Does the Effect of a 3-Year Lifestyle Intervention on Body Weight and Cardiometabolic Health Differ by Prediabetes Metabolic Phenotype?

Does the Effect of a 3-Year Lifestyle Intervention on Body Weight and Cardiometabolic Health Differ by Prediabetes Metabolic Phenotype? A Post Hoc Analysis of the PREVIEW Study

https://doi.org/10.2337/dc22-0549

Ruixin Zhu,[1] Elli Jalo,[2] Marta P. Silvestre,[3,4] Sally D. Poppitt,[3] Teodora Handjieva-Darlenska,[5] Svetoslav Handjiev,[5] Maija Huttunen-Lenz,[6] Kelly Mackintosh,[7] Gareth Stratton,[7] Santiago Navas-Carretero,[8,9,10] Kirsi H. Pietiläinen,[11,12] Elizabeth Simpson,[13] Ian A. Macdonald,[13] Roslyn Muirhead,[14] Jennie Brand-Miller,[14] Mikael Fogelholm,[2] Kristine Færch,[15,16] J. Alfredo Martinez,[9,17,18] Margriet S. Westerterp-Plantenga,[19] Tanja C. Adam,[19] and Anne Raben[1,15]

OBJECTIVE

To examine whether the effect of a 3-year lifestyle intervention on body weight and cardiometabolic risk factors differs by prediabetes metabolic phenotype.

RESEARCH DESIGN AND METHODS

This post hoc analysis of the multicenter, randomized trial, PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World (PREVIEW), included 1,510 participants with prediabetes (BMI ≥25 kg · m^{-2}; defined using oral glucose tolerance tests). Of these, 58% had isolated impaired fasting glucose (iIFG), 6% had isolated impaired glucose tolerance (iIGT), and 36% had IFG+IGT; 73% had normal hemoglobin A_{1c} (HbA_{1c}; <39 mmol · mol^{-1}) and 25% had intermediate HbA_{1c} (39–47 mmol · mol^{-1}). Participants underwent an 8-week diet-induced rapid weight loss, followed by a 148-week lifestyle-based weight maintenance intervention. Linear mixed models adjusted for intervention arm and other confounders were used.

RESULTS

In the available-case and complete-case analyses, participants with IFG+IGT had greater sustained weight loss after lifestyle intervention (adjusted mean at 156 weeks −3.5% [95% CI, −4.7%, −2.3%]) than those with iIFG (mean −2.5% [−3.6%, −1.3%]) relative to baseline ($P = 0.011$). Participants with IFG+IGT and iIFG had similar cardiometabolic benefits from the lifestyle intervention. The differences in cardiometabolic benefits between those with iIGT and IFG+IGT were minor or inconsistent in different analyses. Participants with normal versus intermediate HbA_{1c} had similar weight loss over 3 years and minor differences in cardiometabolic benefits during weight loss, whereas those with normal HbA_{1c} had greater improvements in fasting glucose, 2-h glucose (adjusted between-group difference at 156 weeks −0.54 mmol · L^{-1} [95% CI −0.70, −0.39], $P < 0.001$), and triglycerides (difference −0.07 mmol · L^{-1} [−0.11, −0.03], $P < 0.001$) during the lifestyle intervention.

CONCLUSIONS

Individuals with iIFG and IFG+IGT had similar improvements in cardiometabolic health from a lifestyle intervention. Those with normal HbA_{1c} had greater improvements than those with intermediate HbA_{1c}.

[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, Department of Medicine, School of Biological Sciences, University of Auckland, Auckland, New Zealand
[4]Center for Health Technology and Services Research (CINTESIS), NOVA Medical School (NMS), Universidade Nova de Lisboa, Lisboa, Portugal
[5]Department of Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria
[6]Institute for Nursing Science, University of Education Schwäbisch Gmünd, Schwäbisch Gmünd, Germany
[7]Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre, Swansea University, Swansea, U.K.
[8]Centre for Nutrition Research, University of Navarra, Pamplona, Spain
[9]Centro de Investigacion Biomedica en Red Area de Fisiologia de la Obesidad y la Nutricion (CIBEROBN), Madrid, Spain
[10]Instituto de Investigación Sanitaria de Navarra (IdiSNA) Instituto for Health Research, Pamplona, Spain
[11]Obesity Research Unit, Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Prediabetes is an intermediate state with glycemic parameters above normal but below the threshold of type 2 diabetes (1,2). The prevalence of prediabetes, classified as an intermediate hyperglycemia or intermediate hemoglobin A_{1c} (HbA_{1c}) level, has been increasing worldwide, posing a threat to global health (3). Moreover, prediabetes is associated with an increased risk of cardiovascular disease (CVD) compared with normal glucose tolerance (4,5). The increased CVD risk may be mainly driven by abnormal levels of plasma glucose and cardiometabolic risk factors (e.g., high blood pressure and elevated total cholesterol) (6). Lifestyle interventions with a combination of energy restriction or healthy diets and increased physical activity (PA) may improve cardiometabolic health in individuals with prediabetes (5,7,8).

Prediabetes is a heterogeneous condition; a large variation in the relative contributions of β-cell dysfunction and insulin resistance exists among prediabetes metabolic phenotypes (i.e., isolated impaired fasting glucose [iIFG], isolated impaired glucose tolerance [iIGT], and both IFG and IGT [i.e., IFG+IGT]) (9). Previous studies have suggested that not all individuals with prediabetes reduce the risk of developing type 2 diabetes following a lifestyle intervention compared with traditional therapy (10). Indeed, research has shown that lifestyle interventions may not be effective in reducing diabetes incidence in individuals with iIFG (10–12). However, longitudinal evidence remains limited regarding cardiometabolic benefits from lifestyle interventions in prediabetes metabolic phenotypes. In addition, according to the American Diabetes Association (ADA) criteria, prediabetes can be defined using plasma glucose or HbA_{1c} (2), despite it being consistently shown that the overlap of individuals with intermediate HbA_{1c}, iIFG, and iIGT is poor (13,14). Whether there are differences in response to a lifestyle intervention between individuals with both intermediate hyperglycemia and HbA_{1c} versus those with intermediate hyperglycemia, but normal HbA_{1c}, remains unknown.

The PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World (PREVIEW) study was a 3-year randomized trial using low-energy diet replacement and a lifestyle-based weight maintenance intervention to prevent type 2 diabetes in individuals with prediabetes (15). The main aim of the present post hoc analysis was to examine whether the effect of a lifestyle intervention on body weight and cardiometabolic risk factors differed by baseline prediabetes metabolic phenotype (iIFG, iIGT, and IFG+IGT). Furthermore, changes in outcomes of interest in participants with intermediate hyperglycemia when stratified by normal HbA_{1c} levels (HbA_{1c} <39 mmol $\cdot$ mol^{-1}) versus intermediate levels (HbA_{1c} 39–47 mmol $\cdot$ mol^{-1}) were compared.

RESEARCH DESIGN AND METHODS

Study Design

The present secondary analysis used data from the PREVIEW study (ClinicalTrials.gov, NCT01777893). The study protocol and main findings have been published (15,16). In short, the PREVIEW study was a large-scale, multicenter, randomized controlled trial seeking to ascertain an effective diet and PA combined lifestyle intervention for type 2 diabetes prevention. The primary outcome was diabetes incidence in the two dietary intervention arms. The study was conducted between June 2013 and March 2018 at eight intervention sites in Denmark, Finland, the Netherlands, the U.K., Spain, Bulgaria, Australia, and New Zealand and was conducted in line with the Declaration of Helsinki. The study protocol and procedures were approved by the Human Ethics Committees at each intervention site (Supplementary Table 1).

