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Relationship between dietary macronutrient composition and non-alcoholic fatty liver disease in lean and non-lean populations: a cross-sectional study

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Abstract

Objective: The current study aimed to customize dietary changes for lean patients with non-alcoholic fatty liver disease (NAFLD).

Design: The current study was done with a population-based cross-sectional design. The FFQ was used to analyse dietary macronutrient intake and ultrasonography results for NAFLD diagnosis. The study subjects were divided into the lean and non-lean groups based on their BMI (< 25 and ≥ 25). Multivariable logistic regression was used to evaluate the relationship between dietary macronutrients and NAFLD. Substitution analyses were also performed.

Setting: Amol and its suburban areas in Iran.

Participants: Adults in the age range of 18 to < 65 with full relevant data.

Results: Among the total study subjects (2308), 46·7 % had fatty liver. The substitution of polysaccharides for animal protein and SFA in the lean group resulted in a significant NAFLD reduction, whereas the substitution of SFA for all types of macronutrients, except for *n*-6 and mono-disaccharides, led to a significant increase in NAFLD ($P < 0·05$). In non-lean participants, the substitution of MUFA for mono-disaccharides resulted in a significant reduction of NAFLD ($P < 0·05$). In this group, the substitution of SFA and mono-disaccharides for MUFA, and *n*-6 for all macronutrients, except vegetable protein and SFA, were significantly related to an increase in NAFLD ($P < 0·05$).

Conclusions: Lower lean NAFLD is correlated with increasing polysaccharides in exchange for SFA and animal protein intake, whereas lower non-lean NAFLD is correlated with increasing MUFA in exchange for mono-disaccharides and reducing *n*-6 and SFA.

Keywords
Macronutrient
Lean
Non-lean
Non-alcoholic fatty liver

Non-alcoholic fatty liver disease (NAFLD) is defined as excessive fat accumulation in the liver. The majority of patients with NAFLD are either obese or overweight. However, a few of them had normal body weight, which was called lean NAFLD[1]. Lean NAFLD is characterised as the presence of NAFLD when BMI < 25. The prevalence range of lean NAFLD is 7 % in the USA and 19 % in Asia[2,3]. A cohort study in India reported a high prevalence (54 %) of patients with normal weight and waist circumference[4]. The prevalence of lean NAFLD among an Iranian sample was 17·5 %[5].

A recent meta-analysis study reported that the metabolic profile of the lean NAFLD patients was similar to that of the obese NAFLD patients[6], which was attributed to body fat distribution and visceral adiposity increase in lean patients[6–8]. However, some studies revealed a weaker prognosis for lean NAFLD than non-lean despite a similar metabolic profile. For example, the cumulative survival rate was lower in lean NAFLD compared with non-lean NAFLD[9]. In a cohort study with a mean follow-up period of 19·3 years conducted by Hagström *et al.*, patients with lean NAFLD were more prone to severe liver disease than

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the overweight and obese NAFLD patients despite their better metabolic profile and fibrosis level at baseline[10]. However, there are inadequate data on lean NAFLD, its pathogenesis and its natural history.

To date, losing weight is the primary treatment for NAFLD, that 7–10 % weight loss through diet and physical activity can lead to liver enzyme and histology improvement[11,12]. Therefore, it should be established how these changes can be customized for NAFLD patients within the normal range of body weight. A few studies have investigated the difference in dietary nutrient profile between lean and non-lean NAFLD patients and reported different results, which can probably be attributed to differences in the age, sample size and ethnic properties that could affect dietary habits and nutrient metabolism of the participants[13,14]. For example, a study reported that the dietary carbohydrate energy content and physical activity, less than moderate level, could be an independent predictor of NAFLD in lean patients[15]. Another study found a significant relationship between high animal protein intake and NAFLD in an overweight aged population, which was independent of well-known risk factors[14]. Few studies have compared the relationship of dietary macronutrient intake with NAFLD between lean and non-lean patients on a large scale. For example, a study in the Netherlands investigated this issue; however, it was only concentrated on an elderly population[14].

Since age and ethnicity can affect dietary habits and given the high prevalence of lean NAFLD in Iran[5], the current study compared the relationship of dietary macronutrient profile and NAFLD between lean and non-lean adult Iranian population, considering all important risk factors and substitution models.

Methods

Study population

This population-based cross-sectional study was conducted on the second phase of the Amol cohort study. All individuals between 18 and 65 with full relevant data, including demographic, biochemical, anthropometric, medical, dietary and physical activity data, were consecutively enrolled in the study.

The details of the Amol cohort study were completely explained in another article[16]. The current study was carried out in Amol, a city in the northern area of Iran, in two different periods: 2009–2010 (phase 1) and 2016–2017 (phase 2). The study subjects were selected from twenty-five rural and sixteen urban primary health care centers among those aged between 10 and 90 years old. Then, the subjects were stratified into sixteen strata based on their gender and age with 10-year intervals of 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and 80–89. The selection of study subjects in each stratum was done, using a simple randomization method, proportional to the population size in the same stratum.

Exclusion criteria

The exclusion criteria were the presence of acute or chronic liver diseases, such as viral hepatitis, cirrhosis, hereditary hepatic disorders and drug-related steatosis, except for NAFLD; alcohol consumption of more than 30 g/d in men and more than 20 g/d in women; a daily energy intake of ≤ 3347·2 kJ or ≥ 17 572·8 kJ; patients with cognitive diseases; and individuals incapable of making a communication.

Definition of non-alcoholic fatty liver

The assessment of steatosis was done using abdominal ultrasound. A 3e5MHz transducer was used to obtain sagittal, longitudinal, lateral and intercostal views. NAFLD is defined as a considerable increase in hepatic echogenicity and an abnormal appearance of hepatic vessels and diaphragm, without a history of excess alcohol consumption, drug-related steatosis, or viral or hereditary steatogenic hepatic conditions. Ultrasound imaging procedures were conducted by a sonographer not involved in the study.

Clinical data

Data collection details of the Amol cohort study were thoroughly explained in another article[16]. In summary, the clinical histories, past medical histories, alcohol consumption and drug history of all the participants were assessed using a standardized questionnaire after obtaining the informed consent of the participants. Weight (kg) and height (m), waist circumference, and hip circumference were measured according to the standard protocol[17]. The calculation of BMI was through dividing body weight (kg) by square of height (m). Blood pressure was measured in a quiet room after a 5-min rest by a mercury sphygmomeeter. The mean value of two measurements was used as the blood pressure of the participants, either systolic blood pressure or diastolic blood pressure. Hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 and/or using antihypertensive medication.

Ten-hour fasting venous blood samples of all participants were drawn to measure their laboratory parameters using an auto-analyzer (Biosystem kits). These parameters included serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, TAG, LDL, HDL, total cholesterol, fasting blood glucose, hepatitis B virus surface antigens and hepatitis C virus antibodies.

Definition of metabolic syndrome

Based on the National Cholesterol Education Program Adult Treatment Panel III[18], metabolic syndrome was diagnosed when three out of the following five risk factors were met:

- Fasting blood glucose ≥ 100 mg/dl or drug treatment for elevated blood glucose

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- Waist circumference > 102 cm in men or > 88 cm in women
- Serum TAG ≥ 150 mg/dl or drug treatment for elevated TAG
- Serum HDL < 40 mg/dl in men or < 50 mg/dl in women or drug treatment for low HDL
- Blood pressure ≥ 130/or ≥ 85 mmHg or drug treatment for elevated blood pressure.

