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Mediterranean and low-fat diets are equally effective in MASLD resolution at 12 weeks regardless of PNPLA3 genotype: A randomized controlled trial

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Abstract

Background: Dietary interventions are key for managing metabolic dysfunction–associated steatotic liver disease (MASLD), yet optimal diets and the role of PNPLA3 in modulating response to diet remain unclear. We evaluated the efficacy of a Mediterranean diet (MD) versus a low-fat diet (LFD) on hepatic fat and fibrosis, assessing interactions with PNPLA3 genotype.

Methods: Two hundred fifty adults with MASLD with BMI ≥ 25 kg/m^2 were randomized to a 12-week moderately hypocaloric MD or LFD intervention. Individuals with excess alcohol intake and other etiologies of steatosis were excluded. Subjects were genotyped for PNLPA3 single-nucleotide polymorphism. Anthropometric measures, blood tests, and liver assessments [controlled attenuation parameter (CAP) and liver stiffness measurement (LSM)] were conducted at baseline and follow-up. Essential food items were provided, and adherence was tracked using validated questionnaires. The primary outcome was CAP, analyzed using linear mixed models adjusted for age and metabolic syndrome.

Results: Both diets significantly reduced CAP, LSM, and body weight at follow-up, with no significant differences between groups. The mean difference between MD and LFD was −0.13 dB/m for CAP ($p = 0.976$, 95% CI: −8.54, 8.28), −0.19 kPa for LSM ($p = 0.355$, 95% CI: −0.58, 0.21), and 3.01 kg for weight ($p = 0.159$, 95% CI: −7.21, 1.19). PNPLA3 genotype did

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled-attenuation parameter; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HFF, hepatic fat fraction; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IPAQ, International Physical Activity Questionnaire; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LFD, low-fat diet; LFDAS, low-fat diet adherence score; LSM, liver stiffness measurement; MAR, missing at random; MASLD, metabolic dysfunction–associated steatotic liver disease; MD, Mediterranean diet; MEDAS, Mediterranean diet adherence screener; METS, metabolic syndrome; PNPLA3, patatin like phospholipase 3; TAG, triglycerides; TC, total cholesterol; VCTE, vibration-controlled transient elastography.

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not significantly interact with diet for CAP, LSM, or weight ($p = 0.286$, $p = 0.464$, $p = 0.622$, respectively).

Conclusions: Weight reduction achieved by MD and LFD is similarly efficient in steatosis and fibrosis reduction, while PNPLA3 genotype does not affect the response to diet. Further studies investigating the impact of diet and nutrigenetics on liver-related outcomes are warranted.

Keywords: fatty liver, low-fat diet, MASLD, Mediterranean diet, NAFLD, PNPLA3

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) is estimated to affect ~30%–38% of the global adult population, with its prevalence steadily increasing.[1] As a progressive condition, MASLD encompasses a spectrum of liver abnormalities that can advance to cirrhosis and hepatocellular carcinoma, making it the leading cause of chronic liver disease worldwide.[2] Despite many developments in targeted pharmacological therapeutics, weight loss, achieved by dietary modifications, remains the cornerstone of therapy.[3] A diet tailored to an individual's lifestyle, personal preferences, and nutritional requirements is most likely to promote long-term adherence and sustainability.

Various dietary strategies have been recommended for managing MASLD. A growing body of evidence from observational studies[4–7] and clinical trials[8–16] suggests that increased adherence to a Mediterranean diet (MD) can improve steatosis levels, fibrosis, insulin resistance, and other metabolic risk markers in MASLD. Researchers have investigated the relative superiority of the MD to other dietary approaches; however, the results remain inconclusive. Some studies have shown that an MD rich in healthy fats results in greater hepatic fat loss than conventional fat-restricted diets.[17–19] Others found no differences between hepatic changes induced by diets with different amounts of fat and carbohydrate.[12,20,21] Interestingly, the low-fat diet (LFD) significantly reduced hepatic steatosis, transaminases, and insulin resistance in MASLD subjects following an intervention of 12 weeks, in contrast to an isocaloric MD.[22] Methodological heterogeneity and limited sample sizes contribute to the inconclusive nature of findings within the existing literature. Taken together, although the MD is widely recognized for its health benefits in MASLD management, consensus on the most effective form of medical nutrition therapy has yet to be established.

While dietary interventions are central to MASLD management, not all patients respond favorably. Factors such as genetic predispositions and nutrient–gene interactions may contribute to this inter-individual variability in response.[23] Recently, a single-nucleotide polymorphism (SNP) characterized by a C to G substitution encoding an isoleucine to methionine substitution at the amino acid position 148 in the patatin-like phospholipase 3 (PNPLA3) gene, was found to interact with the factors that induce hepatic fat accumulation. One study found that individuals homozygous for the G allele are more susceptible to increased hepatic fat accumulation when their dietary carbohydrate intake, particularly sugar, is high.[24] A randomized clinical trial reported that the PNPLA3 GG genotype negatively affected changes in steatosis during an 18-month omega-3 supplementation.[25] On the contrary, dietary modification is suggested to be more effective in decreasing steatosis content in PNPLA3 G-allele carriers compared with wildtype.[26] These findings collectively underline the consideration of including PNPLA3 genotypes into MASLD treatment strategies to optimize therapeutic outcomes. However, no clinical trial to date has specifically examined the interaction between PNPLA3 genotypes and dietary interventions. Consequently, there remains debate about which, if any, diet or diets are most effective for steatosis and fibrosis reduction in G-allele carriers, with limited evidence available on nutrigenetic strategies in MASLD.

In the present study, we aimed to investigate whether similarly hypocaloric MD and LFD differ in their capacity to induce steatosis resolution, and secondly, if PNPLA3 genotype moderates the improvements in hepatic and cardiometabolic parameters.

