Online-Only Supplemental Material

Intervention

The 2 diets were either a high-protein diet with 25 E% protein, 30 E% fat, 45 E% carbohydrates, and low glycemic index (GI; <50), or a moderate-protein diet with 15 E% protein, 30 E% fat, 55 E% carbohydrates, and moderate GI (56–70). The diets were consumed ad libitum without energy restriction; instead, participants were given advice on meal portion sizes to maintain weight loss. The PA programs consisted of either a high-intensity PA for 75 min·week^{-1} or a moderate-intensity PA for 150 min·week^{-1}. In order to improve the diet and PA compliance, participants were supported in behavior change with group counselling visits, using the PREVIEW Behavior Modification Intervention Toolbox (PREMIT) (1,2).

1. Kahlert D, Unyi-Reicherz A, Stratton G, et al. PREVIEW behavior modification intervention toolbox (PREMIT): a study protocol for a psychological element of a multicenter project. Front Psychol 2016;7:1136

2. Huttunen-Lenz M, Hansen S, Christensen P, et al. PREVIEW study-influence of a behavior modification intervention (PREMIT) in over 2300 people with pre-diabetes: intention, self-efficacy and outcome expectancies during the early phase of a lifestyle intervention. Psychol Res Behav Manag 2018;11:383-394

Statistical Analyses

Differences in baseline characteristics among prediabetes metabolic phenotypes (e.g. iIFG, iIGT, or IFG+IGT) or between those with normal vs intermediate HbA_{1c} levels were examined using an independent-samples *t* test or a 1-way ANOVA for approximately normally-distributed variables, a Mann−Whitney *U* or a Kruskal−Wallis *H* non-parametric test for non-normally-distributed variables, and a χ^2 test for categorical variables.

Cumulative incidence of type 2 diabetes by prediabetes metabolic phenotypes was calculated using the Kaplan–Meier method, without adjustment. Because of the visit windows, some participants had a longer (>156 weeks) survival time and we assumed that their last status was observed at 156 weeks. Diabetes incidence across prediabetes metabolic phenotypes was determined using a time-dependent Cox hazards regression model, adjusted for Ln(time)×phenotype, ethnicity, baseline smoking status, baseline alcohol drinking, baseline BMI, intervention arm and intervention site. The proportional hazards assumption was evaluated using a Wald test of the interaction of prediabetes metabolic phenotypes and time.

Supplementary Table 1. Human Ethics Committees for each intervention site

Intervention sites	Human Ethics Committees
Denmark (University of Copenhagen)	The Research Ethics Committees of the Capital Region
Finland (University of Helsinki)	Coordinating Ethical Committee of HUS (Helsinki and Uusimaa Hospital District)
The Netherlands (University of Maastricht)	Medical Ethics Committee of the Maastricht University Medical Centre
The UK (University of Nottingham)	UK National Research Ethics Service (NRES) and East Midlands (Leicester) Ethics Committee
Spain (University of Navarra)	Research Ethics Committee of the University of Navarra
Bulgaria (Medical University of Sofia)	Commission on Ethics in Scientific Research with the Medical University-Sofia (KENIMUS)
Australia (University of Sydney)	The University of Sydney, Human Research Ethics Committee (HREC)
New Zealand (University of Auckland)	Health and Disability Ethics Committees (HDEC)

Resource: Zhu, R., Craciun, I., Bernhards-Werge, J. *et al.* Age- and sex-specific effects of a long-term lifestyle intervention on body weight and cardiometabolic health markers in adults with prediabetes: results from the diabetes prevention study PREVIEW. *Diabetologia* (2022). https://doi.org/10.1007/s00125-022-05716-3; Springer Nature

Supplementary Table 2. Overview of data collection

	0 weeks	8 weeks	26 weeks	52 weeks	78 weeks	104 weeks	156 weeks
Socio-demographics (age, sex, ethnicity, smoking habits, and alcohol drinking)	×						
Anthropometry (body weight and waist circumference)	×	×	×	×	×	×	×
Body composition (fat mass and fat-free mass)	×	×	×	×		×	×
Glucose metabolism (fasting plasma glucose, HbA_{1c}, and fasting insulin)	×	×	×	×		×	×
Glucose metabolism (2-hour plasma glucose)	×		×	×		×	×
Blood pressure (systolic blood pressure and diastolic blood pressure)	×	×	×	×		×	×
Lipid metabolism (total cholesterol, high-density lipoprotein cholesterol, and fasting triglycerides)	×	×	×	×		×	×
Dietary intake*	×		×	×		×	×
Physical activity*	×		×	×		×	×

HbA_{1c}, hemoglobin A_{1c}. *Baseline dietary intake and physical activity and changes in dietary intake and physical activity from baseline were calculated and added to the linear mixed model. The macronutrient composition of the low-energy diet (3400 $kJ \cdot day^{-1}$, protein 43.7 E%, carbohydrate 41.2 E%, fat 15.1 E%, fiber 13.3 $g \cdot day^{-1}$) will be used to estimate dietary intake at 8 weeks. Physical activity at 0 weeks was used to estimate physical activity at 8 weeks, assuming that physical activity did not change from during the weight loss phase. Average dietary intake at 52 and 104 weeks was used to estimate dietary intake at 78 weeks. Average physical activity at 52 and 104 weeks was used to estimate physical activity at 78 weeks.

