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Effect of weight loss through dietary interventions on cardiometabolic health in older adults

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BACKGROUND: With the increasing prevalence of obesity and its negative consequences on health, weight management emerges as a priority for public health, especially in older adults, in whom obesity is linked to increased risks of chronic diseases such as cardiovascular disease. We performed a study investigating the association of intentional weight loss through dietary intervention on cardiometabolic health among older adults participating in the MIND trial.

METHODS: The MIND trial enrolled overweight individuals aged 65–84 who self-reported a suboptimal diet. Participants were randomized to the MIND or a control diet for 3 years; both diets promoted weight loss through mild caloric restriction (250 kcal). Of 604 individuals enrolled in the trial, 518 were included in the analysis. We calculated the percentage of weight loss based on measured weight at the baseline and year 3 and categorized individuals into four groups: no weight loss (e.g., weight gain), <5%, 5–10%, and >10% weight loss. Cardiometabolic health included traditional lipid biomarkers, biomarkers of inflammation, and glycosylated hemoglobin. Linear mixed-effect models were used to evaluate the associations of weight loss with cardiometabolic health.

RESULTS: At the baseline, mean age was 70 (SD = 4.1) years, 332 (65%) were women, and BMI was 33.8 (SD = 5.9) kg/m2. Compared to people who did not lose weight, those with >10% weight loss significantly improved their biomarkers of cardiometabolic health at the year 3 visit as follows: LDL cholesterol levels decreased by 8.3%, triglycerides by 28.2%, and HDL increased by 12.4%. As for biomarkers of inflammation, GlycA decreased by 7.5%, hs-IL6 by 33.0%, hs-CRP by 59.4%, and adiponectin increased by 53.7%. These improvements in biomarkers of cardiometabolic health did not differ by dietary intervention.

CONCLUSION: Weight loss through dietary interventions with mild calorie restriction resulted in favorable changes in cardiometabolic risk factors among older adults with overweight and obesity.

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INTRODUCTION

With the increasing obesity epidemic and its associated health risks–including dyslipidemia, inflammation, and diabetes–there is a strong public interest in finding effective strategies for achieving clinically meaningful weight loss [1–5]. These strategies include lifestyle modifications [6–11], pharmacological therapies [12, 13], and bariatric surgery [14]. While pharmacological therapies and bariatric surgery can be effective, high costs, limited insurance coverage, and limited accessibility (e.g., only 1% of eligible individuals undergo bariatric surgery each year) [15, 16] make them unlikely solutions on a population level. In contrast, lifestyle modifications, such as calorie-restricted healthy diets, may offer a more feasible and widely applicable approach to addressing the growing obesity epidemic [17, 18]. In the recently completed MIND trial, which compared the effects of the Mediterranean–DASH Intervention for Neurodegenerative Delay,

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the MIND diet, with a control diet–each incorporating a mild caloric restriction of 250 kcal per day–on cognition in individuals aged 65–84 years with overweight and obesity, we found that a 3-year dietary intervention resulted in clinically meaningful weight loss, independently of the diet group [19]. In the present study, we extend our prior work by examining whether weight loss that MIND trial participants achieved through dietary interventions is associated with better cardiometabolic risk factors, including traditional lipid biomarkers, markers of inflammation, and glucose regulation. This study will address whether, in people aged 65 years and older, intentional weight loss through calorie-restricted dietary intervention improves cardiovascular health.

METHODS

Recruitment, randomization, and treatment groups

The MIND study is a three-year, two-site, randomized, controlled trial that evaluated the effect of the MIND diet intervention on changes in cognitive function and structural changes in the brain [19, 20]. From January 2017 through April 2018, 604 individuals aged 65 years and older with overweight or obesity (BMI ≥ 25), suboptimal diet quality (MIND score < 8 as based on a 14-item dietary screener), no cognitive impairment (MOCA > 22), and with a self-reported family history of Alzheimer's dementia were enrolled in the trial. Participants were randomly assigned to follow the MIND diet with mild caloric restriction for weight loss (intervention) or their usual diet with the same mild caloric restriction for weight loss (control). The caloric restriction consisted of consuming 250 kcal less per day.

Dietary counseling was led by registered dietitians and provided by telephone to all participants at the same frequency. For the MIND diet group, it consisted of instructions on incorporating foods from the MIND diet and strategies to lose weight while keeping exercise levels the same as at baseline. The MIND diet intervention consisted of promoting 9 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans/legumes, whole grains, fish, poultry, extra-virgin olive oil) and limiting consumption of 5 unhealthy food groups (red and processed meats, fried foods, pastries and sweets, butter, and full-fat cheese). Dietary counseling for the control diet group was focused on calorie tracking, portion control, and behavioral strategies to lose weight without changing the types of foods consumed. At the end of the 3-year intervention, both groups experienced, on average, clinically meaningful weight loss (~5.2% weight loss from the baseline weight) [19].