METHODS

This 12-week, single-center, parallel-group randomized controlled nutritional intervention was conducted between October 2023 and September 2024 at the Endocrinology Clinic of Istanbul University-Cerrahpasa Research Hospital. The study protocol was reviewed and approved by the Clinical Research Ethics Committee of Istanbul University-Cerrahpasa

(ref. 2023/134) and adhered to the ethical principles outlined in the Declaration of Helsinki. All participants were thoroughly informed about the study's objectives and implications and provided written consent to participate. The study was prospectively registered with the National Health Institute records (ClinicalTrials.gov, ID: NCT06220695).

Subjects and design

The study included individuals aged 18–80 years who had been diagnosed with liver steatosis within the past 6 months using FibroScan and had a body mass index (BMI) of at least 25 kg/m^2. Exclusion criteria included excessive alcohol consumption (>20 g/d for women, >30 g/d for men), other etiologies of liver diseases (viral, autoimmune, storage), secondary steatosis, celiac disease, pregnancy, breastfeeding, recent bariatric surgery, or cancer.

Subjects were randomized in a 1:1 ratio by blocks of 4 with a computer-generated random allocation. Contrary to the original protocol plan, stratification by PNPLA3 during randomization was not feasible due to practical issues with the genetic test provider, which delayed genotyping until after randomization. After randomization, all patients underwent anthropometric measurements, blood tests, Fibroscan, and baseline nutritional and physical activity assessments. All participants were then invited to their initial dietitian appointment.

Assessments

Steatosis and fibrosis

Steatosis and fibrosis were assessed using vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (CAP), performed with the FibroScan. For each examination, the M probe was applied first, switching to XL if recommended. Exams required ≥ 3 hours fasting, ≥ 10 valid liver stiffness measurements (LSMs), and an IQR to median ratio $<30\%$. Steatosis was defined as CAP ≥ 248 dB/m, and significant fibrosis as LSM ≥ 8 kPa in accordance with current clinical guidance[1] and previous evidence.[27–30]

Anthropometric assessment

Body weight was measured to the nearest 0.05 kg with participants in light clothing, fasting, and shoeless, using a calibrated bioelectrical impedance scale (Tanita, Japan). Height was measured to 0.1 cm, and BMI was calculated as weight/height^2 (kg/m^2).

Genotyping

PNPLA3 rs738409 was genotyped using the real-time PCR method (CFX Connect Real-Time PCR System, Bio-Rad Laboratories, United States). Genotypes were successfully determined for 247 of the 250 individuals included in the study and randomized.

Biochemical assessments

Blood samples were collected at baseline and follow-up. Liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TAG), high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol] levels were analyzed using a biochemistry analyzer (Cobas, Roche Diagnostics, Basel, Switzerland) and commercial Roche diagnostics kits. Fasting insulin level was measured using the electrochemiluminescence immunoassay method (Cobas, Roche Diagnostics, Basel, Switzerland). Fasting insulin and glucose concentrations were used to calculate insulin resistance from the HOMA-IR model.

Diet and physical activity assessment

At baseline, participants completed dietary and lifestyle questionnaires. Dietary intake was assessed at baseline and follow-up with a validated food frequency questionnaire[31] and Mediterranean Diet Adherence Screener (MEDAS), validated for the Turkish population.[32,33] Physical activity was assessed at baseline using the short form of the International Physical Activity Questionnaire (IPAQ), also validated in Turkish.[34] Participants were advised to maintain usual activity levels throughout the intervention.

Dietary intervention

Both the MD and LFD were designed to create a moderate caloric deficit (1500–1800 kcal/d for men, 1200–1400 kcal/d for women) to achieve a gradual 7%–10% weight loss. Similar restrictions on trans fats and simple carbohydrates were put in place, while promoting a higher intake of vegetables. In addition, in both groups, saturated fats accounted for $\leq 10\%$ of total energy.

The LFD followed dietary guidelines from the American Heart Association,[35] the American Diabetes Association, and the Turkey Nutrition Guide,[36] targeting ~50% energy from carbohydrates, 20% from protein, and $<30\%$ from fat. In contrast, the MD, as extensively described,[37] emphasized high consumption of olive oil,

olives, fatty fish, and nuts. It also included high amounts of fruits, vegetables, whole grains, legumes, moderate consumption of eggs, poultry, and dairy products, and limited intake of red meat. The MD provided at least 40% of total energy from fat, primarily from monounsaturated fatty acids, with carbohydrates contributing $<40\%$ and protein making up 20% of total energy intake. Detailed recommendations for both dietary protocols are presented in Supplemental Table S1, http://links.lww.com/HC9/C192, with sample menus provided in Supplemental Table S2, http://links.lww.com/HC9/C192.

Both groups received a 1-hour nutrition education session, accompanied by informational handouts and brochures outlining the core principles of their respective diets and cooking tips. Personalized weekly menus were created for each participant, adjusted for basal metabolic rate and energy needs, while maintaining the calorie deficit. Adherence was supported by accounting for individual preferences. The nutritional intervention consisted of standardized weekly face-to-face sessions across both groups, ensuring consistency in meeting frequency, session duration, and the quality of educational content.

Food supplies

To eliminate differences in purchasing power, all participants were provided with monthly food packages tailored to their assigned group. The specific contents of the packages are detailed in Supplemental Table S3, http://links.lww.com/HC9/C192. The required quantity per person was calculated for a 12-week period, based on the estimated average daily caloric needs of individuals following the calorie-restricted MD or LFD. Packages were sourced from a food sales center capable of supplying all necessary nutritional products.

