reported energy intake (kcal · day^{-1}) and dietary components including percentage of energy from fat, protein, fiber, or carbohydrate, and alcohol (all in E%) as fixed effects and with participant identifier and intervention center as random effects. For markers of glycemic status, the models were additionally adjusted for time-varying weight change. Time-by-tertile group interaction terms were added. Main effects, time effects, and time-by-tertile group interaction were reported. Post hoc analyses with multiple comparisons with Bonferroni adjustment were performed to compare the tertiles at each time point where appropriate. Values with different lowercase letters (a, b, and c) are significantly different ($P < 0.05$).

CONCLUSIONS

In this secondary analysis of individuals with a high risk of type 2 diabetes from a large international, multiethnic cohort, we show that higher cumulative average GI and GL were associated with increases in BW and markers of glycemic status. Specifically, the associations of GI and GL with HbA_{1c} were independent of weight change. Participants in the highest GI and GL tertiles had significantly greater weight regain and increases in HbA_{1c} than those in the lowest tertiles. Greater fiber intake was associated with decreases in WC, whereas the association of fiber with weight regain, FM, and glycemic status did not remain robust in different analyses.

To date, there are few large-scale clinical trials and observational studies focusing on long-term WLM, especially after rapid diet-induced WL. Regarding clinical trials, in the intention-to-treat analysis of the Diet, Obesity, and Genes (Diogenes) study, there was a difference between the high-GI (GI = 63, 51 E% carbohydrate and 20 E% protein) and low-GI (GI = 58, 51 E% carbohydrate and 18 E% protein) groups in weight regain, FM, and WC at 6 months (16) but not the 1-year follow-up (7). The difference in GI may not have been sufficient for detection of an effect on outcomes. By contrast, in our tertile analysis, we observed larger differences between the highest and lowest tertiles of GI (45 vs. 61) and GL (58 vs. 125). Other clinical trials have reported mixed findings on GI, GL, and WL (27). The lack of reliable data on GI of local foods is another limitation. The relative postprandial glycemic response to mixed meals or diets will be affected by many factors in addition to the GI of each meal component. This includes the fat and protein, as well as carbohydrate content (28), meal preparation methods, and serving temperature (29). In the current study and other studies (7,16), GI and GL were calculated based on food composition and GI databases and the outcomes were adjusted for other macronutrients, which may cause bias.

Considering observational studies, previous cohort studies have simply evaluated baseline GI or GL intake and subsequent changes in BW or body composition (30–32). Causal inference is therefore more limited. For instance,