Of 604 individuals enrolled in the MIND trial, 520 had measured weight at the year 3 visit (i.e., study exit). From 520 individuals, we excluded 2 people with similar weight at year 3 compared to the baseline weight. Five hundred eighteen (n = 518) participants experienced weight changes (i.e., gained or lost weight) and, consequently, were included in the analysis. The baseline characteristics, including demographics, lifestyle factors, and genetics, of people included in the study (n = 518) from those excluded from the study (n = 86) were similar (p > 0.1), as shown in Supplementary Table 1.

Assessment of weight and calculation of weight loss

Using standard protocols, trained research staff measured body weight at the baseline, month 6, year 1, year 2, and year 3. We used data on participants' weight at the baseline and end of the study/study exit (i.e., year 3) to calculate the 3-year weight loss percentage. To calculate the percentage weight change, we subtracted participants' weight at year 3 (i.e., study exit) from their baseline weight, divided this difference by their baseline weight, and multiplied the result by 100. Based on the sample distribution and the trial goals for planned weight loss, as well as clinically meaningful weight loss, participants were categorized into four groups: those who did not lose weight (i.e., weight gainers), those who lost less than 5% of their baseline weight, those who lost between 5% and 10%, and those who achieved a weight loss of more than 10%.

Assessment of covariates

Age at baseline was computed by subtracting the date enrolled in the study from the birthdate. Race, sex, and education (years of formal schooling) were self-reported at the baseline visit. Apolipoprotein E gene (APOE) e4 allele was assessed via genetic testing. Physical activity was assessed through the Yale Physical Activity Survey, where participants reported time spent in activities, including brisk walking, calisthenics, cycling, and swimming [21]. Smoking status was self-reported, and participants were categorized as ever and never smokers. Dietary behavior and calorie intake were assessed by a validated food frequency questionnaire estimating how often, on average, a participant had consumed specified amounts of foods during the previous year. The diet quality was determined using the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) diet score [22, 23]. Body mass index (BMI) was calculated based on weight and height at the baseline. Medication use was self-reported. We specifically considered diabetes medications, including metformin and insulin, as well as statin medications for dyslipidemia, such as Lovastatin, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin, and Atorvastatin. Hypertension was defined as being told by a healthcare provider that he/she had high blood pressure or hypertension or being advised by a healthcare provider to take medication for high blood pressure.

Assessment of lipid biomarkers, inflammation, and glucose regulation

Traditional lipid biomarkers included high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and total cholesterol. Total cholesterol and triglyceride concentrations were measured using the Beckman Coulter Cholesterol reagent on the Beckman Coulter AU5800 series automated chemistry analyzer. HDL cholesterol concentration was determined after precipitating all apoB-containing lipoprotein particles [intermediate density Lipoprotein (IDL), low-density lipoprotein (LDL), and lipoprotein (a)] using 50 kDa dextran sulfate with magnesium ions ($MgCl_2$) as the precipitation agent. Cholesterol was then measured in the supernatants only containing HDL particles using the Beckman Coulter cholesterol reagent. LDL cholesterol was calculated using the Friedewald formula: LDL cholesterol = Total Cholesterol – HDL cholesterol – (triglycerides/5) [24].

Biomarkers of inflammation included high-sensitive C-reactive protein (hs-CRP), high-sensitive Interleukin-6 (hs-IL6), GlycA, and adiponectin. Measurements of hs-CRP were performed using Siemens reagent on a Siemens BN2 nephelometer. Measurements of hs-IL6 were performed by a sandwich ELISA method using a monoclonal antibody specific for IL6 as a capturing antibody and a biotinylated polyclonal antibody specific for IL6 as a detecting antibody (R&D Systems Quantikine kit). GlycA was assessed in serum via the Nightingale Health platform using established protocols, as described previously [25, 26]. GlycA was assessed in serum via the Nightingale Health platform using established protocols, as described previously [25, 26]. Briefly, GlycA is a composite biomarker of systemic inflammation that reflects both acute and chronic inflammatory states. Elevated GlycA levels have been associated with subclinical atherosclerosis and an increased risk of cardiovascular disease [27]. Total adiponectin concentration was measured by Enzyme-Linked Immunosorbent Assay (ELISA) using Quantikine® Human Total Adiponectin/Acrp30 ELISA Assay kit (DRP300) by R & D Systems.

Hemoglobin A1c (HbA1c) was assessed by high-performance liquid chromatography (HPLC) using the Tosoh G8 automated glycohemoglobin analyzer.

All these biomarkers were assessed in blood samples collected after overnight fasting and stored in −80 °C freezers at each clinical trial site until shipment to the Northwest Lipid Metabolism and Diabetes Research Laboratories at the University of Washington and Medpace Reference Laboratories, for measurements of total cholesterol, HDL cholesterol, triglycerides, hs-CRP, hs-IL6, adiponectin, and HbA1c. Measurement of GlycA was performed by Nightingale Health Laboratories.