Assessment of adherence

Dietary adherence was assessed at baseline and follow-up by MEDAS in the MD group and Low-Fat Diet Adherence Screening (LFDAS) in the LFD group. Both questionnaires are scored 0 or 1 per item. MEDAS ranges from 0 to 14, with a score of ≥ 10 indicating high adherence, 6–9 reflecting moderate adherence, and <5 indicating low adherence to the MD.[38] LFDAS ranges from 0 to 9, with ≥ 6 points indicating high adherence, 4–5 points representing moderate adherence, and 0–3 points reflecting low adherence to the low-fat diet.[38]

Statistical analysis

The primary outcome was CAP (dB/m), and secondary outcomes were LSM (kPa), weight (kg), FBG (mg/dL), HOMA-IR, liver function tests (ALT, AST), and serum lipids [TC, LDL, HDL, TAG (mg/dL)]. Analyses of secondary outcomes were not corrected for multiple testing. The original sample size calculation for the registered protocol was based on estimated effect sizes (large, medium, small) across PNPLA3 genotypes, as no prior clinical data were available. A total of 150 participants was required to detect a clinically meaningful difference with 80% power at a 5% significance level. After protocol registration and before data collection, additional funding allowed larger recruitment, leading to a revised calculation. The new requirement was 218 participants, with power 80%, Bonferroni corrected significance level 2.5%, and Cohen $d=0.8$ (large effect size) for wildtype and $d=0.5$ (medium effect size) for G-allele carriers. Sample size was calculated using G*power (v3.1) for a 2-tailed t test aiming to detect differences in mean CAP between diet groups at follow-up within each PNPLA3 level. The target sample size was set at 244, to allow for about 10% dropout. Continuous variables were expressed as means $\pm$ SD, and categorical variables as counts and percentages. Normality was assessed with histograms and PP-plots. Hardy–Weinberg equilibrium of genotypes was tested with chi-square.

Outcome missingness was explored with logistic regression of outcome missingness at follow-up, predicted from diet group and all the variables in Table 1. Linear mixed models were used to assess the differences between the diet groups and the presence of an interaction between PNPLA3 genotype and diet groups. This method accounts for the correlation between repeated outcome measures, retains dropouts in accordance with the intention-to-treat (ITT) principle by employing a likelihood-based approach for handling missing outcome data without the need for imputation, which is valid under the missing-at-random (MAR) assumption and is a natural missing data approach for RCTs with (almost) complete baseline covariates. The fixed part of the linear mixed models included diet group, PNPLA3 genotype, time, and all 2-way and 3-way interactions. In addition, variables related to missing outcome data were included in the fixed part of the model to support the plausibility of the MAR assumption, while variables associated with the outcomes and showing substantial baseline differences between groups were included as covariates to enhance power and precision. For the random part of the models, an unstructured covariance matrix was initially assumed for the repeated measures, which was simplified to a compound symmetry structure if it resulted in a lower Bayesian Information Criterion. A top-down strategy was used to simplify the fixed part of the linear mixed models. The procedure started by testing the 3-way interaction (group$*$time$*$genotype). If significant, the procedure stopped. If not significant, the 3-way interaction was removed, and the remaining variables were tested stepwise, while adhering to the

TABLE 1 Baseline characteristics of the study groups

	MD (n = 125)	LFD (n = 125)
Demographics		
Age (y)	52.6 (12.18)	52.8 (12.7)
Male (%)	37.5%	35.2%
BMI (kg/m^2)	34.4 (5.6)	35.1 (6.3)
Weight (kg)	92.6 (18.1)	94.6 (18.6)
Education (y)	9.3 (5.0)	9.7 (4.9)
Married (%)	80%	84%
Low income (%)	11.2%	10.4%
Medium income (%)	60%	69.6%
High income (%)	28.8%	20.0%
Lifestyle		
Active drinkers (%)	15.2%	16.0%
Active smokers (%)	20%	25.6%
IPAQ score (metmin/week)	532.2 (730.0)	533.4 (894.7)
Assessments		
CAP (db/m)	313.1 (35.8)	310.9 (35.5)
LSM (kPa)	6.1 (1.8)	6.4 (2.5)
ALT (U/L)	24.5 (19.1)	22.4 (14.6)
AST(U/L)	20.4 (12.2)	18.8 (7.9)
FBG (mg/dL)	112.0 (43.8)	114.1 (48.4)
HOMA-IR	5.2 (3.4)	5.4 (5.7)
HDL (mg/dL)	43.5 (13.4)	45.2 (14.2)
TAG (mg/dL)	184.9 (117.7)	176.7 (136.0)
Medical conditions		
Obesity (%)	76.8%	76.8%
Central obesity (%)	82.4%	84.8%
Hypertension (%)	62.4%	74.4%
Diabetes (%)	64%	56.8%
Dyslipidemia (%)	84.8%	84.0%
MetS (IDF criteria) (%)	80.8%	74.4%
GG or CG (%)	44.0% (n = 123)	56.8% (n = 124)
Dietary intake		
Energy (kcal/day)	2582.9 (245.3)	2629.1 (335.6)
Carbohydrates (g/day)	251.1 (43.9)	267.1 (52.4)
Fat (g/day)	120.5 (19.2)	118.9 (17.4)
Protein (g/day)	123.5 (20.1)	123.0 (33.0)
Fiber (g/day)	20.9 (4.8)	18.3 (6.1)
Added sugars (g/day)	51.0 (27.6)	61.3 (23.8)
Alcohol (g/day)	9.3 (11.6)	9.9 (13.3)

Note: Values are presented as mean (SD).
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; FBG, fasting blood glucose; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; LFD, low-fat diet; LSM, liver stiffness measurement; MD, Mediterranean diet; MetS, metabolic syndrome; TAG, triglycerides; TC, total cholesterol.

hierarchical principle by avoiding tests of lower-order terms of a significant interaction. This continued until only statistically significant variables remained in the model, except for group (retained to address the main research question) and variables associated with missing outcome data (retained to ensure MAR). Three subjects with unsuccessful genotyping were excluded from analyses that included PNPLA3 as a factor. All *p*-values were 2-sided, with $p < 0.05$. The SPSS statistical software package, version 29.0 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Baseline characteristics

Of 459 screened subjects, 250 were recruited and randomized to receive either MD (n = 125, 47 male, 78 female) or LFD (n = 125, 45 male, 80 female) (Figure 1). The mean age of the study population was 52.7 ± 12.4 years. A total of 63.6% participants were women, with a mean BMI of 34.7 ± 5.9 kg/m^2. At trial entry, there were no significant differences between groups regarding age or laboratory indices that might affect response to dietary treatment. Lifestyle habits, reported dietary intake, and underlying health conditions were also comparable across the groups (Table 1).

