Title Page

Associations of obesity phenotypes with weight change, cardiometabolic benefits, and type 2 diabetes incidence during a lifestyle intervention: results from the PREVIEW study

Running title: metabolically healthy obesity and lifestyle intervention

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Competing interests

Anne Raben has received honoraria from Nestlé, the International Sweeteners Association and Unilever. Jennie Brand-Miller is President and Director of the Glycemic Index Foundation, oversees of a glycemic index testing service at the University of Sydney and is a co-author of books about diet and diabetes. She is also a member of the Scientific Advisory Board of the Novo Foundation and of ZOE Global. Sally D. Poppitt was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. No relevant disclosures from other authors.

ABSTRACT

BACKGROUND/OBJECTIVES: Some individuals with overweight/obesity may be relatively metabolically healthy (MHO) and have a lower risk of cardiovascular disease than those with metabolically unhealthy overweight/obesity (MUO). We aimed to compare changes in body weight and cardiometabolic risk factors and type 2 diabetes incidence during a lifestyle intervention between individuals with MHO vs MUO.

METHODS: This post-hoc analysis included 1012 participants with MHO and 1153 participants with MUO at baseline in the randomized trial PREVIEW. Participants underwent an eight-week low-energy diet phase followed by a 148-week lifestyle-based weight-maintenance intervention. Adjusted linear mixed models and Cox proportional hazards regression models were used.

RESULTS: There were no statistically significant differences in weight loss (%) between participants with MHO vs MUO over 156 weeks. At the end of the study, weight loss was 2.7% (95% CI, 1.7%–3.6%) in participants with MHO and 3.0% (2.1%–4.0%) in those with MUO. After the low-energy diet phase, participants with MHO had smaller decreases in triglyceride (mean difference between MHO vs MUO 0.08 $mmol \cdot L^{-1}$ [95% CI, 0.04–0.12]; $P<0.001$) but similar reductions in fasting glucose and HOMA-IR than those with MUO. However, at the end of weight maintenance, those with MHO had greater reductions in triglyceride (mean difference -0.08 $mmol \cdot L^{-1}$ [-0.12–-0.04]; $P<0.001$), fasting glucose, 2-hour glucose (difference -0.28 $mmol \cdot L^{-1}$ [-0.41–-0.16]; $P<0.001$), and HOMA-IR than those with MUO. Participants with MHO had smaller decreases in diastolic blood pressure and

HbA_{1c} and greater decreases in HDL cholesterol after weight loss than those with MUO, whereas the statistically significant differences disappeared at the end of weight maintenance. Participants with MHO had lower 3-year type 2 diabetes incidence than those with MUO (adjusted hazard ratio 0.37 [0.20–0.66]; $P<0.001$).

CONCLUSIONS: Individuals with MUO had greater improvements in some cardiometabolic risk factors during the low-energy diet phase, but had smaller improvements during long-term lifestyle intervention than those with MHO.

Keywords: metabolic syndrome; cardiovascular disease; low-energy diet; weight loss; type 2 diabetes

INTRODUCTION

The prevalence of overweight and obesity is increasing worldwide (1). Generally, overweight and obesity lead to impaired glucose tolerance, dyslipidemia, and hypertension (2), a cluster of the components of the metabolic syndrome (3). Metabolic syndrome, in turn, increases the risk of developing cardiovascular disease (CVD) and type 2 diabetes (4). Some individuals with overweight or obesity, however, have a normal metabolic profile, which is referred to in the current literature as metabolically healthy overweight/obesity (MHO) (5). Compared with those with metabolically unhealthy overweight/obesity (MUO) or metabolic syndrome, individuals with MHO have been shown to have a lower risk of CVD and type 2 diabetes (4).

Previous observational studies have found that individuals with MHO are still at higher CVD and type 2 diabetes risk than those with metabolically healthy normal weight (6, 7). Moreover, those with MHO, without any intervention, were found to develop metabolic abnormalities and converted to MUO during 10-30 year follow-up (8-10). Accordingly, a very recent prospective study suggested that the term 'MHO' may be misleading (7) and a review suggested that obesity treatment was also needed in individuals with MHO for prevention of the natural course of transition to MUO with aging (5). In the present study, we still used MHO to refer to those with overweight or obesity but without metabolic syndrome, for better consistency with previous studies.

As the first-line treatment for obesity, lifestyle interventions have been shown to aid weight loss and improve cardiometabolic outcomes in several large-scale, long-term (≥1 year) trials (11-15). However, whether long-term lifestyle interventions have similar effects

in individuals with different metabolic phenotypes (i.e. MHO and MUO) is unclear (5). The concepts of MHO and MUO were not introduced in the abovementioned large-scale studies and only a few small-scale short- or medium-term (<1 year) studies compared the effects of lifestyle or diet interventions on cardiometabolic outcomes between MHO and MUO (9).

The PREVIEW study was a multi-center, lifestyle intervention consisting of an 8-week low-energy diet-induced weight loss phase followed by a 148-week lifestyle-based weight-maintenance phase (16). In previous papers, we examined the associations of age, sex, and prediabetes phenotypes with health outcomes (17, 18). The aim of the present analysis was to compare type 2 diabetes incidence and changes in body weight and cardiometabolic risk factors between PREVIEW participants with baseline MHO (or without metabolic syndrome) and MUO (or with metabolic syndrome).

MATERIALS AND METHODS

Study design and participants

The PREVIEW study (ClinicalTrials.gov, NCT01777893) was a multi-center, two-by-two factorial, randomized controlled trial for diabetes prevention. The detailed study protocol and main findings have previously been published (16, 19). In brief, the PREVIEW study was conducted between June 2013 and March 2018 at eight intervention sites in Denmark, Finland, the Netherlands, the UK, Spain, Bulgaria, Australia, and New Zealand. The aim of the PREVIEW study was to examine the effects of lifestyle interventions (two diets combined with two physical activity programs) on type 2 diabetes incidence. The study was conducted

in line with the Declaration of Helsinki and its amendments. The study protocol and procedures were approved by the Human Ethics Committees (**Supplementary Table 1**).