Statistical Analysis

Characteristics of the study participants are summarized as mean and standard deviation (SD), median and interquartile [IQR], or as number (n) and percentages (%) of participants. Linear mixed-effect models with a random intercept were used to estimate the association of weight loss with 3-year changes in biomarkers of cardiometabolic health, including traditional lipid biomarkers, markers of inflammation, and glucose regulation. The proportion of weight loss at year 3 (i.e., study exit) relative to baseline (i.e., study entry) was evaluated as a categorical variable with people who did not lose weight as reference category. Other weight loss categories included those who lost less than 5% of their weight, those who lost between 5% and 10%, and those who achieved a weight loss of more than 10%. Biomarkers of cardiometabolic health were log10 transformed to normalize the distribution. To simplify the interpretation, we back-transformed the beta coefficients (i.e., 10^{beta}) into relative differences. The relative difference can be interpreted as a percentage lower (negative value) or higher (positive value) in

cardiometabolic biomarkers attributed to the weight loss categories [28]. In addition, to enable clinical interpretation of our findings, we calculated the means of these biomarkers at the baseline and year 3 by each category of weight loss. Models were adjusted by age (years), sex (male vs. female), race (White vs. non-White), education (years), APOE e4 carriership (yes vs. no), body mass index (kg/m2), physical activity (hours/week), smoking history (never vs. ever), MIND diet score (points), and dietary assignment (MIND diet group vs control diet group).

We conducted several sensitivity analyses to test the strength of the associations between weight loss groups and cardiometabolic biomarkers. First, we excluded people who did not lose weight (i.e., weight gainers) as nonadherent to the trial interventions. In this analysis, the reference category was the group of people with a weight loss of less than 5%. In addition, by changing the reference category to those who lost less than 5% and comparing people with weight loss 5–10 and >10%, we address the question of whether clinically meaningful weight loss (i.e., >5%) [29] is necessary for improving cardiometabolic health. Second, we investigated the influence of caloric restriction on the association between weight loss and cardiometabolic health. Individuals who substantially reduce their calorie intake are more likely to achieve greater weight loss. Therefore, to address whether the association of weight loss with cardiometabolic health is attributed exclusively to caloric restriction, we conducted an additional sensitivity analysis by adjusting our models for total calorie intake at baseline and year 3. Third, we evaluated the role of medication, specifically statin use for dislipidemia and metformin and insulin use for diabetes treatment, by adjusting the multivariable model with medication at the baseline and year 3 and evaluating the association of weight loss with biomarkers of cardiometabolic health. Fourth, we adjusted the multivariable model by the laboratory (i.e., Medpace and the University of Washington) to evaluate whether potential variations in lab settings could influence our results—despite the same investigator directed measures of these biomarkers in both laboratories. Lastly, we examined the role of intervention (MIND diet vs. control diet) in associations of weight loss with cardiometabolic health by assessing the significance of the interaction between weight loss and dietary intervention in association with 3-year changes in cardiometabolic biomarkers.

Analyses were performed using R statistical computing, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) [30].

Study protocol approval and patient consent

The institutional review board of Rush University Medical Center, Harvard School of Public Health, and Brigham and Women's Hospital approved the MIND study protocol and all participants provided written informed consent.

RESULTS

Table 1 shows the baseline characteristics of the overall study sample (n = 518) and by weight loss categories. The mean age at baseline was 70 years, 332 (65%) were women, and BMI was 34 kg/m^2. There were no significant differences in demographic, lifestyle factors, or biomarkers across weight loss categories at the baseline. At year 3, weight change ranged from an average increase of 3.6 kg in the no weight loss group [n = 112 (21.6%)] to a decrease of 15.0 kg in people with >10% weight loss [n = 114 (22%)]. Total calorie intake decreased for all weight change groups, including those in the no-weight loss group.

Table 2 shows the association of weight loss with 3-year changes in traditional lipid biomarkers. Compared to people who did not lose weight (i.e., weight gain), those with 5–10% and >10% weight loss significantly improved levels of HDL and decreased triglycerides at the year 3 visit (i.e., study exit). In addition, LDL cholesterol levels decreased in individuals with >10% weight loss compared to those who did not lose weight. Specifically, levels of LDL cholesterol decreased by 8.3% (β=−0.038, SE = 0.018, p = 0.039), triglycerides levels decreased by 28.2% (β=−0.144; SE = 0.020, p < 0.001), and HDL cholesterol levels increased by 12.4% (β=0.051, SE = 0.009, p < 0.001) for individuals who experienced over 10% weight loss compared to those with no weight loss at the end of the study (i.e., year 3).

Table 3 shows the association of weight loss with 3-year changes in biomarkers of inflammation. Compared to people who did not lose weight, those with 5–10% and >10% weight loss had lower levels of hs-CRP, hs-IL6, and higher levels of adiponectin hormone at the year 3 visit (i.e., study exit). People with >10% weight loss also decreased levels of GlycA. Specifically, compared to individuals who did not lose weight, individuals with more than 10% weight loss had a decrease in levels of hs-CRP by 59.5% (β=−0.392, SE = 0.052, p < 0.001), hs-IL6 levels by 33.1% (β=−0.175; SE = 0.038, p < 0.001), GlycA levels by 7.5% (β=−0.034, SE = 0.011, p = 0.003) and an increase adiponectin hormone levels by 53.5% (B = 0.186, SE = 0.018, p < 0.001).