Dietary and physical activity data

Dietary intake was measured using a 168-item semi-quantitative FFQ, validated in Tehran Lipid and Glucose Study[19]. Each questionnaire was completed by a trained dietitian by asking the frequency of consuming each food on a daily, weekly or monthly basis and the amount of consumption at each time in household measures, which were then converted to grams and analyzed based on the US Department of Agriculture Food Composition Table[20]. Since the Iranian Food Composition Table[21] remains incomplete with limited data on the nutrient content of raw foods and beverages, US Department of Agriculture Food Composition Table was employed as the primary source for analysis. The Iranian Food Composition Table was also employed for some native foods and beverages[22]. Unreliable FFQ with a daily energy intake of ≤ 3347·2 kJ or ≥ 17 572·8 kJ were removed from the analysis[23,24]. The nutrient density method was used to adjust the dietary intake of macronutrients and their subtypes for energy intake. This method presents the daily macronutrient intakes in the form of energy content percentage to total daily energy intake (%E). Energy content for 1 g of carbohydrate, protein, fat and fibre was, respectively, set at 16·7, 16·7, 37·6 and 8·37 kJ[14,25]. Calculated macronutrient subtypes were polysaccharide and mono-disaccharide for total dietary carbohydrate, animal and vegetable proteins for total dietary protein, SFA, MUFA, PUFA and *n*-3, *n*-6 and *trans*-fatty acid (TFA) for total dietary fat.

Rapid Assessment of Physical Activity form was used for the assessment of physical activity level[26]. In addition, the participants were categorized into five physical activity levels of sedentary, under light, light, regular and active.

Statistical analysis

Data are, respectively, presented in the form of mean ± SD or median (interquartile range) for parametric and non-parametric variables. Shapiro–Wilks test was used to determine the continuous variables' normality; moreover, the arithmetic transformations were applied if necessary. The χ^2 test, Student's *t* test or Mann–Whitney *U* test were, respectively, used to analyze categorical, parametric and non-parametric continuous variables between participants with and without NAFLD.

The participants were then divided into two groups of participants with BMI < 25 and BMI ≥ 25. Three separate multivariable logistic regression models were used to determine the relationship between dependent variables (dietary macronutrient intakes in %E) and dependent variable (NAFLD). The demographic model (model 1) included age and gender for adjustment. In addition to these factors, the lifestyle model (model 2) included smoking status (never *v.* past/current), energy intake (kcal) and physical activity level too. Finally, the metabolic model (model 3) also included the presence of diabetes, metabolic syndrome and total serum cholesterol (mg/dl). The analyses for dietary carbohydrates were adjusted for fibre intake and vice versa. In addition, all subtypes of each macronutrient were adjusted for each other. These assessments were applied to the total population and the two subgroups of participants with BMI < 25 and BMI ≥ 25. The multivariable logistic regression was used to assess the interaction effects of dietary macronutrient intakes and BMI subgroups on NAFLD. These results were presented in the form of odds ratio (OR) with 95 % CI.

Substitution analysis was used in the metabolic model (model 3) to establish whether the relationship observed for each macronutrient was because of the higher intake of that specific macronutrient or the lower intake of another macronutrient. For example, the substitution analysis of total carbohydrate for total protein included the dietary covariates of total carbohydrates, total fibre and total fat, excluded total protein and their subtypes in addition to the covariates in model 3, and total energy intake[27]. A *P*-value < 0·05 was considered to be the significance level. All analyses were performed in SPSS 24.

Results

Characteristics of study population

A total of 2308 participants (50·8 % women) were enrolled in the study. Among the participants, 1078 (46·7 %) had NAFLD. The prevalence of NAFLD in lean and non-lean participants was, respectively, 15·3 and 59·3 %.

In the current study, age, BMI, waist circumference, waist to hip ratio, systolic blood pressure, diastolic blood pressure, fasting blood glucose, serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total cholesterol, LDL, TAG, the prevalence of metabolic syndrome and its components, diabetes and high blood pressure were significantly higher, whereas serum HDL level was significantly lower in the fatty liver group ($P < 0·001$). On the other hand, smoking prevalence ($P = 0·03$) was significantly lower in the group with fatty liver than in the healthy group (Table 1).

Dietary macronutrient profile of study population

The total intake of dietary protein ($P = 0·02$) was significantly higher, whereas the dietary polysaccharide intake ($P = 0·01$) was significantly lower in the fatty liver group. Total dietary energy and other macronutrient intakes were not significantly different between the two groups (Table 1).

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Table 1 Characteristics of the study population

	Without NAFLD (*n* 1230)	CI	With NAFLD (*n* 1078)	CI	*P*
Demographics					
Age (years)	41·00	29·00–52·00	47·0	39·00–55·00	0·000**
Female (%)	49·50		52·30		0·17
Smoking status (%)					
Never	87·00		89·80		0·03*
Past or current	13·00		10·20		
Physical activity					
Sedentary	13·20		15·00		0·33
Under light	3·70		4·60		
Light	51·50		52·00		
Regular	16·30		14·70		
Active	15·20		13·50		
Physical examination					
BMI (kg/m^2)	25·50	22·70–28·50	30·10	27·54–33·46	0·000**
Waist circumference (cm)					
Men	83·00	78·00–90·00	94·0	89·00–100·00	0·000**
Women	81·00	73·00–88·00	94·00	86·25–101·00	0·000**
W/H ratio					
Men	0·86 ± 0·07		0·91 ± 0·05		0·000**
Women	0·80 ± 0·07		0·87 ± 0·07		0·000**
Blood pressure					
SBP	107·50	97·50–117·50	115·00	105·00–125·00	0·000**
DBP	70·00	60·00–75·00	75·00	65·00–80·00	0·000**
Biochemistry					
AST (U/L)	18·70	15·77–23·00	20·30	16·90–25·10	0·000**
ALT (U/L)	17·00	12·00–24·00	23·00	16·00–33·00	0·000**
GGT (U/L)	19·00	15·00–26·00	25·00	19·00–34·00	0·000**
FBS (mg/dl)	92·00	86·00–100·00	99·00	91·00–110·00	0·000**
Total cholesterol (mg/dl)	172·00	149·00–197·00	182·00	156·75–207·00	0·000**
HDL-cholesterol (mg/dl)	44·00	37·00–50·00	41·00	36·00–47·00	0·000**
LDL-cholesterol (mg/dl)	94·00	78·75–111·0	99·00	83·00–118·00	0·000**
TAG (mg/dl)	95·00	72·00–130·00	135·00	96·00–187·00	0·000**
Comorbidities					
Metabolic syndrome (%)	12·00		41·20		0·000**
WC > 88 cm (♀) or>120 cm(♂)	13·40		43·30		0·000**
TAG >150 mg/dl	17·60		41·80		0·000**
HDL-C < 40 mg/dl(♂) or 50 mg/dl(♀)	53·80		65·00		0·000**
Blood pressure ≥ 130/85 mmHg	11·80		27·00		0·000**
FBS > 100 mg/dl	27·40		48·50		0·000**
Diabetes mellitus (%)	7·60		19·70		0·000**
Hypertension (%)	6·30		15·90		0·000**
Dietary data					
Total energy (kJ/d)	10 136·45	8172·94–12 412·58	9986·49	7968·59–12 111·63	0·15
Total carbohydrate (%E)	47·03	42·51–51·12	46·66	42·76–50·54	0·19
Polysaccharides (%E)	23·02	20·41–25·60	22·44	20·18–25·04	0·01*
Mono-disaccharide (%E)	23·69	20·31–26·88	23·99	20·43–27·01	0·19
Fibre (%E)	3·24	2·36–4·014	3·25	2·50–4·10	0·47
Total protein (%E)	16·64 ± 3·78		17·05 ± 4·43		0·02*
Animal protein (%E)	9·57 ± 5·15		9·65 ± 3·96		0·68
Vegetable protein (%E)	7·20 ± 3·48		7·40 ± 4·05		0·21
Total fat (%E)	33·75 ± 16·15		33·61 ± 13·47		0·81
SFA (%E)	12·03 ± 3·32		12·28 ± 3·79		0·09
MUFA (%E)	11·38 ± 3·44		11·50 ± 6·21		0·55
PUFA (%E)	6·26 ± 1·98		6·32 ± 2·17		0·49
n-3 (%E)	0·52 ± 0·22		0·52 ± 0·24		0·42
n-6 (%E)	4·84 ± 1·93		4·82 ± 1·90		0·80
TFA (%E)	0·17 ± 0·21		0·17 ± 0·30		0·54

NAFLD, non-alcoholic fatty liver disease; W/H, waist circumference to hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; FBS, fasting blood sugar; WC, waist circumference; E, energy; TSF, *trans*-fatty acid.
*The difference between the two groups (with and without NAFLD) is statistically significant at $P < 0·05$.
**The difference between the two groups (with and without NAFLD) is statistically significant at $P < 0·001$.