Table 2 illustrates weight, CAP, and LSM values according to PNPLA3 genotype. The alleles of PNPLA3 were in Hardy–Weinberg equilibrium ($p = 0.464$), and the frequency of the G allele was 29.6%.

Adherence to diet

Of 250 subjects recruited, 173 completed the intervention. One subject with unsuccessful genotyping was excluded from analyses that included PNPLA3 as a factor. All retained participants had eligible follow-up tests. Overall, the dropout rate was 30.8% with no difference between groups ($p = 0.839$; Statistical Supplement 1, http://links.lww.com/HC9/C192). Among the baseline characteristics in Table 1, a logistic regression of outcome missingness at follow-up showed that age was predictive of dropout (OR = 0.959, $p < 0.001$, 95% CI: 0.937–0.981; Statistical Supplement 1, http://links.lww.com/HC9/C192). Dropouts were, on average, younger than completers (48.23 ± 13.03 vs. 54.73 ± 11.61).

At week 6, the mean MEDAS in the MD group was 8.8 ± 1.9, while the mean LFDAS in the LFD group was 5.3 ± 1.9. Dietary adherence from baseline to the end of the study has improved more in MD than in LFD (Figure 2).

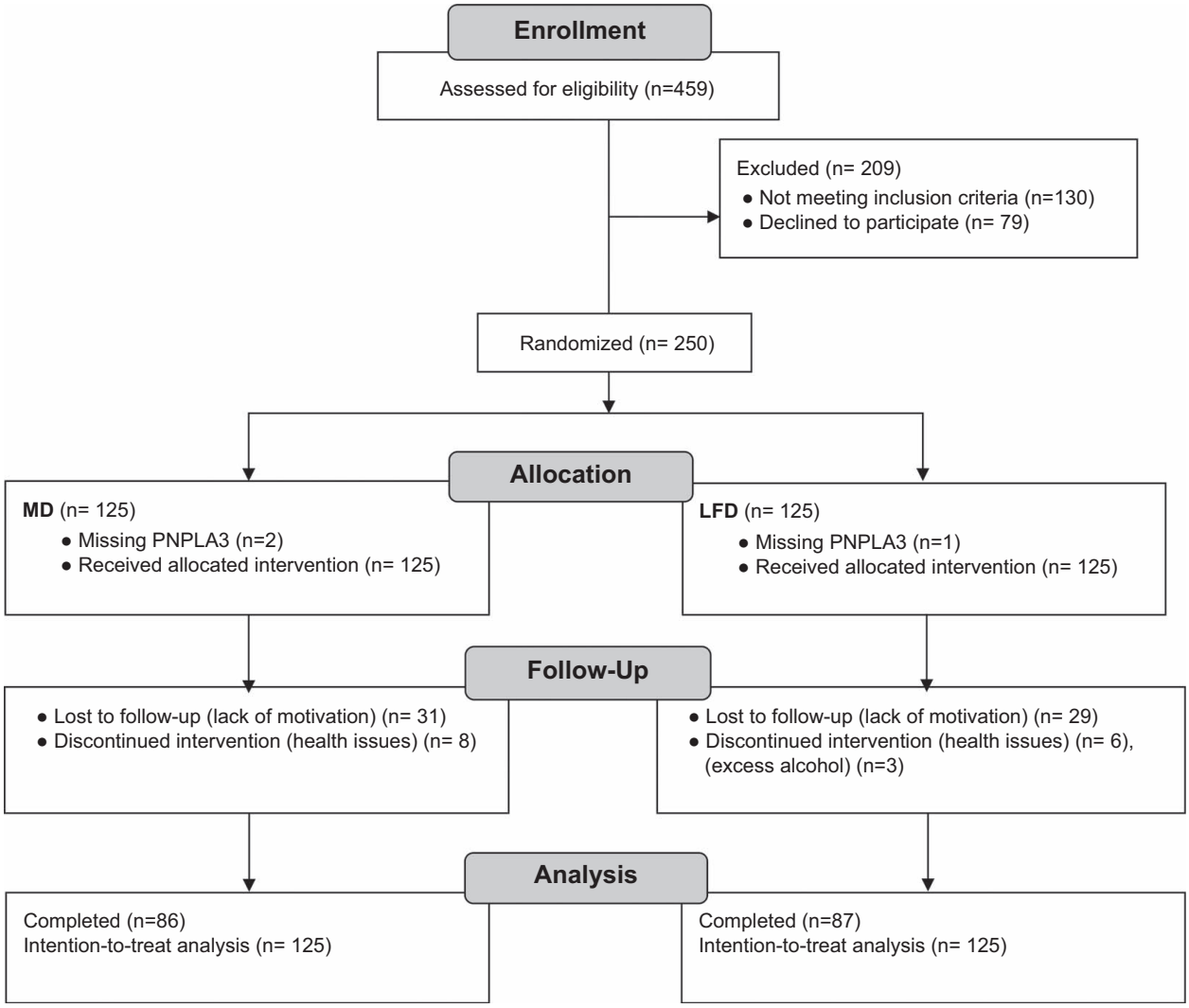

FIGURE 1 CONSORT flowchart. Abbreviations: LFD, low-fat diet; MD, Mediterranean diet; PNPLA3, patatin-like phospholipase 3.