Participants were enrolled from June 2013 to April 2015. Eligible participants were those aged 25–70 years and with overweight or obesity (BMI≥25 $kg \cdot m^{-2}$) and prediabetes. Prediabetes was identified at the screening visit as fasting plasma glucose of 5.6–6.9 $mmol \cdot L^{-1}$ and/or 2-hour plasma glucose of 7.8–11.0 $mmol \cdot L^{-1}$ after a 75-g oral glucose tolerance test, according to the American Diabetes Association criteria (20). Hemoglobin A_{1c} (HbA_{1c}) was not used to define prediabetes because it was not widely used when the study protocol was drafted. Those with pre-existing type 1 or 2 diabetes were excluded. All eligible participants provided written informed consent.

Interventions

The PREVIEW study comprised two phases. Phase 1 was an 8-week low-energy diet phase to lose weight and phase 2 was a 148-week weight-maintenance intervention (21). All participants were provided with low-energy diet meal replacement products with 3400 kJ (810 kcal) in phase 1, but those who lost≤8% of initial body weight after the low-energy diet phase were excluded from phase 2. During phase 1, the participants were asked to maintain their usual physical activity habits. In phase 2, participants were randomized into four intervention groups (The randomization was stratified by sex and age group): a high-protein/low-glycaemic index diet or a moderate-protein/moderate-glycaemic index diet combined with either high- or moderate-intensity physical activity. The moderate intensity

group aimed to achieve 3–5.9 metabolic equivalents of task for 150 min/week; the high intensity group aimed to achieve ≥6 metabolic equivalents of task for 75 min/week. The diets were consumed ad libitum, without an individual target for daily energy intake, but participants were encouraged to self-monitor their portion sizes. To improve diet and physical activity compliance, group counselling visits were performed throughout the study. Diet compliance was evaluated using 4-day food records and physical activity compliance was evaluated using 7-day accelerometry.

The primary outcome of the PREVIEW study was type 2 diabetes between the two diets. The sample size calculation was based on the primary outcome. The current analysis is a post-hoc and exploratory analysis. The primary outcomes of the present paper were type 2 diabetes incidence and weight change. The secondary outcomes were changes in body composition and cardiometabolic risk factors. The primary and secondary outcomes did not change during the post-hoc analysis. The outcomes were measured at seven clinical investigation days (0, 8, 26, 52, 78, 104, and 156 weeks, respectively) (**Supplementary Table 2**). We allowed the following 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.

Body weight and cardiometabolic risk factors

Measurements of body weight, waist circumference, fat mass, fat-free mass, fasting plasma glucose, 2-hour plasma glucose, fasting insulin, HbA_{1c}, total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting triglycerides, systolic blood pressure, and diastolic

blood pressure were described previously (16). In brief, blood samples were drawn from the antecubital vein. All measures were determined after a fasting state (>10 hours) and were initially stored at −80℃ at each site. Then the samples were transported to the Finnish Institute for Health and Welfare for analysis. We calculated the homeostasis model for assessment of insulin resistance (HOMA-IR) using the following equation: HOMA-IR=fasting insulin in $mU \cdot L^{-1}$×fasting plasma glucose in $mmol \cdot L^{-1}/22.5$. We also calculated the triacylglycerol-glucose (TyG) index, a new predictor of CVD events, using the formula: TyG= $\log_e$[triacylglycerols ($mg \cdot dL^{-1}$)×fasting plasma glucose ($mg \cdot dL^{-1}$)/2] (22).

Type 2 diabetes ascertainment

Type 2 diabetes was diagnosed either 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 centers or by a medical doctor, according to the WHO and the American Diabetes Association criteria (20, 23).

Definition of MHO and MUO

MHO was defined according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) (24), as having BMI≥25 $kg \cdot m^{-2}$ and with two or less of the following abnormal metabolic risk factors: 1) waist circumference (>102 cm in men or >88 cm in women). Waist circumference was used to identify the body weight component of the metabolic syndrome, because compared with elevated BMI, abdominal obesity is more highly correlated with metabolic syndrome (24). It is suggested that if BMI is over 30 $kg \cdot m^{-2}$,

abdominal obesity can be assumed and waist circumference does not need to be measured (25). Nonetheless, as the existence of individuals with overweight (BMI≥25 and <30 $kg \cdot m^{-2}$) in the PREVIEW study, in the present analysis waist circumference was still used as one of the abnormal metabolic risk factors; 2) fasting triglycerides (≥1.7 $mmol \cdot L^{-1}$); 3) HDL cholesterol (<1.03 $mmol \cdot L^{-1}$ in men or <1.30 $mmol \cdot L^{-1}$ in women); 4) blood pressure (systolic blood pressure≥130 mmHg or diastolic blood pressure≥85 mmHg), and 5) fasting plasma glucose (≥6.1 $mmol \cdot L^{-1}$; the WHO criteria; 1112 PREVIEW participants had fasting plasma glucose<6.1 $mmol \cdot L^{-1}$ at baseline). Those with three or more of abnormal clinical measures were identified as having MUO. Those with some CVDs including angina, myocardial infarction, stroke, heart failure, symptomatic peripheral vascular disease, etc and those who had systolic blood pressure>160 mmHg and/or diastolic blood pressure>100 mmHg were excluded at the screening visit. Those with missing baseline data for risk factors for metabolic syndrome were excluded from the present analysis.

For conversion from MUO to MHO, converters were defined as those who achieved conversion from MUO at baseline to MHO at each time point respectively; and non-converters were defined as those who did not convert from MUO at baseline to MHO at aforementioned time points. In the present analysis, all participants were merged into one intervention group and re-classified according to their baseline obesity phenotype, because 1) no statistically significant interaction of intervention group and obesity phenotypes was observed; and 2) diet and physical activity compliance was lower than expected (16).

