Title Page

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

Running title: prediabetes phenotype and lifestyle intervention

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

[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 Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria

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

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

[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]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

[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, 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

[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), CEI UAM + 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 (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）

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ABSTRACT

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 multi-center, randomized trial, PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World (PREVIEW), included 1510 participants with prediabetes (BMI≥25 $kg \cdot m^{-2}$; 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 HbA_{1c} (<39 $mmol \cdot mol^{-1}$) and 25% had intermediate HbA_{1c} (39–47 $mmol \cdot mol^{-1}$). 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

vs intermediate HbA_{1c} had similar WL 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-hour glucose (adjusted between-group difference at 156 weeks -0.54 $mmol \cdot L^{-1}$ [-0.70, -0.39]; $P<0.001$), and triglycerides (difference -0.07 $mmol \cdot L^{-1}$ [-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}.

INTRODUCTION

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 in comparison to 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 either

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} vs those with intermediate hyperglycemia, but normal HbA_{1c} remains unknown.

The 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 HbA_{1c} (normal vs intermediate HbA_{1c} levels; HbA_{1c} <39 mmol·mol^{-1} vs HbA_{1c} 39–47 mmol·mol^{-1}) were compared.

RESEARCH DESIGN AND METHODS

Study Design

The present secondary analysis used data from the PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World (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, multi-center, 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 2 dietary intervention arms. The study was conducted between June 2013 and March 2018 at 8 intervention sites in Denmark, Finland, the Netherlands, the UK, 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 males and females aged 25–70 years with a body mass index (BMI)≥25 $kg \cdot m^{-2}$ and prediabetes. Prediabetes was assessed at the screening visit in the local labs 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, Switzerland; or EML105 Radiometer, Copenhagen). Fasting plasma glucose and 2-hour plasma glucose were estimated by multiplying whole blood glucose by 1.11. HbA_{1c} was not used to identify prediabetes at screening. Those with pre-existing diabetes or significant CVD were excluded during enrolment.

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 weight-loss phase, all participants were given total low-energy diet replacement products (810 kcal or 3400 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 1 of 4 intervention arms and were eligible to commence the weight-maintenance phase. The intervention arms were a combination of 2 diets and 2 PA programs. The detailed information about intervention arms is included in **Supplemental Material**. Diet compliance was mainly evaluated using 4-day food records and 24-hour urine nitrogen (biomarker for protein), and PA compliance was primarily evaluated using 7-day accelerometry at baseline and 26, 52, 104, and 156 weeks (**Supplementary Table 2**).

Outcomes Measures

Outcome measures were body weight, fat mass, fat-free mass, fasting plasma glucose, 2-hour plasma glucose, fasting insulin, HbA_{1c}, total cholesterol, low-density lipoprotein (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 hours of fasting. Blood samples were drawn from the antecubital vein and initially stored at −80℃ 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, USA). The outcomes were collected at 7 clinical investigation

days (at 0, 8, 26, 52, 78, 104 and 156 weeks, respectively) (see **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. Homeostasis model for assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin in $mU \cdot L^{-1}$×fasting plasma glucose in $mmol \cdot L^{-1}/22.5$ (18). The triglyceride-glucose (TyG) index, a predictor of CVD events, was calculated as Ln[triglycerides ($mg \cdot dL^{-1}$)× fasting plasma glucose ($mg \cdot dL^{-1}$)/2] (19).

Type 2 diabetes ascertainment

Type 2 diabetes was diagnosed by an OGTT (fasting plasma glucose≥7.0 $mmol \cdot L^{-1}$ and/or 2-hour plasma glucose≥11.1 $mmol \cdot L^{-1}$) conducted at the intervention site or 2) 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 baseline fasting plasma glucose and 2-hour plasma glucose analyzed at the Finnish Institute for Health and Welfare, regardless of the data collected at screening using local glucose analyzers. HbA_{1c} was not used to define prediabetes at the study commencement in 2013. Using the ADA criteria (2), participants with prediabetes were stratified into metabolic phenotypes having iIFG (fasting plasma glucose 5.6–6.9 $mmol \cdot L^{-1}$ and 2-hour plasma glucose <7.8 $mmol \cdot L^{-1}$), iIGT (fasting plasma glucose<5.6 $mmol \cdot L^{-1}$ and 2-hour plasma glucose 7.8–11.0 $mmol \cdot L^{-1}$), or IFG+IGT (fasting