Dietary macronutrient profile and non-alcoholic fatty liver disease in total population

Carbohydrate and fibre intake

In model 1, an increase in total carbohydrate (OR = 0·98, $P = 0·03$) and polysaccharide (OR = 0·97, $P = 0·02$) intake were significantly related to lower OR for NAFLD; moreover, an increase in fibre intake (OR = 1·12, $P = 0·009$) was significantly related to higher OR for NAFLD. However, no significant relationship was observed between mono-disaccharide intake and NAFLD.

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These relationships remained the same in model 2. In model 3, only polysaccharide (OR = 0·97, $P = 0·02$) intake was significantly related with lower OR for NAFLD after adjusting for metabolic confounders. Total carbohydrate and fibre intake were not significantly correlated with NAFLD (Table 2).

Protein intake

There was no significant correlation between NAFLD and total intake of dietary protein and its subtypes, that is, animal and vegetable proteins, in all three models (Table 2).

Fat intake

In model 1, an increase in dietary intake of SFA was significantly correlated with an increase in OR (OR = 1·03, $P = 0·01$) for NAFLD. The same significant correlation was observed in the other models too. In model 3, dietary intake of *n*-6 was also significantly correlated with an increase in OR (OR = 1·06, $P = 0·04$) for NAFLD. There was not any significant correlation between dietary intake of total fat, MUFA, PUFA, *n*-3 and TFA with NAFLD in all models (Table 2).

Table 2 Stepwise logistic regression models between dietary macronutrients as independent variables and NAFLD as the dependent variable

	BMI < 25 (*n* 660)			BMI ≥ 25 (*n* 1648)			Total (*n* 2308) Main effect			*P* for interaction effect†
Macronutrients	OR	95 % CI		OR	95 % CI		OR	95 % CI		
Model 1 (demographic)‡										
Total carbohydrate (%E)	0·96	0·93, 0·99	0·01*	1·00	0·98, 1·01	0·87	0·98	0·97, 0·99	0·03*	0·005**
Mono-disaccharide (%E)	0·97	0·94, 1·01	0·16	1·01	0·99, 1·02	0·30	0·99	0·98, 1·01	0·94	0·04*
Polysaccharide (%E)	0·93	0·88, 0·98	0·01*	0·99	0·96, 1·01	0·36	0·97	0·95, 0·99	0·02*	0·03*
Fibre (%E)	0·93	0·83, 1·05	0·29	0·98	0·94, 1·03	0·54	1·12	1·03, 1·22	0·009*	0·06
Total protein (%E)	0·99	0·94, 1·05	0·87	1·01	0·99, 1·04	0·21	1·01	0·99, 1·03	0·21	0·97
Animal protein (%E)	0·99	0·95, 1·04	0·91	1·00	0·97, 1·03	0·66	1·00	0·98, 1·02	0·59	0·78
Vegetable protein (%E)	0·97	0·91, 1·04	0·48	1·01	0·98, 1·05	0·24	1·01	0·98, 1·03	0·46	0·27
Total fat (%E)	1·00	0·99, 1·01	0·76	1·00	0·99, 1·01	0·59	0·99	0·99, 1·00	0·57	0·42
SFA (%E)	1·08	1·01, 1·16	0·02*	1·02	0·98, 1·05	0·20	1·03	1·00, 1·06	0·01*	0·02*
MUFA (%E)	1·04	0·97, 1·11	0·23	0·98	0·96, 1·01	0·25	0·97	0·94, 1·00	0·14	0·02*
PUFA (%E)	1·09	0·96, 1·23	0·16	1·05	0·99, 1·11	0·07	1·04	0·99, 1·09	0·10	0·81
n-3 (%E)	0·86	0·23, 3·26	0·83	0·87	0·50, 1·53	0·64	0·87	0·53, 1·42	0·59	0·32
n-6 (%E)	1·09	0·93, 1·27	0·25	1·06	0·99, 1·14	0·09	1·04	0·98, 1·10	0·18	0·93
TFA (%E)	0·39	0·07, 2·02	0·26	1·06	0·73, 1·55	0·72	1·12	0·79, 1·60	0·50	0·56
Model 2 (lifestyle)§										
Total carbohydrate (%E)	0·96	0·93, 0·99	0·01*	1·00	0·98, 1·01	0·85	0·98	0·97, 1·00	0·04*	0·008**
Mono-disaccharide (%E)	0·97	0·94, 1·01	0·22	1·01	0·99, 1·02	0·27	1·00	0·98, 1·01	0·92	0·06
Polysaccharide (%E)	0·93	0·88, 0·98	0·009**	0·98	0·96, 1·01	0·35	0·97	0·95, 0·99	0·02*	0·03*
Fibre (%E)	0·93	0·82, 1·05	0·24	0·98	0·94, 1·03	0·52	1·11	1·01, 1·21	0·017**	0·67
Total protein (%E)	0·99	0·94, 1·05	0·89	1·01	0·99, 1·04	0·17	1·01	0·99, 1·04	0·19	0·96
Animal protein (%E)	0·99	0·95, 1·04	0·90	1·00	0·98, 1·03	0·59	1·00	0·98, 1·02	0·56	0·82
Vegetable protein (%E)	0·97	0·91, 1·04	0·50	1·02	0·98, 1·05	0·21	1·01	0·98, 1·03	0·48	0·30
Total fat (%E)	1·00	0·99, 1·01	0·69	1·00	0·99, 1·01	0·57	0·99	0·99, 1·00	0·62	0·40
SFA (%E)	1·08	1·01, 1·16	0·02*	1·02	0·98, 1·05	0·19	1·03	1·01, 1·06	0·008**	0·02*
MUFA (%E)	1·04	0·97, 1·11	0·25	0·98	0·96, 1·01	0·26	0·97	0·94, 1·00	0·10	0·03*
PUFA (%E)	1·09	0·96, 1·23	0·15	1·05	0·99, 1·11	0·08	1·04	0·99, 1·09	0·09	0·88
n-3 (%E)	0·82	0·22, 3·11	0·78	0·87	0·49, 1·53	0·63	0·85	0·52, 1·39	0·52	0·38
n-6 (%E)	1·10	0·94, 1·29	0·19	1·06	0·98, 1·14	0·09	1·04	0·98, 1·11	0·15	0·86
TFA (%E)	0·41	0·08, 2·10	0·28	1·07	0·73, 1·55	0·72	1·14	0·80, 1·63	0·44	0·62
Model 3 (metabolic)‖										
Total carbohydrate (%E)	0·96	0·93, 0·99	0·01*	1·00	0·98, 1·01	0·88	0·98	0·97, 1·00	0·07	0·01*
Mono-disaccharide (%E)	0·97	0·94, 1·01	0·20	1·01	0·99, 1·03	0·22	1·00	0·98, 1·01	0·93	0·04*
Polysaccharide (%E)	0·93	0·88, 0·98	0·01*	0·98	0·96, 1·01	0·26	0·97	0·95, 0·99	0·02*	0·11
Fibre (%E)	0·92	0·82, 1·04	0·22	0·97	0·92, 1·02	0·27	1·07	0·98, 1·18	0·11	0·62
Total protein (%E)	0·99	0·94, 1·05	0·85	1·01	0·99, 1·04	0·21	1·01	0·98, 1·03	0·27	0·89
Animal protein (%E)	0·99	0·95, 1·04	0·83	1·00	0·97, 1·03	0·70	1·00	0·98, 1·02	0·75	0·97
Vegetable protein (%E)	0·97	0·91, 1·04	0·50	1·02	0·98, 1·05	0·21	1·01	0·98, 1·03	0·44	0·34
Total fat (%E)	1·00	0·99, 1·01	0·67	1·00	0·99, 1·01	0·45	0·99	0·99, 1·00	0·80	0·44
SFA (%E)	1·08	1·01, 1·16	0·02*	1·02	0·99, 1·05	0·14	1·03	1·00, 1·06	0·01*	0·04*
MUFA (%E)	1·04	0·97, 1·11	0·24	0·98	0·95, 1·00	0·20	0·97	0·93, 1·00	0·14	0·03*
PUFA (%E)	1·09	0·96, 1·24	0·15	1·05	0·99, 1·11	0·10	1·04	0·99, 1·10	0·08	0·62
n-3 (%E)	0·75	0·19, 2·91	0·68	0·75	0·41, 1·36	0·35	0·68	0·40, 1·16	0·16	0·32
n-6 (%E)	1·11	0·95, 1·30	0·16	1·07	0·99, 1·16	0·05	1·06	1·00, 1·13	0·04*	0·86
TFA (%E)	0·41	0·08, 2·11	0·29	1·15	0·78, 1·68	0·47	1·17	0·81, 1·68	0·38	0·76

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SFA, saturated fatty acid; MUFA, mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; TSF, *trans*-fatty acid.