Statistical analyses

Difference in change in outcomes of interest from baseline to 156 weeks between participants with baseline MHO and MUO were examined using linear mixed models. The available-case analysis included all participants, whether they lost >8% of initial weight or not. Missing data were accounted for using expectation maximization algorithm. The linear models were adjusted for fixed covariates including age, sex, ethnicity, baseline BMI, smoking habits, alcohol drinking, and physical activity, changes in physical activity from baseline, baseline values of the outcome being considered, time (categorical), interaction of time and metabolic phenotype, and intervention group and random effects including participant identifier and intervention site. If the interaction was statistically significant, post hoc pairwise comparisons (independent *t* tests) were conducted at each time point. The justification of selection of covariates is included in **Supplementary Material**. We also conducted several sensitivity analyses: 1) by additionally adjusting for dietary intake (e.g. baseline intakes of carbohydrate, protein, fiber, and fat and time-varying intakes of carbohydrate, protein, fiber, and fat); the definition of time-varying is changes over time; 2) by additionally adjusting for percentage weight change from baseline; 3) by repeating the main analysis in participants who completed the whole study (complete-case analysis); we did not impute missing data as most of the participants had full data; 4) by repeating the main analysis in participants who lost >8% of initial weight and successfully entered the weight maintenance phase; 5) by repeating the main analysis in the highest 75% of MHO according to baseline BMI vs the lowest 75% of MUO according to baseline BMI (**Supplementary Table 3**). The differences

in weight change between converters and non-converters were examined using linear mixed models. The detailed information is described in **Supplementary Material**.

Cumulative incidence of type 2 diabetes was calculated using the Kaplan–Meier method. Because of the visit windows, some participants had a longer (>156 weeks) survival time. In this case, we assumed that their last status was observed at 156 weeks. Diabetes incidence was compared between the groups using a Cox proportional hazards regression model adjusted for age, sex, ethnicity, baseline smoking status, baseline alcohol consumption, baseline BMI, baseline physical activity, changes in physical activity from baseline, intervention arm and intervention site as covariates.

The normality of risk factors for metabolic syndrome at each time point and changes in outcomes from baseline to each time point was examined using histograms and p-p plots. Non-normally-distributed variables were log transformed, imputed, and then back transformed. Homogeneity of variance was diagnosed using residual plot. Data analyses were based on IBM SPSS version 28.0 (Chicago, IL, USA) and OriginPro 2020 software (OriginLab, Northampton, MA, USA). The statistical test was two-sided and at the 0.05 level of significance.

RESULTS

Participants

The present analysis included 2165 participants who started the low-energy diet phase (**Supplementary Figure 1**). Of these, 1012 were MHO and 1153 were MUO at baseline.

1822 participants successfully entered the weight maintenance phase. Baseline characteristics of all participants are shown in **Table 1** and **Supplementary Table 4**. Participants' dietary intake and physical activity during the study are shown in **Supplementary Table 5.**

Changes in body weight and body composition

In the available-case analysis, the adjusted models showed that there were no statistically significant differences in weight loss (kg and %), or fat mass (kg and %) between participants with MHO vs MUO over 156 weeks (**Supplementary Figure 2** and **Supplementary Figure 3**). After the low-energy diet phase, body weight of participants with MHO reduced by 10.5% (9.6%–11.5%) compared with 10.5% (9.5%–11.4%) in those with MUO (ns). At the end of the study, participants with MHO retained 2.7% (1.7%–3.6%) weight loss, while MUO retained 3.0% (2.1%–4.0%) relative to pre-intervention baseline. Compared with those with MUO, participants with MHO had greater overall reduction in waist circumference over 156 weeks (**Supplementary Figure 2**) (adjusted mean between-group difference over 156 weeks -0.6 cm [95%CI, -1.1–-0.1]; *P*=0.011) and a greater regain of fat-free mass (kg) at 156 weeks (difference 0.2 kg [0.02–0.5]; *P*=0.035) (**Supplementary Figure 2**). In the complete-case analysis, there were no statistically significant differences in weight change (kg and %) over 156 weeks in participants with MHO vs MUO (**Supplementary Figure 4**).

Change in cardiometabolic risk factors

In the available-case analysis, after adjustment for confounding factors, participants with baseline MHO and MUO had a similar decrease in fasting plasma glucose and HOMA-IR

after the low-energy diet phase, whereas those with MHO had a greater decrease at 78, 104, and 156 weeks (difference in fasting plasma glucose at 156 weeks -0.17 $mmol \cdot L^{-1}$ [95% CI, -0.21–-0.13]; $P<0.001$; HOMA-IR -0.15 [-0.28–-0.03]; $P=0.012$; **Figure 1**). Compared with those with MUO, participants with MHO had a smaller decrease in 2-hour plasma glucose at 26 weeks, but a greater decrease at 104 and 156 weeks (difference at 156 weeks -0.28 $mmol \cdot L^{-1}$ [95% CI, -0.41–-0.16]; $P<0.001$). Participants with MHO had a smaller decrease in HbA_{1c} and diastolic blood pressure and a greater decrease in HDL cholesterol than those with MUO at 8 weeks (difference in HbA_{1c} 0.36 $mmol \cdot mol^{-1}$ [0.19–0.53]; $P<0.001$; diastolic blood pressure 0.72 mmHg [95% CI, 0.11–1.33]; $P=0.020$; HDL -0.04 $mmol \cdot L^{-1}$ [-0.05–-0.02]; $P<0.001$), whereas the statistically significant differences disappeared by 156 weeks. Greater overall reduction in low-density lipoprotein (LDL) cholesterol during 156 weeks were observed in MHO vs MUO. Participants with MHO had a smaller decrease in triglycerides and TyG (**Supplementary Figure 5**) at 8 weeks (difference in triglycerides 0.08 $mmol \cdot L^{-1}$ [95% CI, 0.04–0.12]; $P<0.001$; TyG 0.05 $mmol \cdot L^{-1}$ [95% CI, 0.02–0.07]; $P<0.001$), but a greater decrease at 52, 78, 104, and 156 weeks (difference in triglycerides at 156 weeks -0.08 $mmol \cdot L^{-1}$ [-0.12–-0.04]; $P<0.001$; TyG -0.05 $mmol \cdot L^{-1}$ [95% CI, -0.07–-0.03]; $P<0.001$). There were no statistically significant differences in changes in systolic blood pressure between participants with MHO and MUO over 156 weeks (**Supplementary Figure 5**).

