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Relationship of three different types of low-carbohydrate diet to cardiometabolic risk factors in a Japanese population: the INTERMAP/INTERLIPID Study

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Abstract

Purpose—Low-carbohydrate diets (LCD) are a popular dietary strategy for weight reduction. The effects of LCD on long-term outcome vary depending on type of LCD, possibly due to the

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Compliance with Ethical Standards

Conflict of interest None.

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fact that effects on cardiometabolic risk factors may vary with different types of LCD. Accordingly, we studied these relations.

Methods—We assessed serum concentrations of high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), high-sensitivity C-reactive protein (CRP), total cholesterol, glycated hemoglobin, and uric acid, and nutrient intakes by standardized methods in men and women ages 40–59 years from four population samples of Japanese in Japan (553 men and 544 women, combined). For people consuming usual, animal-based, and plant-based LCDs, we calculated LCD scores, based on relative level of fat, protein, and carbohydrate, by modifying the methods of Halton et al. Instead of calculating scores based on animal or vegetable fat, we used saturated fatty acids (SFA) or monounsaturated fatty acids (MUFA) + polyunsaturated fatty acids (PUFA).

Results—In multivariate regression analyses with adjustment for site, age, sex, BMI, smoking, alcohol intake, physical activity, and years of education, all three LCD scores were significantly positively related to HDLc (all $P < 0.001$), but not to LDLc. The plant-based LCD score was significantly inversely related to log CRP (coefficient = −0.010, $P = 0.018$).

Conclusions—All three LCD scores were significantly positively related to HDLc. The plant-based LCD score was significantly inversely related to CRP. Carbohydrate intake below 50 % of total energy with higher intakes of vegetable protein and MUFA + PUFA, and lower intakes of SFA may be favorable for reducing cardiometabolic risk factors.

Keywords

Low-carbohydrate diet; C-reactive protein; Cardiometabolic risk factors; High-density lipoprotein cholesterol

Introduction

Low-carbohydrate diets (LCD) are a popular dietary strategy for weight reduction [1]. The term LCD is generally applied to diets that restrict carbohydrates to <20 % of caloric intake [1], but can also refer to diets that simply restrict or limit carbohydrates to less than recommended proportions (generally <45 % of total energy coming from carbohydrates). Effectiveness for weight loss and reduction in cardiometabolic risk factors (CMRF) [including obesity (particularly central), hyperglycemia, hypertension, insulin resistance, dyslipoproteinemia] of LCD has been reported in several review and meta-analysis studies [2–5]. However, Sacks et al. [6] reported that reduced-calorie diets result in clinically meaningful weight loss regardless of the macronutrients they emphasize. Although dropout in this study was low (20 %), the dietary goals were only partially achieved as judged from objective biomarkers [6]. LCDs often involve high intake of saturated fatty acids (SFA) or diet patterns with adverse lipid composition, leading to increase in low-density lipoprotein cholesterol (LDLc). It has been suggested that LCDs may be associated with increased risk of cardiovascular disease (CVD) morbidity and mortality [7–11]. Recently, a meta-analysis of observational studies on the association of LCD with total mortality has been carried out by Noto et al. [12]. This study showed LCD to be associated with significantly higher risk of total mortality without significant differences in CVD mortality and incidence. Although

differential effects of animal-based and plant-based LCDs on health outcomes have been noted [7, 11], actual data are sparse on the effects on CMRF with different types of LCD.

In observational studies, dichotomizing participants into those who are on and those who are not on an LCD is difficult. Halton et al. [11] devised a system to classify women in the Nurses' Health Study according to their relative levels of fat, protein, and carbohydrate intake and created a summary score designated the LCD score. One type of LCD score is based on dietary patterns involving varied mixes of both vegetable and animal products; we call this type the usual LCD score. Halton et al. calculated two other types of LCD score based on animal or vegetable fat. With use of INTERLIPID/INTERMAP data collected from 1997 to 1999 [13, 14], we assessed relationships of usual, animal-based, and plant-based LCD score to CMRF including serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), LDLc, uric acid (UA), and an inflammatory marker, high-sensitivity C-reactive protein (CRP), in population-based samples of Japanese residing in Japan. In contrast to Halton et al., we here used SFA, or monounsaturated fatty acids (MUFA) + polyunsaturated fatty acids (PUFA), given available data on harmful effects of SFA and beneficial effects of MUFA + PUFA on serum lipids and health. We designate these other two LCD scores as animal-based LCD score and plant-based LCD score. In these three LCD scores, usual, animal-based, and plant-based, higher scores indicate lower carbohydrate intake.