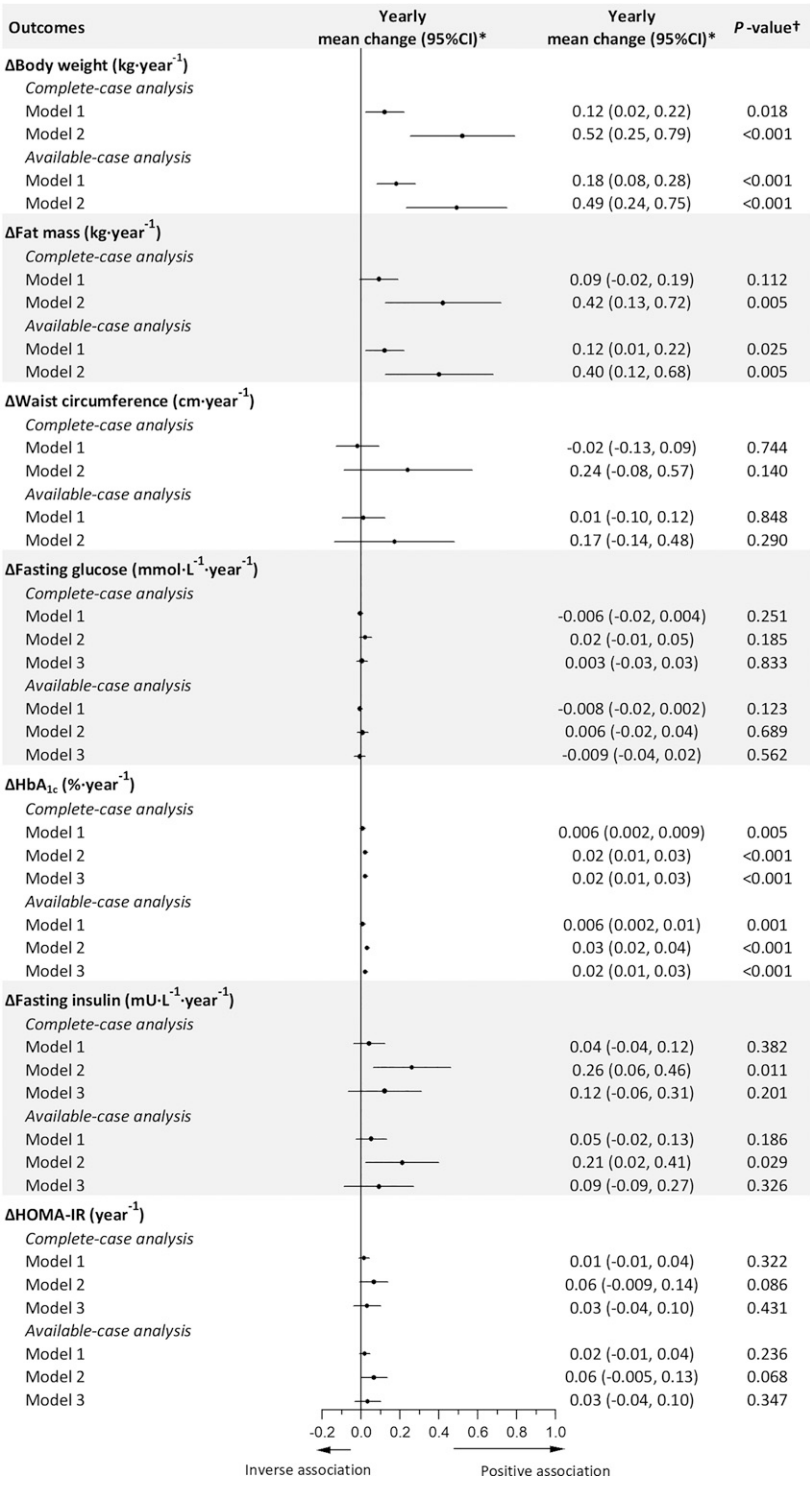

Figure 3—Longitudinal associations of cumulative average GL (each 20 unit) with yearly weight regain and changes in markers of glycemic status during WLM. Analyses were performed with use of a linear mixed model with repeated measurements. Model 1 was adjusted for age, sex, ethnicity, weight- or glycemic status–related outcomes at the start of WLM (8 weeks), BMI at 8 weeks, and time as fixed effects and intervention center and participant identifier as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured PA and time-varying self-reported energy intake (kcal · day^{-1}) and dietary components including intake of fat, protein, fiber, and alcohol (all in E%). Model 3 was additionally adjusted for time-varying yearly changes in BW. *Yearly mean change and 95% CI of main effects indicating the amount of increase in anthropometric outcomes or body composition or markers of glycemic status increased per year by 20-unit increment in GL. †*P* values for main effects.

Salari-Moghaddam et al. (31) reported that dietary GI was positively related to abdominal obesity in women in a cross-sectional study. Hare-Bruun et al. (30) found positive associations between baseline GI and subsequent 6-year changes in BW, percentage body fat, and WC in women. Unlike these studies, we analyzed long-term, updated, cumulative average GI and GL with concurrent BW changes, which may provide new insights into the causally relevant associations.

Our findings are in line with previous observational studies on GI or GL and glucose metabolism, especially HbA_{1c}. Cheng et al. (33) reported that GI and GL were positively associated with HbA_{1c} in 3,918 Chinese without diabetes. In addition, Wang et al. (34) found a positive longitudinal association between change in GI and change in HbA_{1c} in a 1-year intervention trial without a WL phase. That secondary analysis was based on those classified as having Latino ethnicity and having diabetes, whereas PREVIEW participants were mainly of Caucasian (90%) ethnicity with overweight or obesity and prediabetes. In the present analysis, unlike HbA_{1c}, fasting insulin and HOMA-IR did not show significant associations after adjustment for BW change. This may be because HbA_{1c}, a marker reflecting longer-term glycemic status, is more influenced by postprandial glycemia in individuals with prediabetes (as opposed to individuals with type 2 diabetes) and because fasting insulin and HOMA-IR, markers of shorter-term glycemic status, are less disturbed.

In the available-case analysis, we did not find a link between fiber and BW but we found inverse associations between self-reported fiber and WC, which implies that fiber may be more relevant to central obesity. In a secondary, observational analysis in an RCT with 30-month WLM (18) investigators also found no effect of greater fiber intake on weight. Regarding glucose metabolism, the association of fiber intake with glycemic outcomes in the present analysis failed to remain robust after adjustment for weight change or in the tertile analysis. In contrast, in a cross-sectional study it was found that, after adjustment for age, sex, BMI, and other confounders, the odds ratios for poor glycemic control were reduced with

increasing tertiles of fiber intake (35). The casual inference of that study was, however, limited because of its cross-sectional nature. Type of fiber may also be relevant. Different types or sources of fiber, e.g., soluble and insoluble fiber, have different physiological effects. In the primary PREVIEW RCT, participants in the two diet groups were advised not only to select foods from the different food groups in different proportions but also to select different foods from certain food groups for achievement of the differences in percentage of total energy from each macronutrient and GI. This may have resulted in a greater divergence in the types of fiber consumed (and their subsequent functional effects) than would otherwise be expected across the continuum of total fiber intake. Results from large prospective cohort studies have suggested that high insoluble cereal fiber intake may reduce the type 2 diabetes risk, whereas the association with soluble fiber intake is either weak or absent (36). The present analysis focused on total fiber only, so this distinction could not be made. With these factors taken together, the present findings on fiber, WLM, and glucose metabolism should be interpreted with caution.