Table 4 shows the association of weight loss with 3-year changes in HbA1c. Compared to people who did not lose weight, those with <5%, 5–10%, and >10% weight loss had a decrease in levels of HbA1c, respectively, by 2.9% (β=−0.013, SE = 0.004, p = 0.002), 4.0% (β=−0.018, SE = 0.004, p < 0.001), and 6.4% (β=−0.029, SE = 0.004, p < 0.001) at the study exit (i.e., year 3).

To simplify the clinical interpretation of our findings, in Fig. 1, we present the estimated means of traditional lipid biomarkers (*Panel A*), biomarkers of inflammation (*Panel B*), and HbA1c (*Panel C*) across weight loss groups at baseline and year 3 to enable further clinical interpretation of our findings. At the baseline, the levels of these biomarkers were similar, but at year 3 (i.e., study exit), people with 10% or more in weight loss experienced a notable decrease in LDL cholesterol, triglycerides, hsCRP, hsIL6, GlycA, HbA1c, and increased levels of HDL cholesterol and adiponectin hormone.

Sensitivity analyses

Supplementary Tables 2–4 show associations between weight loss groups and traditional lipid biomarkers, biomarkers of inflammation, and HbA1c with a focus only on people (n = 406) who experienced weight loss during 3 years of dietary intervention – excluding people who did not lose weight (i.e., weight gainers). Compared to people who lost less than 5% of their baseline weight, those who achieved >10% loss in weight had a 19.0% decrease in triglyceride levels and a 10.2% increase in HDL cholesterol levels (Supplementary Table 2). Similar findings to the primary analysis were observed for inflammatory biomarkers (Supplementary Table 3) and HbA1c (Supplementary Table 4). Specifically, hs-CRP decreased by 48.6%, hs-IL6 decreased by 24.6%, GlycA decreased by 5.0%, and Adiponectin increased by 38.5% during 3 years of dietary intervention in people with 10% or more weight loss compared to those who lost less than 5% of their baseline weight. Additional adjustments for baseline and year 3 calorie intake, baseline and year 3 medication use (i.e., statin, metformin, and insulin), as well as laboratory location, yielded results consistent with the primary analysis (Supplementary Tables 5–13).

The associations between weight loss groups and cardiometabolic biomarkers did not differ by dietary intervention (*p-for-interaction* > 0.131).

DISCUSSION

In this study of adults 65 years and older with overweight and obesity and residing in metropolitan areas of Chicago and Boston in the United States, a 10% or more weight loss during a 3-year intervention with mild-calorie restriction diets was associated with improved cardiometabolic health, including traditional lipid biomarkers, biomarkers of inflammation, and glucose regulation (i.e., Hb1Ac) compared to people who did not lose weight (i.e., weight gainers) or to individuals who lost less than 5% of their baseline weight. These findings suggest that weight management through dietary interventions with mild calorie restriction may help improve cardiometabolic health in older adults with overweight and obesity.

In this analysis, we explored the association of achieved weight loss with 3-year changes in cardiometabolic biomarkers. Although we used data from a randomized clinical trial, we caution that these findings do not have the validity of the primary analysis for the randomized controlled trial, which compared the MIND diet versus

Table 1. Baseline characteristics of the study population.