Methods

Participants

Detailed methods of the INTERMAP Study have been described [13, 14]. INTERLIPID participants aged 40–59 years were five INTERMAP population samples: four in Japan and one in Hawaii [15–17]; for the present study, the four samples in Japan were used. They were: (1) Japanese factory workers in Toyama, central Japan (149 men and 150 women); (2) Japanese factory workers in Sapporo, northern Japan (149 men and 148 women); (3) Japanese residents in Aito-town, a rural town in Shiga Prefecture, central Japan (129 men and 129 men); (4) Japanese factory workers in Wakayama, central Japan (145 men and 143 women). Among these four research sites, 32 persons (11 men and 21 women) were excluded because volume of their stored serum specimen was not enough to measure CRP and serum lipids; 13 persons (8 men and 5 women) were excluded because their CRP concentrations were more than 10 mg/L, leaving 1097 individuals (553 men and 544 women). Ethics committees of the Shiga University of Medical Science, the Pacific Health Research Institute, and Northwestern University approved the study protocol. Written informed consent was obtained from all participants.

Anthropometric and lifestyle assessment

Participants visited the research centers four times on two pairs of consecutive days on average 3 weeks apart. Height and weight with light clothes were measured at each visit; the four measurements of height and weight were averaged. Two standardized blood pressure (BP) measurements were made on each of the four different days; these eight measurements were averaged. Using a questionnaire, trained observers inquired about physical activity,

smoking status, previous medical history of CVDs/diabetes, and use of medication (including anti-hypertensive medication). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). To evaluate physical activity, questions were posed about number of hours per day spent in heavy activity, moderate activity, light activity, watching TV, other sedentary and no activity (sleeping); the interviewer ensured that the total time added up to 24 h. A physical activity index score was calculated by multiplying the times spent in different activities by corresponding weighting factors that parallel the increased rate of oxygen consumption associated with increasingly more intense physical activity; for this, the procedure in the Framingham Offspring Study [18] was followed.

Dietary assessment

Four in-depth multi-pass 24-h dietary recalls per participant were conducted during the four visits by specially trained and certified dietary interviewers. All participants attended all four study visits; their energy intakes from all 24-h dietary recalls were between 500 and 5000 kcal/day. Validation of the methods has been reported [14]. For each person, means of individual nutrients from the four 24-h dietary recalls were used in the analyses. Data are presented as the contribution to total energy intake (percentage of kcal [% kcal]) from total carbohydrates, total protein, animal protein, plant protein, total fats, SFA, MUFA, PUFA, and alcohol (% kcal). Keys dietary lipid score, predictive of serum TC, was calculated as $1.35 \times (2 \times \text{SFA} - \text{PUFA}) + 1.5 \times C^{1/2}$, where SFA is % kcal from SFA; PUFA, % kcal from PUFA; and C, dietary cholesterol in mg/1000 kcal [19].

Biochemical measurements

For the INTERLIPID Study, non-fasting blood was drawn ad libitum time after last meal on the second day of the first 2-day visit pair [15–17]. We used data on analytes measured in these blood samples, as well as data from INTERMAP. Serum and plasma were obtained by centrifugation within 30 min of blood drawing and immediately refrigerated. Within 24-h, all specimens were frozen and stored locally at −70 °C. Samples were sent to a central laboratory in Japan on dry ice. TC, HDLc, LDLc, triglycerides (TG), and UA were directly measured by enzymatic methods on an auto-analyzer (Hitachi 7107; Hitachi, Tokyo, Japan). TGs were analyzed for inclusion as a covariate in the models, not as an outcome variable in this study. Serum CRP was measured by immunoturbidimetric assay. Percentage of glycated hemoglobin A1c (HbA1c) was measured using the standard method of the Japan Diabetes Society.