Participants

Participants were enrolled from June 2013 to April 2015. All provided written informed consent before taking part in the study. Detailed inclusion and exclusion criteria have been published previously (16), but briefly, eligible participants were men and women aged 25–70 years with a BMI $\geq$25 kg $\cdot$ m^{-2} and prediabetes. Prediabetes was assessed at the screening visit in the local laboratories using a 75 g oral glucose tolerance test (OGTT) according to the ADA criteria (2). Whole-blood glucose was measured at each intervention site using glucose analyzers (HemoCue, Angelholm, Sweden; Reflotron, Roche Diagnostics, Basel, Switzerland; or EML105, Radiometer, Copenhagen, Denmark). Fasting plasma glucose and 2 h plasma glucose were estimated by multiplying whole-blood glucose by 1.11. HbA_{1c} was not used to identify prediabetes at screening. Those with preexisting diabetes or significant CVD were excluded during enrollment.

Intervention

The PREVIEW study consisted of an 8-week rapid weight-loss phase, followed by a 148-week weight-maintenance phase via lifestyle interventions (17). During the

[12]Abdominal Center, Endocrinology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[13]Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, Queen's Medical Centre, Medical Research Council (MRC)/Alzheimer's 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, Nottingham, U.K.
[14]School of Life and Environmental Sciences and Charles Perkins Centre, The University of Sydney, Sydney, Australia
[15]Clinical Research, Copenhagen University Hospital—Steno Diabetes Center Copenhagen, Herlev, Denmark
[16]Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark
[17]Department of Nutrition and Physiology, University of Navarra, Pamplona, Spain
[18]Precision Nutrition and Cardiometabolic Health Program, IMDEA-Food Institute (Madrid Institute for Advanced Studies), Campus of International Excellence (CEI) Universidad Autónoma de Madrid (UAM) + Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain
[19]Department of Nutrition and Movement Sciences, NUTRIM, School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands
Corresponding author: Anne Raben, ara@nexs.ku.dk

Received 18 March 2022 and accepted 25 April 2022
This article contains supplementary material online at https://doi.org/10.2337/figshare.19762549.
Clinical trial reg. no. NCT1777893, clinicaltrials.gov

See accompanying article, p. XXX.

weight-loss phase, all participants were given total low-energy diet replacement products (810 kcal or 3,400 kJ). During this phase, participants were allowed to consume low-starch vegetables. Participants who met the requirement of ≥8% weight loss after the weight loss phase were randomized, according to age and sex, into one of four intervention arms and were eligible to commence the weight-maintenance phase. The intervention arms were a combination of two diets and two PA programs. The detailed information about intervention arms is included in the Supplementary Material. Diet compliance was mainly evaluated using 4 day food records and 24 h urine nitrogen (biomarker for protein), and PA compliance was primarily evaluated using 7 day accelerometry data at baseline and at 26, 52, 104, and 156 weeks (Supplementary Table 2).

Outcome Measures

Outcome measures were body weight, fat mass, fat-free mass, fasting plasma glucose, 2-h plasma glucose, fasting insulin, HbA_{1c}, total cholesterol, LDL cholesterol, fasting triglycerides, systolic blood pressure, and diastolic blood pressure, as described previously (15,17). Briefly, all outcomes were determined after at least 10 h of fasting. Blood samples were drawn from the antecubital vein and initially stored at −80°C at each site prior to transportation to a central laboratory of the Finnish Institute for Health and Welfare, Helsinki, for analysis, using an Architect ci8200 integrated system (Abbott Laboratories, Abbott Park, IL). The outcomes were collected at seven clinical investigation days (at 0, 8, 26, 52, 78, 104 and 156 weeks, respectively) (Supplementary Table 2**)**. The following visit windows were allowed for data collection *1*) at 8 weeks: −3 to +5 days; *2*) at 26 weeks: ±1 week; *3*) at 52 weeks: ± 2 weeks; and *4*) remaining time points: ± 4 weeks. HOMA of insulin resistance (HOMA-IR) was calculated as fasting insulin in mU · L^{-1} × fasting plasma glucose in mmol · L^{-1}/22.5 (18). The triglyceride-glucose (TyG) index, a predictor of CVD events, was calculated as Ln [triglycerides (mg · dL^{-1}) × fasting plasma glucose (mg · dL^{-1})/2] (19).

Type 2 Diabetes Ascertainment

Type 2 diabetes was diagnosed by an OGTT (fasting plasma glucose ≥7.0 mmol · L^{-1} and/or 2-h plasma glucose ≥11.1 mmol · L^{-1}) conducted at the intervention site or by a medical doctor, according to World Health Organization and ADA criteria (2,20).

Definition of Prediabetes Metabolic Phenotypes

Prediabetes metabolic phenotypes were defined using local glucose analyzers from baseline fasting plasma glucose and 2-h plasma glucose analyzed at the Finnish Institute for Health and Welfare, regardless of the data collected at screening. HbA_{1c} was not used to define prediabetes at the study commencement in 2013. The ADA criteria (2) were used to stratify participants with prediabetes into metabolic phenotypes having iIFG (fasting plasma glucose 5.6–6.9 mmol · L^{-1} and 2-h plasma glucose <7.8 mmol · L^{-1}), iIGT (fasting plasma glucose <5.6 mmol · L^{-1} and 2 h plasma glucose 7.8–11.0 mmol · L^{-1}), or IFG+IGT (fasting plasma glucose 5.6–6.9 mmol · L^{-1} and 2 h plasma glucose 7.8–11.0 mmol · L^{-1}). Additionally, participants with prediabetes were stratified in groups having normal HbA_{1c} (<39 mmol · mol^{-1}) or intermediate HbA_{1c} (39–47 mmol · mol^{-1}). Participants with missing baseline fasting plasma glucose and/or 2-h plasma glucose data from the central laboratory (unidentifiable glycemic status) were excluded from the present analysis. We merged all participants into one intervention group and reclassified them according to baseline prediabetes metabolic phenotypes, because *1*) there were no significant differences in primary or secondary outcomes between the intervention groups; *2*) there was no significant interaction of intervention arm and prediabetes metabolic phenotypes; and *3*) diet and PA compliance was lower than expected (15).

Statistical Analyses

Differences in changes in outcomes of interest from baseline over 3 years among the prediabetes metabolic phenotypes (iIFG, iIGT, or IFG+IGT) or between those with normal versus intermediate HbA_{1c} levels were examined using linear mixed models. In the models, we adjusted for the following covariates, which may influence outcomes of interest (21–23): fixed covariates, including age, sex, race/ethnicity (Caucasian, Asian, Black, Arabic, Hispanic, or other), baseline BMI, baseline smoking habits (daily, less than weekly, or no smoking), baseline alcohol drinking (yes or no), baseline values of the outcome being considered (baseline body weight in kg was added as an explanatory variable when the percentage of weight loss was added as a dependent variable), time (categorical; week), intervention arms, and random effects, including participant identifier and intervention site. A two-way interaction of time and prediabetes metabolic phenotype was added. If the interaction was significant, post hoc multiple comparisons with Bonferroni correction or pairwise comparisons (independent-samples *t* test) were conducted at each time point. The normality of the residuals of changes in outcomes of interest from over 3 years was assessed by visual inspection of histograms and probability–probability plots. Missing data were accounted for using the expectation maximization algorithm. The above analyses were conducted in available participants (e.g., participants who entered the rapid weight loss phase, whether with ≥8% of weight loss or not at the end of the weight loss phase). Several sensitivity analyses were conducted *1*) by additionally adjusting for percentage weight change from baseline in the models with cardiometabolic risk factors as dependent variables, if there were significant differences in the percentage of weight change between groups; *2*) by including completers only; *3*) by only including participants who lost ≥8% of initial weight and successfully entered the weight maintenance phase; and *4*) by additionally adjusting for PA and dietary intake, as diet and PA may also influence the results (24).