There are many strengths in the current study. First, we provide new evidence of the associations in question during longer-term WLM, which is more likely to address a lifelong problem, particularly for individuals with obesity. Second, unlike some studies providing standardized meals with fixed caloric content, we determined the associations in a "free-living" context with ad libitum diets. Further, we found that most results, especially regarding GI and GL, from participants who started the WLM were also applicable to completers (who were older and relatively healthier than the available-case population), which implies that selection bias should not be a concern and that the results may be generalizable. Finally, in the main PREVIEW RCT (37), no differences were observed in primary or secondary outcomes between the two diet randomization arms or among the four diet-PA intervention groups. This null result may have occurred because some participants adhered less strictly to their dietary prescriptions and PA protocols, resulting in overlap between arms, especially toward the end. The present analysis merged participants into one group and explored longitudinal associations. In addition, we divided participants into tertiles of GI, GL, and fiber and determined dose-dependent associations and robustness of longitudinal associations.

The current study has several limitations. The GI, GL, and fiber were calculated from self-reported 4-day food diaries. Although food diaries outperform food-frequency questionnaires on estimates of dietary intakes, misreporting is inevitable (38). It is possible that weight regain and dietary misreporting are correlated, which may create bias. Moreover, as food diaries were not collected at the end of the WL phase, we used food intake at 26 weeks to estimate the average food intake from 8 to 26 weeks, which may not be accurate. Finally, GI is a proxy for a certain type of diet, including fruit, vegetables, legumes, berries, and dairy. Although we have correctly adjusted for dietary macronutrient composition, there are several dietary components (e.g., vitamins, minerals, and antioxidants) that we could not adjust for, and, hence, residual and unmeasured confounders may exist. Cigarette smoking has been found to be related to BW (39), and the evidence from epidemiologic studies has demonstrated a clear association between cigarette smoking and increased diabetes risk (40). It is possible that smoking could have affected the results, but this was not measured during WLM and therefore not adjusted for.

In conclusion, this secondary analysis addresses the prevention of weight regain after a period of rapid WL in a large international population with a high risk of diabetes. It may have implications for the lifelong problem of incremental weight gain creep and may provide new evidence that the quality and quantity of carbohydrates are linked to longer-term WLM and glycemic status. Due to the observational nature of the study and residual and unmeasured confounders, the findings should be interpreted with caution. Future research based on large-scale, long-term RCTs should investigate whether diets with lower GI or GL can be recommended to individuals with overweight or obesity and higher risk of diabetes.

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Duality of Interest. T.M.L. is an advisor for "Sense" diet program. J.B.-M. is President and Director of the Glycemic Index Foundation, oversees a GI testing service at the University of Sydney, and is a co-author of books about diet and diabetes. She is also a member of the Scientific Advisory Board of ZOE Global. S.D.P. was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. I.A.M. is a member of the Mars Scientific Advisory Council, member of the Mars Europe Nutrition Advisory Board, and Scientific Adviser to the Waltham Centre for Pet Nutrition. He was also a member of the Nestle Research Scientific Advisory Board and of the Novozymes Scientific Advisory Board. He is now Scientific Director of the Nestle Institute of Health Sciences. A.R. has received honorariums from Unilever and the International Sweeteners Association. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. The PREVIEW project was designed by M.F., M.S.W.-P., J.B-.M., A.R., Wolfgang Schlicht (W.S.), and Edith Feskens. The protocol for the PREVIEW adult intervention study was written by T.M.L., M.F., and A.R. W.S., S.D.P., G.S., S.H., J.A.M., I.A.M., and M.S.W.-P. were involved in developing the study design. L.M.V. designed the eight postprandial studies to obtain the GI and GL values and led the compilation work for the estimated GI and GL databases of the Fineli database used in the study. R.Z., T.M.L., J.B-.M., and A.R. conceived the research question of this secondary analysis. R.Z., T.M.L., J.B-.M., and A.R. designed the analysis plan. R.Z. performed the data analysis. C.R. provided statistical supervision. R.Z., J.B-.M., and A.R. formed the writing group. R.Z. drafted the manuscript with supervision from A.R. and J.B-.M. All authors contributed to the implementation of the experimental trial and contributed to analysis and interpretation of the data. All authors contributed to critical revision of the manuscript for important intellectual content. All authors agreed that the accuracy and integrity of the work have been appropriately investigated and resolved, and all approved the final version of the manuscript. A.R. attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. A.R. and R.Z. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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