Resource: Zhu, R., Craciun, I., Bernhards-Werge, J. *et al.* Age- and sex-specific effects of a long-term lifestyle intervention on body weight and cardiometabolic health markers in adults with prediabetes: results from the diabetes prevention study PREVIEW. *Diabetologia* (2022). https://doi.org/10.1007/s00125-022-05716-3; Springer Nature

Supplementary Table 3. Ethnicity

	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†**
Ethnicity				<0.001			<0.001
Caucasian	773 (89.0%)	70 (75.3%)	488 (89.1%)	–	1012 (91.5%)	300 (78.1%)	–
Asian	16 (1.8%)	11 (11.8%)	13 (2.4%)	–	19 (1.7%)	21 (5.5%)	–
Black	13 (1.5%)	1 (1.1%)	6 (1.1%)	–	10 (0.9%)	10 (2.6%)	–
Arabic	2 (0.2%)	0 (0%)	2 (0.4%)	–	1 (0.1%)	3 (0.8%)	–
Hispanic	22 (2.5%)	2 (2.2%)	9 (1.6%)	–	23 (2.1%)	10 (2.6%)	–
Other	43 (4.9%)	9 (9.7%)	30 (5.5%)	–	41 (3.7%)	40 (10.4%)	–

Data are n (%). iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance. **P* for differences in ethnicity between participants with different prediabetes metabolic phenotypes, examined using a χ^2 test. †*P* for differences in ethnicity between participants with normal vs intermediate HbA_{1c}, examined using a χ^2 test.

Supplementary Table 4. Completer and non-completer characteristics at baseline

	Completers (n=685)	**Non-completers† (n=825)**	***P*-value‡**
Prediabetes phenotypes			–
iIFG	402 (58.7%)	467 (56.6%)	0.055
iIGT	31 (4.5%)	62 (7.5%)	
IFG+IGT	252 (36.8%)	296 (35.9%)	
Normal HbA_{1c}	508 (74.6%)	598 (73.9%)	0.493
Intermediate HbA_{1c}	173 (25.4%)	211 (26.1%)	
Socio-demographics			
Age, years	58 (49, 63)	50 (40, 59)	<0.001
Sex			<0.001
Women	421 (61.5%)	579 (70.2%)	–
Men	264 (38.5%)	246 (29.8%)	–
Ethnicity			<0.001
Caucasian	641 (93.6%)	690 (83.6%)	–
Other*	44 (6.4%)	135 (16.4%)	–
Smoking			<0.001
No	617 (90.1%)	662 (80.2%)	–
Yes, but less than weekly	20 (2.9%)	122 (14.8%)	–
Yes, at least daily	40 (5.8%)	30 (3.6%)	–
Missing	8 (1.2%)	11 (1.3%)	–
Drinking			<0.001
No	173 (25.3%)	308 (37.3%)	–
Yes	505 (73.7%)	505 (61.2%)	–
Missing	7 (1.0%)	12 (1.5%)	–
Anthropometry and body composition			
Body weight, kg	93.5 (83.6, 105.1)	100.3 (87.3, 116.5)	<0.001
Height, m	1.68 (1.62, 1.76)	1.67 (1.61, 1.74)	0.003
BMI, $kg \cdot m^{-2}$	32.6 (30.0, 36.1)	35.4 (31.7, 40.7)	<0.001
Fat mass, kg	37.9 (31.3, 46.3)	43.3 (35.5, 53.9)	<0.001
Fat-free mass, kg	53.0 (47.4, 64.1)	55.3 (48.2, 65.0)	0.088
Glucose metabolism			
Fasting plasma glucose, $mmol \cdot L^{-1}$	6.2 (0.4)	6.1 (0.4)	0.034
2-hour plasma glucose, $mmol \cdot L^{-1}$	7.4 (1.8)	7.5 (1.7)	0.235
Fasting insulin, $mU \cdot L^{-1}$	10.7 (8.0, 15.0)	12.8 (9.3, 17.8)	<0.001
HOMA-IR	3.0 (2.2, 4.2)	2.9 (2.2, 4.2)	<0.001
HbA_{1c}, $mmol \cdot mol^{-1}$	36.6 (3.1)	36.6 (3.3)	0.650
HbA_{1c}, %	5.5 (0.3)	5.5 (0.3)	0.720

Lipid metabolism			
Fasting triglycerides, mmol·L^{-1}	1.3 (1.0, 1.7)	1.4 (1.1, 1.8)	0.028
Total cholesterol, mmol·L^{-1}	5.2 (1.0)	5.2 (1.0)	0.077
HDL cholesterol, mmol·L^{-1}	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	0.101
LDL cholesterol, mmol·L^{-1}	3.3 (2.6, 3.8)	3.2 (2.7, 3.8)	0.979
Blood pressure			
Systolic blood pressure, mmHg	130.1 (15.5)	129.2 (15.6)	0.292
Diastolic blood pressure, mmHg	79.0 (72.7, 85.3)	79.0 (70.0, 85.7)	0.226

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; LDL cholesterol, low-density lipoprotein cholesterol. *Including Asian, Black, Arabic, Hispanic, and other. χ^2 test was based on full categories. †Non-completers are the same as dropouts. ‡*P* for differences in baseline characteristics between completers and non-completers, examined using independent-sample t tests, a Mann−Whitney *U* non-parametric test, and a χ^2 test.