Cumulative incidence of type 2 diabetes by prediabetes phenotypes was calculated using the Kaplan-Meier method. Diabetes incidence across prediabetes phenotypes was determined using a time-dependent Cox hazards regression model. Detailed information is included in the Supplementary Material.

Descriptive statistics are described in the Supplementary Material. Data analyses were performed using IBM SPSS 28.0 (Armonk, NY). Statistical significance was determined as $P \leq 0.05$ in two-sided tests.

RESULTS

Participants

The present analysis included 1,510 participants (Supplementary Fig. 1). Of

these, 869 (58%) had iIFG, 93 (6%) had iIGT, and 548 (36%) had IFG+IGT; 1,106 (73%) had normal HbA_{1c} levels, and 384 (25%) had intermediate HbA_{1c} levels. The present analysis excluded 5 participants with diabetic HbA_{1c} and 15 with missing HbA_{1c} at baseline. A total of 1,268 participants commenced the weight maintenance phase, and 685 completed the study. The reasons for drop out were weight loss <8% and personal reasons such as time constraints, moving away, or illness. Participants' baseline characteristics are shown in Table 1 and Supplementary Tables 3 and 4. Participants with normal or intermediate HbA_{1c} had similar lipid profile and blood pressure at baseline. Compared with noncompleters, completers were older and had lower BMI but higher fasting plasma glucose. Participants' dietary intake and PA during the weight maintenance phase is shown in Supplementary Table 5.

Changes in Outcomes in iIFG, iIGT, and IFG+IGT

In the available-case analysis with adjustment for age, sex, and baseline outcomes of interest, participants with iIFG, iIGT, and IFG+IGT had a similar weight loss (adjusted mean $\sim$ −10.3 kg or −10.3%) at 8 weeks (the rapid weight loss period using a low-energy diet) (Fig. 1). After lifestyle-based weight maintenance, participants with IFG+IGT maintained a greater weight loss relative to baseline (−3.7 kg [95% CI, −4.9, −2.5] or −3.5% [−4.7, −2.3]), compared with those with iIFG (−2.5 kg [−3.7, −1.3] or −2.5% [−3.6, −1.3]; adjusted mean between-group difference 1.2 kg [0.5, 2.0], $P < 0.001$; or 1.0% [0.3, 1.8], $P = 0.002$). Those with IFG+IGT also lost more fat-free mass after weight maintenance than those with iIFG (between-group difference −0.7 kg [−1.1, −0.4], $P < 0.001$). The results regarding changes in weight and fat-free mass were similar in the complete-case analysis (Supplementary Fig. 2) or after further adjustment for PA and dietary intake.

In the available-case analysis with adjustment for baseline differences, participants with IFG+IGT had a greater decrease in fasting plasma glucose after rapid weight loss (at 8 weeks) than those with iIFG (adjusted mean between-group difference at 8 weeks −0.06 mmol · L^{-1} [95% CI, −0.12, −0.005], $P = 0.029$) (Fig. 2), whereas there were no differences among participants with all prediabetes metabolic phenotypes at the end of weight maintenance (156 weeks). Participants with iIGT or IFG+IGT had greater reductions in HbA_{1c} than those with iIFG at 8 weeks (difference between iIGT vs. iIFG −0.63 mmol · mol^{-1} [95% CI, −1.10, −0.17], $P = 0.004$), and differences between those with iIGT and iIFG remained significant at 52, 78, 104, and 156 weeks (between-group difference at 156 weeks −0.75 mmol · mol^{-1} [−1.21, −0.28], $P < 0.001$). There were no differences in changes in other cardiometabolic risk factors over 3 years (Fig. 1 and Supplementary Table 6). Results were similar in participants who entered the weight maintenance phase or after further adjustment for PA and dietary intake. In the complete-case analysis, only the difference in change in HbA_{1c} remained significance between participants with IFG+IGT versus iIFG (Supplementary Fig. 3). After subsequent adjustment for weight loss (%), there was a greater decrease in 2-h plasma glucose at 104 and 156 weeks in participants with iIGT versus IFG+IGT and a greater increase in HDL cholesterol over 3 years in participants with iIFG versus IFG+IGT (Supplementary Fig. 4**).**

Changes in Outcomes in Participants With Normal and Intermediate HbA_{1c}

In the available-case analysis with adjustment for baseline differences, there were no differences in weight change (kg or %) over 3 years between participants with prediabetes and normal versus intermediate HbA_{1c} over 3 years (Fig. 3), whereas those with intermediate HbA_{1c} lost more fat-free mass at 156 weeks than those with normal HbA_{1c} (adjusted mean between-group difference −0.4 kg [95% CI, −0.7, −0.1], $P = 0.005$). Compared with those with normal HbA_{1c}, those with intermediate HbA_{1c} had a smaller decrease in fasting plasma glucose, 2-h plasma glucose, and TyG at 26, 54, 104, and 156 weeks (adjusted mean between-group difference in fasting plasma glucose at 156 weeks 0.15 mmol · L^{-1} [95% CI, 0.10, 0.20], $P < 0.001$; in 2-h plasma glucose at 156 weeks 0.54 mmol · L^{-1} [0.39, 0.70], $P < 0.001$; in TyG at 156 weeks 0.06 [0.03, 0.10], $P < 0.001$) (Fig. 3 and Supplementary Table 6) and had a smaller reduction in triglycerides over 156 weeks (between-group difference 0.07 mmol · L^{-1} [0.03, 0.11], $P < 0.001$). Those with intermediate HbA_{1c} had a greater decrease in LDL cholesterol at 8 weeks (between-group difference −0.07 mmol · L^{-1} [95% CI, −0.13, −0.01], $P = 0.018$) and a greater decrease in HbA_{1c} at 8, 26, and 52 weeks (between-group difference at 8 weeks −0.54 mmol · mol^{-1} [−0.82, −0.25], $P < 0.001$) than those with normal HbA_{1c}, whereas the differences disappeared at the end of weight maintenance. The above results remained robust in participants who entered the weight maintenance phase or after adjustment for PA and dietary intake. In the complete-case analysis, the differences in fasting plasma glucose, 2-h plasma glucose, triglycerides and TyG at 156 weeks still remained robust (Supplementary Fig. 5).

Type 2 Diabetes Incidence

The total number of participants with type 2 diabetes was 29 (13 iIFG, 2 iIGT, and 14 IFG+IGT. Of these, 13 were normal HbA_{1c} and 15 were intermediate HbA_{1c}. The 3-year cumulative incidence was 3.2% in iIFG, 5.1% in iIGT, and 5.5% in IFG+IGT and was 2.6% in those with normal HbA_{1c} and 7.9% with intermediate HbA_{1c} (Supplementary Fig. 6). There were no differences in diabetes incidence across iIFG, iIGT, and IFG+IGT. The adjusted hazard ratio was 11.66 (95% CI 0.97, 140.54) for those with intermediate HbA_{1c} versus normal HbA_{1c} ($P = 0.053$).

