# 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

Zhu, Ruixin

2021-07

Zhu , R , Larsen , T M , Fogelholm , M , Poppitt , S D , Vestentoft , P S , Silvestre , M P , Jalo , E , Navas-Carretero , S , Huttunen-Lenz , M , Taylor , M A , Stratton , G , Swindell , N , Drummen , M , Adam , T C , Ritz , C , Sundvall , J , Valsta , L M , Muirhead , R , Brodie , S , Handjieva-Darlenska , T , Handjiev , S , Martinez , J A , Macdonald , I A , Westerterp-Plantenga , M S , Brand-Miller , J & Raben , A 2021 , ' 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 ' , Diabetes Care , vol. 44 , no. 7 , pp. 1672-1681 . https://doi.org/10.2337/dc2(

http://hdl.handle.net/10138/354526
https://doi.org/10.2337/dc20-3092

## Title Page

# 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 PREVIEW diabetes prevention study

Running title: GI, GL, fiber and weight and glucose control

Authors: Ruixin Zhu, Msc[1]; Thomas M. Larsen, PhD[1]; Mikael Fogelholm, PhD[2]; Sally D. Poppitt, PhD[3]; Pia S. Vestentoft, PhD[1]; Marta P. Silvestre, PhD[3,4]; Elli Jalo, MSc[2]; Santiago Navas-Carretero, PhD[5,6,7]; Maija Huttunen-Lenz, PhD[8]; Moira A. Taylor, PhD[9]; Gareth Stratton, PhD[10]; Nils Swindell, PhD[10]; Mathijs Drummen, PhD[11]; Tanja C. Adam, PhD[11]; Christian Ritz, PhD[1]; Jouko Sundvall, MSc[12]; Liisa M. Valsta, PhD[13]; Roslyn Muirhead, PhD[14]; Shannon Brodie, MSc[14]; Teodora Handjieva-Darlenska, PhD[15]; Svetoslav Handjiev, PhD[15]; J. Alfredo Martinez, PhD[5,6,7]; Ian A. Macdonald, PhD[16]; Margriet S. Westerterp-Plantenga, PhD[11]; Jennie Brand-Miller, PhD[14]; Anne Raben, PhD[1,17]

[1]Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark

[2]Department of Food and Nutrition, University of Helsinki, Helsinki, Finland

[3]Human Nutrition Unit, School of Biological Sciences, Department of Medicine, University of Auckland, New Zealand

[4]CINTESIS, NOVA Medical School, NMS, Universidade Nova de Lisboa, Lisboa, Portugal

[5]Department of Nutrition, University of Navarra, Pamplona, Spain

[6]CIBER obn, Instituto de Salud Carlos III, Madrid, Spain

[7]Precision Nutrition and Cardiometabolic Health Program. IMDEA-Food Institute (Madrid Institute for Advanced Studies), CEI UAM + CSIC, Madrid, Spain

[8]Institute for Nursing Science, University of Education Schwäbisch Gmünd, Germany

[9]Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, Queen's Medical Centre, Nottingham, UK

[10]Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre, Swansea University, Swansea, UK

[11]Department of Nutrition and Movement Sciences, NUTRIM, School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

[12]Department of Government Services, Forensic Toxicology Unit, Biochemistry Laboratory, Finnish Institute for Health and Welfare, Helsinki, Finland

[13]Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland

[14]School of Life and Environmental Sciences and Charles Perkins Centre, the University of Sydney, Sydney, Australia

[15]Department of Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria

[16]Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, Queen's Medical Centre, MRC/ARUK Centre for Musculoskeletal Ageing Research, ARUK Centre for Sport, Exercise and Osteoarthritis, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham, UK

[17]Steno Diabetes Center Copenhagen, Gentofte, Denmark

Corresponding author: Anne Raben

Current address: Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Rolighedsvej 30, 1958 Frederiksberg C, Denmark.

Phone/Fax: +45 21 30 69 12

E-mail: ara@nexs.ku.dk

Clinical trial reg. no. NCT01777893, clinicaltrials.gov.

Word count-abstract: 250

Word count-main text: 4,000

Number of tables and figures: 1 table and 3 figures in main text; 3 tables and 4 figures in Online-Only Supplemental Material

References: 40

**ABSTRACT**

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 high-risk adults.