Supplementary Table 5. Dietary intake and physical activity by prediabetes metabolic phenotype

	Prediabetes phenotype	0 weeks	26 weeks	52 weeks	104 weeks	156 weeks	*P* for interaction of group and time	*P* for group main effect	*P* for time main effect
Carbohydrate, E%	iIFG	39.6 (0.3)	40.0 (0.3)	40.2 (0.3)	40.3 (0.4)	38.9 (0.4)	0.001	–	–
	iIGT	43.8 (0.8) †‡	40.4 (1.0)	41.8 (1.1)	41.4 (1.2)	43.9 (1.3) †‡			
	IFG+IGT	39.9 (0.4)	40.4 (0.4)	40.3 (0.4)	39.5 (0.4)	39.5 (0.5)			
	Normal HbA_{1c}	39.9 (0.3)	40.0 (0.3)	40.2 (0.3)	40.0 (0.3)	39.0 (0.3)	0.412	0.173	<0.001
	Intermediate HbA_{1c}	40.2 (0.4)	40.9 (0.5)	40.8 (0.5)	40.2 (0.5)	40.3 (0.5)			
Protein, E%	iIFG	17.7 (0.2)	20.5 (0.2)	20.1 (0.2)	19.9 (0.2)	20.1 (0.2)	0.304	0.601	<0.001
	iIGT	17.1 (0.5)	21.2 (0.6)	20.0 (0.6)	20.8 (0.7)	19.4 (0.7)			
	IFG+IGT	17.9 (0.2)	20.6 (0.2)	20.1 (0.2)	20.2 (0.2)	20.2 (0.3)			
	Normal HbA_{1c}	17.6 (0.1)	20.5 (0.2)	20.1 (0.2)	20.0 (0.2)	20.1 (0.2)	0.741	0.439	<0.001
	Intermediate HbA_{1c}	18.0 (0.2)	20.7 (0.3)	20.1 (0.3)	20.1 (0.3)	20.0 (0.3)			
Fat, E%	iIFG	37.2 (0.3)	33.6 (0.3)	33.9 (0.3)	34.5 (0.3)	35.3 (0.3)	0.109	0.155	<0.001
	iIGT	35.4 (0.8)	33.4 (0.9)	34.3 (1.0)	33.2 (1.1)	32.0 (1.2)			
	IFG+IGT	37.0 (0.3)	33.8 (0.4)	34.4 (0.4)	35.2 (0.4)	34.9 (0.4)			
	Normal HbA_{1c}	36.8 (0.2)	33.7 (0.3)	34.1 (0.3)	34.6 (0.3)	35.0 (0.3)	0.650	0.517	<0.001
	Intermediate HbA_{1c}	37.4 (0.4)	33.4 (0.4)	34.1 (0.5)	34.8 (0.5)	35.0 (0.5)			
Fiber, $g \cdot day^{-1}$	iIFG	22.2 (0.3)	23.4 (0.4)	22.9 (0.4)	21.8 (0.4)	21.2 (0.4)	0.029	–	–
	iIGT	23.2 (0.9)	22.1 (1.1)	25.6 (1.2) ‡	23.4 (1.3)	23.0 (1.4)			
	IFG+IGT	22.4 (0.4)	22.1 (0.4)	22.3 (0.5)	20.8 (0.5)	21.1 (0.5)			
	Normal HbA_{1c}	22.2 (0.3)	22.9 (0.3)	22.6 (0.3)	21.1 (0.4)	21.0 (0.4)	0.077	0.205	
	Intermediate HbA_{1c}	22.8 (0.5)	22.4 8 (0.5)	23.5 (0.6)	22.4 (0.6)	21.8 (0.6)			
Energy, $kcal \cdot day^{-1}$	iIFG	8925.3 (87.7)	7116.6 (98.7)	7009.6 (103.6)	6832.5 (110.4)	6804.3 (111.6)	0.289	0.106	<0.001
	iIGT	8761.1 (257.5)	7108.9 (306.7)	7682.0 (332.3)	7314.6 (355.2)	7417.8 (381.4)			
	IFG+IGT	8686.9 (106.5)	6828.3 (119.3)	6801.5 (126.6)	6707.1 (133.4)	6577.7 (137.5)			

	Normal HbA_{1c}	8824.9 (76.7)	7102.1 (86.1) §	6958.6 (91.1)	6758.6 (97.4)	6757.9 (99.1)	0.029	–	–
	Intermediate HbA_{1c}	8817.8 (126.9)	6741.7 (144.1)	6986.7 (152.0)	6965.1 (157.6)	6717.7 (162.6)			
Total physical activity, counts·min^{-1}	iIFG	301.9 (4.5)	336.5 (5.1)	318.6 (5.4)	314.4 (5.8)	304.1 (6.0)	0.138	0.038	<0.001
	iIGT	283.9 (14.0)	330.9 (16.4)	335.3 (16.9)	317.5 (18.9)	308.3 (21.0)			
	IFG+IGT	278.3 (5.6)	317.5 (6.3)	316.0 (6.7)	308.9 (7.0)	292.0 (7.4)			
	Normal HbA_{1c}	297.7 (4.0)	333.3 (4.5)	319.0 (4.8)	316.9 (5.1)	301.5 (5.3)	0.174	0.036	<0.001
	Intermediate HbA_{1c}	277.0 (6.8)	317.5 (7.7)	317.9 (8.1)	302.4 (8.3)	295.8 (8.8)			