CONCLUSIONS

We found that participants with iIFG versus IFG+IGT had similar cardiometabolic benefits from the lifestyle intervention, although those with IFG+IGT had greater sustained weight loss. The differences in cardiometabolic benefits between participants with iIGT versus IFG+IGT were minor or inconsistent in different analyses. Participants with prediabetes and normal versus intermediate HbA_{1c} had similar weight changes over 3 years and only minor differences in cardiometabolic benefits during rapid weight loss. In contrast, during weight maintenance, those with normal HbA_{1c} levels had greater improvements in fasting plasma glucose, 2-h plasma glucose, triglycerides, and TyG during the lifestyle intervention compared with those with intermediate HbA_{1c}. Participants

Table 1—Participant characteristics at baseline

	iIFG (n = 869)	iIGT (n = 93)	IFG+IGT (n = 548)	P value†	Intermediate hyperglycemia but normal HbA_{1c} level (n = 1,106)	Intermediate hyperglycemia and intermediate HbA_{1c} level (n = 384)	P value‡
Sociodemographics							
Age, years	55 (43, 61)	45 (37, 58)	56 (45, 63)	<0.001	55 (42, 61)	56 (46, 62)	<0.001
Sex, n (%)				0.003			0.002
Women	554 (63.8)	75 (80.6)	371 (67.7)	—	733 (66.3)	254 (66.1)	—
Men	315 (36.2)	18 (19.4)	177 (32.3)	—	373 (33.7)	130 (33.9)	—
Race/ethnicity, n (%)				<0.001			<0.001
Caucasian	773 (89.0)	70 (75.3)	488 (89.1)	—	1012 (91.5)	300 (78.1)	—
Other*	96 (11.0)	23 (24.7)	60 (10.9)	—	94 (8.5)	84 (21.9)	—
Smoking, n (%)				0.600			0.079
No	730 (84.0)	84 (90.3)	465 (84.9)	—	931 (84.2)	340 (88.5)	—
Yes, but less than weekly	31 (3.6)	2 (2.2)	17 (3.1)	—	41 (3.7)	7 (1.8)	—
Yes, at least daily	97 (11.2)	6 (6.5)	59 (10.8)	—	119 (10.8)	33 (8.6)	—
Missing	11 (1.3)	1 (1.1)	7 (1.3)	—	15 (1.4)	4 (1.0)	—
Drinking, n (%)				0.001			0.001
No	255 (29.3)	44 (47.3)	182 (33.2)	—	327 (29.6)	148 (38.5)	—
Yes	603 (69.4)	48 (51.6)	359 (65.5)	—	765 (69.2)	231 (60.2)	—
Missing	11 (1.3)	1 (1.1)	7 (1.3)	—	14 (1.3)	5 (1.3)	—
Anthropometry and body composition							
Body weight, kg	97.1 (85.5, 110.7)	95.5 (83.5, 106.3)	97.1 (85.2, 111.7)	0.232	96.3 (84.5, 110.2)	99.4 (87.0, 112.0)	0.025
Height, m	1.68 (1.62, 1.76)	1.65 (1.60, 1.69)	1.66 (1.61, 1.74)	<0.001	1.68 (1.62, 1.75)	1.67 (1.61, 1.74)	0.080
BMI, $kg \cdot m^{-2}$	33.7 (30.4, 38.1)	34.4 (30.7, 38.3)	34.1 (31.4, 39.0)	0.045	33.6 (30.4, 38.1)	35.0 (31.6, 39.3)	<0.001
Fat mass, kg	40.0 (32.8, 50.3)	41.7 (34.3, 49.2)	41.9 (33.8, 50.4)	0.145	40.1 (32.7, 49.9)	42.3 (34.4, 51.0)	0.011
Fat-free mass, kg	55.1 (48.1, 66.1)	52.1 (45.6, 58.6)	53.5 (47.2, 64.1)	<0.001	54.2 (47.5, 64.3)	55.1 (48.5, 65.9)	0.226
Glucose metabolism							
Fasting plasma glucose, $mmol \cdot L^{-1}$	6.1 (0.4)	5.3 (0.3)	6.3 (0.4)	<0.001	6.1 (0.4)	6.3 (0.4)	<0.001
2-h plasma glucose, $mmol \cdot L^{-1}$	6.2 (1.0)	9.0 (0.9)	9.1 (0.9)	<0.001	7.3 (1.7)	8.0 (1.7)	<0.001
Fasting insulin, $mU \cdot L^{-1}$	11.2 (8.4, 15.4)	11.4 (7.9, 16.4)	12.9 (9.3, 17.9)	<0.001	11.2 (8.3, 15.5)	13.9 (10.0, 18.6)	<0.001
HOMA-IR	3.0 (2.3, 4.3)	2.7 (1.9, 3.9)	3.6 (2.6, 5.1)	<0.001	3.0 (2.2, 4.2)	3.8 (2.8, 5.3)	<0.001
HbA_{1c}, %	5.5 (0.3)	5.4 (0.3)	5.6 (0.3)	<0.001	5.4 (0.2)	5.9 (0.2)	<0.001
HbA_{1c}, $mmol \cdot mol^{-1}$	36.1 (3.0)	35.6 (3.3)	37.6 (3.4)	<0.001	35.1 (2.2)	40.6 (1.7)	<0.001
Lipid metabolism							
Fasting triglycerides, $mmol \cdot L^{-1}$	1.3 (1.0, 1.7)	1.3 (1.0, 2.0)	1.5 (1.1, 1.9)	<0.001	1.3 (1.0, 1.8)	1.4 (1.1, 1.8)	0.131
Total cholesterol, $mmol \cdot L^{-1}$	5.2 (1.0)	4.9 (1.0)	5.2 (1.0)	0.017	5.2 (1.0)	5.1 (1.0)	0.047
HDL cholesterol, $mmol \cdot L^{-1}$	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	<0.001	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	0.059
LDL cholesterol, $mmol \cdot L^{-1}$	3.3 (2.7, 3.8)	3.1 (2.4, 3.5)	3.2 (2.6, 3.8)	0.025	3.3 (2.7, 3.8)	3.2 (2.5, 3.8)	0.057
TyG index	8.8 (0.4)	8.6 (0.5)	8.9 (0.4)	<0.001	8.8 (0.4)	8.9 (0.4)	0.006
Blood pressure							
Systolic, mmHg	129.4 (15.3)	127.8 (15.1)	130.2 (15.9)	0.314	129.2 (15.7)	130.5 (15.1)	0.158
Diastolic, mmHg	79.7 (72.3, 85.7)	75.7 (68.8, 80.8)	79.0 (71.0, 85.7)	0.003	79.3 (72.0, 85.7)	78.3 (70.7, 85.3)	0.166

Data are mean (SD) or median (25th, 75th percentiles), unless indicated as n (%). *Including Asian, Black, Arabic, Hispanic, and other. χ^2 Test was based on full categories. †P for differences in baseline characteristics among participants with different prediabetes metabolic phenotypes, examined using one-way ANOVA, a Kruskal-Wallis H nonparametric test, and a χ^2 test. ‡P for differences in baseline characteristics between participants with normal vs. intermediate HbA_{1c}, examined using an independent-samples t test, a Mann-Whitney U nonparametric test, and a χ^2 test.