*Statistically significant at $P < 0·05$.

**Statistically significant at $P < 0·01$.

†Interaction effect: the interaction effect of dietary macronutrients and lean/non-lean variable on NAFLD.

‡Model 1 (demographics): adjusted for age and gender.

§Model 2 (lifestyle): in addition to the previous model, adjusted for past or current smoking, physical activity and energy intake.

‖Model 3 (metabolic): in addition to the previous models, adjusted for serum total cholesterol, metabolic syndrome and diabetes mellitus.

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Substitution analysis

The significant reduction in OR of polysaccharide intake for NAFLD was achieved after substitution for all macronutrients (total protein (OR = 0·96, $P = 0·003$), animal protein (OR = 0·96, $P = 0·002$), vegetable protein (OR = 0·96, $P = 0·004$), mono-disaccharide (OR = 0·96, $P = 0·003$), total fat (OR = 0·97, $P = 0·005$) and SFA (OR = 0·96, $P = 0·01$)) except for fibre, PUFA, *n*-6 and *n*-3.

The significant increase in OR of SFA and *n*-6 intake for NAFLD was observed after substitution for almost all macronutrients (total protein (OR = 1·04, $P = 0·009$; OR = 1·07, $P = 0·03$), animal protein (OR = 1·05, $P = 0·007$; OR = 1·07, $P = 0·03$), vegetable protein (OR = 1·05, $P = 0·009$; OR = 1·07, $P = 0·04$), total carbohydrate (OR = 1·05, $P = 0·002$; OR = 1·07, $P = 0·03$), polysaccharide (OR = 1·05, $P = 0·001$; OR = 1·09, $P = 0·01$), mono-disaccharide (OR = 1·03, $P = 0·04$; OR = 1·10, $P = 0·007$) and MUFA (OR = 1·05, $P = 0·002$; OR = 1·07, $P = 0·03$)). Substitution of SFA for PUFA (OR = 1·04, $P = 0·01$), *n*-6 (OR = 1·04, $P = 0·01$) and *n*-3 (OR = 1·05, $P = 0·004$) was also correlated with a significant increase in OR for NAFLD.

The substitution of PUFA for mono-disaccharide (OR = 1·05, $P = 0·04$) and polysaccharide (OR = 1·06, $P = 0·02$) and MUFA (OR = 1·05, $P = 0·04$) caused a significant increase in OR of NAFLD (Table 3).

Interaction effects

In model 1, the interaction effects of dietary macronutrients and the BMI groups (lean and non-lean) on NAFLD were statistically significant for total carbohydrate ($P = 0·005$), mono-disaccharide ($P = 0·04$), polysaccharide ($P = 0·03$), SFA ($P = 0·02$) and MUFA ($P = 0·02$). Except for mono-disaccharide ($P = 0·06$), these interactions remained significant in model 2: total carbohydrate ($P = 0·008$), polysaccharide ($P = 0·03$), SFA ($P = 0·02$) and MUFA ($P = 0·03$). Significant interactions were observed for total carbohydrate ($P = 0·01$), mono-disaccharide ($P = 0·04$), SFA ($P = 0·03$) and MUFA ($P = 0·04$) in model 3 (Table 2).

Dietary macronutrient profile and non-alcoholic fatty liver disease in lean participants

Carbohydrate and fibre intake

Increased total carbohydrate (OR = 0·96, $P = 0·01$) and polysaccharide (OR = 0·93, $P = 0·01$) intake were significantly correlated with reduced OR for NAFLD. In contrast, no significant relationship was observed between dietary fibre or mono-disaccharide intake and NAFLD.

These relationships were also observed in model 2 and model 3 after adjusting for lifestyle and metabolic confounders (Table 2).

Protein intake

There was no significant correlation between NAFLD and total intake of dietary protein and its subtypes, that is, animal and vegetable proteins, in all three models (Table 2).

Fat intake

An increase in dietary intake of SFA was significantly correlated with an increase in OR (OR = 1·08, $P = 0·02$) for NAFLD. The same significant correlation was observed in the other models too. No significant relationship was observed between dietary intake of total fat, MUFA, PUFA, *n*-3, *n*-6 and TFA with NAFLD (Table 2).

Substitution analysis

A significant reduction in OR of total carbohydrate intake was observed after substitution for total fat (OR = 0·96, $P = 0·02$). Substitution of polysaccharides for total fat (OR = 0·93, $P = 0·03$), animal protein (OR = 0·94, $P = 0·03$) and SFA (OR = 0·92, $P = 0·04$) also had a significant lower OR for NAFLD. According to these results, the substitution of total dietary fat for total carbohydrate (OR = 1·03, $P = 0·02$) and polysaccharide (OR = 1·06, $P = 0·03$) can significantly increase OR for NAFLD. The significant increase in OR of SFA for NAFLD was achieved after substitution for all types of macronutrients except for *n*-6 and mono-disaccharides (Table 3, Fig. 1): animal protein (OR = 1·08, $P = 0·04$), vegetable protein (OR = 1·09, $P = 0·03$), total carbohydrate (OR = 1·09, $P = 0·01$), polysaccharides (OR = 1·10, $P = 0·01$), MUFA (OR = 1·08, $P = 0·04$) and *n*-3 (OR = 1·08, $P = 0·04$).

Dietary macronutrient profile and non-alcoholic fatty liver disease in non-lean participants

Carbohydrate and fibre intake

No significant correlation was observed between total dietary carbohydrate intake and its subtypes, namely dietary polysaccharide and mono-disaccharide intake, or dietary fibre intake with NAFLD in none of the models (Table 2).

Protein intake

No significant correlation was observed between total intake of dietary protein and its subtypes, namely animal and vegetable protein, with NAFLD in none of these three models (Table 2).

Fat intake

No significant correlation was observed between total intake of dietary fat or its subtypes, namely SFA, MUFA, PUFA, *n*-3, *n*-6 and TFA, with NAFLD in none of these models; however, the higher OR of *n*-6 dietary intake for NAFLD (OR = 1·07, $P = 0·05$) was very close to a significant level in model 3 (Table 2).