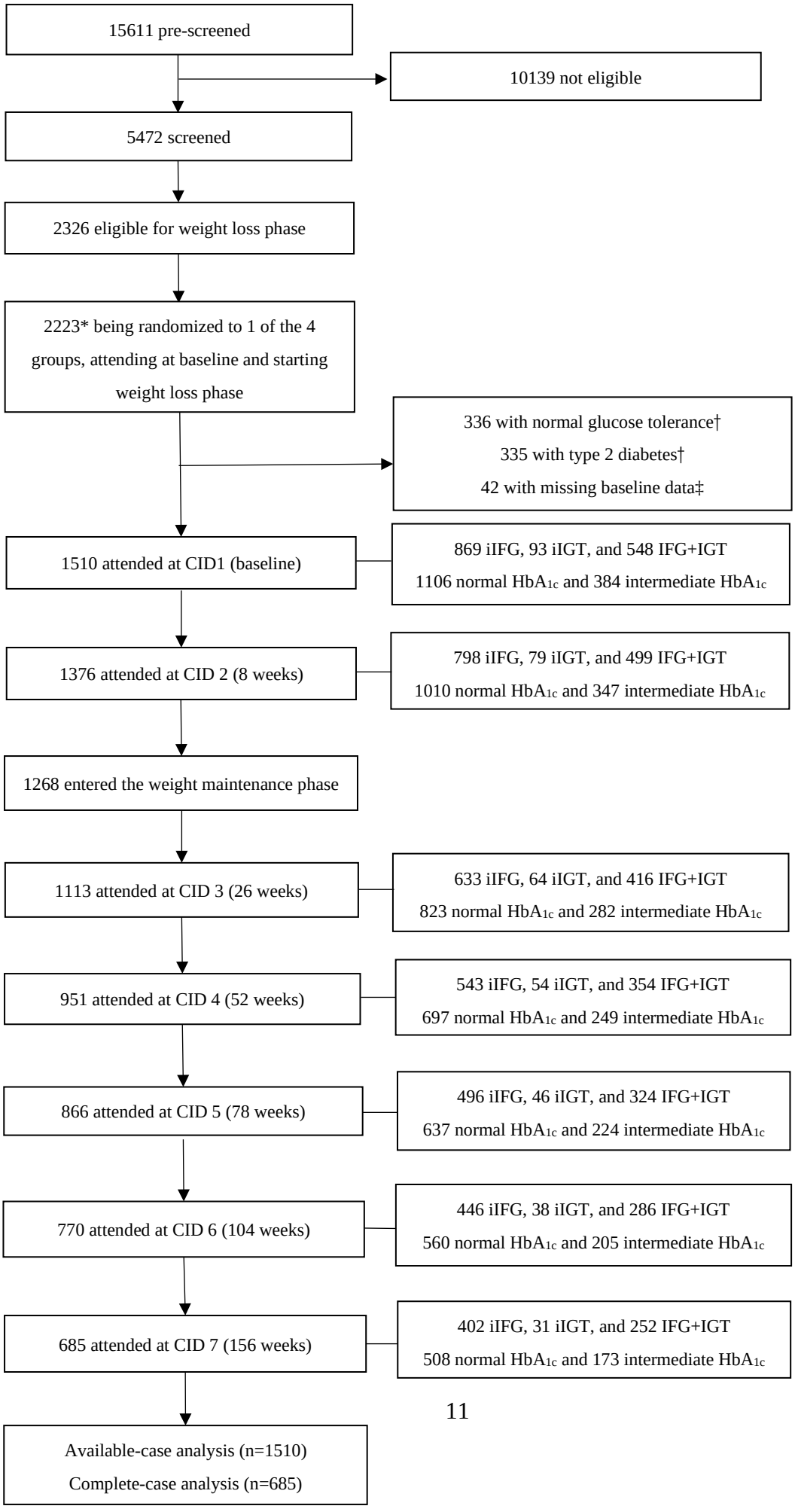
Data are estimated marginal mean (SE). Analyses were performed using a linear mixed model adjusted for time as fixed effects and participant identifier and intervention site as random effects. Time by group interaction terms were added. Post hoc analyses with multiple comparisons with Bonferroni correction were performed to compare groups at each time point, where appropriate. HbA_{1c}, hemoglobin A_{1c}; iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance; prediabetes metabolic phenotypes were defined at baseline. iIFG vs IFG+IGT $^{*}P < 0.05$; iIFG vs iIGT $^{\dagger}P < 0.05$; iIGT vs IFG+IGT $^{\ddagger}P < 0.05$; normal vs intermediate HbA_{1c} $^{\S}P < 0.05$.

Supplementary Table 6. Changes in triglyceride-glucose index by prediabetes metabolic phenotype