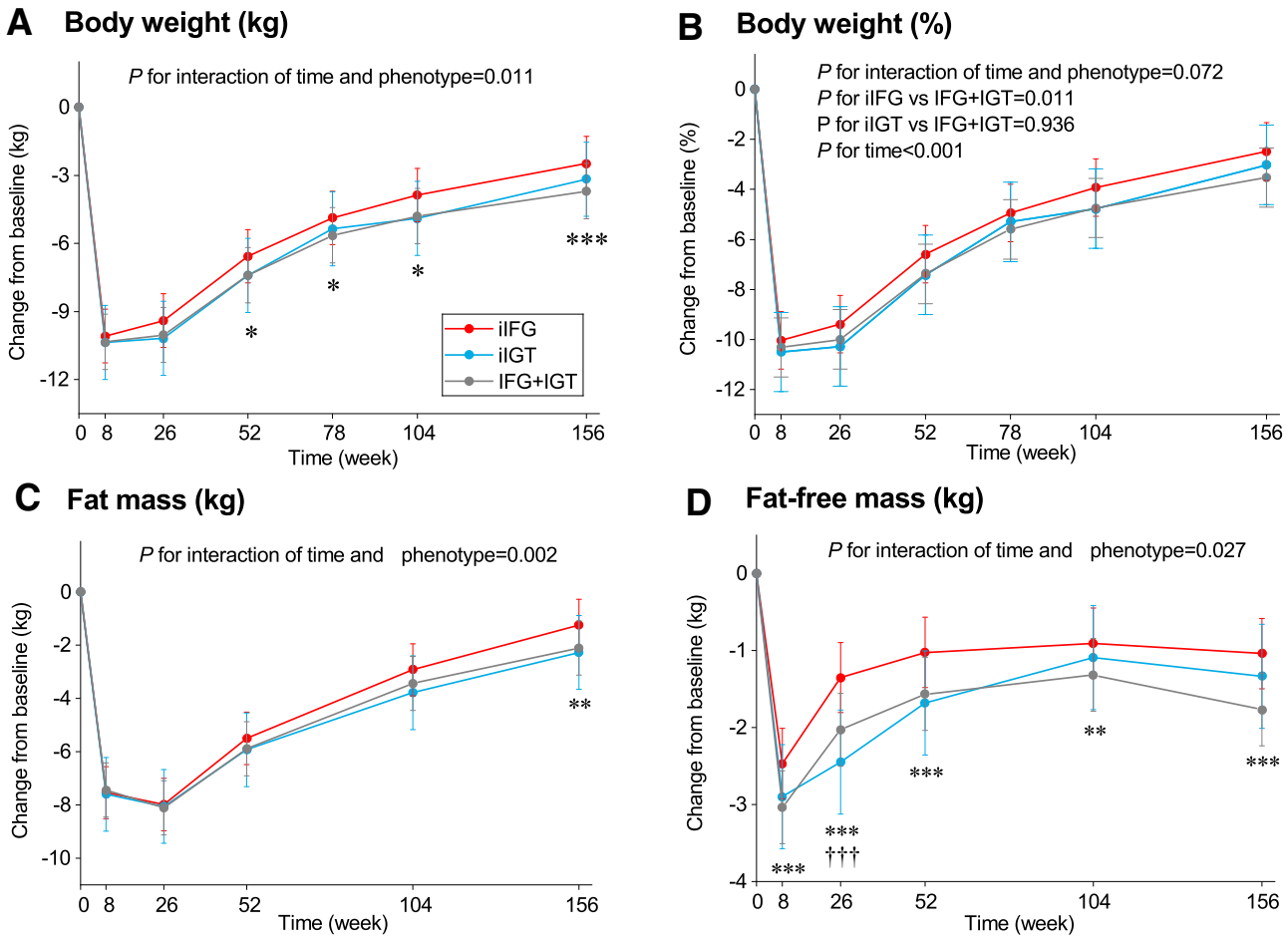

Figure 1—Changes in body weight and body composition by prediabetes metabolic phenotype. Values are estimated marginal mean and 95% CI in changes in body weight in kg (*A*), body weight in percentage (*B*), fat mass in kg (*C*), and fat-free mass in kg (*D*) from baseline in different prediabetes metabolic phenotypes. Prediabetes metabolic phenotypes were defined at baseline. Analyses were performed using a linear mixed model adjusted for age, sex, race/ethnicity, baseline BMI, baseline smoking habits, and baseline alcohol drinking, baseline values of the outcome being considered (baseline body weight in kg was added as a explanatory variable when percentage weight loss was added as a dependent variable), intervention arm, and time as fixed covariates, and participant identifier and intervention site as random effects. Time-by-prediabetes metabolic phenotype interaction terms were added. Post hoc multiple comparisons with Bonferroni correction were performed to compare prediabetes metabolic phenotypes at each time point, where appropriate. iIFG vs. IFG+IGT: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$; iIFG vs. iIGT: $\dagger\dagger\dagger P < 0.001$.

with prediabetes and normal HbA_{1c} levels had lower incidence of type 2 diabetes than those with intermediate HbA_{1c}.

Prediabetes metabolic phenotypes display different metabolic abnormalities despite both being accompanied by impaired β-cell function (10). IGT is characterized by skeletal muscle insulin resistance, and IFG has marked hepatic insulin resistance, although both are below the diabetes thresholds (10). Individuals with iIFG also have a decreased early-phase (first 30 min) but a normal late-phase (60–120 min) plasma insulin response during OGTT, while those with iIGT have a defect in early-phase insulin secretion and an even more severe defect in late-phase insulin secretion during OGTT (25).

There was a statistically significant difference in weight loss at the end of the 3 year intervention between participants with iIFG versus IFG+IGT, and those with IFG+IGT had greater sustained weight loss. The effect size of the difference, however, was small (∼1%), and whether the difference was clinically significant needs to be confirmed by future studies. Notably, participants with IFG+IGT also had greater loss of fat-free mass compared with those with iIFG. Greater fat-free mass loss may be related to adverse CVD outcomes. Khazem et al. (26) showed that lower fat-free mass increased the odds of having CVD in men. In addition, Spahillari et al. (27) reported an association of increased fat-free mass with reduced cardiovascular mortality in the elderly. Therefore, future lifestyle intervention design should mainly focus on fat mass loss, instead of total body mass, and should also aim to prevent fat-free mass loss.

In the current study, the 8-week low-energy diet induced great improvements in cardiometabolic outcomes (e.g., HbA_{1c}) compared with baseline in all prediabetes phenotypes, but the improvements were not sustainable, especially at the end of the 3 year study. It is therefore necessary for individuals with prediabetes to maintain improvements in metabolic outcomes through more intensive lifestyle interventions or other treatments. We did not find clinically significant differences in improvements in cardiometabolic risk factors between participants