	Weight change groups					
	Overall	**No weight loss**	**<5% weight loss**	**5–10% weight loss**	**>10% weight loss**	***p***
n	518	112	163	129	114	
Demographics						
Age, years	70.3 (4.11)	69.4 (4.0)	70.6 (4.1)	70.75 (4.7)	70.2 (4.2)	0.038
Sex, male, *n* (%)	186 (35.9)	33 (29.5)	64 (39.3)	49 (38.0)	40 (35.1)	0.377
Race, white, *n* (%)	457 (88.2)	95 (84.8)	147 (90.2)	113 (87.6)	102 (89.5)	0.558
Education, years	17.0 (2.6)	17.3 (2.8)	17.0 (2.3)	16.6 (2.4)	17.0 (2.8)	0.251
Genetics						
APOE e4 carrier, *n* (%)	148 (28.6)	32 (28.6)	41 (25.2)	39 (30.2)	36 (31.6)	0.656
Lifestyle						
Smoking history, *n* (%)						0.496
Never	242 (46.7)	48 (42.9)	73 (44.8)	58 (45.0)	63 (55.3)	
Current	15 (2.9)	4 (3.6)	4 (2.5)	3 (2.3)	4 (3.5)	
Former	261 (50.4)	60 (53.6)	86 (52.8)	68 (52.7)	47 (41.2)	
Physical activity, h/week	2.50 [0.58, 4.67]	2.71 [1.00, 4.27]	2.50 [0.67, 4.88]	2.50 [0.75, 4.50]	2.00 [0.27, 4.94]	0.788
MIND diet, score	7.7 (1.8)	7.8 (1.8)	7.5 (1.8)	7.7 (1.8)	7.7 (1.8)	0.506
Medication						
Statin use, *n* (%)	235 (45.4)	49 (43.8)	70 (42.9)	61 (47.3)	55 (48.2)	0.783
Antidiabetic medications (metformin and/or insulin use), *n* (%)	59 (11.4)	14 (12.5)	16 (9.8)	14 (10.9)	15 (13.2)	0.819
Hypertension, *n* (%)	283 (54.6)	57 (50.9)	88 (54.0)	79 (61.2)	59 (51.8)	0.346
Intervention						
Diet assignment, MIND, *n* (%)	251 (48.5)	50 (44.6)	83 (50.9)	63 (48.8)	55 (48.2)	0.787
Weight, BMI, and calorie intake, at the baseline and year 3						
Weight, kg	93.5 (18.6)	91.9 (15.9)	94.1 (20.8)	91.4 (16.5)	96.6 (19.9)	0.130
Weight Year 3, kg	88.6 (18.6)	95.5 (17.0)	91.7 (20.3)	84.8 (15.3)	81.6 (17.9)	<0.001
BMI, kg/m^2	33.8 (5.9)	33.4 (5.1)	33.8 (6.7)	33.0 (5.2)	34.8 (6.3)	0.121
BMI Year 3, kg/m^2	32.0 (6.0)	34.8 (5.6)	32.9 (6.5)	30.6 (4.9)	29.4 (5.5)	<0.001
Total calories, kcal/d	2026.9 (712.8)	1966.1 (781.6)	1998.7 (662.1)	2071.4 (671.2)	2077.2 (758.8)	0.546
Total calories Year 3, kcal/d	1871.5 (564.5)	1874.3 (610.2)	1935.0 (600.3)	1855.0 (505.7)	1795.0 (522.6)	0.246
Weight change, kg	−4.92 (7.3)	3.60 (3.4)	−2.37 (1.4)	−6.67 (1.8)	−14.98 (6.3)	<0.001
Traditional lipid biomarkers						
Total cholesterol, mmol/L	4.90 [4.14, 5.57]	4.71 [4.22, 5.45]	4.91 [4.20, 5.66]	4.77 [4.07, 5.48]	4.93 [4.16, 5.64]	0.733
HDL cholesterol, mmol/L	1.40 [1.14, 1.74]	1.45 [1.17, 1.74]	1.41 [1.12, 1.74]	1.40 [1.16, 1.69]	1.32 [1.06, 1.70]	0.407
LDL cholesterol, mmol/L	2.72 [2.20, 3.34]	2.62 [2.23, 3.21]	2.72 [2.27, 3.34]	2.67 [2.10, 3.35]	2.90 [2.23, 3.44]	0.705
Triglyceride, mmol/L	1.25 [0.95, 1.72]	1.24 [0.94, 1.61]	1.33 [0.94, 1.80]	1.19 [0.92, 1.54]	1.24 [0.96, 1.78]	0.372
Inflammatory biomarkers						
C-reactive protein, mg/L	2.18 [1.09, 4.67]	2.04 [0.98, 3.73]	2.10 [1.03, 4.98]	2.04 [1.10, 4.70]	2.78 [1.10, 5.12]	0.565
Interleukin-6, pg/mL	2.60 [1.77, 3.68]	2.49 [1.77, 3.47]	2.58 [1.76, 3.65]	2.62 [1.63, 3.94]	2.72 [1.93, 3.81]	0.507
GlycA, mmol/l	0.96 [0.88, 1.06]	0.94 [0.87, 1.04]	0.98 [0.90, 1.07]	0.95 [0.88, 1.05]	0.98 [0.89, 1.07]	0.308
Total adiponectin, µg/mL	7.73 [4.68, 12.32]	7.88 [4.56, 12.77]	7.46 [5.18, 13.07]	7.52 [4.34, 11.46]	8.12 [4.86, 12.11]	0.917
Glycosylated hemoglobin						
Hemoglobin A1c, %	5.50 [5.30, 5.80]	5.60 [5.30, 5.80]	5.50 [5.30, 5.80]	5.50 [5.30, 5.80]	5.60 [5.40, 5.88]	0.704

MIND Mediterranean-DASH Intervention for Neurodegenerative Delay, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein.
Baseline values are shown unless otherwise specified.
Medication use was self-reported. We specifically considered diabetes medications, including metformin and insulin, as well as medications for dyslipidemia, such as Lovastatin, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin, and Atorvastatin. Metformin accounted for 85% of antidiabetic medication use, including treatments involving metformin and/or insulin. Hypertension was defined as a self-report of being told they had high blood pressure by a healthcare provider or to take medication for high blood pressure.

Table 2. Association between weight loss and 3-year changes in traditional lipid biomarkers.