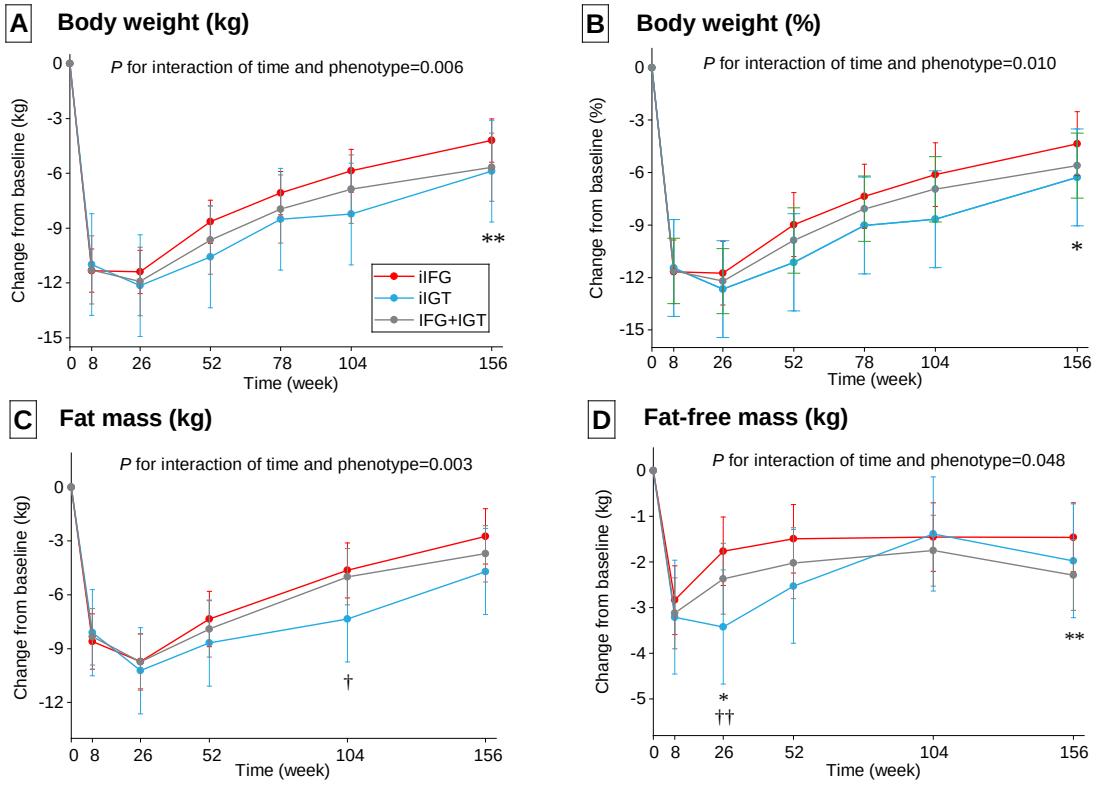
	Group	0–8 weeks	0–26 weeks	0–52 weeks	0–78 weeks	0–104 weeks	0–156 weeks	*P* for interaction of group and time	*P* for group main effect	*P* for time main effect
Available-case analysis, weight-unadjusted	iIFG	-0.33 (0.03)	-0.22 (0.03)	-0.13 (0.03)	-0.07 (0.03)	-0.10 (0.03)	-0.08 (0.03)	0.154	0.384	<0.001
	iIGT	-0.31 (0.04)	-0.26 (0.04)	-0.17 (0.04)	-0.09 (0.04)	-0.16 (0.04)	-0.13 (0.04)			
	IFG+IGT	-0.35 (0.03)	-0.23 (0.03)	-0.15 (0.03)	-0.07 (0.03)	-0.11 (0.03)	-0.11 (0.03)			
Available-case analysis, weight-adjusted	iIFG	-0.27 (0.02)	-0.17 (0.02)	-0.15 (0.02)	-0.13 (0.02)	-0.18 (0.02)	-0.19 (0.02)	0.146	0.620	<0.001
	iIGT	-0.23 (0.04)	-0.19 (0.04)	-0.17 (0.04)	-0.14 (0.04)	-0.22 (0.04)	-0.23 (0.04)			
	IFG+IGT	-0.27 (0.03)	-0.16 (0.03)	-0.14 (0.03)	-0.11 (0.03)	-0.17 (0.03)	-0.19 (0.03)			
Complete-case analysis, weight-unadjusted	iIFG	-0.43 (0.05)	-0.30 (0.05)	-0.21 (0.05)	-0.12 (0.05)	-0.16 (0.05)	-0.13 (0.05)	0.138	0.636	<0.001
	iIGT	-0.38 (0.08)	-0.33 (0.08)	-0.24 (0.08)	-0.10 (0.08)	-0.28 (0.08)	-0.27 (0.08)			
	IFG+IGT	-0.43 (0.05)	-0.30 (0.05)	-0.22 (0.05)	-0.11 (0.05)	-0.17 (0.05)	-0.17 (0.05)			
Available-case analysis, weight-adjusted	Normal HbA_{1c}	-0.35 (0.03)	-0.25** (0.03)	-0.17** (0.03)	-0.10*** (0.03)	-0.13* (0.03)	-0.12*** (0.03)	<0.001	–	–
	Intermediate HbA_{1c}	-0.35 (0.03)	-0.20 (0.03)	-0.11 (0.03)	-0.03 (0.03)	-0.08 (0.03)	-0.06 (0.03)			

Complete-case analysis, weight-adjusted	Normal HbA_{1c}	-0.43 (0.05)	-0.33* (0.05)	-0.26*** (0.05)	-0.15** (0.05)	-0.20* (0.05)	-0.19* (0.05)	<0.001	–	–
	Intermediate HbA_{1c}	-0.48 (0.05)	-0.27 (0.05)	-0.16 (0.05)	-0.06 (0.05)	-0.14 (0.05)	-0.12 (0.05)			