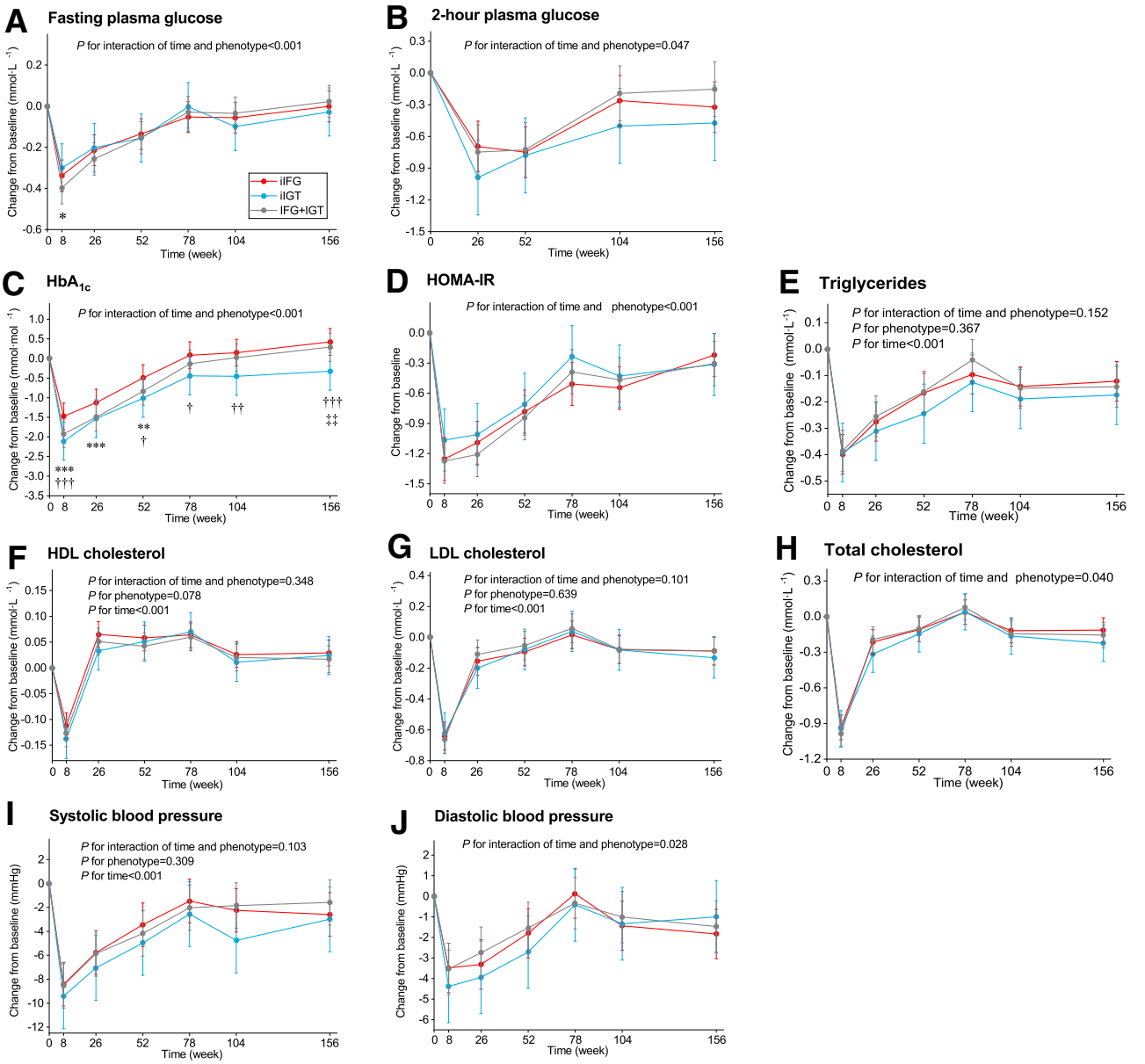

Figure 2—Changes in cardiometabolic risk factors by prediabetes metabolic phenotype. Values are estimated marginal mean (95% CI) in changes in fasting plasma glucose (*A*), 2-h plasma glucose (*B*), HbA_{1c} (*C*), HOMA-IR (*D*), triglycerides (*E*), HDL cholesterol (*F*), LDL cholesterol (*G*), total cholesterol (*H*), diastolic blood pressure (*I*), and systolic blood pressure (*J*) from baseline in different prediabetes metabolic phenotypes. Prediabetes metabolic phenotypes were defined at baseline. Analyses were performed using a linear mixed model adjusted for age, sex, race/ethnicity, baseline BMI, baseline smoking habits, baseline alcohol drinking, baseline values of the outcome being considered, intervention arm, and time as fixed covariates, and participant identifier and intervention site as random effects. Time-by-prediabetes metabolic phenotype interaction terms were added. Post hoc multiple comparisons with Bonferroni correction were performed to compare prediabetes metabolic phenotypes at each time point, where appropriate. iIFG vs. IFG+IGT: $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$; iIFG vs. iIGT: $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, and $\dagger\dagger\dagger P < 0.001$; iIGT vs. IFG+IGT: $\ddagger\ddagger P < 0.01$.

with iIFG and IFG+IGT, despite significant differences in weight-related outcomes between the groups. The differences in outcomes in participants with iIGT versus other prediabetes metabolic phenotypes were minor and disappeared in the available-case analysis. This may be attributed to the small effect size and indeed small sample size of participants with iIGT. In the present analysis, iIFG and IFG+IGT accounted for 93.8% of the PREVIEW participants with prediabetes, while iIGT accounted for 6.2% only. A review of seven studies in Caucasian participants showed that according to the ADA criteria, the average proportional prevalences for iIFG, iIGT, and IFG+IGT were 58.0%, 20.3%, and 19.8%, respectively (28). Balion et al. (29) demonstrated that the reproducibility was lower for IGT compared with IFG.

Very few previous studies have investigated prediabetes metabolic phenotype and cardiometabolic benefits from long-term lifestyle interventions, but some studies reported differences between individuals with IFG+IGT versus iIFG in type 2 diabetes incidence. In the Innovative Medicines Initiative Diabetes Research on Patient Stratification (IMI DIRECT) study, without intervention,

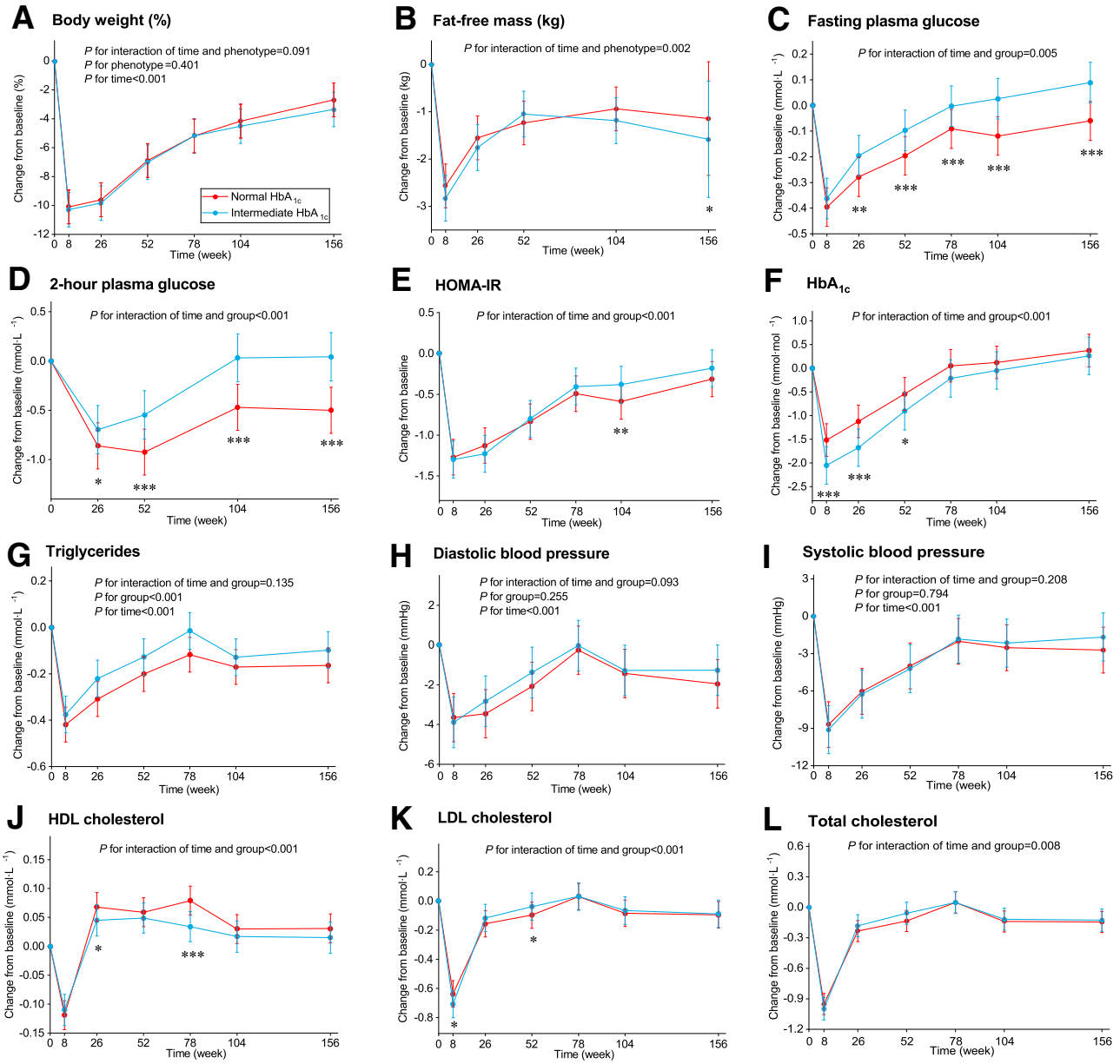

Figure 3—Changes in body weight and cardiometabolic risk factors in prediabetes with normal or intermediate HbA_{1c}. Values are estimated marginal mean (95% CI) in changes in body weight in percentage (*A*), fat-free mass (*B*), fasting plasma glucose (*C*), 2-h plasma glucose (*D*), HOMA-IR (*E*), HbA_{1c} (*F*), triglycerides (*G*), diastolic blood pressure (*H*), systolic blood pressure (*I*), HDL cholesterol (*J*), LDL cholesterol (*K*), and total cholesterol (*L*) from baseline in prediabetes with normal or intermediate HbA_{1c}. Analyses were performed using a linear mixed model adjusted for age, sex, race/ethnicity, baseline BMI, baseline smoking habits, baseline alcohol drinking, baseline values of the outcome being considered (baseline body weight in kg was added as an explanatory variable when percentage weight loss was added as a dependent variable), intervention arm, and time as fixed covariates, and participant identifier and intervention site as random effects. Time-by-group interaction terms were added. Post hoc pairwise comparisons (independent-samples *t* test) were performed to compare groups at each time point, where appropriate. Normal vs intermediate HbA_{1c}: $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