Percent changes from baseline in total energy intake, protein, fiber, added sugars, saturated fatty acids, polyunsaturated fatty acids, trans fatty acids, and alcohol consumption were comparable between groups. However, carbohydrate reduction was greater in the MD group, while monounsaturated fatty acid intake increased in the MD but decreased in the LFD group. In addition, the reduction in total fat intake was greater in the LFD compared with the MD group (Supplemental Table S4, http://links.lww.com/HC9/C192).

Changes in outcome measures, between-group differences, and the impact of PNPLA3 on response to diet

After 12 weeks, changes in weight, CAP, and LSM from baseline to follow-up were comparable between groups and between wildtypes and minor allele carriers (Figure 3) (Supplemental Tables S5, S6, http://links.lww.com/HC9/C192).

TABLE 2 Baseline measurements of the primary outcomes according to PNPLA3 genotype

	Weight (kg)		CAP (db/m)		LSM (kPa)		N	
	MD	LFD	MD	LFD	MD	LFD	MD	LFD
CC	93.2 (17.1)	94.7 (19.1)	312.9 (30.9)	314.1 (40.3)	6.1 (1.9)	6.6 (3.1)	70	52
CG or GG	92.5 (19.3)	93.9 (17.9)	317.7 (34.3)	309.6 (30.8)	7.1 (7.7)	6.3 (2.0)	53	72

Abbreviations: CAP, controlled attenuation parameter; LFD, low-fat diet; LSM, liver stiffness measurement; MD, Mediterranean diet.

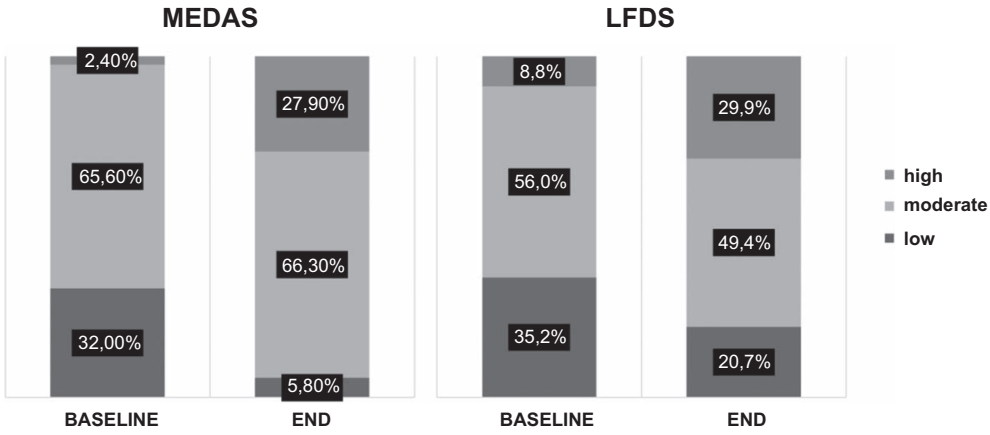

FIGURE 2 The percentage of participants falling into each adherence category at baseline and end-of-study, defined by MD and LFD adherence scores. Abbreviations: LFDS, low-fat diet adherence score; MEDAS, Mediterranean diet adherence screener.

Primary outcome: CAP

Table 3 shows the linear mixed model results for CAP. CAP reduced significantly in the full cohort at follow-up (−45.80 dB/m, $p < 0.001$, 95% CI: −52.32, −39.27) with no difference between groups with a mean CAP difference between MD and LFD of −0.13 dB/m ($p = 0.976$, 95% CI: −8.54, 8.28) after controlling for time, metabolic syndrome at baseline, and age. No interactions were found between group, genotype, and time ($p = 0.449$ of Group∗Genotype∗Time) or between group and genotype ($p = 0.286$, not shown). The mean CAP difference between wildtypes and G-allele carriers was −1.55 dB/m ($p = 0.709$, 95% CI: −9.75, 6.64) when adjusted for group, time, metabolic syndrome at baseline, and age.

For the models in Table 3, all assumptions were met (Statistical Supplement 2, http://links.lww.com/HC9/C192).

Secondary outcomes

Linear mixed models examining LSM, FBG, HOMA-IR, ALT, AST, HDL, TAG (with unstructured covariance matrix), and weight, TC, LDL (with compound symmetry covariance matrix) showed significant reductions at follow-up in the full cohort in LSM ($B = -1.06$, $p < 0.001$), weight ($B = -4.46$, $p < 0.001$), FBG ($B = -7.66$, $p < 0.001$), HOMA-IR ($B = -1.25$, $p < 0.001$), AST ($B = -3.48$, $p < 0.001$), ALT ($B = -13.65$, $p < 0.001$), TC ($B = -8.57$, $p < 0.001$), LDL ($B = -7.20$, $p = 0.006$), HDL ($B = -1.54$, $p = 0.027$), and TAG ($B = -26.50$, $p < 0.001$) with no significant difference between groups (Supplemental Table S7, http://links.lww.com/HC9/C192). Differences in LSM and weight between wildtypes and G-allele carriers were nonsignificant (LSM: 0.26 kPa, $p = 0.199$, weight: 1.67, $p = 0.443$). No group∗genotype∗time interactions were observed except for HOMA-IR ($p = 0.019$, 95% CI: −5.03, −0.45; Statistical Supplement 3, http://links.lww.com/HC9/C192). However, pairwise comparisons showed no significant differences between diets within PNPLA3 subgroups at follow-up (wildtypes: 0.1, $p = 0.88$, 95% CI −1.2, 1.4; G-allele carriers: 1.248, $p = 0.069$, 95% CI −0.099, 2.594; Statistical Supplement 3, http://links.lww.com/HC9/C192).