	Cholesterol ($n = 516$)			LDL cholesterol ($n = 514$)			HDL cholesterol ($n = 516$)			Triglyceride ($n = 516$)		
	Beta ± SE	**RD**	***P***	**Beta ± SE**	**RD**	***P***	**Beta ± SE**	**RD**	***P***	**Beta ± SE**	**RD**	***P***
No weight loss	reference			reference			reference			reference		
<5% weight loss	−0.015 ± 0.01	−3.4	0.129	−0.023 ± 0.017	−5.2	0.17	0.009 ± 0.009	2.2	0.279	−0.054 ± 0.018	−11.7	0.004
5–10% weight loss	−0.006 ± 0.01	−1.4	0.55	−0.021 ± 0.018	−4.7	0.239	0.031 ± 0.009	7.5	0.001	−0.082 ± 0.019	−17.1	<0.001
>10% weight loss	−0.02 ± 0.011	−4.6	0.057	−0.038 ± 0.018	−8.3	0.039	0.051 ± 0.009	12.4	<0.001	−0.144 ± 0.02	−28.2	<0.001

SE standard error, *RD* relative difference, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein.
RD can be interpreted as a percent lower (negative value) or higher (positive value).
Models were adjusted by age (years), sex (male vs. female), race (White vs. non-White), education (years), APOE e4 carriership (yes vs. no), body mass index (kg/m^2), physical activity (hours/week), smoking history (never vs. ever), MIND diet score (points), and dietary assignment (MIND diet group vs control diet group).

Table 3. Association between weight loss and 3-year changes in inflammatory biomarkers.

	C-reactive protein ($n = 515$)			Interleukin-6 ($n = 515$)			GlycA ($n = 454$)			Total adiponectin ($n = 509$)		
	Beta ± SE	**RD**	***P***	**Beta ± SE**	**RD**	***P***	**Beta ± SE**	**RD**	***P***	**Beta ± SE**	**RD**	***P***
No weight loss	reference			reference			reference			reference		
<5% weight Loss	−0.102 ± 0.048	−21.0	0.034	−0.051 ± 0.035	−11.0	0.15	−0.011 ± 0.011	−2.5	0.295	0.044 ± 0.017	10.8	0.009
5−10% weight loss	−0.200 ± 0.051	−36.9	<0.001	−0.086 ± 0.037	−17.9	0.021	−0.014 ± 0.011	−3.1	0.207	0.096 ± 0.018	24.7	<0.001
>10% weight loss	−0.392 ± 0.052	−59.5	<0.001	−0.175 ± 0.038	−33.1	<0.001	−0.034 ± 0.011	−7.5	0.003	0.186 ± 0.018	53.5	<0.001

SE standard error, *RD* relative difference.
RD can be interpreted as a percent lower (negative value) or higher (positive value).
Models were adjusted by age (years), sex (male vs. female), race (White vs. non-White), education (years), APOE e4 carriership (yes vs. no), body mass index (kg/m^2), physical activity (hours/week), smoking history (never vs. ever), MIND diet score (points), and dietary assignment (MIND diet group vs control diet group).

a control diet in relation to changes in global cognitive function and brain structure [19]. For the current study, we combined both randomized groups because the MIND diet and control diet promoted the same calorie restriction (i.e., 250 kcal), and participants in each arm, on average, experienced the same weight loss during the trial period [19]. Nevertheless, despite promoting the same calorie restriction (i.e., 250 kcal) and achieving similar weight loss, there were distinctions in the intervention plan between the MIND diet and the control diet worth noting. The MIND diet intervention promoted brain-healthy food groups of the MIND diet (e.g., green leafy vegetables, fish, extra-virgin olive oil), while the dietary counseling for the control diet group consisted of portion control to reduce calorie intake without changing the types of foods consumed. However, while the interventions differed, both randomized groups showed an improvement in their MIND diet scores by the end of the trial, although a greater improvement was observed in the MIND group as expected and planned [19]. Therefore, for this study, due to improvement in diet quality during the intervention, we posit that the association between weight loss and favorable cardiometabolic health could be attributed to a healthy diet, whether it is a MIND diet or a more generic dietary approach. This argument for a healthy diet is further supported by a sensitivity analysis, which demonstrated that the association between weight loss and cardiometabolic health was independent of total calorie intake–that is, calorie restriction alone did not explain the association between weight loss and improvements in cardiometabolic health.

The findings of our study that weight loss is associated with favorable cardiometabolic health align with several other clinical trials on weight loss. For example, a one-year, multicenter,

Table 4. Association between weight loss and 3-year changes in hemoglobin A1c.

	Hemoglobin A1c ($n = 518$)		
	Beta ± SE	***P***	**RD**
No weight loss	reference		
<5% weight loss	−0.013 ± 0.004	0.002	−2.9
5–10% weight loss	−0.018 ± 0.004	<0.001	−4.0
>10% weight loss	−0.029 ± 0.004	<0.001	−6.4

SE standard error, *RD* relative difference.
RD can be interpreted as a percent lower (negative value) or higher (positive value).
Models were adjusted by age (years), sex (male vs. female), race (white vs. non-white), education (years), APOE e4 carriership (yes vs. no), body mass index (kg/m^2), physical activity (hours/week), smoking history (never vs. ever), MIND diet score (points), and dietary assignment (MIND diet group vs control diet group).