diabetes incidence was higher in individuals with IFG+IGT versus iIFG (30). This pattern, however, did not change after the lifestyle intervention. We found that individuals with IFG+IGT had higher 3 year incidence of type 2 diabetes (5.5%) than those with iIFG (3.2%), but with no statistical significance. Similarly, Saito et al. (12) showed that after the lifestyle intervention, 3 year cumulative diabetes incidence was almost 20% in IFG+IGT and only 7% in iIFG. In addition, they found that compared with the control therapy, the lifestyle intervention was more effective in reducing diabetes incidence in IFG+IGT, whereas there was no effect in iIFG (12). As diabetes is one of the drivers of CVD (31) and IGT has been shown to be more strongly associated with CVD risk than IFG (32), individuals with iIGT may need more intensive or additional interventions (e.g., lifestyle intervention plus pharmacotherapy) for prevention of diabetes and CVD.

In accord with previous studies (13,14), the agreement of prediabetes defined

using 2-h OGTT and HbA_{1c} was poor in the present analysis, with only 25% of participants having both prediabetic hyperglycemia and intermediate HbA_{1c}. This means that if prediabetes had been defined by using only HbA_{1c}, >70% of participants would not have met the criteria for enrollment and not been eligible for the intervention. In the IMI DIRECT study, individuals with prediabetic hyperglycemia, but normal HbA_{1c}, had higher risk of developing type 2 diabetes than those with normal glucose tolerance (30). Accordingly, in diabetes and CVD prevention, individuals with prediabetic hyperglycemia but normal HbA_{1c} should also be considered a target population and should not be ignored. Moreover, in the IMI DIRECT study, individuals with both prediabetic hyperglycemia and intermediate HbA_{1c}, especially with intermediate HbA_{1c}+IFG+IGT, had more severe impairments of both β-cell function and insulin sensitivity and higher risk of developing diabetes, compared with those with iIFG and iIGT (30). In the Whitehall II Study, while Vistisen et al. (33) demonstrated that prediabetes phenotypes influenced CVD risk, the risk was primarily explained by the clustering of cardiometabolic risk factors associated with hyperglycemia (e.g., elevated total cholesterol, reduced HDL cholesterol, or high systolic blood pressure). In the present analysis, however, we found that those with intermediate HbA_{1c} had smaller improvements in cardiometabolic risk factors, despite similar baseline lipid profiles and blood pressure compared with those with normal HbA_{1c}. Thus, for CVD prevention in prediabetes, risk stratification based on both plasma glucose and HbA_{1c}, or even multiple metabolic parameters, may be needed.

Recently, several studies have paid attention to risk stratification and personalized prevention of type 2 diabetes and CVD (34). Our findings suggest that high-risk participants (i.e., those with IFG+IGT or those with both prediabetic hyperglycemia and intermediate HbA_{1c}) had comparable or smaller improvements during the lifestyle intervention compared with low-risk counterparts (i.e., those with iIFG or iIGT or those with prediabetic hyperglycemia but normal HbA_{1c}). This is consistent with Stefan et al. (35) who reported that high-risk participants (i.e., those with IFG+IGT) had a smaller reduction in 2 h plasma glucose after a 9 month lifestyle intervention. Fritsche et al. (36) demonstrated that an intensified lifestyle intervention with doubling of required exercise in high-risk individuals with prediabetes improved cardiometabolic risk factors. In the current study, we also showed that individuals with both prediabetic hyperglycemia and intermediate HbA_{1c} had a higher diabetes incidence than those with normal HbA_{1c}. In a retrospective observational study, Armato et al. (37) showed that in high-risk individuals with prediabetes, lifestyle interventions plus drugs markedly reduced the development of diabetes and improved cardiometabolic risk factors. Taken together, the available evidence implies that risk stratification and personalized interventions may be needed.

There are numerous strengths of the current study. Indeed, inclusion of both sexes across a wide age range (25–70 years) resulted in relatively representative sample. Moreover, the large sample size enabled us to make comparisons between those with iIFG and IFG+IGT and between those with normal and intermediate HbA_{1c}.

However, the current study is not without limitations. First, it is pertinent to note that the attrition rate at intervention cessation was high, and selection bias may be a concern. Nonetheless, to minimize the bias, missing data were imputed and a complete-case analysis was conducted. Most results were robust in the complete-case analysis.

Second, PREVIEW was a multiethnic study, but as it was conducted in European countries, Australia, and New Zealand, >80% of participants were Caucasian, resulting in an underrepresentation of participants from other races/ethnicities. Future research is therefore required to ascertain whether these findings can be generalized to individuals from other races/ethnicities.

Moreover, the subgroups in the current study were not prespecified in the PREVIEW protocol. Specifically, the sample size of the IGT subgroup was much smaller than the other subgroups, and therefore, undetectable differences between IGT and other groups are possible. In addition, the baseline characteristics of subgroups were not balanced (e.g., the iIGT group was younger than the other subgroups). Although we adjusted for age, it was not possible to completely remove all age-related confounders (e.g., CVD risk at baseline), which may have influenced the results.

Finally, the day-to-day variation of fasting plasma glucose may affect the classification of prediabetes phenotypes and cause bias. The 7 day average of fasting plasma glucose determined using continuous glucose monitoring may reduce the bias on classification of phenotype. Taken together, our findings therefore need to be interpreted with caution and require further verification.

In conclusion, the present analyses show that individuals with iIFG and IFG+IGT had similar improvements in cardiometabolic risk factors after the lifestyle intervention, despite greater sustained weight loss in those with IFG+IGT. Individuals with prediabetic hyperglycemia but normal HbA_{1c} had a lower incidence of type 2 diabetes and greater improvements in cardiometabolic health than those with intermediate HbA_{1c}. For individuals with prediabetes, risk stratification based on both plasma glucose and HbA_{1c} and personalized CVD prevention may be needed, and those with intermediate HbA_{1c} may needed more intensive interventions.

Acknowledgments. The PREVIEW consortium would like to thank all study participants at every intervention site 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 the Supplementary Materials. Specifically, the authors would like to thank Edith Feskens (Wageningen University), who contributed to designing the PREVIEW project, Thomas Meinert Larsen, who contributed to writing the protocol for the PREVIEW adult intervention study, Pia Siig Vestentoft (University of Copenhagen), and Wolfgang Schlicht (University of Stuttgart), who contributed to designing the PREVIEW project and to designing the study.