Compared with the primary analyses, the results from the sensitivity analyses were similarly robust after adjustment for percentage weight change (**Supplementary Figure 6**) or

adjustment for intakes of carbohydrate, protein, fiber, and fat. The results were also robust in 1) completers only (**Supplementary Figure 4**), 2) participants who entered the weight maintenance phase, and 3) those with MHO and higher baseline BMI vs those with MUO but lower baseline BMI (**Supplementary Figure 7**).

Conversion from MUO to MHO

With 10.5% (95% CI, 9.6%–11.5%) weight loss, 60% of participants with MUO at baseline converted to MHO after the low-energy diet phase, of which only 38% maintained MHO at the end of the study, despite 4.3% (3.3%–5.3%) sustained weight loss (**Figure 2**). Compared with converters, non-converters had significantly less weight loss (adjusted mean 10.0% [95% CI, 9.1%–11.0%]; mean between-group difference -0.5% [-0.9%–-0.1%], *P*=0.005) after the low-energy diet phase and comprised a lower proportion of men (26.2% vs 42.6%; *P*<0.001), were older (median 56 years [25th and 75th percentiles, 44, 63] vs 55 years [43, 61]; *P*=0.027), and with higher baseline BMI (36.5 [32.9, 40.8] vs 34.0 [31.1, 38.5]; *P*<0.001) than converters.

Type 2 diabetes incidence

The total number of type 2 diabetes incidence cases was 66 (5 during the low-energy diet phase and 61 during the weight maintenance phase; 16 baseline MHO and 50 baseline MUO). The 3-year cumulative incidence was 3.2% in those with MHO and 9.2% in those with MUO (**Figure 3**). The adjusted hazard ratio was 0.37 (95% CI, 0.20–0.66) for individuals with baseline MHO vs MUO (*P*<0.001).

DISCUSSION

In the present study, we found that after adjustment for confounding factors, compared with those with baseline MHO, individuals with baseline MUO had greater improvements in cardiometabolic risk factors during the low-energy diet phase, but had smaller improvements during the 3-year lifestyle intervention, despite similar weight change between the two obesity phenotypes throughout the study. Participants with MUO had higher 3-year cumulative type 2 diabetes incidence than those with MHO.

Similar to our findings, previous short-term studies have shown no statistically significant differences in weight change between individuals with baseline MHO and MUO during an energy-restricted diet- or lifestyle weight-loss interventions (26-32). The response to energy-restricted diets in weight change between individuals with baseline MHO and MUO has been mostly investigated in women (i.e. premenopausal women only, postmenopausal women only, or both) (26-28). Also, the aforementioned studies did not find different changes in waist circumference, fat mass, or fat-free mass between those with MHO and MUO during the interventions (28-30, 32). Differences in changes in waist circumference and fat-free mass were detectable in the present study, but the effect sizes were very small (differences between MHO vs MUO<1% baseline values of weight-related outcomes). Taking all the available evidence together, energy-restricted diets or lifestyle interventions may not induce clinically significant differences in body weight or body composition changes between individuals with MHO vs MUO.

In terms of improvements in cardiometabolic risk factors, previous studies have demonstrated that individuals with MHO may benefit to the same extent or less from short-term (3 to 9 months) diet- or lifestyle-based weight-loss interventions (26-32). We are the first to explore longer-term effects of lifestyle-based weight maintenance in participants with MHO and MUO. We found clinically significant changes in cardiometabolic risk factors between participants with MHO vs MUO. Specifically, participants with MUO benefited more or similarly in almost all the cardiometabolic risk factors during the low-energy diet, especially in triglycerides and HDL cholesterol (differences between MHO vs MUO: 3%–7% baseline values), but the greater benefits in cardiometabolic risk factors in those with MUO disappeared during the first year of the weight-maintenance intervention. Moreover, in the long-term, participants with MHO had greater improvements in cardiometabolic risk factors, especially in 2-hour plasma glucose, HOMA-IR, and triglycerides (differences between MHO vs MUO: 4%–7% baseline values), than those with MUO. Our findings still remained robust in multiple sensitivity analyses.

In previous cohort studies, without interventions, individuals with baseline MHO are less likely to develop type 2 diabetes than those with baseline MUO, although those with MHO are at increased type 2 diabetes risk than healthy individuals with normal body weight (5, 7, 33). Our study is the first to compare type 2 diabetes incidence after a long-term lifestyle intervention and we found that participants with MHO still had lower type 2 diabetes risk. For individuals with MUO, a review suggested that 10% weight loss is necessary to move from MUO to MHO (34). However, in the present study some participants with MUO (four

in ten), with 10% weight loss after the low-energy diet, failed to convert to MHO. Compared with non-converters, converters had greater weight loss (10.5%), a higher proportion of men, and lower age and baseline BMI, although the difference in weight loss between converters and non-converters was small. Regarding individuals with MHO, conversion from MHO to MUO with aging has been found by several large observational studies (8-10). The conversion from MHO to MUO based on the PREVIEW database will be investigated in the future.