Calculation of the LCD score

Usual LCD score was calculated by modifying the methods of Halton et al. [11]. Data are shown as percentage of total energy. Men and women considered together were analyzed into 11 strata for fat, protein, and carbohydrate intake. For fat and protein, participants in the highest stratum received 10 points for that macronutrient, down to participants in the lowest stratum, who received 0 points. For carbohydrate, the order of the strata was reversed. The points for each of the three macronutrients were then summed to create the overall diet score, which ranged from 0 to 30. Type of dietary lipid influences serum lipids; previous studies also showed differential effects of animal-based and plant-based LCD on health outcomes [7, 11]. Accordingly, we also generated two additional LCD scores. One was

calculated according to the percentage of energy as carbohydrate, animal protein (from egg, meat, chicken, other poultry, seafood, and dairy products), and SFA. Although some SFA, like myristic and palmitic acids, have been reported as more harmful than the others [20], we did not subdivide SFA in this study. The other LCD score was calculated according to the percentage of energy as carbohydrate, vegetable protein (from soy, other legumes, nuts, grains, and other non-animal sources), and MUFA plus PUFA. The former is called animal-based LCD score; the latter, plant-based LCD score.

Data analyses

SAS version 9.4 for Windows (SAS Institute, Cary, NC) was used. As the distribution of CRP values was positively skewed, logarithmic transformation was used to normalize them. We divided participants into quintiles as well as deciles according to their LCD score. The Mantel–Haenszel Chi-square statistical test for nominal variables and the “contrast” option for analysis of variance for continuous variables were used to assess whether there were significant differences in variables across quintiles of LCD score. Trend *P* values were obtained. Multiple linear regression analysis with adjustment for confounders was used to examine relationships of deciles of LCD score to CRP (log CRP), HDLc, LDLc, TC, UA, and HbA1c. Model 1 included site (site 1–4; site 4 as reference), age, sex, BMI, and decile of LCD score. Model 2 included model 1 covariates + cigarettes/day, alcohol (% kcal), physical activity index, and years of education (≤9, 10–12, 13–15, ≥16 year; ≤9 year as reference). In sensitivity analyses, TG was entered into model 2 analyses for relation of LCD scores to LDLc, because TG may influence the relation even though LDLc was measured by the direct method. Interaction *P* values for sex-LCD were not significant; hence, all results are presented for both sexes combined. Finally, for guidance in identifying a cut point for designating a diet as LCD, we scrutinized successive plant-based LCD scores in descending order to find where significant differences occurred in CRP or HDLc using age- and sex-adjusted analysis of variance. All *P* values were two tailed; $P < 0.05$ was considered significant.

Results

Descriptive statistics

Data on the criteria for determining the three LCD scores are shown in Table 1. On average, about 54 % of energy intake was from carbohydrate, 16 % from protein, 25 % from fat, and 4.8 % from alcohol. For participants in the lowest carbohydrate stratum, carbohydrate intake ranged from 29.3 to 44.1 (mean 40.2) % kcal; in the highest stratum, from 63.7 to 78.6 (mean 66.6) % kcal.

Characteristics of participants by quintile of the three types of LCD score are shown in Table 2. Mean age was lower in higher LCD score groups of the three types (trend *P*s = 0.007–0.040). Percentage of men was lower in higher plant-based LCD score groups (trend *P* = 010), and mean BMI was greater in higher usual LCD score groups (trend *P* = 0.039). Mean HDLc was greater with higher values of all three LCD score groups (trend *P*s < 0.001); increments from quintile 1 to quintile 5 were similar in all three groups (about +11 %). Median CRP values were lower in higher usual and plant-based LCD score groups (trend *P*s

= 0.044 and 0.003), slightly more so in plant-based LCD score groups (−15.2 % in usual vs −17.7 % in plant-based LCD score groups). Mean cigarettes smoked were lower in higher usual and plant-based LCD score groups (trend *P*s = 0.039 and <0.001). Mean physical activity score was lower with higher LCD score for all three LCD score groups (trend *P*s <0.001), and percentage of participants with ≥16 years of education was greater with higher LCD score for all three LCD score groups (trend *P*s = 0.007 to <0.001). Other variables were not different across the groups.

Nutritional variables of participants by quintile of the three types of LCD score are shown in Table 3. Mean energy intake was greater in higher animal-based LCD score groups (trend *P* = 0.003). Alcohol intakes were greater in higher usual and animal-based LCD score groups (trend *P*s < 0.001). Keys dietary lipid scores were greater with higher LCD scores in all three LCD groups (trend *P*s < 0.001); the increment was greatest in animal-based LCD score groups (+54 %) and least in plant-based LCD score groups (+12 %). Means of all dietary lipid variables were significantly higher (trend *P*s < 0.001), and means of dietary carbohydrate variables were lower with higher LCD score for all three LCD scores groups (trend *P*s < 0.001). Although the findings were qualitatively similar, quantitatively there were differences in dietary lipids among the three groups: the increment of SFA was the most in animal-based LCD score groups (+71 % from quintile 1–5) and least in plant-based LCD score groups (+38 %); the increment of dietary cholesterol was the most in animal-based LCD score groups (+126 %) and least in plant-based LCD score groups (+19 %); the increment of PUFA was the least in animal-based LCD score groups (+19 %) and greatest in plant-based LCD score groups (+62 %).