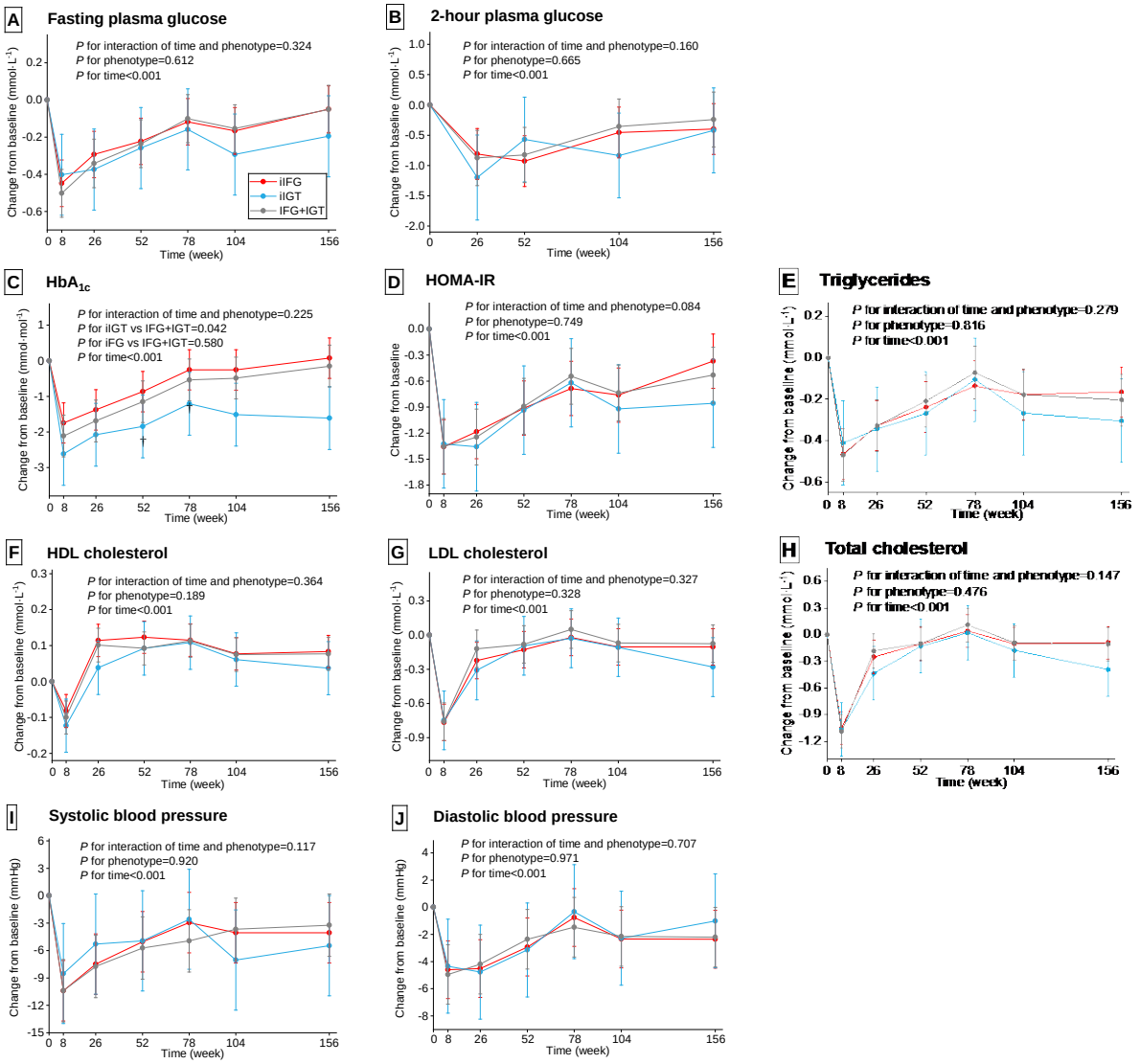
Data are estimated marginal mean (SE) in changes in triglyceride-glucose index from baseline in different prediabetes metabolic phenotypes. HbA_{1c}, hemoglobin A_{1c}; iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired 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 triglyceride-glucose index, 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 multiple comparisons with Bonferroni correction 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.


15611 pre-screened
10139 not eligible
5472 screened
2326 eligible for weight loss phase
2223* being randomized to 1 of the 4 groups, attending at baseline and starting weight loss phase
336 with normal glucose tolerance†
335 with type 2 diabetes†
42 with missing baseline data‡
1510 attended at CID1 (baseline)
869 iIFG, 93 iIGT, and 548 IFG+IGT
1106 normal HbA1c and 384 intermediate HbA1c
1376 attended at CID 2 (8 weeks)
798 iIFG, 79 iIGT, and 499 IFG+IGT
1010 normal HbA1c and 347 intermediate HbA1c
1268 entered the weight maintenance phase
1113 attended at CID 3 (26 weeks)
633 iIFG, 64 iIGT, and 416 IFG+IGT
823 normal HbA1c and 282 intermediate HbA1c
951 attended at CID 4 (52 weeks)
543 iIFG, 54 iIGT, and 354 IFG+IGT
697 normal HbA1c and 249 intermediate HbA1c
866 attended at CID 5 (78 weeks)
496 iIFG, 46 iIGT, and 324 IFG+IGT
637 normal HbA1c and 224 intermediate HbA1c
770 attended at CID 6 (104 weeks)
446 iIFG, 38 iIGT, and 286 IFG+IGT
560 normal HbA1c and 205 intermediate HbA1c
685 attended at CID 7 (156 weeks)
402 iIFG, 31 iIGT, and 252 IFG+IGT
508 normal HbA1c and 173 intermediate HbA1c
Available-case analysis (n=1510)
Complete-case analysis (n=685)