Our findings suggest that risk stratification may be important and individualized type 2 diabetes or CVD prevention may be needed. For long-term type 2 diabetes or CVD prevention, traditional lifestyle interventions failed to show more favorable or at least similar effects in individuals with MUO compared with those with MHO. Individuals with MUO (with metabolic syndrome) might need more intensive lifestyle interventions (e.g. high-intensity physical activity and energy-restricted diets) or even pharmacologic therapy/bariatric surgery than those with MHO. Also, our findings support the Edmonton Obesity Staging System and the obesity classification based on metabolic status (35). Individuals with obesity or obesity might need to be classified. For obesity-related chronic disease (e.g. type 2 diabetes), intensive obesity treatments (e.g. all psychological interventions and pharmacological and surgical treatment options) are needed (35).

Notably, currently there is no universally accepted definition of MHO, although the definition of metabolic syndrome is used in most previous studies. The cut-off points of each metabolic syndrome components are not always the same in different studies (e.g. a cut-off

point of 5.6 or 6.1 or 7.0 mmol·L^{-1} for fasting plasma glucose) (5, 36). The diversity of the definition may cause conflicting findings. The present analysis used the harmonized MHO definition proposed by the BioShare-EU project (37) and used 6.1 mmol·L^{-1} as the cut-off point of fasting plasma glucose. This cut-off point enabled us to have similar numbers of participants in each metabolic subgroup and have a large enough sample size to conduct a complete-case analysis.

The present analysis is exploratory and the findings need to be interpreted with caution. The higher-than-expected attrition rate at the end of the study should be regarded as a limitation. A high percentage of missing data at the end of the study may cause selection bias. To minimize the bias, we imputed the missing data and conducted a complete-case analysis. Furthermore, the sample was mostly Caucasian (87%), which may limit the generalizability of the present results for other ethnicities. Finally, in the present analysis participants with MUO had significant lower baseline BMI than those with MHO. To minimize this limitation, we included baseline BMI as a confounder in the statistical models. We also did a sensitivity analysis based on MHO (with higher baseline BMI) and MUO (with lower baseline BMI) subgroups and the results were similar. In addition, given that the magnitude of changes in outcomes from baseline may be correlated to baseline values, we adjusted for baseline outcomes of interest.

In conclusion, individuals with baseline MUO had greater improvements in cardiometabolic risk factors during the low-energy diet phase, but had smaller improvements during a 3-year lifestyle intervention than those with baseline MHO, despite similar weight

change between the two obesity phenotypes throughout the study. Risk stratification according to obesity phenotypes might be important and individualized CVD prevention in individuals with overweight or obesity might be needed.

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AUTHOR CONTRIBUTIONS

Ruixin Zhu: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. Anne Raben: Funding acquisition; Conceptualization, Supervision; Investigation, Writing - review & editing. Maija Huttunen-Lenz, Gareth Stratton, Teodora Handjieva-Darlenska, Svetoslav Handjiev, Jouko Sundvall[e], Marta P. Silvestre, Elli Jalo, Kirsi H. Pietiläinen, Tanja C. Adam, Mathijs Drummen, Elizabeth J. Simpson, Moira A. Taylor, Sally D. Poppitt, Santiago Navas-Carretero, J. Alfredo Martinez, Wolfgang Schlicht, Mikael Fogelholm, Jennie Brand-Miller: Investigation, Writing - review & editing.

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COMPETING INTERESTS

Anne Raben has received honorariums from the International Sweeteners Association and Unilever. Jennie Brand-Miller is President and Director of the Glycemic Index Foundation, oversees of a glycemic index testing service at the University of Sydney and is a co-author of

books about diet and diabetes. She is also a member of the Scientific Advisory Board of the Novo Foundation and of ZOE Global. Sally D. Poppitt was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. No relevant disclosures from other authors.

ETHICS STATEMENT

The study was approved by Research Ethics Committees of the Capital Region, Coordinating Ethical Committee of HUS (Helsinki and Uusimaa Hospital District), Medical Ethics Committee of the Maastricht University Medical Centre, UK National Research Ethics Service (NRES) and East Midlands (Leicester) Ethics Committee, Research Ethics Committee of the University of Navarra, Commission on Ethics in Scientific Research with the Medical University-Sofia (KENIMUS), The University of Sydney, Human Research Ethics Committee (HREC), and Health and Disability Ethics Committees (HDEC).

DATA AVAILABILITY STATEMENT

The study protocol and the datasets analysed during the current study are available from the corresponding author on reasonable request.

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564 **Table 1.** Participant characteristics at baseline

	All participants (n=2165)	**MHO (n=1012)**	**MUO (n=1153)**
Socio-demographics			
Age range, years	25 to 70	25 to 70	25 to 70
Age, years	55 (43, 61)	51 (41, 60)	55 (44, 62)
Sex			
Women	1469 (67.9%)	731 (72.2%)	738 (64.0%)
Men	696 (32.1%)	281 (27.8%)	415 (36.0%)
Anthropometry and body composition			
Body weight, kg	96.8 (84.7, 110.8)	93.0 (81.8, 105.8)	100.5 (88.2, 114.4)
Height, m	1.67 (1.61, 1.74)	1.67 (1.61, 1.73)	1.68 (1.62, 1.75)
BMI, $kg \cdot m^{-2}$	33.9 (30.7, 38.5)	32.9 (29.8, 37.4)	35.0 (31.7, 39.2)
Waist circumference, cm	110.4 (14.7)	106.4 (14.7)	114.0 (13.7)
Fat mass, kg	40.9 (33.5, 50.4)	39.0 (31.9, 48.1)	42.5 (34.8, 51.5)
Fat-free mass, kg	54.0 (47.7, 64.1)	51.9 (46.6, 61.2)	56.3 (48.7, 66.4)
Glucose metabolism			
Fasting plasma glucose, $mmol \cdot L^{-1}$	6.2 (0.7)	5.8 (0.6)	6.4 (0.7)
2-hour plasma glucose, $mmol \cdot L^{-1}$	7.7 (2.2)	7.0 (1.9)	8.2 (2.3)
Fasting insulin, $mU \cdot L^{-1}$	11.5 (8.4, 16.4)	9.9 (7.1, 13.9)	13.3 (9.8, 18.7)
HOMA-IR	3.2 (2.2, 4.6)	2.6 (1.8, 3.7)	3.8 (2.7, 5.4)
HbA_{1c}, %	5.5 (0.4)	5.4 (0.3)	5.6 (0.4)
HbA_{1c}, $mmol \cdot mol^{-1}$	36.7 (4.0)	35.6 (3.4)	37.7 (4.2)
Lipid metabolism			
Fasting triglycerides, $mmol \cdot L^{-1}$	1.3 (1.0, 1.8)	1.1 (0.9, 1.4)	1.7 (1.2, 2.1)
Triglyceride-glucose index	9.5 (0.5)	9.2 (0.4)	9.7 (0.4)
Total cholesterol, $mmol \cdot L^{-1}$	5.2 (1.0)	5.1 (1.0)	5.3 (1.0)
HDL cholesterol, $mmol \cdot L^{-1}$	1.2 (1.1, 1.4)	1.4 (1.2, 1.5)	1.2 (1.0, 1.3)
LDL cholesterol, $mmol \cdot L^{-1}$	3.2 (2.6, 3.8)	3.2 (2.6, 3.7)	3.2 (2.7, 3.8)
Blood pressure			
Systolic blood pressure, mmHg	129 (16)	123 (14)	135 (15)
Diastolic blood pressure, mmHg	79 (71, 85)	75 (68, 81)	82 (75, 89)