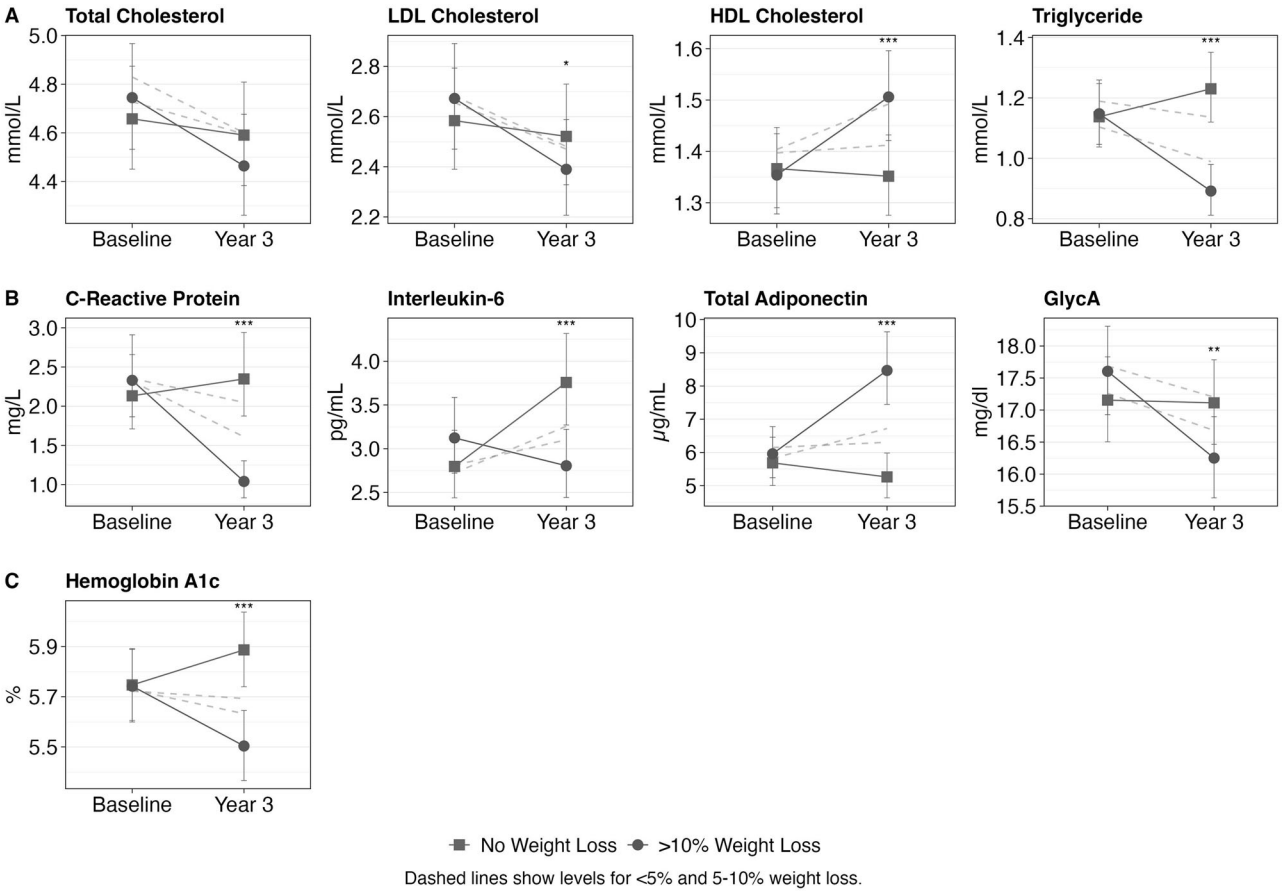

Fig. 1 Estimated means of cardiometabolic biomarkers across weight change groups at the baseline and year 3. Panels **A**–**C** show the estimated means for traditional lipid biomarkers, inflammatory biomarkers, and HbA1c, respectively, by weight loss group at baseline and year 3. Asterisk (*) indicate the *p* value ($p < 0.001$ ***; $p < 0.01$ **; $p < 0.05$ *) for the difference between changes in biomarkers for people who lost more than 10% of their baseline weight (>10% weight loss) compared to those who did not lose weight (no weight Loss). *P* values, including comparison between people in <5% and 5–10% weight loss versus those in the no weight loss group, are shown in Tables 2–4. Estimated means were adjusted by age (years), sex (male vs. female), race (White vs. non-White), education (years), APOE e4 carriership (yes vs. no), body mass index (kg/m^2), physical activity (hours/week), smoking history (never vs. ever), MIND diet score (points), and dietary assignment (MIND diet group vs control diet group).