DISCUSSION

This 12-week randomized, parallel-group dietary intervention demonstrated that both MD and LFD effectively reduced hepatic steatosis, without an influence of the PNPLA3 polymorphism on the response to either dietary intervention. To our knowledge, this is the first study to investigate the potential genotype-specific responses to dietary treatment protocols designed for MASLD management.

The finding that the MD was not superior to the LFD in resolving steatosis aligns with certain previous studies, although the overall evidence remains mixed. A 12-week trial comparing an ad libitum MD to an LFD in MASLD patients reported significant steatosis reductions in both groups without between-group differences.[12] Similarly, another study conducted in Australia reported comparable outcomes for MD and LFD.[22] While other studies have suggested greater benefits of MD, limited sample sizes[9,18–20] and the absence of a healthy control diet[11,14,15] may constrain the generalizability of their findings. A recent systematic review and meta-analysis, pooling data from randomized controlled trials, concluded that both MD and LFD exhibit similar therapeutic effects on liver enzymes and liver fat content,[39] similar to our findings. One of the multiple explanations for the comparable results in our study is that the prescribed MD and LFD were quite similar in several respects, particularly fiber content—a

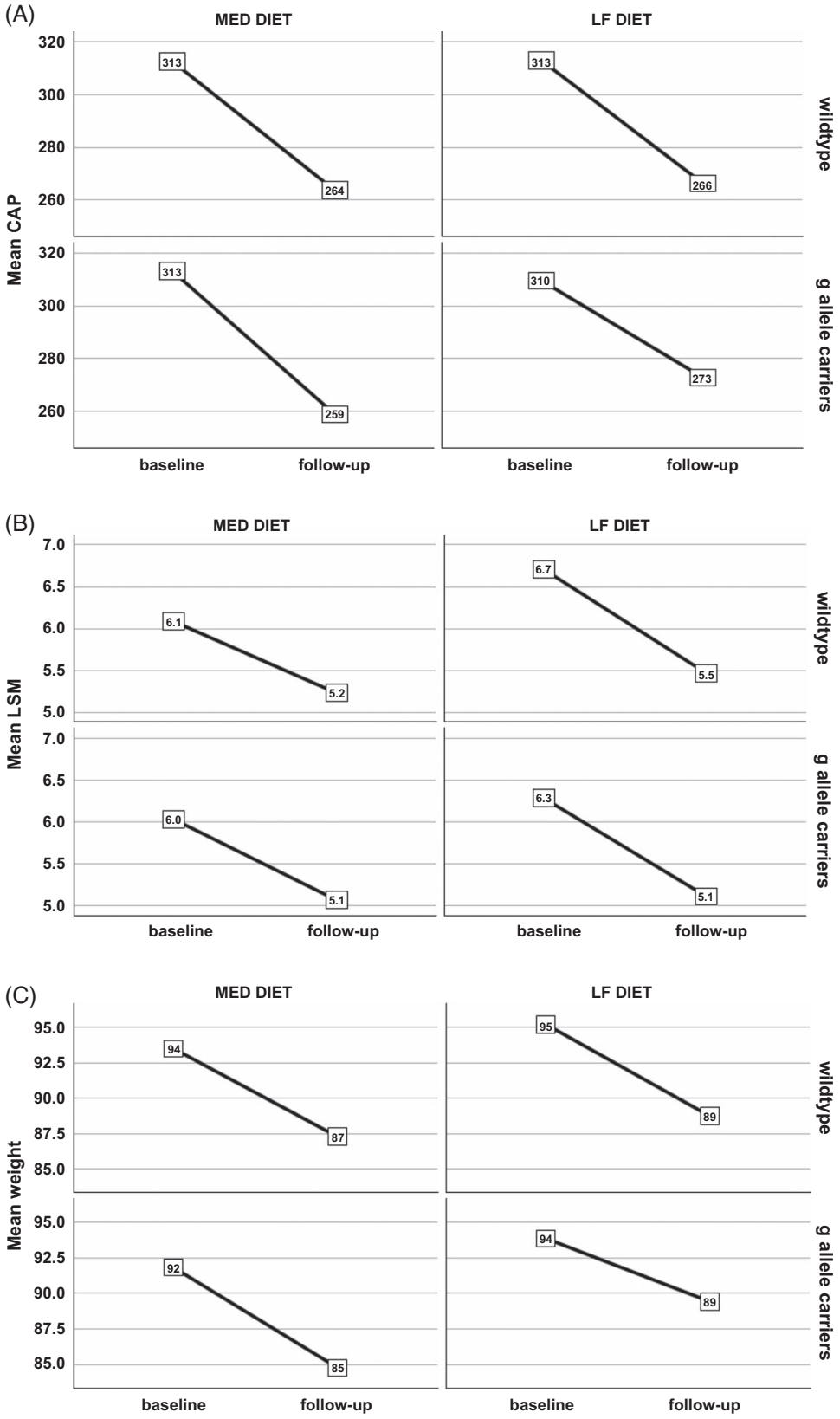

FIGURE 3 Unadjusted mean changes in outcome measures by PNPLA3 minor allele carriage: (A) mean CAP (db/m), (B) mean LSM (kPa), and (C) mean body weight (kg). Abbreviations: CAP, controlled attenuation parameter; LF diet, low-fat diet; LSM, liver stiffness measurement; PNPLA3, patatin-like phospholipase 3; MED diet, Mediterranean diet