RESEARCH DESIGN AND METHODS

This secondary analysis used pooled data from the PREVIEW randomized controlled trial, which was designed to test the effects of four diet and physical activity interventions. 1,279 participants with overweight or obesity (aged 25–70 years; BMI≥25 $kg \cdot m^{-2}$) and pre-diabetes at baseline were included. Multi-adjusted linear mixed models with repeated measurements were used 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 and complete-case analyses, each 10-unit increment in GI was associated with a greater regain of weight (0.46 $kg \cdot year^{-1}$; 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 $kg \cdot year^{-1}$; 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 higher 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.

Type 2 diabetes is a global health problem and is related to multiple comorbidities such as cardiovascular disease (1). Substantial evidence supports that type 2 diabetes may be largely prevented by managing body weight (BW) and improving glucose homeostasis by 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 the PREVIEW study (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). As well as carbohydrate quantity, carbohydrate quality is also of interest (10), but the effect of GI, a marker of carbohydrate glycemic effect (11) and GL, a marker combining carbohydrate quality and quantity (12), remains controversial. A recent meta-analysis of four randomized controlled trials (RCT) 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 one year (15-17), hence 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 non-communicable 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 with excessive BW, but 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 present 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 high-risk adults in the PREVIEW study, a randomized controlled trial designed to examine the effects of four diet and physical activity interventions on diabetes prevention.

## RESEARCH DESIGN AND METHODS

### Study Design

The PREVIEW study 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 physical activity (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 diet (HP-LGI; 25 E% 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 followed the latest revision of the Declaration of Helsinki.

The present study is a secondary observational analysis based on the data on WLM (8–156 weeks) of the PREVIEW study, 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, homeostatic model assessment of insulin resistance (HOMA-IR), and type 2 diabetes events 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, and 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, with overweight or obesity, and pre-diabetes (19). Overweight and obesity were defined as BMI 25–29.9 kg·m$^{-2}$ and BMI≥30 kg·m$^{-2}$, respectively. Pre-diabetes was

evaluated in accordance with American Diabetes Association (ADA) criteria (20). Eligible 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 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 unclear cases 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 (Supplemental Materials). The GI of each food was obtained using 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 van Woudenbergh et al. (23):

$$Dietary\ GI = \frac{\sum_{i=1}^{n}(GI_i \times carbohydrates_i)}{\sum_{i=1}^{n}(carbohydrates_i)}$$

$$Dietary\ GL = \frac{\sum_{i=1}^{n}(GI_i \times carbohydrates_i)}{100}$$

Protein intake was also objectively assessed by 24-h urine collection (nitrogen or urea) with the following formula: dietary protein ($g \cdot day^{-1}$)=[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**

Body weight was measured when participants were in a fasting state with an empty bladder and wearing light clothing or underwear. FM was measured by dual X ray absorptiometry or 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 ℃ and transported to the Finnish Institute for Health and Welfare in Helsinki for determination of FPG, $HbA_{1c}$, and fasting insulin. HOMA-IR was calculated using the following formula: HOMA-IR=(fasting insulin in $mU \cdot L^{-1}$×FPG in $mmol \cdot L^{-1}$)/22.5. The diagnosis of type 2 diabetes and cardiovascular disease (CVD) incidence is described in Supplementary Materials.

**Covariates Assessment**

Age, sex, and ethnicity were collected using self-administered questionnaires at week 0. Stature was measured at week 0. BMI was calculated as BW in kg divided by height in $m^2$. 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 Materials.

Participants were merged into one group to assess longitudinal associations between 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. To best represent 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. 26-week diet and PA were used to estimate the average dietary intake and PA from 8 to 26 weeks (Supplementary Materials 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-ID as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured PA (continuous) and self-reported energy intake ($kcal \cdot day^{-1}$) 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 using 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 Gl, GL, and fiber with type 2 diabetes or CVD incidence is described in Supplementary Materials.