Substitution analysis

Substitution of total dietary carbohydrate (OR = 1·02, $P = 0·03$), mono-disaccharides (OR = 1·04, $P = 0·006$), total protein (OR = 1·03, $P = 0·04$), SFA (OR = 1·04, $P = 0·04$) and PUFA (OR = 1·07, $P = 0·03$) for MUFA, substitution of *n*-6 for animal protein (OR = 1·08, $P = 0·04$), total carbohydrate (OR = 1·08, $P = 0·03$), polysaccharides (OR = 1·11,

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Table 3 Substitution analyses of macronutrients in the metabolic model

	BMI < 25 (*n* 660)			BMI ≥ 25 (*n* 1648)			Total (*n* 2308)		
	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Substitution for: total protein intake									
Total carbohydrate	0·97	0·91, 1·04	0·46	0·99	0·96, 1·02	0·56	0·98	0·96, 1·00	0·07
Mono-disaccharides	0·98	0·92, 1·04	0·60	0·99	0·96, 1·03	0·90	0·99	0·97, 1·01	0·55
Polysaccharide	0·94	0·87, 1·02	0·19	0·97	0·93, 1·01	0·15	0·96	0·93, 0·98	0·003**
Fibre	0·95	0·83, 1·08	0·46	0·96	0·91, 1·02	0·27	1·08	0·98, 1·19	0·08
Total fat	1·01	0·95, 1·07	0·65	0·98	0·95, 1·01	0·43	0·99	0·98, 1·00	0·55
SFA	1·07	0·98, 1·16	0·10	1·01	0·97, 1·06	0·48	1·04	1·01, 1·08	0·009**
MUFA	1·00	0·90, 1·10	0·96	0·96	0·93, 1·00	0·09	0·97	0·93, 1·02	0·26
PUFA	1·13	0·99, 1·29	0·06	1·06	0·99, 1·13	0·06	1·07	0·99, 1·10	0·08
n-3	0·76	0·19, 2·98	0·70	0·71	0·38, 1·33	0·29	0·72	0·41, 1·27	0·26
n-6	1·11	0·95, 1·30	0·16	1·08	1·00, 1·16	0·05	1·07	1·00, 1·14	0·03*
TFA	0·43	0·08, 2·15	0·30	1·24	0·83, 1·84	0·28	1·18	0·82, 1·70	0·35
Substitution for: animal protein intake									
Total carbohydrates	0·97	0·91, 1·03	0·39	0·99	0·96, 1·02	0·65	0·98	0·97, 1·00	0·06
Mono-disaccharides	0·97	0·94, 1·01	0·22	1·01	0·99, 1·03	0·26	0·99	0·97, 1·01	0·57
Polysaccharides	0·94	0·88, 0·99	0·03*	0·98	0·96, 1·01	0·24	0·96	0·93, 0·98	0·002**
Fibre	0·95	0·83, 1·08	0·44	0·97	0·91, 1·02	0·29	1·08	0·98, 1·19	0·11
Total fat	1·00	0·94, 1·07	0·84	0·99	0·95, 1·02	0·55	0·99	0·98, 1·00	0·51
SFA	1·08	1·00, 1·17	0·04*	1·03	0·99, 1·07	0·13	1·05	1·01, 1·08	0·007**
MUFA	1·01	0·91, 1·12	0·80	0·98	0·95, 1·01	0·38	0·97	0·93, 1·02	0·35
PUFA	1·12	0·98, 1·27	0·09	1·05	0·99, 1·12	0·08	1·04	0·99, 1·10	0·08
n-3	0·68	0·16, 2·79	0·60	0·71	0·38, 1·32	0·28	0·65	0·38, 1·12	0·12
n-6	1·13	0·96, 1·33	0·13	1·08	1·00, 1·17	0·04*	1·07	1·00, 1·14	0·03*
TFA	0·44	0·09, 2·22	0·32	1·19	0·80, 1·77	0·37	1·18	0·82, 1·70	0·36
Vegetable protein	0·98	0·91, 1·05	0·62	1·00	0·97, 1·04	0·65	1·00	0·98, 1·03	0·63
Substitution for: vegetable protein intake									
Animal protein	0·99	0·95, 1·04	0·94	0·98	0·95, 1·02	0·42	0·99	0·97, 1·01	0·86
Total carbohydrates	0·98	0·98, 1·04	0·49	0·98	0·94, 1·02	0·34	0·98	0·97, 1·00	0·08
Mono-disaccharides	0·98	0·91, 1·05	0·58	0·98	0·94, 1·03	0·47	0·99	0·97, 1·01	0·53
Polysaccharides	0·94	0·86, 1·03	0·21	0·96	0·91, 1·01	0·08	0·96	0·93, 0·99	0·004*
Total fat	1·01	0·95, 1·08	0·69	0·98	0·94, 1·02	0·27	0·98	0·98, 1·01	0·55
SFA	1·09	1·01, 1·17	0·035*	1·03	0·98, 1·07	0·21	1·05	1·01, 1·08	0·009*
MUFA	1·01	0·91, 1·12	0·83	0·98	0·95, 1·02	0·34	0·97	0·93, 1·02	0·29
PUFA	1·12	0·98, 1·28	0·09	1·05	0·99, 1·12	0·11	1·05	0·99, 1·10	0·09
n-3	0·76	0·19, 2·98	0·69	0·71	0·37, 1·33	0·28	0·64	0·37, 1·11	0·11
n-6	1·11	0·95, 1·30	0·16	1·08	0·99, 1·16	0·052	1·07	1·01, 1·15	0·04*
TFA	0·44	0·08, 2·19	0·31	1·19	0·80, 1·77	0·38	1·18	0·82, 1·70	0·35
Fibre	0·94	0·82, 1·08	0·44	0·95	0·89, 1·01	0·16	1·09	0·99, 1·19	0·07
Substitution for: total carbohydrate intake									
Total protein	1·02	0·96, 1·08	0·46	1·00	0·97, 1·04	0·56	1·01	0·99, 1·04	0·24
Animal protein	1·00	0·96, 1·04	0·84	1·00	0·97, 1·03	0·92	1·00	0·98, 1·02	0·61
Vegetable protein	0·99	0·92, 1·06	0·85	1·01	0·97, 1·05	0·59	1·00	0·97, 1·03	0·61
Total fat	1·03	1·01, 1·07	0·02*	0·99	0·98, 1·01	0·69	1·00	0·99, 1·01	0·94
SFA	1·09	1·01, 1·17	0·01*	1·01	0·98, 1·05	0·28	1·05	1·01, 1·08	0·002*
MUFA	1·03	0·95, 1·11	0·42	0·97	0·95, 1·00	0·13	0·98	0·95, 1·02	0·53
PUFA	1·12	0·98, 1·28	0·07	1·04	0·98, 1·11	0·11	1·05	0·99, 1·10	0·06
n-3	0·81	0·20, 3·28	0·77	0·74	0·41, 1·36	0·34	0·70	0·41, 1·20	0·20
n-6	1·10	0·94, 1·29	0·19	1·08	1·01, 1·17	0·03*	1·07	1·01, 1·15	0·03*
TFA	0·45	0·09, 2·24	0·33	1·20	0·80, 1·79	0·36	1·19	0·83, 1·72	0·32
Fibre	0·97	0·86, 1·08	0·61	0·97	0·92, 1·02	0·29	1·08	0·99, 1·19	0·06
Substitution for: mono and disaccharide intake									
Polysaccharides	0·96	0·89, 1·02	0·25	0·97	0·94, 1·01	0·10	0·96	0·94, 0·98	0·003*
Total protein	1·01	0·95, 1·08	0·60	1·00	0·97, 1·03	0·90	1·01	0·98, 1·03	0·86
Animal protein	1·00	0·96, 1·04	0·99	0·99	0·96, 1·02	0·68	1·00	0·98, 1·02	0·99
Vegetable protein	0·99	0·93, 1·07	0·94	1·00	0·96, 1·05	0·75	1·01	0·98, 1·04	0·38
Total fat	1·02	0·98, 1·06	0·22	0·98	0·96, 1·01	0·18	0·99	0·98, 1·01	0·41
SFA	1·07	0·99, 1·16	0·07	1·00	0·96, 1·04	0·78	1·03	1·01, 1·07	0·04*
MUFA	1·01	0·92, 1·10	0·80	0·96	0·93, 0·99	0·04*	0·97	0·93, 1·01	0·18
PUFA	1·13	0·99, 1·29	0·06	1·05	0·99, 1·11	0·10	1·05	1·01, 1·11	0·04*
n-3	0·73	0·18, 3·03	0·67	0·60	0·32, 1·14	0·12	0·58	0·33, 1·02	0·06
n-6	1·12	0·96, 1·32	0·14	1·11	1·02, 1·21	0·009**	1·10	1·02, 1·18	0·007*
TSF	0·43	0·08, 2·18	0·31	1·22	0·82, 1·82	0·31	1·22	0·85, 1·75	0·28
Fibre	0·97	0·86, 1·08	0·62	0·97	0·92, 1·02	0·25	1·06	0·96, 1·17	0·17
Substitution for: polysaccharide intake									
Mono-disaccharide	1·04	0·97, 1·11	0·25	1·02	0·99, 1·06	0·10	1·00	0·98, 1·02	0·74
Total protein	1·05	0·97, 1·15	0·19	1·02	0·98, 1·07	0·155	1·01	0·99, 1·04	0·23