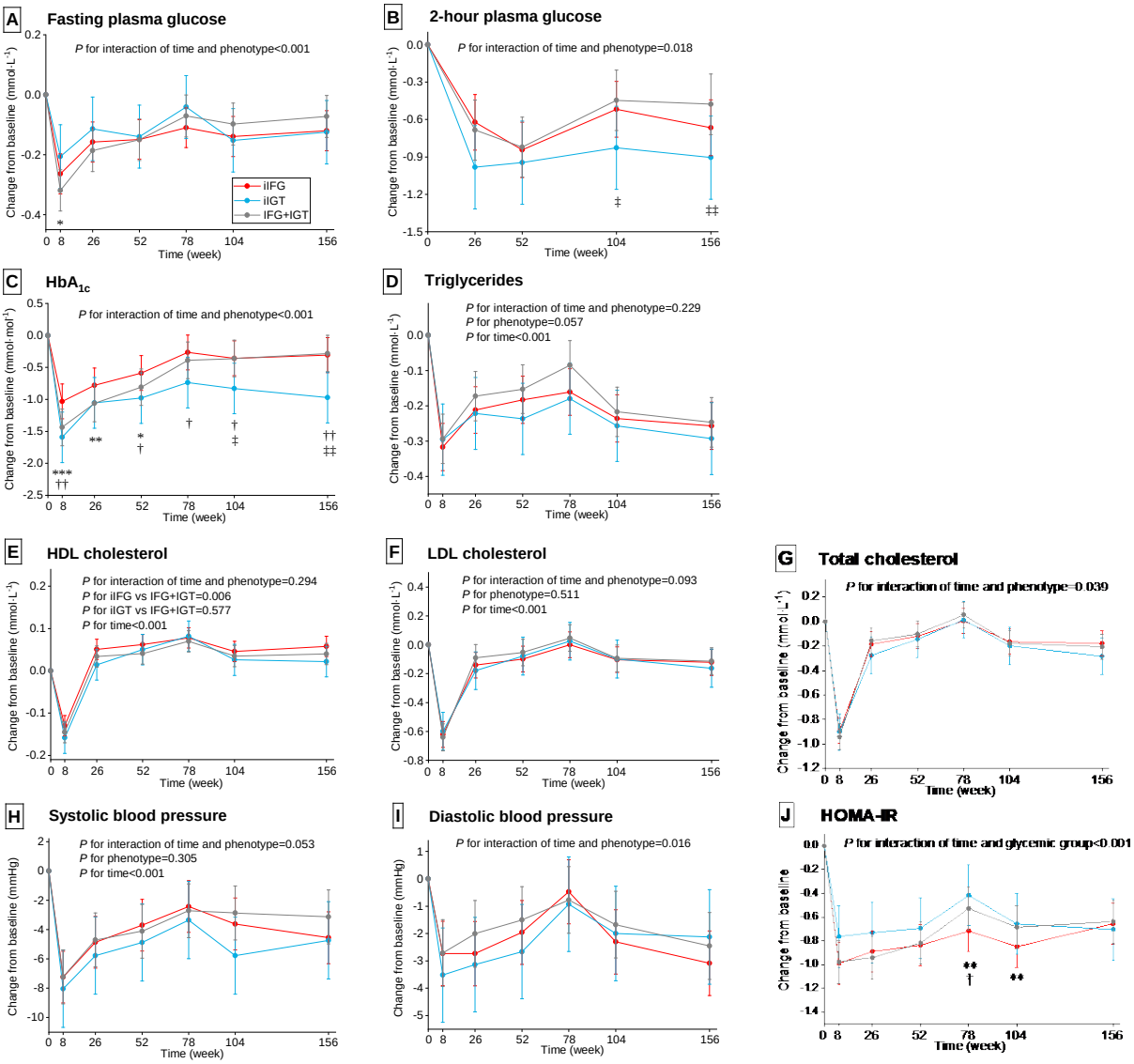
Supplementary Figure 1. Study flow diagram. CID, clinical investigation day; iIFG, isolated impaired fasting glucose; iIGT, isolated impaired glucose tolerance; IFG+IGT, both impaired fasting glucose and impaired glucose tolerance; prediabetes metabolic phenotype was defined at baseline. *A total of 2224 participants started the weight loss phase, but 1 withdrew consent and requested data deletion. †Normal glucose tolerance and type 2 diabetes were defined using fasting plasma glucose and 2-hour plasma glucose. ‡Participants with normal glucose tolerance or type 2 diabetes at baseline or missing baseline fasting plasma glucose and/or 2-hour plasma glucose data (unidentifiable glycemic status) were excluded from the present analysis. Visit windows for data collection: at 8 weeks: –3 to 5 days; at 26 weeks: ±1 week; at 52 weeks: ±2 weeks; remaining time points: ±4 weeks



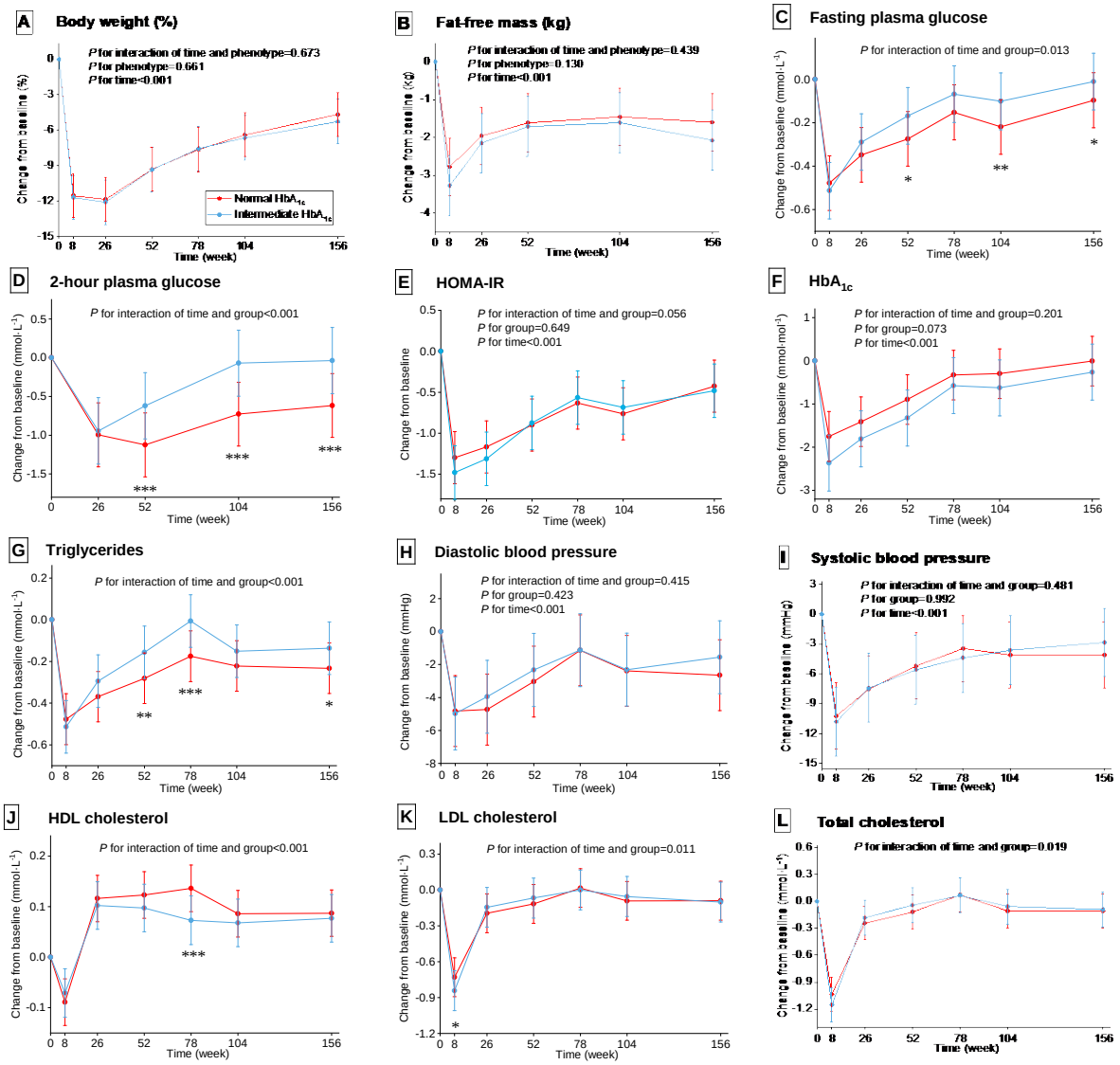
Supplementary Figure 2.·Complete-case analysis: changes in body weight and body composition by prediabetes metabolic phenotype . Values are estimated marginal mean and 95% CI in changes in body weight in kg (A), body weight in % (B), fat mass in kg (C), and fat-free mass in kg (D) from baseline in different prediabetes metabolic phenotypes (complete-case analysis). 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, 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 $^{\ddagger}P < 0.05$, $^{\ddagger\ddagger}P < 0.01$, and $^{\ddagger\ddagger\ddagger}P < 0.001$.