We did sensitivity analyses by: 1) replacing self-reported protein intake (E%) with protein intake from urinary nitrogen ($g \cdot day^{-1}$); 2) further adjusting for intervention group as fixed effect; 3) assuming that data were not missing at random (26) (results were reported if they were modified). All data analyses were performed by IBM Statistical Package for the Social Sciences v26.0 (SPSS, Chicago, IL). Statistical significance was set at a 2-tailed *P* values 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 (range: 25–70) years (Table 3) and the median ($25^{th}$, $75^{th}$ percentiles) values were 83.0 (74.1, 94.4) kg for BW and 29.2 (26.6, 32.8) $kg \cdot m^{-2}$ for BMI at 8 weeks. The mean±standard deviation values were 5.3%±0.3% (34.6±3.1 $mmol \cdot mol^{-1}$) for $HbA_{1c}$ at 8 weeks and 53.5±8.2 for GI, 90.5±35.6 for GL, and 22.6±8.2 $g \cdot day^{-1}$ for fiber at 26 weeks. Compared with non-completers, 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.

Fig. 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 higher 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. 2A and B). Specifically, compared with those in the lowest tertile (GI~45; ~52% of participants from the HP-LGI group), participants in the highest GI tertile (GI~61; ~48% from HP-LGI) had higher weight regain and increases in $HbA_{1c}$ (Supplementary Fig. 3A and B).

Fig. 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 adding protein intake from urinary nitrogen as a covariate, WC showed significant association with GL and the associations of fasting insulin, and $HbA_{1c}$ and 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. 2C and D). Specifically, compared with those in the lowest tertile (GL~58), participants in the highest GL tertile (GL~125) had higher weight regain and increases in $HbA_{1c}$ (Supplementary Fig. 3A 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 adjusting 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. 2F and Supplementary Fig. 3F) 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, and fiber with type 2 diabetes or CVD incidence (Supplementary Table 3).

## CONCLUSIONS

In this secondary analysis of individuals with a high risk of type 2 diabetes from a large international, multi-ethnic 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 higher weight regain and increases in $HbA_{1c}$ than

those in the lowest tertiles. Higher 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 DIOGenes study, there was a difference between the high (GI=63, 51 E% carbohydrate and 20 E% protein) and low GI groups (GI=58, 51 E% carbohydrate and 18 E% protein) 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 to detect 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 components. This includes the fat and protein, as well as carbohydrate content (28), meal preparation methods, and serving temperature (29). In the present 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, 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-y changes in BW, percentage body fat, and waist circumference 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 non-diabetic Chinese. 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 Latinos ethnicity with diabetes, whereas PREVIEW participants were mainly of Caucasians (90%) ethnicity with overweight or obesity and pre-diabetes. In the present analysis, unlike $HbA_{1c}$, fasting insulin and HOMA-IR did not show significant associations after adjusting 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 pre-diabetes (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. A secondary, observational analysis in an RCT with 30-month WLM (18) also found no effect of higher fiber intake on weight. Regarding glucose

metabolism, the association of fiber intake with glycemic outcomes in the present analysis failed to remain robust after adjusting for weight change or in the tertile analysis. In contrast, a cross-sectional study found that, after adjusting 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 eg, 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, in order to achieve the differences in percentage of total energy from each macronutrient and GI. This may have resulted in a greater divergence in the types of fibre consumed (and their subsequent functional effects) than would otherwise be expected, across the continuum of total fibre 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. Taken together, the present findings on fiber and 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 life-long 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 and 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 towards 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 present 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) 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 life-long problem of incremental weight gain creep and may provide new evidence that the quality and quantity of carbohydrate are linked to longer-term WLM and glycemic status. The observational nature and residual and unmeasured confounders mean that 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, obesity and higher risk of diabetes.

**Acknowledgments.** The PREVIEW consortium would like to thank all study participants at every intervention center for their time and commitment and all scientists, advisors, and students for their dedication and contributions to the study. A full list of investigators of the PREVIEW study is available in Supplementary Materials, in addition to the list below. We would like to thank Louise Dye (chairman of the Scientific Advisory Board, SAB), University of Leeds, UK, Richard Atkinson (Ethical Officer of the SAB), Virginia Commonwealth University, USA, and medical expert and consultant Stephen Colagiuri (University of Sydney, Australia). Meyers Madhus A/S is acknowledged for providing