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Table 3 *Continued*

	BMI < 25 (*n* 660)			BMI ≥ 25 (*n* 1648)			Total (*n* 2308)		
	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Animal protein	1·00	0·97, 1·04	0·76	1·01	0·97, 1·05	0·40	1·00	0·98, 1·02	0·60
Vegetable protein	0·99	0·92, 1·07	0·98	1·02	0·98, 1·08	0·247	1·00	0·97, 1·03	0·61
Total fat	1·06	1·00, 1·12	0·03*	1·01	0·98, 1·03	0·33	1·00	0·99, 1·01	0·88
SFA	1·10	1·02, 1·18	0·01*	1·03	0·99, 1·06	0·09	1·05	1·02, 1·09	0·001**
MUFA	1·05	0·95, 1·16	0·27	0·98	0·95, 1·02	0·51	1·01	0·90, 1·05	0·55
PUFA	1·15	0·99, 1·32	0·06	1·08	1·01, 1·15	0·02*	1·06	1·01, 1·12	0·02*
n-3	0·81	0·20, 3·30	0·77	0·74	0·40, 1·35	0·32	0·71	0·42, 1·21	0. 21
n-6	1·10	0·94, 1·29	0·19	1·11	1·02, 1·20	0·01*	1·09	1·01, 1·16	0·01*
TSF	0·44	0·08, 2·20	0·32	1·29	0·86, 1·93	0·21	1·21	0·84, 1·75	0·29
Fibre	1·00	0·87, 1·15	0·95	0·99	0·94, 1·05	0·93	1·09	0·99, 1·19	0·06
Substitution for: total fat intake									
Total carbohydrates	0·96	0·93, 0·99	0·02*	1·00	0·98, 1·019	0·69	0·98	0·97, 1·00	0·13
Polysaccharides	0·93	0·88, 0·99	0·03*	0·98	0·96, 1·01	0·33	0·97	0·94, 0·99	0·005*
Mono-disaccharide	0·97	0·94, 1·01	0·22	1·01	0·99, 1·03	0·18	1·00	0·98, 1·01	0·96
Total protein	0·98	0·92, 1·04	0·65	1·01	0·98, 1·04	0·43	1·00	0·98, 1·03	0·46
Animal protein	0·98	0·93, 1·04	0·67	1·00	0·97, 1·03	0·82	1·00	0·98, 1·02	0·91
Vegetable protein	0·97	0·90, 1·04	0·46	1·01	0·97, 1·05	0·48	1·00	0·97, 1·03	0·70
Fibre	1·00	0·98, 1·02	0·81	0·98	0·94, 1·02	0·49	1·07	0·97, 1·17	0·13
Substitution for: SFA intake									
Total carbohydrates	0·96	0·90, 1·01	0·16	1·00	0·98, 1·03	0·58	0·98	0·95, 1·01	0·25
Polysaccharides	0·92	0·85, 0·99	0·04*	0·98	0·95, 1·01	0·31	0·96	0·92, 0·99	0·01*
Mono-disaccharide	0·97	0·91, 1·04	0·47	1·02	0·99, 1·05	0·17	0·99	0·97, 1·02	0·91
Total protein	0·98	0·90, 1·06	0·63	1·01	0·98, 1·05	0·33	1·00	0·97, 1·04	0·76
Animal protein	0·98	0·91, 1·05	0·62	1·00	0·97, 1·04	0·72	0·99	0·97, 1·02	0·83
Vegetable protein	0·96	0·88, 1·05	0·48	1·01	0·97, 1·06	0·48	1·00	0·97, 1·03	0·98
MUFA	0·98	0·87, 1·10	0·75	0·99	0·95, 1·02	0·61	0·97	0·92, 1·03	0·41
PUFA	1·08	0·95, 1·23	0·19	1·04	0·98, 1·11	0·13	1·02	0·97, 1·08	0·26
n-3	0·96	0·24, 3·72	0·95	0·81	0·42, 1·54	0·527	0·77	0·44, 1·34	0·36
n-6	1·08	0·93, 1·27	0·28	1·06	0·99, 1·15	0·09	1·05	0·98, 1·12	0·12
TFA	0·46	0·10, 2·16	0·32	1·20	0·80, 1·80	0·35	1·16	0·81, 1·67	0·39
Fibre	0·91	0·8, 1·05	0·22	0·97	0·92, 1·03	0·41	1·06	0·97, 1·17	0·17
Substitution for: MUFA intake									
Total carbohydrates	0·98	0·94, 1·02	0·45	1·02	1·00, 1·05	0·03*	1·01	0·99, 1·02	0·32
Polysaccharides	0·96	0·90, 1·02	0·23	1·01	0·97, 1·04	0·55	0·98	0·96, 1·01	0·43
Mono-disaccharide	0·99	0·94, 1·04	0·86	1·04	1·01, 1·07	0·006*	1·01	0·99, 1·04	0·08
Total protein	0·99	0·93, 1·06	0·94	1·03	1·00, 1·07	0·04*	1·02	0·99, 1·05	0·06
Animal protein	0·99	0·94, 1·04	0·71	1·02	0·98, 1·06	0·21	1·00	0·98, 1·03	0·43
Vegetable protein	0·99	0·92, 1·06	0·80	1·03	0·99, 1·08	0·10	1·01	0·98, 1·04	0·24
SFA	1·08	1·01, 1·17	0·04*	1·04	1·00, 1·09	0. 04*	1·05	1·02, 1·09	0·002*
PUFA	1·12	0·98, 1·28	0·08	1·07	1·01, 1·15	0·03*	1·05	1·01, 1·12	0·04*
n-3	0·69	0·17, 2·83	0·61	0·82	0·44, 1·51	0·52	0·72	0·42, 1·24	0·243
n-6	1·12	0·96, 1·31	0·12	1·08	1·01, 1·17	0·03*	1·07	1·00, 1·14	0·03*
TSF	0·45	0·09, 2·27	0·34	1·26	0·84, 1·88	0·25	1·20	0·84, 1·72	0·29
Fibre	0·99	0·86, 1·14	0·67	1·01	0·94, 1·07	0·74	1·07	0·98, 1·18	0·12
Substitution for: PUFA intake									
Total carbohydrates	0·98	0·91, 1·05	0·64	1·01	0·98, 1·04	0·43	1·00	0·97, 1·03	0·73
Polysaccharides	0·97	0·88, 1·06	0·50	0·98	0·94, 1·03	0·62	0·98	0·94, 1·02	0·41
Mono-disaccharide	0·98	0·92, 1·05	0·71	1·01	0·98, 1·04	0·35	1·00	0·97, 1·04	0·58
Total protein	0·99	0·91, 1·09	0·98	1·02	0·98, 1·06	0·31	1·02	0·98, 1·06	0·22
Animal protein	0·99	0·93, 1·05	0·73	1·00	0·96, 1·04	0·73	1·00	0·97, 1·02	0·84
Vegetable protein	0·98	0·90, 1·07	0·73	1·02	0·97, 1·06	0·39	1·01	0·97, 1·04	0·50
SFA	1·06	0·99, 1·15	0·08	1·02	0·98, 1·06	0·26	1·04	1·01, 1·08	0·01*
MUFA	1·03	0·90, 1·17	0·65	1·00	0·95, 1·04	1·00	1·01	0·95, 1·07	0·69
TSF	0·65	0·16, 2·63	0·55	1·24	0·82, 1·86	0·30	1·20	0·83, 1·72	0·32
Fibre	1·00	0·97, 1·03	0·74	0·97	0·81, 1·16	0·77	1·08	0·98, 1·18	0·10
Substitution for: *n*-6 intake									
Total carbohydrates	0·98	0·92, 1·04	0·60	1·01	0·97, 1·06	0·54	1·00	0·97, 1·04	0·71
Polysaccharides	0·96	0·88, 1·05	0·44	0·98	0·93, 1·04	0·70	0·98	0·94, 1·02	0·42
Mono-disaccharide	0·98	0·92, 1·05	0·66	1·01	0·97, 1·06	0·49	1·00	0·97, 1·04	0·62
Total protein	0·99	0·92, 1·07	0·94	1·02	0·96, 1·08	0·38	1·02	0·98, 1·06	0·24
Animal protein	0·99	0·94, 1·04	0·80	1·01	0·96, 1·06	0·58	1·00	0·97, 1·02	0·90
Vegetable protein	0·98	0·91, 1·05	0·59	1·02	0·97, 1·08	0·32	1·01	0·97, 1·04	0·53
SFA	1·07	0·99, 1·16	0·06	1·03	0·98, 1·08	0·15	1·04	1·01, 1·08	0·01*
MUFA	1·03	0·91, 1·16	0·60	1·00	0·92, 1·08	0·98	1·01	0·95, 1·08	0·68
n-3	1·35	0·45, 4·03	0·58	1·16	0·68, 1·98	0·58	1·03	0·65, 1·61	0·89
TSF	0·62	0·15, 2·58	0·51	1·27	0·84, 1·92	0·25	1·20	0·83, 1·72	0·32
Fibre	1·15	0·86, 1·54	0·32	1·09	0·95, 1·26	0·19	1·08	0·98, 1·19	0·08