Funding. Funding was received from the European Union Framework Programme 7 (FP7/2007-2013) grant agreement no. 312057, the National Health and Medical Research Council—European Union 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 no. 4/191), and University of Auckland Faculty Research Development Fund. The Cambridge Weight Plan donated all products for the 8-week weight loss period. Funding was received from the Danish Agriculture & Food Council and the Danish Meat and Research Institute. Funding was received from the National Institute for Health Research Biomedical Research

Centre (U.K.), the Biotechnology and Biological Sciences Research Council (U.K.), and the Engineering and Physical Sciences Research Council (U.K.). Nutritics (Dublin. Ireland) donated all dietary analyses software used by University of Nottingham. Support was received from the Juho Vainio Foundation (Finland), 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 (Finland), Jenny and Antti Wihuri Foundation (Finland), Emil Aaltonen Foundation (Finland), and the China Scholarship Council.

Duality of Interest. A.R. has received honorariums from the International Sweeteners Association and Unilever. I.A.M. was 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, and was also a member of the Nestlé Research Scientific Advisory Board, and of the Novozymes Scientific Advisory Board. He withdrew from all of these roles in 2020 and on 1 August 2020 became Professor Emeritus at the University of Nottingham and took up the post of Scientific Director of the Nestlé Institute of Health Sciences in Lausanne, Switzerland. J.B.-M. is President and Director of the Glycemic Index Foundation, oversees a glycemic index testing service at the University of Sydney. She is also a member of the Scientific Advisory Board of the Novo Nordisk Foundation and of ZOE Global. S.D.P. was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.Z. drafted the manuscript. S.D.P., S.H., G.S., I.A.M., J.A.M., and M.S.W.-P., were involved in developing the study design. J.B.-M., M.F., M.S.W.-P., and A.R., designed the PREVIEW project. M.F. and A.R. wrote the protocol for the PREVIEW adult intervention study. R.Z., A.R., T.C.A., J.B.-M., M.F., M.S.W.-P., S.D.P., S.H., G.S., I.A.M., J.A.M., E.J., M.P.S., T.H.-D., M.H.-L., K.M., S.N.-C., K.H.P., E.S., R.M., and K.F. 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. R.Z., T.C.A., A.R., and M.S.W.-P. designed the current post hoc analysis. 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.

References

1. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012;379:2279–2290
2. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1): S17–S38
3. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119
4. Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ 2020;370:m2297
5. Færch K, Vistisen D, Johansen NB, Jørgensen ME. Cardiovascular risk stratification and management in pre-diabetes. Curr Diab Rep 2014;14:493
6. Welsh C, Welsh P, Celis-Morales CA, et al. Glycated hemoglobin, prediabetes, and the links to cardiovascular disease: data from UK Biobank. Diabetes Care 2020;43:440–445
7. Diabetes Prevention Program Outcomes Study Research Group; Orchard TJ, Temprosa M, Barrett-Connor E, et al. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013;30:46–55
8. Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019;7:452–461
9. Faerch K, Hulmán A, Solomon TP. Heterogeneity of pre-diabetes and type 2 diabetes: implications for prediction, prevention and treatment responsiveness. Curr Diabetes Rev 2016;12:30–41
10. Campbell MD, Sathish T, Zimmet PZ, et al. Benefit of lifestyle-based T2DM prevention is influenced by prediabetes phenotype. Nat Rev Endocrinol 2020;16:395–400
11. Sathish T, Tapp RJ, Shaw JE. Do lifestyle interventions reduce diabetes incidence in people with isolated impaired fasting glucose? Diabetes Obes Metab 2021;23:2827–2828
12. Saito T, Watanabe M, Nishida J, et al.; Zensharen Study for Prevention of Lifestyle Diseases Group. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med 2011;171:1352–1360
13. Saukkonen T, Cederberg H, Jokelainen J, et al. Limited overlap between intermediate hyperglycemia as defined by A1C 5.7-6.4%, impaired fasting glucose, and impaired glucose tolerance. Diabetes Care 2011;34:2314–2316
14. Chatzianagnostou K, Vigna L, Di Piazza S, et al. Low concordance between HbA1c and OGTT to diagnose prediabetes and diabetes in overweight or obesity. Clin Endocrinol (Oxf) 2019;91:411–416
15. Raben A, Vestentoft PS, Brand-Miller J, et al. The PREVIEW intervention study: 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;23:324–337
16. Fogelholm M, Larsen TM, Westerterp-Plantenga M, 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;9:632
17. Christensen P, Meinert Larsen T, Westerterp-Plantenga M, 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;20:2840–2851
18. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004; 27:1487–1495
19. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. The TyG index may predict the development of cardiovascular events. Eur J Clin Invest 2016;46:189–197
20. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. 21 April 2006. Accessed 19 July 2017. Available from https://www.who.int/publications/i/item/definition-and-diagnosis-of-diabetes-mellitus-and-intermediate-hyperglycaemia
21. Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. JAMA 2019;322:642–650
22. Chiva-Blanch G, Badimon L. Benefits and risks of moderate alcohol consumption on cardiovascular disease: current findings and controversies. Nutrients 2019;12:108
23. Malik MO, Govan L, Petrie JR, et al.; Scottish Diabetes Research Network Epidemiology Group. Ethnicity and risk of cardiovascular disease (CVD): 4.8 year follow-up of patients with type 2 diabetes living in Scotland. Diabetologia 2015;58: 716–725
24. Barbaresko J, Rienks J, Nöthlings U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. Am J Prev Med 2018;55:555–564
25. Nathan DM, Davidson MB, DeFronzo RA, et al.; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–759
26. Khazem S, Itani L, Kreidieh D, et al. Reduced lean body mass and cardiometabolic diseases in adult males with overweight and obesity: a pilot study. Int J Environ Res Public Health 2018;15:2754
27. Spahillari A, Mukamal KJ, DeFilippi C, et al. The association of lean and fat mass with all-cause mortality in older adults: the Cardiovascular Health Study. Nutr Metab Cardiovasc Dis 2016;26: 1039–1047
28. Yip WCY, Sequeira IR, Plank LD, Poppitt SD. Prevalence of pre-diabetes across ethnicities: a review of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) for classification of dysglycaemia. Nutrients 2017;9:1273
29. Balion CM, Raina PS, Gerstein HC, et al. Reproducibility of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) classification: a systematic review. Clin Chem Lab Med 2007;45: 1180–1185
30. Tura A, Grespan E, Göbl CS, et al.; IMI DIRECT Consortium. Profiles of glucose metabolism in different prediabetes phenotypes, classified by fasting glycemia, 2-hour OGTT, glycated hemoglobin, and 1-hour OGTT: an IMI DIRECT Study. Diabetes 2021;70:2092–2106
31. Almourani R, Chinnakotla B, Patel R, Kurukulasuriya LR, Sowers J. Diabetes and cardiovascular disease: an update. Curr Diab Rep 2019;19:161

32. Abdul-Ghani M, DeFronzo RA, Jayyousi A. Prediabetes and risk of diabetes and associated complications: impaired fasting glucose versus impaired glucose tolerance: does it matter? Curr Opin Clin Nutr Metab Care 2016;19:394–399
33. Vistisen D, Witte DR, Brunner EJ, et al. Risk of cardiovascular disease and death in individuals with prediabetes defined by different criteria: the Whitehall II study. Diabetes Care 2018;41:899–906
34. Stefan N, Fritsche A, Schick F, Häring HU. Phenotypes of prediabetes and stratification of cardiometabolic risk. Lancet Diabetes Endocrinol 2016;4:789–798
35. Stefan N, Staiger H, Wagner R, et al. A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. Diabetologia 2015;58:2877–2884
36. Fritsche A, Wagner R, Heni M, et al. Different effects of lifestyle intervention in high- and low-risk prediabetes: results of the randomized controlled Prediabetes Lifestyle Intervention Study (PLIS). Diabetes 2021;70:2785–2795
37. Armato JP, DeFronzo RA, Abdul-Ghani M, Ruby RJ. Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES). Lancet Diabetes Endocrinol 2018;6:781–789