training and producing the two cooking books. Furthermore, we gratefully thank the research staff from each center. From University of Copenhagen (Denmark): Laura Pastor-Sanz, Grith Møller, Lone Vestergaard Nielsen, Kasper Nowak, Arne Astrup, Finn Sandø-Pedersen, Morten Bo Johansen, Ulla Skovbæch Pedersen, Maria Roed Andersen, Marianne Juhl Hansen, Jane Jørgensen, Sofie Skov Frost, Lene Stevner. From University of Helsinki (Finland): Heikki Tikkanen, Saara Kettunen, Tiia Kunnas, Sanna Ritola, Laura Korpipää, Heini Hyvärinen, Karoliina Himanen, Tiina Pellinen, Elina Malkamäki, Heidi Jokinen, Pauliina Kokkonen, Liisi Korhonen, Jaana Valkeapää, Heli Pikkarainen, Martta Nieminen, Tuulia Ingman, Pihla Mäkinen, and Sonja Toijonen. From University of Nottingham (the U.K.): Clare Randa ll, Nicky Gilbert, Shelley Archer, Sally Maitland, Melanie Marshall, Cheryl Percival, Jakki Pritchard, Laura Helm and Peter Mansell. From University of Navarra (Spain): Blanca Martinez de Morentin, Maria Hernandez Ruiz de Eguilaz, Salome Perez Diez, Veronica Ciaurriz, Angels Batlle, Maria Jose Cobo. From Medical University of Sofia (Bulgaria): Georgi Bogdanov, Pavlina Gateva, Rossica Metodieva, Galia Dobrevska. From Swansea University (the U.K.): Kelly Mackintosh, Melitta McNarry, Jeff Stephens, Gareth Dunseath, Steve Luzio, Masoumeh Minou. From Finnish Institution for Health and Welfare (Finland): Merja Tukiainen, Ira Greinert, Laura Karjalainen, Jukka Lauronen. From University of Sydney (Australia): Fiona Atkinson, Michele Whittle, Jessica Burke, Kylie Simpson, Kimberley Way, Sally McClintock, Radhika Seimon, Shelly Keating, Kirsten Bell, Tania Markovic, Cathy Corry, Evalyn Eldering, Ian Caterson. From University of Auckland (New Zealand): Amy Liu, Anne-Thea McGill, Katya Volkova, Madhavi Bollineni, Clarence

Vivar, Kelly Storey, Niamh Brennan, Audrey Tay, Lindsay Plank, Nicholas Gant, Jon Woodhead.

**Conflicts of Interest.** A.R. has received honorariums from Unilever and the International Sweeteners Association. J.B.-M. is President and Director of the Glycemic Index Foundation, oversees of a glycemic index 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 the Novo Foundation and of ZOE Global. I.A.M. is member of the UK Government Scientific Advisory Committee on Nutrition, Treasurer of the Federation of European Nutrition Societies, Treasurer of the World Obesity Federation, 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. S.D.P. was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. T.M.L. is advisor for "Sense" diet program. No other potential conflicts of interest relevant to this article were reported.

**Funding.** EU framework programme 7 (FP7/2007-2013) grant agreement # 312057. National Health and Medical Research Council - EU Collaborative Grant, AUS 8, ID 1067711). The Glycemic Index Foundation Australia through royalties to the University of Sydney. The New Zealand Health Research Council (grant #14/191) and University of

Auckland Faculty Research Development Fund. The Cambridge Weight Plan© donated all products for the 8-weeks LED period. The Danish Agriculture & Food Council. The Danish Meat and Research Institute. National Institute for Health Research Biomedical Research Centre (NIHR BRC) (UK). Biotechnology and Biological Sciences Research Council (BBSRC) (UK). Engineering and Physical Sciences Research Council (EPSRC) (UK). Nutritics (Dublin) donated all dietary analyses software used by UNOTT. Juho Vainio Foundation (FIN), Academy of Finland (grant numbers: 272376, 314383, 266286, 314135), Finnish Medical Foundation, Gyllenberg Foundation, Novo Nordisk Foundation, Finnish Diabetes Research Foundation, University of Helsinki, Government Research Funds for Helsinki University Hospital (FIN), Jenny and Antti Wihuri Foundation (FIN), Emil Aaltonen Foundation (FIN). China Scholarship Council. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Author Contributions.** The PREVIEW project was designed by A.R., J.B-.M., M.W.-P., M.F., Wolfgang Schlicht (W.S.), and Edith Feskens. The protocol for the PREVIEW adult intervention study was written by M.F., T.M.L., and A.R. M.W.-P., and I.A.M., J.A.M., S.D.P., W.S., G.S., and S.H. were involved in developing the study design. L.M.V. designed the 8 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. T.M.L., R.Z., A.R., and J.B-.M. conceived the research question of this secondary analysis. T.M.L., R.Z., A.R., and J.B-.M. designed the analysis plan. R.Z. performed the data analysis. C.R. provided statistical supervision. R.Z., A.R., and J.B-.M. 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 has 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 of the data in the study and take responsibility for the integrity of the data. R.Z. takes responsibility for the accuracy of the data analysis.