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Table 3 *Continued*

	BMI < 25 (*n* 660)			BMI ≥ 25 (*n* 1648)			Total (*n* 2308)		
	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Substitution for: *n*-3 intake									
Total carbohydrates	0·97	0·91, 1·04	0·48	1·02	0·97, 1·06	0·33	1·01	0·97, 1·04	0·51
Polysaccharides	0·95	0·86, 1·04	0·27	0·99	0·94, 1·04	0·812	0·98	0·94, 1·02	0·48
Mono-disaccharide	0·98	0·92, 1·04	0·53	1·02	0·98, 1·07	0·21	1·01	0·98, 1·05	0·34
Total protein	0·99	0·92, 1·06	0·82	1·04	0·98, 1·10	0·14	1·03	0·99, 1·08	0·10
Animal protein	0·99	0·94, 1·04	0·81	1·02	0·97, 1·08	0·27	1·00	0·98, 1·03	0·64
Vegetable protein	0·97	0·91, 1·04	0·49	1·04	0·98, 1·09	0·14	1·01	0·98, 1·04	0·41
SFA	1·08	1·01, 1·17	0·04*	1·04	0·99, 1·09	0·06	1·05	1·01, 1·09	0·004*
MUFA	1·01	0·89, 1·14	0·85	1·00	0·92, 1·08	0·96	1·01	0·94, 1·07	0·74
n-6	1·09	0·96, 1·24	0·14	1·07	1·01, 1·14	0·04*	1·05	0·99, 1·11	0·06
TSF	0·46	0·09, 2·30	0·35	1·28	0·84, 1·93	0·23	1·19	0·83, 1·72	0·33
Fibre	1·13	0·85, 1·52	0·38	1·10	0·96, 1·27	0·15	1·07	0·97, 1·18	0·14

BMI, body mass index; SFA, saturated fatty acid; MUFA, mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; TSF, *trans*-fatty acid.
*Statistically significant at $P < 0·05$.
**Statistically significant at $P < 0·01$.

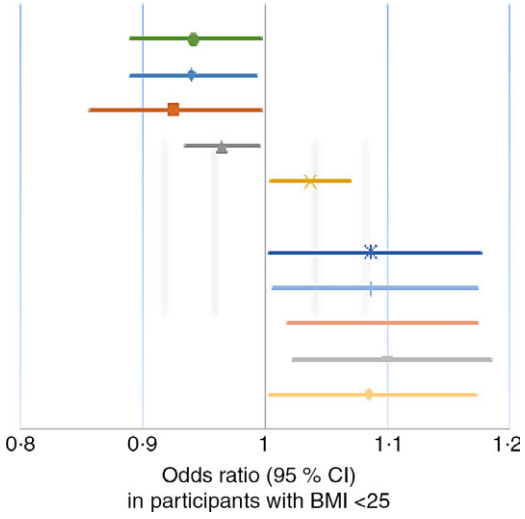

Fig. 1 (colour online) Significant macronutrient substitution analysis for non-alcoholic fatty liver disease (in the metabolic model) in lean participants (BMI < 25). Odds ratios were adjusted for age and gender, past or current smoking, physical activity, energy intake, total serum cholesterol, metabolic syndrome and diabetes mellitus. **Abbreviations:** BMI, body mass index; MUFA, mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; SFA, saturated fatty acid; TSF, *trans*-fatty acid. —, polysaccharide for animal protein; —, polysaccharides for total fat; —, polysaccharide for SFA; —, total carbohydrate for total fat; —, total fat for total carbohydrate; —, SFA for animal protein; —, SFA for vegetable protein; —, SFA for total carbohydrate; —, SFA for polysaccharide; —, SFA for MUFA

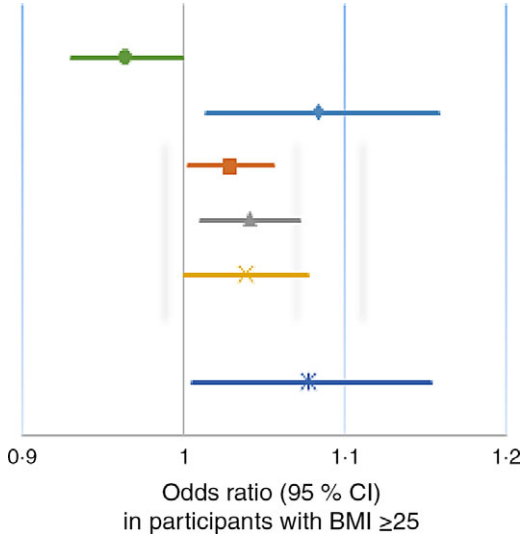

Fig. 2 (colour online) Significant macronutrient substitution analysis for non-alcoholic fatty liver disease (in the metabolic model) in non-lean participants (BMI ≥ 25). Odds ratios were adjusted for age and gender, past or current smoking, physical activity, energy intake, total serum cholesterol, metabolic syndrome and diabetes mellitus. **Abbreviations:** BMI, body mass index; MUFA, mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; SFA, saturated fatty acid; TSF, *trans*-fatty acid. —, MUFA for mono and disaccharide; —, PUFA for polysaccharide; —, total carbohydrate for MUFA; —, mono-disaccharide for MUFA; —, total protein for MUFA; —, PUFA for MUFA

$P = 0·01$), mono-disaccharides (OR = 1·11, $P = 0·009$), MUFA (OR = 1·08, $P = 0·03$) and *n*-3 (OR = 1·07, $P = 0·04$) and substitution of PUFA for polysaccharides (OR = 1·08, $P = 0·02$) significantly increased OR for NAFLD. The only significant reduction of OR for NAFLD was observed after the substitution of dietary MUFA for mono-disaccharides (OR = 0·96, $P = 0·04$) (Table 3, Fig. 2).

Discussion

Although obesity is typically associated with NAFLD, it can also happen in individuals with normal weight. These lean NAFLD conditions do not necessarily result in high health improvement than obese NAFLD[6]. However, there are limited studies with adequate sample size on lean NAFLD.

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It was a large-scale community-based cross-sectional study. The relationship of macronutrient intake with NAFLD between two groups of lean and non-lean participants was investigated in the present study. The results suggested that dietary macronutrient composition is correlated with NAFLD regardless of demographic, lifestyle and metabolic characteristics, and energy intake. However, this pattern is not similar in the lean and non-lean patients.

In lean subjects, NAFLD prevalence significantly reduces with increasing dietary polysaccharide intake (independent of fibre) when it is substituted for animal protein, total fat and SFA. In contrast, dietary polysaccharide intake was not significantly correlated with NAFLD prevalence in non-lean participants.