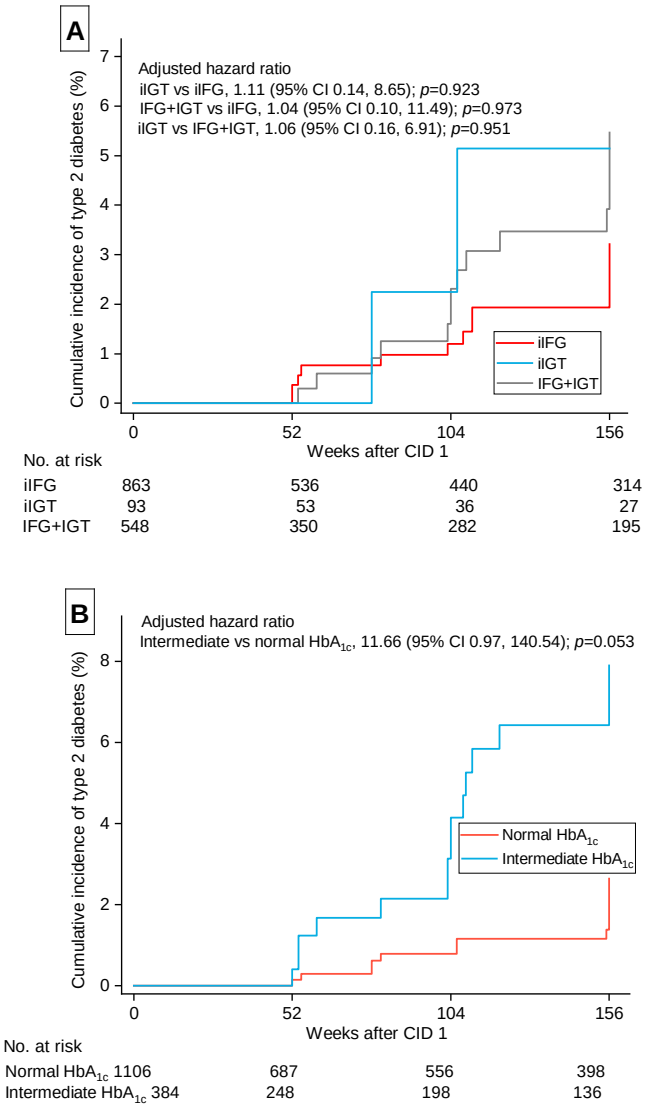
Supplementary Figure 3. Complete-case analysis: changes in cardiometabolic risk factors by prediabetes metabolic phenotype. Values are estimated marginal mean (95% CI) in changes in fasting plasma glucose (A), 2-hour plasma glucose (B), HbA_{1c} (C), HOMA-IR (D), triglycerides (E), HDL cholesterol (F), LDL cholesterol (G), total cholesterol (H), diastolic blood pressure (I), and systolic blood pressure (J) from baseline in different prediabetes metabolic phenotypes (complete-case analysis). 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 $^{\ddagger}P < 0.05$, $^{\ddagger\ddagger}P < 0.01$, and $^{\ddagger\ddagger\ddagger}P < 0.001$.



Supplementary Figure 4. Weight-adjusted 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), triglycerides (D), HDL cholesterol (E), LDL cholesterol (F), total cholesterol (G), diastolic blood pressure (H), systolic blood pressure (I), and HOMA-IR (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 $^{\ddagger}P < 0.05$, $^{\ddagger\ddagger}P < 0.01$, and $^{\ddagger\ddagger\ddagger}P < 0.001$.



Supplementary Figure 5. Complete-case analysis: 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} (complete-case analysis). 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, 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 $^{***}P < 0.001$.



Supplementary Figure 6. Cumulative incidence of type 2 diabetes. CID, clinical investigation day. Values are cumulative incidence of type 2 diabetes at each time point. Cumulative incidence was calculated using the Kaplan–Meier method, without adjustment. The incidence of type 2 diabetes was compared among subgroups using a time-dependent Cox hazards regression model adjusted for Ln(time)×subgroup, ethnicity, baseline smoking status, baseline alcohol consumption, baseline BMI, intervention arm and intervention site as covariates.

Appendices

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