## References


1. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-51.
2. Merlotti C, Morabito A, Pontiroli A. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. Diabetes Obes Metab. 2014;16(8):719-27.
3. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA. 2014;312(9):923-33.
4. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet. 2014;383(9933):1999-2007.
5. Gudzune KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, et al. Efficacy of commercial weight-loss programs: an updated systematic review. Ann Intern Med. 2015;162(7):501-12.
6. Christensen P, Meinert Larsen T, Westerterp-Plantenga M, Macdonald I, Martinez JA, Handjiev S, et al. Men and women respond differently to rapid weight loss: Metabolic outcomes of a multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW). Diabetes Obes Metab. 2018;20(12):2840-51.
7. Aller EE, Larsen TM, Claus H, Lindroos AK, Kafatos A, Pfeiffer A, et al. Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. Int J Obes (Lond). 2014;38(12):1511-7.
8. Ebbeling CB, Feldman HA, Klein GL, Wong JMW, Bielak L, Steltz SK, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. BMJ. 2018;363:k4583.
9. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the

management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr. 2018;72(3):311-25.
10. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 2019;393(10170):434-45.
11. Wolever T. Is glycaemic index (GI) a valid measure of carbohydrate quality? Eur J Clin Nutr. 2013;67(5):522-31.
12. Monro JA, Shaw M. Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: definitions, distinctions, and implications. Am J Clin Nutr. 2008;87(1):237S-43S.
13. van Baak MA, Mariman ECM. Dietary Strategies for Weight Loss Maintenance. Nutrients. 2019;11(8):1916.
14. Livesey G, Taylor R, Livesey HF, Buyken AE, Jenkins DJA, Augustin LSA, et al. Dietary Glycemic Index and Load and the Risk of Type 2 Diabetes: A Systematic Review and Updated Meta-Analyses of Prospective Cohort Studies. Nutrients. 2019;11(6).
15. Sloth B, Due A, Larsen TM, Holst JJ, Heding A, Astrup A. The effect of a high-MUFA, low-glycaemic index diet and a low-fat diet on appetite and glucose metabolism during a 6-month weight maintenance period. Br J Nutr. 2009;101(12):1846-58.
16. Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med. 2010;363(22):2102-13.
17. Philippou E, Neary NM, Chaudhri O, Brynes AE, Dornhorst A, Leeds AR, et al. The effect of dietary glycemic index on weight maintenance in overweight subjects: a pilot study. Obesity. 2009;17(2):396-401.
18. Champagne CM, Broyles ST, Moran LD, Cash KC, Levy EJ, Lin PH, et al. Dietary intakes associated with successful weight loss and maintenance during the Weight Loss Maintenance trial. J Am Diet Assoc. 2011;111(12):1826-35.
19. Fogelholm M, Larsen TM, Westerterp-Plantenga M, Macdonald I, Martinez JA, Boyadjieva N, et al. PREVIEW: prevention of diabetes through lifestyle intervention and population studies in Europe and around the world. design, methods, and baseline participant description of an adult cohort enrolled into a three-year randomised clinical trial. Nutrients. 2017;9(6):632.
20. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2017;40(Suppl 1):S11-S24.
21. Bhupathiraju SN, Tobias DK, Malik VS, Pan A, Hruby A, Manson JE, et al. Glycemic index, glycemic load, and risk of type 2 diabetes: results from 3 large US cohorts and an updated meta-analysis. Am J Clin Nutr. 2014;100(1):218-32.
22. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. Am J Clin Nutr. 2006;83(6):1306-12.
23. van Woudenbergh GJ, Kuijsten A, Sijbrands EJ, Hofman A, Witteman JC, Feskens EJ. Glycemic index and glycemic load and their association with C-reactive protein and incident type 2 diabetes. J Nutr Metab. 2011;2011.
24. Bingham SA. Urine nitrogen as a biomarker for the validation of dietary protein intake. J Nutr. 2003;133(3):921S-4S.
25. Bingham SA. The use of 24-h urine samples and energy expenditure to validate dietary assessments. Am J Clin Nutr. 1994;59(1):227S-31S.