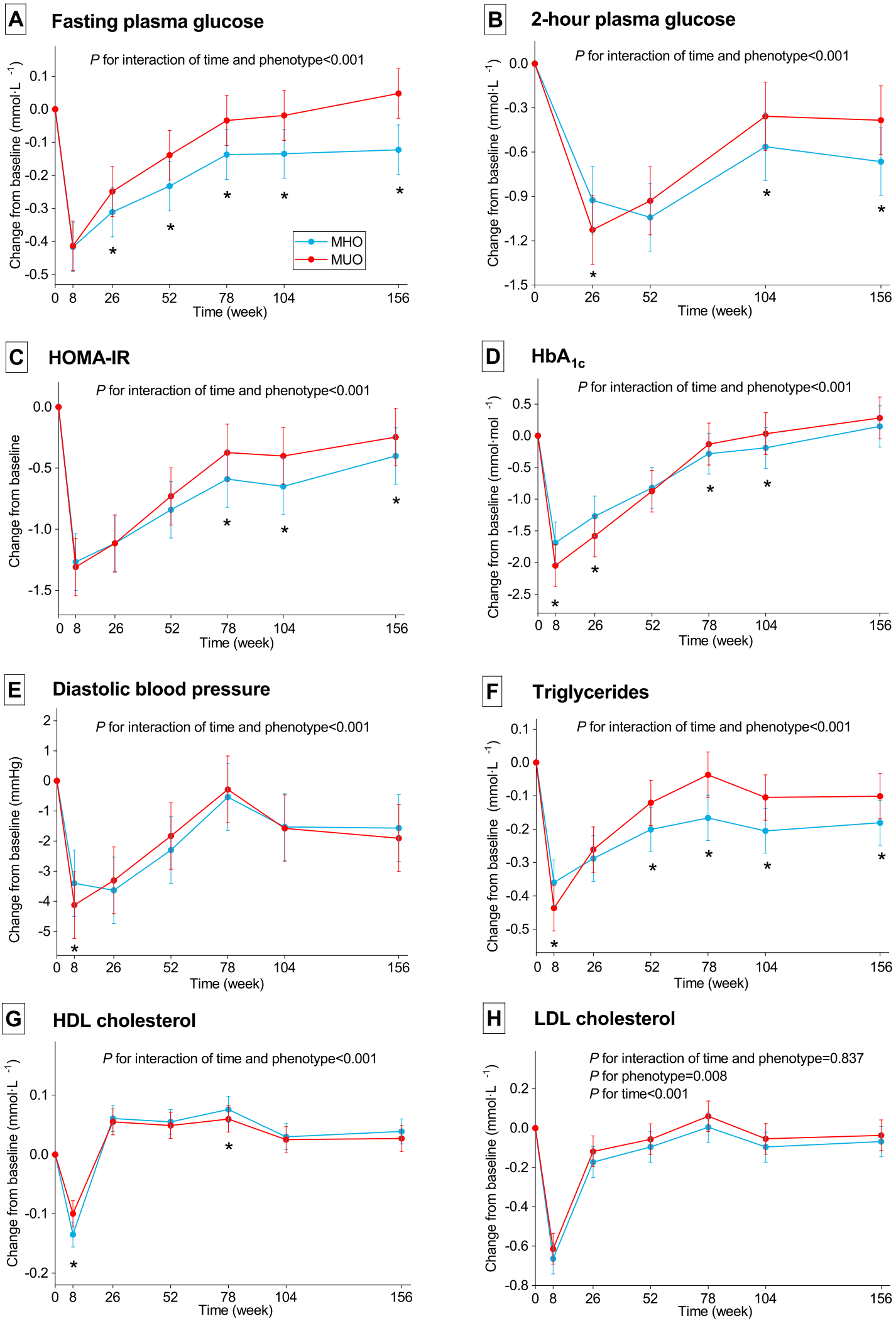
565 Data are mean (SD), median (25th, 75th percentiles), or n (%). HbA_{1c}, haemoglobin A_{1c}; HDL cholesterol, high-
566 density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL
567 cholesterol, low-density lipoprotein cholesterol; MHO, metabolically healthy overweight/obesity; MUO,
568 metabolically unhealthy overweight/obesity.
569