controlled trial of 63 individuals with obesity who were randomly assigned to a low-carbohydrate diet or a conventional diet showed that both diets were associated with weight loss at year one, but no significant differences in weight loss between diets [7]. However, people with the low-carbohydrate diet had greater improvement in cardiometabolic risk factors such as HDL cholesterol and triglycerides, and both diets improved insulin response to an oral glucose load [7]. Similar findings were shown in another trial involving 120 volunteers from the community who were overweight to compare a low-carbohydrate, ketogenic diet versus a low-fat diet [8]. In a more recent randomized clinical trial of 811 adults with overweight, four diets with different compositions of fat, protein, and carbohydrates were compared in relation to weight loss during 2-year intervention. At the end of the trial, participants across all randomized diet groups experienced similar weight loss, averaging 4 kg, along with improvements in cardiometabolic risk factors such as lipid profiles and fasting insulin levels [9]. Another study evaluated the role of 1-year intensive lifestyle intervention consisting of diet and physical activity on weight loss and cardiometabolic risk factors among 130 individuals with severe obesity. This trial showed that lifestyle intervention was associated with clinically significant weight loss and favorable changes in cardiometabolic risk factors [10]. In addition to reinforcing the association between dietary intervention, weight loss, and improved cardiometabolic risk factors, our study contributes novel findings by demonstrating that the MIND diet designed for brain health or a more generic dietary approach could also provide cardiometabolic health benefits and these benefits extend to individuals aged 65 and older–an age group that is particularly vulnerable to unintentional weight loss and its associated adverse health consequences–whereas previous clinical trials utilized other dietary patterns, different intervention period, and primarily enrolled younger participants, averaging 44 to 52 years of age and tested other diets [7–10]. Moreover, our study presented novel findings indicating that weight loss resulting from these diets (e.g., MIND diet) has more significant anti-inflammatory effects compared to other biomarkers of cardiometabolic health, as shown by significantly lower levels of CRP and IL-6 during the dietary interventions. We also presented new data on novel biomarkers of inflammation, such as GlycA, which is a stable and reliable marker of acute and chronic inflammation. Most importantly, higher levels of GlycA have been associated with an increased risk of diabetes, subclinical atherosclerosis, and cardiovascular disease, further supporting findings of weight loss with traditional biomarkers of cardiovascular disease (e.g., total cholesterol, HDL cholesterol, and HbA1c). Taken together, we provide the most up-to-date evidence on the interrelationships among diet, weight loss, and biomarkers of cardiometabolic health. A recently published study from the Women's Health Initiative Observational Study, a prospective cohort with a mean follow-up of 18.6 years that included women aged 50 to 79 at 40 clinical centers in the U.S., among other outcomes, reported that intentional weight loss of 5% or more was associated only with lower cardiovascular mortality [31]. While we studied biomarkers of cardiometabolic health by utilizing 3-year follow-up clinical trial data, the Women's Health Initiative with a longer follow-up observation data further supports our findings that weight loss, potentially through dietary interventions, may have long-lasting effects on cardiovascular health. Another long-term study, Look AHEAD, was a multicenter randomized controlled trial that enrolled 5,145 individuals with overweight or obesity and type 2 diabetes to evaluate the effects of an intensive lifestyle intervention, including caloric restriction and increased physical activity. Over the initial 4 years, participants in the intervention group experienced significant weight loss and had favorable changes in glycemic control, blood pressure, HDL cholesterol, and triglyceride levels [32]. However, the intervention did not result in a significant reduction in cardiovascular morbidity or mortality over a median of 9.6 years of follow-up [33].

This study has limitations. First, the MIND trial was designed to test whether the MIND diet could improve brain health by being positively associated with cognitive function and changes in brain function. Therefore, the trial enrolled people without cognitive impairment at baseline but at risk of cognitive impairment. In addition, individuals enrolled in the trial were highly educated, mostly of European descent. Therefore, the findings of this study may not be generalizable to individuals from more diverse backgrounds or with lower educational levels. Second, although we used clinical trial data, the association between weight loss groups and cardiometabolic risk factors does not imply causal inferences. Third, although we may hypothesize that intentional weight loss through dietary interventions in our study participants could be related to decreasing fat mass, we did not assess body composition changes, and therefore, acknowledge this as a limitation of the study.

In conclusion, the MIND trial showed that weight loss through dietary interventions with mild calorie restriction is associated with favorable changes in cardiometabolic risk factors among older adults with overweight and obesity.

DATA AVAILABILITY

Limited data may be available for investigators upon approval of a research proposal.

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AUTHOR CONTRIBUTIONS

KD performed data analysis, interpreted the findings, and drafted and revised the manuscript. RMV, JV, KBR, XL, PA, and CT critically revised the manuscript and contributed substantial intellectual input. RKD and SMC contributed to the biomarker analysis and reviewed the manuscript and provided intellectual content. NTA, KA, FMS, and LLB were involved in the design of the MIND trial, oversaw data collection, critically reviewed and revised the manuscript, and contributed significant intellectual input to the study.

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COMPETING INTERESTS

Dr. Kaddurah-Daouk in an inventor on a series of patents on use of metabolomics for the diagnosis and treatment of CNS diseases and holds equity in Metabolon Inc., Chymia LLC and PsyProtix.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The MIND trial followed the ethical standards of the 1964 Declaration of Helsinki and its later amendments and was approved by the institutional review boards at Rush University Medical Center, Harvard School of Public Health, and Brigham and Women's Hospital. All the participants provided written informed consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-025-01902-6.

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