TABLE 3 Linear mixed models with primary outcome CAP as the dependent variable

	Model 1 (N = 247)				Model 2 (N = 247)				Model 3 (N = 250)			
Predictors	***B* (SE)**	**95% CI**	***T*-value**	***p*-value**	***B* (SE)**	**95% CI**	***T*-value**	***p*-value**	***B* (SE)**	**95% CI**	***T*-value**	***p*-value**
Intercept	322.34 (9.68)	303.27, 341.41	33.29	< 0.001	325.71 (9.54)	306.91, 344.51	34.13	< 0.001	326.12 (9.88)	306.67, 345.58	33.02	< 0.001
Group												
MD	7.67 (6.06)	−4.27, 19.61	1.26	0.207	1.46 (4.16)	−6.73, 9.65	0.35	0.726	−0.13 (4.27)	−8.54, 8.28	−0.03	0.976
Genotype												
CC	5.70 (6.12)	−6.36, 17.77	0.93	0.353	−1.55 (4.16)	−9.75, 6.64	−0.37	0.709	N/A	N/A	N/A	N/A
Time												
Follow-up	−36.09 (6.20)	−48.32, −23.86	−5.82	< 0.001	−46.18 (3.32)	−52.73, −39.64	−13.92	< 0.001	−45.80 (3.31)	−52.32, −39.27	−13.84	< 0.001
Group∗Time												
MD∗Follow-up	−10.27 (9.74)	−29.50, 8.96	−1.05	0.293	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Group∗Genotype												
MD∗CC	−10.61 (8.64)	−27.63, 6.41	−1.23	0.221	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Genotype∗Time												
CC∗Follow-up	−15.48 (9.39)	−34.00, 3.04	−1.65	0.101	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Group∗Genotype∗Time												
MD∗ CC∗follow-up	10.21 (13.46)	−16.34, 36.77	0.76	0.449	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Covariates												
No MetS	−11.53 (5.02)	−21.42, −1.63	−2.29	0.023	−11.47 (5.01)	−21.34, −1.60	−2.29	0.023	−14.97 (5.16)	−25.14, −4.80	−2.90	0.004
Age	−0.19 (0.17)	−0.52, 0.14	−1.16	0.249	−0.19 (0.17)	−0.52, 0.14	−1.12	0.263	−0.20 (0.17)	−0.55, 0.14	−1.17	0.242

Note: Values are presented as mean (SD).
Model 1: includes all 2-way and 3-way interactions between group, genotype, and time, adjusted for age and metabolic syndrome at baseline.
Model 2: controls the intervention effect for PNPLA3 genotype and time, adjusted for age and metabolic syndrome at baseline.
Model 3: includes only group and time and excludes genotypes for a full intention-to-treat analysis, adjusted for age and metabolic syndrome at baseline.
Using dummy coding for categorical predictors: diet group, genotype, time, metabolic syndrome at baseline, with as reference categories respectively low-fat diet, G-allele carrier, baseline, and having metabolic syndrome at baseline. All models assume an unstructured covariance matrix.
Abbreviations: CAP, controlled attenuation parameter; MD, Mediterranean diet.

putative mediator of the MD's benefits. Thus, the principal difference was largely confined to a relatively modest variation in macronutrients and MUFA versus carbohydrate content, while many other dietary features were relatively aligned. In addition, the weight loss–induced improvements in insulin resistance observed in both arms likely represent the comparable therapeutic efficacy of the 2 diets in our study. Insulin resistance is widely recognized as a key driver of free fatty acids flux to the liver caused by dysregulated adipose lipolysis[40] as well as increased de novo lipogenesis.[41] Its detrimental effects are further exacerbated by decreased hepatic insulin clearance, impaired glucose disposal, and increased hepatic gluconeogenesis seen in MASLD.[41] Both dietary interventions in our study targeted—and successfully limited—the intake of free sugars and saturated fats, 2 major contributors to insulin resistance–associated hyperinsulinemia. Furthermore, weight loss is known to improve liver mitochondrial dynamics and β-oxidation that drive MASLD pathogenesis.[42] By reducing intrahepatic fat and consequently lowering oxidative stress, inflammatory cytokines, and endotoxin-mediated injury, weight loss could represent the principal mechanism driving hepatic improvements. Consistent with this interpretation, previous evidence suggests that a minimal clinically meaningful improvement in steatosis can be achieved with an initial weight loss of ~5 kg, regardless of the dietary method used to achieve it.[43] Collectively, these findings reiterate that multiple dietary approaches can effectively facilitate weight loss and improve MASLD outcomes. Given its robust design, our study provides strong empirical confirmation that energy restriction—and the consequent weight loss—plays a pivotal role in the management of MASLD.[44] Future studies stratifying outcomes by weight-loss status may help clarify whether dietary composition exerts additional benefits beyond caloric restriction.

Interestingly, liver fibrosis was significantly reduced in both groups in this study, although fibrosis regression typically requires a longer intervention period.[45] For example, a study of similar length found no significant changes in fibrosis in either the MD or LFD groups.[22] Another 12-week dietary intervention likewise reported no significant fibrosis improvements in either group.[12] Notably, participants in those studies did not experience weight loss $>5\%$ of body weight, while a reduction of 7%–10% is known to correlate with fibrosis improvement.[1] Indeed, a 52-week weight-loss trial reported improved fibrosis scores in 71% of subjects that achieved a weight loss $>7\%$, with greater changes in patients with weight reduction of $>10\%$.[44] In our study, both the relatively short duration and the achieved weight loss of ~5% in both groups are initially anticipated to be insufficient to trigger meaningful fibrosis regression. Although our results indicate a statistically significant change, the absolute decrease of 1.06 kPa remains too small to be considered clinically relevant. More extensive, long-term studies are needed to clarify how dietary patterns and weight reduction influence liver fibrosis.