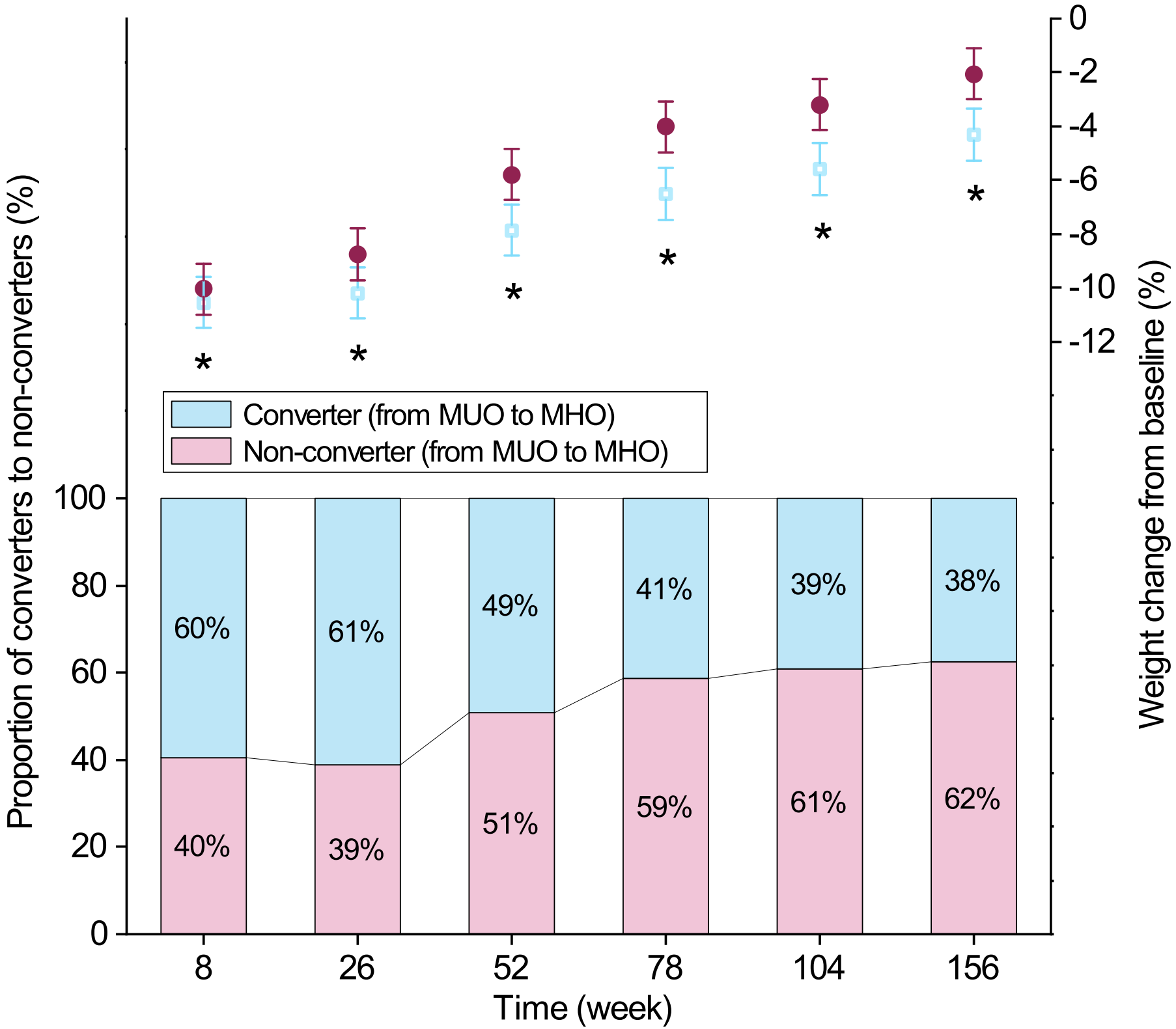
Figure 1. Changes in cardiometabolic risk factors (n=2165). Values are estimated marginal mean (95% CI) in changes in fasting plasma glucose (A), 2-hour plasma glucose (B), HOMA-IR (C), HbA_{1c} (D), diastolic blood pressure (D), triglycerides (F), HDL cholesterol (G), and LDL cholesterol (H) from baseline. Analyses were performed using a linear mixed model adjusted for age, sex, ethnicity, baseline BMI, smoking, alcohol drinking, and physical activity, time-varying change in physical activity from baseline, baseline outcomes, intervention group, time by metabolic phenotype interaction, and time as fixed covariates and participant identifier and intervention site as random effects. *Statistically significantly different, $P<0.05$. HbA_{1c}, haemoglobin A_{1c}; HDL cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein cholesterol; MHO, baseline metabolically healthy overweight/obesity; MUO, baseline metabolically unhealthy overweight/obesity.