plasma glucose 5.6–6.9 mmol·L^{-1} and 2-hour 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-hour plasma glucose data from the central laboratory (unidentifiable glycemic status) were excluded from the present analysis. We merged all participants into 1 intervention group and re-classified 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 vs 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, 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 percentage weight loss was added as a dependent variable), time (categorical; week), intervention arms, and

random effects including participant identifier and intervention site. A 2-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 p-p plots. Missing data were accounted for using the expectation maximization algorithm. The above analyses were conducted in available cases (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 percentage 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; 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 **Supplemental Material**.

Descriptive statistics is described in **Supplemental Material**. Data analyses were performed using IBM SPSS 28.0 (Chicago, IL, USA). Statistical significance was determined as $P \leq 0.05$ in 2-sided tests.

RESULTS

Participants

In total, 1510 participants were included in the present analysis (**Supplementary Figure 1**). Of these, 869 (58%) had iIFG, 93 (6%) had iIGT and 548 (36%) had IFG+IGT; 1106 (73%) had normal HbA_{1c} levels and 384 (25%) had intermediate HbA_{1c} levels. Five participants with diabetic HbA_{1c} and 15 with missing HbA_{1c} at baseline were excluded from the present analysis. 1268 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 non-completers, 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, baseline outcomes of interest, participants with iIFG, iIGT, and IFG+IGT had a similar weight loss (adjusted mean~-10.3 kg or -10.3%) at 8 weeks (the rapid weight loss period using a low-energy diet; **Figure 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 Figure 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 $mmol \cdot L^{-1}$ [95% CI, -0.12, -0.005]; P=0.029; **Figure 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 $mmol \cdot mol^{-1}$ [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 $mmol \cdot mol^{-1}$ [-1.21, -0.28]; P<0.001). There were no differences in changes in other

cardiometabolic risk factors over 3 years **Figure 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 vs iIFG (**Supplementary Figure 3**). After subsequent adjustment for weight loss (%), there was a greater decrease in 2-hour plasma glucose at 104 and 156 weeks in participants with iIGT vs IFG+IGT and a greater increase in HDL cholesterol over 3 years in participants with iIFG vs IFG+IGT (**Supplementary Figure 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 vs intermediate HbA_{1c} over 3 years (**Figure 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-hour 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 $mmol \cdot L^{-1}$ [95% CI, 0.10, 0.20]; *P*<0.001; in 2-hour plasma glucose at 156 weeks 0.54 $mmol \cdot L^{-1}$ [0.39, 0.70]; *P*<0.001; in TyG at 156 weeks 0.06 [0.03, 0.10]; *P*<0.001; **Figure 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-hour plasma glucose, triglycerides and TyG at 156 weeks still remained robust (**Supplementary Figure 5**).

Type 2 diabetes incidence

The total number of cases of type 2 diabetes was 29 (13 iIFG, 2 iIGT, and 14 IFG+IGT; 13 normal HbA_{1c} and 15 intermediate HbA_{1c}). The 3-year cumulative incidence was 3.2% in iIFG, 5.1% in iIGT and 5.5% in IFG+IGT; and 2.6% in those with normal HbA_{1c} and 7.9% with intermediate HbA_{1c} (**Supplementary Figure 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} vs normal HbA_{1c} (*P*=0.053).