One of the key findings of this study is that PNPLA3 G-allele carriage did not modulate the treatment response in MASLD. Consistent with our results, previous research found that the presence of the G allele did not impair steatosis improvement achieved through a 4-month calorie-restricted diet, despite its strong association with increased baseline MASLD risk.[46] Similarly, a cross-sectional analysis of Mexican-origin adults with overweight or obesity reported no interaction between PNPLA3 genotype, dietary intake, or hepatic steatosis.[47] Furthermore, a community-based dietary intervention observed no correlation between the G allele and changes in LSM, although it did find an association with reductions in intrahepatic triglyceride content.[26] While that study demonstrated an interaction between the G allele and steatosis, caution should be exercised in interpreting the findings, as GG homozygous individuals in the control group showed 3 times greater intrahepatic fat reduction than CC homozygotes, though it was not statistically significant. Other studies investigating the role of PNPLA3 in MASLD have yielded findings that are different from our study. A randomized controlled trial of omega-3 fatty acid supplementation in MASLD patients reported an increase in steatosis among G-allele carriers from baseline to follow-up, in contrast to a reduction observed in wildtypes.[25] In another study involving children, the hepatic fat fraction was associated with the dietary n-6/n-3 ratio only in GG homozygous subjects.[48] Taken together, the evidence regarding the role of PNPLA3 in MASLD remains inconclusive. In our study, we followed a dominant genetic model and grouped CG and GG carriers together, as has been done in several previous studies, because the number of GG homozygous individuals was too small to allow for meaningful independent analysis. Moreover, as mentioned in the methodology, we were unable to implement the original protocol plan to stratify the trial by genotype, leading to an unequal distribution of genotypes across the groups. This imbalance may have contributed to the absence of a detectable genotype–diet interaction. Furthermore, the relatively short duration of the dietary intervention may not have provided sufficient time for dietary effects to interact with MASLD and genetic factors. Further large-scale and PNPLA3-stratified trials with a longer follow-up are warranted to address these inconsistencies and to better define the role of PNPLA3 in the dietary management of MASLD.

The present research has also shown that serum markers of glucose and lipid metabolism have decreased significantly and similarly in both groups. The findings of this investigation complement those of a large randomized controlled trial of high-fat versus low-

fat diet, where a similar decrease in TC, LDL-C, TAG, and FBG in the high-fat group compared with the low-fat group was reported.[49] On the contrary, a meta-analysis of similar randomized controlled trials indicated that low-carbohydrate diets, including the MD, may unfavorably increase serum LDL-C and TC levels compared with LFD at 1–3 months.[50] However, these effects are typically transient, often disappearing after 12 months. Regardless, physicians should consider patients' baseline sugar and lipid profiles and tailor dietary recommendations for managing MASLD accordingly, ensuring an individualized approach to optimize both liver health and cardiometabolic risk.

The strengths of this study include its randomized design, statistical methodology, and the flexibility to achieve dietary targets within the context of participants' personal food preferences. In addition, core foods were provided to all participants, reducing the influence of differences in purchasing power on outcomes. The use of a healthy comparator diet, such as the LFD, instead of a Western diet or standard-of-care further strengthens the validity of conclusions regarding the impact of the MD. However, certain limitations should be acknowledged. First, the study relied on noninvasive diagnostic modalities rather than liver biopsy, which remains the gold standard for assessing liver pathology. Although VCTE is a validated and widely used non-invasive tool for quantifying steatosis and fibrosis, its role in monitoring longitudinal therapeutic effects remains under evaluation. In addition, reductions in LSM should be interpreted with caution, as weight loss and obesity-related factors may partly account for lower LSM values rather than reflecting definitive fibrosis regression. As none of the patients in the current study underwent liver biopsy, we cannot rule out the possibility that the effects of the diets and their interaction with PNPLA3 variants might differ in patients with metabolic dysfunction–associated steatohepatitis. Nonetheless, participants' willingness to undergo liver biopsy is typically low, posing significant challenges for recruitment and the feasibility of such studies. Second, although the dropout rate was relatively high, the linear mixed models retained all dropouts. However, linear mixed models are valid under the MAR assumption. To that end, we adjusted for age in all the linear mixed models, which was associated with missingness at follow-up, thus strengthening the plausibility of the MAR assumption. Furthermore, we adjusted all models for metabolic syndrome to (i) increase power, and (ii) because the difference at baseline between diet groups was considered fairly large, given that metabolic syndrome can be related to the outcomes. Lastly, dietary adherence and alcohol consumption were assessed through self-reported questionnaires, which may introduce bias. To mitigate this limitation, we cross-checked digital diet diary entries and validated them through interviews conducted by dietitians.

In conclusion, a 12-week calorie-restricted MD and LFD were equally effective in achieving weight-loss–induced improvements in MASLD biomarkers, with their efficacy unaffected by the PNPLA3 genotype. These findings underscore the broad applicability of both dietary approaches, irrespective of genetic variation. Further research is warranted to confirm these results and explore long-term outcomes.

DATA AVAILABILITY STATEMENT

The original data and findings presented in this study are available within the article and its Supplementary Material. For additional information, please contact the corresponding author.

AUTHOR CONTRIBUTIONS

Gediz Dogay Us contributed to the conception and design, drafted the study protocol, acquired data, analyzed and interpreted data, drafted the manuscript, revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. Francesco Innocenti designed the statistical methodology, analyzed, and interpreted the data. Ayse Eylul Alagoz recruited participants. Ger H. Koek, Ozgur Muhammet Koc, Zeynep Banu Gungor, and Volkan Demirhan Yumuk reviewed the study protocol and critically revised the manuscript for intellectual content. All authors were involved in the development, review, and editing of the manuscript. All authors had access to the study data, and the corresponding author had final responsibility for publishing the manuscript.

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CONFLICTS OF INTEREST

Volkan Yumuk advises for Novo Nordisk, Eli Lilly, and Regeneron.

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