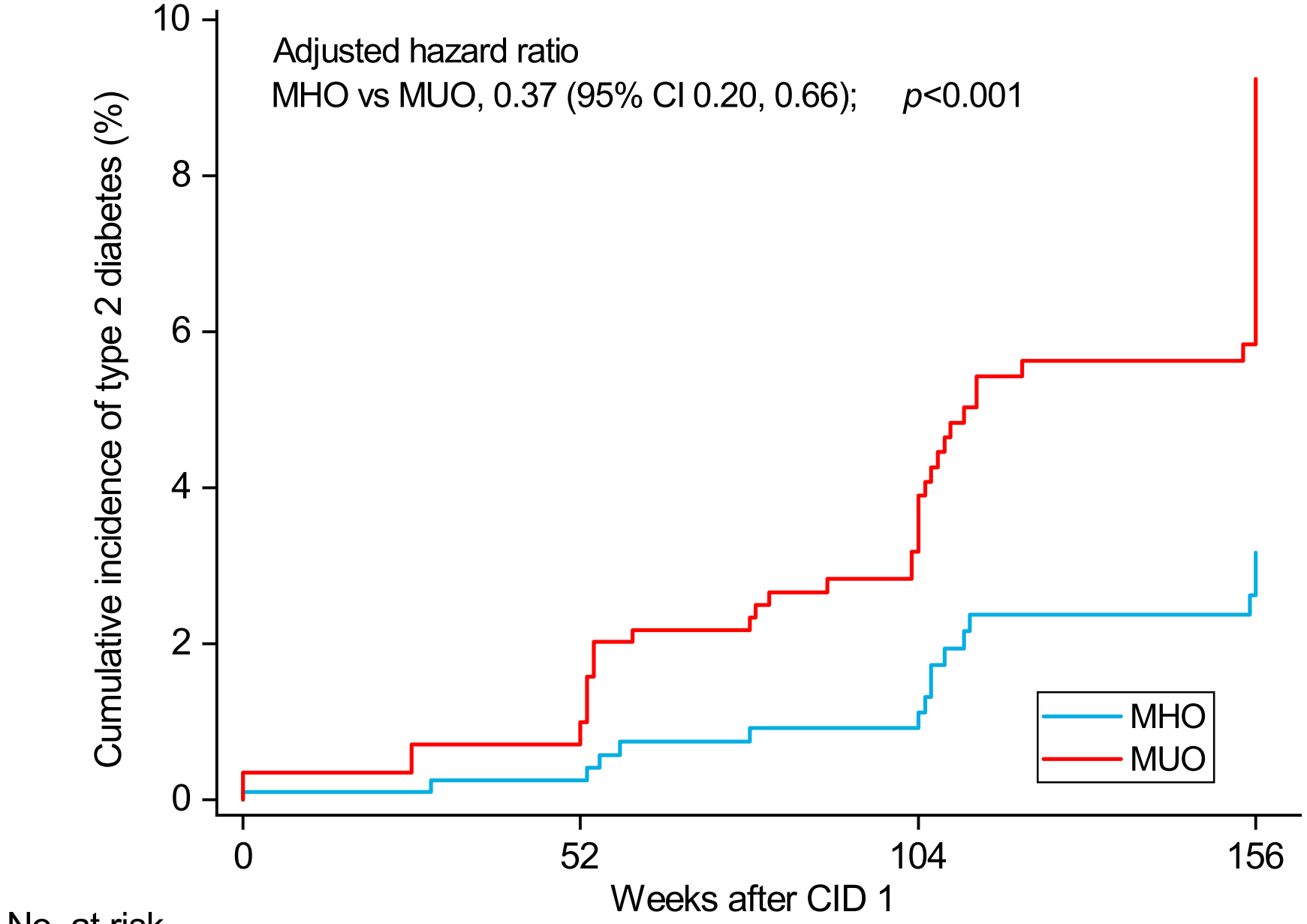
Figure 2. Conversion from metabolically unhealthy to healthy overweight/obesity (n=1153). Values are estimated marginal mean (95% CI) in percentage weight change from baseline and the proportion of converters to non-converters in participants with MUO at baseline. Analyses were performed using a linear mixed model adjusted for age, sex, ethnicity, baseline BMI, smoking, alcohol drinking, and physical activity, time-varying change in physical activity from baseline, baseline outcomes, intervention group, time by metabolic phenotype interaction, and time as fixed covariates and participant identifier and intervention site as random effects. * Statistically significantly different, $P<0.05$. MHO, baseline metabolically healthy overweight/obesity; MUO, baseline metabolically unhealthy overweight/obesity.

Figure 3. Cumulative incidence of type 2 diabetes (n=2165). Values are cumulative incidence of diabetes in participants with MUO vs MHO at each time point. Cumulative incidence was calculated using the Kaplan–

Meier method, without adjustment. The incidence of diabetes was compared between participants with MUO vs MHO using a Cox proportional hazards regression model adjusted for age, sex, ethnicity, baseline smoking status, baseline alcohol consumption, baseline BMI, baseline physical activity, changes in physical activity from baseline, intervention arm and intervention site as covariates. MHO, baseline metabolically healthy overweight/obesity; MUO, baseline metabolically unhealthy overweight/obesity.


A
Fasting plasma glucose
P for interaction of time and phenotype<0.001
Change from baseline (mmol·L -1)
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
MHO
MUO
0 8 26 52 78 104 156
Time (week)
B
2-hour plasma glucose
P for interaction of time and phenotype<0.001
Change from baseline (mmol·L -1)
0.0
-0.3
-0.6
-0.9
-1.2
-1.5
0 26 52 104 156
Time (week)
C
HOMA-IR
P for interaction of time and phenotype<0.001
Change from baseline
0.0
-0.5
-1.0
-1.5
0 8 26 52 78 104 156
Time (week)
D
HbA1c
P for interaction of time and phenotype<0.001
Change from baseline (mmol·mol -1)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
0 8 26 52 78 104 156
Time (week)
E
Diastolic blood pressure
P for interaction of time and phenotype<0.001
Change from baseline (mmHg)
2
1
0
-1
-2
-3
-4
-5
0 8 26 52 78 104 156
Time (week)
F
Triglycerides
P for interaction of time and phenotype<0.001
Change from baseline (mmol·L -1)
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0 8 26 52 78 104 156
Time (week)
G
HDL cholesterol
P for interaction of time and phenotype<0.001
Change from baseline (mmol·L -1)
0.1
0.0
-0.1
-0.2
0 8 26 52 78 104 156
Time (week)
H
LDL cholesterol
P for interaction of time and phenotype=0.837
P for phenotype=0.008
P for time<0.001
Change from baseline (mmol·L -1)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
0 8 26 52 78 104 156
Time (week)


Converter (from MUO to MHO)
Non-converter (from MUO to MHO)
Proportion of converters to non-converters (%)
Weight change from baseline (%)
Time (week)
0
20
40
60
80
100
0
-2
-4
-6
-8
-10
-12
8
26
52
78
104
156
60%
61%
49%
41%
39%
38%
40%
39%
51%
59%
61%
62%
*
*
*
*
*
*



No. at risk

MHO	1012	643	509	366
MUO	1153	705	563	387