CONCLUSIONS

We found that participants with iIFG vs 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 vs IFG+IGT were minor or inconsistent in different analyses. Participants with prediabetes and normal vs 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-hour plasma glucose, and triglycerides, and TyG during the lifestyle intervention compared with those with intermediate HbA_{1c}. Participants 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 vs 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 present study, 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 with iIFG and IFG+IGT, despite significant differences in weight-related outcomes between the groups. The differences in outcomes in participants with iIGT vs 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 7 studies in Caucasian participants showed that according to the ADA criteria, the average proportional prevalence 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 to 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 vs iIFG in type 2 diabetes incidence. In the Innovative Medicines Initiative Diabetes Research on Patient Stratification (IMI DIRECT) study, without intervention, diabetes incidence was higher in individuals with IFG+IGT vs 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 (3.2 %) than those with iIFG (5.5 %), 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-hour 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}, more than 70% of participants would not have met the criteria for enrolment 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, whilst 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-hour 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 present study we also showed that individuals with both prediabetic hyperglycemia and intermediate HbA_{1c} had 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 present 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 present 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 multi-ethnic study, but as it was conducted in European countries, Australia, and New Zealand, more than 80% of participants were Caucasian resulting in an under-representation of participants from other ethnicities. Future research is therefore required to ascertain whether these findings can be generalized to individuals from other ethnicities. Moreover, the subgroups in the present study were not pre-

specified 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. Seven-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 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: those with intermediate HbA_{1c} may needed more intensive interventions.

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Conflict of interest. AR has received honorariums from the International Sweeteners Association and Unilever. IAM was a 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 withdrew from all of these roles in 2020 and on August 1 2020 became Professor Emeritus at the University of Nottingham and took up the post of Scientific Director of the Nestle Institute of Health Sciences in Lausanne, Switzerland. JB-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 Nordisk Foundation and of ZOE Global. SDP was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. No relevant disclosures from other authors.

Author Contributions. The PREVIEW project was designed by AR, JB-M, MW-P, MF, Wolfgang Schlicht (WS), and Edith Feskens. The protocol for the PREVIEW adult

intervention study was written by MF, TML, and AR. MW-P, IM, JAM, SP, WS, GS, and SH were involved in developing the study design. RZ drafted the manuscript. 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. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted. AR and RZ 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. RZ takes responsibility for the accuracy of the data analysis.

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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=1106)**	**Intermediate hyperglycemia and intermediate HbA_{1c} level (n=384)**	***P*-value‡**
Socio-demographics							
Age, years	55 (43, 61)	45 (37, 58)	56 (45, 63)	<0.001	55 (42, 61)	56 (46, 62)	<0.001
Sex				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%)	–
Ethnicity				<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				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				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-hour 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
Triglyceride-glucose 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 blood pressure, 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 blood pressure, 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), median (25th, 75th percentiles), or n (%). HbA_{1c}, hemoglobin A_{1c}; HDL cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance; LDL cholesterol, low-density lipoprotein cholesterol. *Including Asian, Black, Arabic, Hispanic, and other. χ^2 test was based on full categories. $^{\dagger}P$ for differences in baseline characteristics among participants with different prediabetes metabolic phenotypes, examined using 1-way ANOVA, a Kruskal−Wallis *H* non-parametric test, and a χ^2 test. $^{\ddagger}P$ for differences in baseline characteristics between participants with normal vs intermediate HbA_{1c}, examined using an independent-samples *t* test, a Mann−Whitney *U* non-parametric 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 % (B), fat mass in kg (C), and fat-free mass in kg (D) from baseline in different prediabetes metabolic phenotypes. iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance; prediabetes metabolic phenotype was defined at baseline. Analyses were performed using a linear mixed model adjusted for age, sex, ethnicity, baseline BMI, baseline smoking habits, 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 $^{\dagger\dagger\dagger}P < 0.001$.

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-hour 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. HbA_{1c}, hemoglobin A_{1c}; HDL cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance; LDL cholesterol, low-density lipoprotein cholesterol; prediabetes metabolic phenotype was defined at baseline. Analyses were performed using a linear mixed model adjusted for age, sex, 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 $^{\ddagger\ddagger}P < 0.01$.

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 % (A), fat-free mass (B), fasting plasma glucose (C), 2-hour 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}. HbA_{1c}, hemoglobin A_{1c}; HDL cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein cholesterol. Analyses were performed using a linear mixed model adjusted for age, sex, 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 $^{***}P < 0.001$.