26. Son H, Friedmann E, Thomas SA. Application of pattern mixture models to address missing data in longitudinal data analysis using SPSS. Nurs Res. 2012;61(3):195-203.
27. Esfahani A, Wong JM, Mirrahimi A, Villa CR, Kendall CW. The application of the glycemic index and glycemic load in weight loss: A review of the clinical evidence. IUBMB Life. 2011;63(1):7-13.
28. Ballance S, Knutsen SH, Fosvold ØW, Fernandez AS, Monro J. Predicting mixed-meal measured glycaemic index in healthy subjects. Eur J Nutr. 2019;58(7):2657-67.
29. Raben A. Glycemic index and metabolic risks: how strong is the evidence? Am J Clin Nutr. 2014;100:1-3.
30. Hare-Bruun H, Flint A, Heitmann BL. Glycemic index and glycemic load in relation to changes in body weight, body fat distribution, and body composition in adult Danes. Am J Clin Nutr. 2006;84(4):871-9.
31. Salari-Moghaddam A, Keshteli AH, Haghighatdoost F, Esmaillzadeh A, Adibi P. Dietary glycemic index and glycemic load in relation to general obesity and central adiposity among adults. Clin Nutr. 2019;38(6):2936-42.
32. Murakami K, McCaffrey TA, Gallagher AM, Neville CE, Boreham CA, Livingstone MB. Dietary glycemic index and glycemic load in relation to changes in body composition measures during adolescence: Northern Ireland Young Hearts Study. Int J Obes (Lond). 2014;38(2):252-8.
33. Cheng G, Xue H, Luo J, Jia H, Zhang L, Dai J, et al. Relevance of the dietary glycemic index, glycemic load and genetic predisposition for the glucose homeostasis of Chinese adults without diabetes. Sci Rep. 2017;7(1):1-12.
34. Wang ML, Gellar L, Nathanson BH, Pbert L, Ma Y, Ockene I, et al. Decrease in Glycemic Index Associated with Improved Glycemic Control among Latinos with Type 2 Diabetes. J Acad Nutr Diet. 2015;115(6):898-906.
35. Jiang J, Qiu H, Zhao G, Zhou Y, Zhang Z, Zhang H, et al. Dietary fiber intake is associated with HbA1c level among prevalent patients with type 2 diabetes in Pudong New Area of Shanghai, China. PloS One. 2012;7(10):e46552.
36. Weickert MO, Pfeiffer AFH. Impact of Dietary Fiber Consumption on Insulin Resistance and the Prevention of Type 2 Diabetes. J Nutr. 2018;148(1):7-12.
37. Raben A, Vestentoft PS, Brand-Miller J, Jalo E, Drummen M, Simpson L, et al. PREVIEW-Results from a 3-year randomised 2 x 2 factorial multinational trial investigating the role of protein, glycemic index and physical activity for prevention of type-2 diabetes. Diabetes Obes Metab. 2020;23:324-37.
38. Park Y, Dodd KW, Kipnis V, Thompson FE, Potischman N, Schoeller DA, et al. Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers. Am J Clin Nutr. 2018;107(1):80-93.
39. Wang Q. Smoking and body weight: evidence from China health and nutrition survey. BMC Public Health. 2015;15:1238.
40. Aggarwal S, Khandelwal D, Dutta D, Kalra S, Balhara YPS. Diabetes and smoking: the burden of evidence. The Diabetes Textbook: Springer; 2019. p. 611-6.