Evidence shows excessive consumption of dietary carbohydrates plays a major role in the occurrence of NAFLD by affecting *de novo* lipogenesis and the gut microbiome. The majority of these studies concentrated on simple carbohydrates, especially fructose or sucrose[28], and thus there are scant studies on the relationship between dietary macronutrient composition and NAFLD in lean and non-lean individuals. Inconsistent with the present study, Kwak *et al.*[15] showed that carbohydrate intake in the lean group caused an increase in fatty liver prevalence; however, mono-disaccharides and polysaccharides were not analyzed separately in the study. Honarvar *et al.* did not find any significant correlation between total carbohydrate intake and NAFLD in lean or non-lean individuals; however, they did not adjust demographic, lifestyle, or metabolic factors. Two subtypes, namely mono-disaccharides and polysaccharides, were not analyzed separately[29]. Alferink *et al.* did not find any significant correlation between dietary carbohydrate and its subtypes with NAFLD in lean and non-lean participants after adjustment for socio-demographic, lifestyle and metabolic covariates[14]. The current study was conducted on the elderly whose dietary behaviors were different from youths.

Consistent with the present study, Cortez-Pinto *et al.* observed a lower amount of carbohydrate intake in non-alcoholic steatohepatitis patients than healthy controls in lean NAFLD[30]. It was also found that the effectiveness of high carbohydrate, low protein diets depends on the presence or absence of metabolic diseases. High carbohydrate, low protein diets are more beneficial when there is not any other metabolic disorder[31]. The higher polysaccharide intake in lean participants with a lower prevalence of metabolic disorders in the present study may be the cause of lower NAFLD; however, a higher polysaccharide intake was not observed in non-lean participants with a higher prevalence of metabolic disorders.

Evidence suggests that dietary intake of simple carbohydrates, particularly fructose or sucrose, plays an important role in the occurrence of NAFLD[28]. In the present study, mono and disaccharides' dietary intake was not significantly correlated with lean NAFLD; however, it is significantly correlated with a higher prevalence of non-lean NAFLD when substituted for MUFA. This is because the majority of previous studies were concentrated on high-added sugar diets[32,33], whereas fruits were the primary source of dietary mono and disaccharides, especially in lean participants, in the present study.

No significant relationship was observed between the dietary intake of total protein and NAFLD in lean or non-lean participants in the present study. The positive relationship between dietary protein intake and NAFLD was reported in the literature. Alferink *et al.*, for example, found a positive correlation between dietary protein intake from animal subtype and NAFLD in overweight individuals[14]. Chan *et al.* showed that among the possible confounding factors, the rate of red meat consumption in patients with NAFLD was significantly higher than in the control[34]. Moreover, a study on a Dutch population showed a positive correlation between high animal protein intake and fatty liver index[35]. In contrast, some studies did not report any difference in the amount of protein intake between the fatty liver and the control group[13,30] or even the effectiveness of animal/plant protein intake on fatty liver improvement[36]. Different results may be attributed to such factors as different methods used to identify NAFLD (ultrasound[14], fatty liver index[35], proton magnetic resonance spectroscopy[34], etc.), using dietary protein intake as absolute intake in gram rather than energy adjustment form in statistical analysis, or employing different study methods (observational or interventional)[36].

The relationship between fat intake and its subtypes with the development of NAFLD is a widely discussed subject and different results have been reported. It is worth noting that many intervening factors are involved in this field[37]. In the present study, increased dietary SFA was correlated with an increase in NAFLD in lean and non-lean participants when substituted for all macronutrients, except mono-disaccharides and *n*-6 and MUFA, respectively. Consistent with the present study, the positive relationship between SFA and NAFLD can be found in the literature[38,39]. Sobrecases *et al.* showed that the SFA-enriched diet led to higher liver fat than fructose in lean men (~86 % *v.* ~16 %)[40]. Rosqvist *et al.* reported a 53 % increase in hepatic fat content after 7 weeks of an SFA-enriched diet in overweight and obese individuals[41].

However, there was not any significant correlation between other fatty acids (PUFA, *n*-6, *n*-3, MUFA and TFA) and NAFLD in lean participants in the present study. In non-lean participants, an increase in the dietary PUFA (when substituted for polysaccharides and MUFA) and *n*-6 (when substituted for all macronutrients except for vegetable protein and SFA) was significantly correlated with an increase in NAFLD; moreover, an increase in dietary MUFA (when substituted for mono-disaccharides) was significantly correlated with a reduction of NAFLD.

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The positive correlation of dietary PUFA and *n*-6 with NAFLD in non-lean participants was similar to the findings of Honarvar *et al.*, who observed a significant relationship between PUFA and NAFLD; however, the current study did not investigate lean and non-lean individuals separately. Inconsistent with the present study, the literature reported that PUFA (both *n*-6 and *n*-3 PUFA) can improve fatty liver by reducing liver TNF-α expression, insulin resistance[42,43] and hepatic *de novo* lipogenesis[44]. Alferink *et al.* also showed that PUFA reduced NAFLD in overweight individuals; however, this correlation was not significant[14]. Different ratios of *n*-3 and *n*-6 in diets may also influence the way *n*-6 affects liver fat accumulation in different studies.

Consistent with the findings of the current study, the negative correlation of dietary MUFA and NAFLD has also been reported by Bozetto *et al.*, in which MUFA-enriched diet reduced liver fat content in patients with type 2 diabetes[45]. It seems that the MUFA-rich diets increase lipoprotein lipase activity in adipose tissue; therefore, most fatty acids are taken up by adipose tissue and their flux towards the liver is reduced[46].

The dietary intake of *n*-3 was not significantly correlated with NAFLD in lean and non-lean participants of the present study. This finding is different from some literature results, in which *n*-3 has been protective for NAFLD[47]. The low consumption of dietary sources of *n*-3, for example, fatty fish, because of high price, may explain this controversy. A domestic study showed a major difference between the fish consumption rate in Iran and the recommended rate as a healthy diet[48].

The discrepancies between previous findings on the relationship between dietary macronutrient composition and NAFLD maybe because of such factors as different cultural and demographic characteristics that can affect dietary habits, (e.g., low fish consumption in Iran), inaccurate dietary assessment techniques and different adjustments in statistical analysis. However, the current study for the first time used substitution analysis of the relationships in two groups of lean and non-lean participants, with probably different pathologic pathways for NAFLD, separately.

The results showed that the relationship between dietary macronutrients and the prevalence of NAFLD was different in lean and non-lean groups. It seems that an increase in polysaccharides with decreasing SFA and animal protein-derived energy content is correlated with lower lean NAFLD. However, non-lean NAFLD was more correlated with a dietary fatty acid profile. Increasing MUFA-derived energy content to replace almost all types of macronutrients, namely total carbohydrate, total protein, mono-disaccharides, SFA and PUFA, and especially mono-disaccharides, and reducing dietary intake of *n*-6 and SFA can reduce non-lean NAFLD (Fig. 1). These results can be used to regulate dietary compositions and determine their differences between non-lean and lean NAFLD patients. Further in-depth studies are needed to analyze the cause-and-effect relationships and their mechanisms.

Among the strengths of the present study are using a large population-based sample size, using a validated 168-item FFQ for collecting required dietary information[19], and adjusting the results for most of the confounding factors in this field, such as demographics, lifestyle and metabolic characteristics. The results were also adjusted for total energy intake. The aim was to exclude the energy intake effect from the relationships between macronutrients and NAFLD. Separating lean and non-lean participants, with different pathologic pathways for NAFLD, during the analyses and performing substitution analysis for dietary macronutrients to ensure that the observed relationship for one macronutrient is not because of reducing or increasing other macronutrients are among other strong points of the current study.

The current study has some limitations. Due to the cross-sectional design of the current study, it is not possible to determine cause-and-effect relationships. The current study was conducted in the northern part of Iran, where dietary habits are different from western diets. The results should cautiously be generalized to a population with a western diet.

Conclusion

Lean and non-lean NAFLD might be correlated with different dietary macronutrient profiles. In the current study, the higher substitution of polysaccharides for SFA and animal protein intake was correlated with lower lean NAFLD. In contrast, the higher substitution of MUFA for mono-disaccharides and reduction of *n*-6 and SFA intake was correlated with lower non-lean NAFLD.

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research study participants were approved by the ethics committee of Iran University of Medical Sciences, Tehran, Iran by NoIR.IUMS.REC.1397.166. Written informed consent was obtained from all subjects.

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