**Table 1** Characteristics of participants at the start of weight-loss maintenance (8 weeks) or 26 weeks (diet and lifestyle outcomes)

| **Characteristics** | **All participants‡** | **Completers** | **Non-completers** | ***P*-value** |
|---|---|---|---|---|
| N | 1,279 | 847 | 432 | – |
| **Socio-demographics*** | | | | |
| 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*** | | | | |
| Body weight (kg) | 83.0 (74.1, 94.4) | 81.3 (72.8, 90.7) | 86.3 (76.5, 99.7) | <0.001 |
| BMI ($kg \cdot m^{-2}$) | 29.2 (26.6, 32.8) | 28.4 (26.0, 31.7) | 30.8 (28.2, 34.6) | <0.001 |
| Fat mass (kg) | 31.1 (24.5, 39.8) | 29.6 (23.1, 37.0) | 35.2 (28.0, 42.5) | <0.001 |
| Waist circumference (cm) | 98.7±12.4 | 97.4±11.9 | 101.2±13.1 | <0.001 |
| **Glucose tolerance and blood biochemistry*** | | | | |
| Fasting plasma glucose ($mmol \cdot L^{-1}$) | 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 |
| $HbA_{1c}$ ($mmol \cdot mol^{-1}$) | 34.6±3.1 | 34.5±3.1 | 34.8±3.2 | 0.893 |
| Fasting insulin ($mU \cdot L^{-1}$) | 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 |
| Glycemic index from food diary | 53.5±8.2 | 53.9±8.0 | 52.8±8.5 | 0.028 |
| Glycemic load from food diary | 90.5±35.6 | 92.5±35.6 | 86.5±35.5 | 0.005 |
| Dietary fiber from food diary ($g \cdot day^{-1}$) | 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 ($g \cdot day^{-1}$) | 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 |
| Physical activity ($counts \cdot min^{-1}$) | 311.6 (248.2, 396.9) | 315.1 (255.2, 404.1) | 305.2 (228.0, 382.0) | 0.022 |

Values represent mean±standard deviation, median ($25^{th}$, $75^{th}$ percentiles), and the number of participants (%).

*Data were collected at 8 weeks. †Data were collected at 26 weeks. ‡Participants who entered the weight-loss

maintenance phase. Difference between completers and non-completers in characteristics was examined by t-test, Wilcoxon non-parametric test, and Chi-square test. T-test was used for approximately, normally-distributed variables, Wilcoxon non-parametric test was used for non-normally-distributed variables, and Chi-square test was used for categorical variables. BMI, body mass index; $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$; HOMA-IR, homeostatic model assessment of insulin resistance.

**Fig 1** Longitudinal associations of cumulative average glycemic index (GI) (each 10 unit) with yearly weight regain and changes in markers of glycemic status during weight-loss maintenance. Model 1 was adjusted for age, sex, ethnicity, anthropometric outcomes or body composition or markers of glycemic status at 8 weeks, BMI at the start of weight-loss maintenance (8 weeks), and time as fixed effects and intervention center and participant-ID as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured physical activity 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 body weight. *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 10-unit increment in GI. †*P*-values for main effects. BMI, body mass index; $HbA_{1c}$, glycated hemoglobin $A_{1c}$; HOMA-IR, homeostatic model assessment of insulin resistance.

**Fig 2** Changes in body weight and markers of glycemic status overtime during weight-loss maintenance by tertiles of cumulative average glycemic index (GI), glycemic load (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. Analyses were performed using a linear mixed model with repeated measurements adjusted for age, sex, ethnicity, anthropometric outcomes or body composition or markers of glycemic status at the start of weight-loss maintenance (8 weeks), BMI at 8 weeks, time, time-varying accelerometry-measured physical activity, 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 participant-ID and intervention centre 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 tertile by 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 the different lowercase letters (a and b) are significantly different, $P<0.05$. BMI, body mass index; BW, body weight; $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$.

**Fig 3** Longitudinal associations of cumulative average glycemic load (GL) (each 20 unit) with yearly weight regain and changes in markers of glycemic status during weight-loss maintenance. Analyses were performed using 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 weight-loss maintenance (8 weeks), BMI at 8 weeks, and time as fixed effects and intervention center and participant-ID as random effects. Model 2 was additionally adjusted for time-varying accelerometry-measured physical activity 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 body weight. *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. BMI, body mass index; $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$; HOMA-IR, homeostatic model assessment of insulin resistance.