Food group characteristics of participants by quintile of the three types of LCD score are shown in Supplement Table 1. Mean intakes of rice and of fruits were significantly lower with higher LCD scores in all three LCD groups (trend *P*s < 0.001); mean intakes of meats, eggs, and dairy products were greater with higher LCD scores in all three LCD groups (trend *P*s < 0.001). Mean intakes of soy, other beans, and vegetables were greater in higher usual and plant-based LCD score groups (trend *P*s < 0.001). Mean sweets intake was lower and mean fish intake was greater with higher usual and animal-based LCD score groups (trend *P*s < 0.001).

Relations of LCD scores to CMRF

Relations of the three LCD scores to CMRF are shown in Table 4. All three LCD scores were significantly positively related to HDLc in both models (all *P*s < 0.001). The plant-based LCD score alone was significantly inversely related to CRP in both models (coefficient = −0.013 to −0.010, *P* = 0.003–0.018). Animal-based LCD score was positively related to TC in model 1, but the relation was no longer statistically significant after adjustment for other covariates in model 2. The results of model 2 analyses including TG for relation of LCD scores to LDLc did not differ from the initial results (data not shown). The three LCD scores were not significantly related to the other CMRF.

Cutoff carbohydrate intake for designating LCD

Scrutinizing decile cut points of plant-based LCD score in descending order to identify where significant differences in CRP or HDLc occur, we found a significant increment in CRP at decile 6; significant decrement in HDLc at decile 8 (Supplement Table 2). Mean intakes of carbohydrate in decile 6 and decile 8 of plant-based LCD score were 50.4, and 49.5 %, respectively. Thus, <50 % may be suitable for designating a diet as LCD. From Table 1 results, about 300 participants (about 27 %) with carbohydrate intake in strata 8–10 fulfilled this criterion.

Discussion

Main findings here were, in four middle-aged population samples of Japanese in Japan combined, with median carbohydrate intake relatively high (54.6 % of total energy intake), three LCD scores (usual, animal-based, and plant-based) were significantly positively related to non-fasting HDLc. The plant-based LCD score was significantly inversely related to CRP. LCD scores were not related to other CMRF, LDLc, TC, HbA1c, or UA.

Previous studies have shown that LCD was positively related to HDLc [21–23]. No previous studies compared the relation of usual, animal-based, and plant-based LCD to HDLc. Results of our study indicate that all three types of LCD, usual, animal-based, plant-based, related positively to HDLc. The fact that all three types of LCD increase HDLc may be related to the fact that various types of LCD are associated with an increase in fatty acids intake. A meta-analysis by Mensink et al. [24] reported that intake of three classes of fatty acids, SFA, MUFA, and PUFA, increased HDLc relative to carbohydrates.

Although all three LCD scores were significantly positively related to non-fasting HDLc, only the plant-based LCD score significantly inversely related to CRP. Data are available from previous studies on the association of CRP with various dietary patterns. In cross-sectional studies, low concentration of CRP was associated with intake of a Mediterranean diet [25–27], nuts and whole-grain foods [28], and low glycemic index diets [29]. A recent meta-analysis by Schwingshackl et al. [30] of long-term intervention trials with low glycemic index diets showed a decrease in CRP. With regard to MUFA, a recent meta-analysis showed no statistically significant differences in CRP between high-MUFA and low-MUFA diets [31]. Previous meta-analyses of cohort studies reported inconsistent associations of MUFA with coronary heart disease (CHD) [32, 33]. These inconsistencies may be due to the fact that differences in sources of MUFA were not taken into account. Adopting a western diet means that MUFA is predominantly supplied by foods of animal origin, while in south European countries, olive oil is the dominant source of this type of fatty acid [34]. A so-called prudent dietary pattern, characterized by higher intakes of vegetables, legumes, fruits, fish, lean poultry, and whole grains, and lower intakes of red and processed meats, fried foods, refined grains, desserts, and other sweets, had an inverse association with plasma CRP. The Western dietary pattern, characterized by high intakes of red and processed meats, fried foods, refined grains, desserts, and sweets, showed a positive relation with CRP, significant after adjustment for age, BMI, physical activity, smoking status, and alcohol consumption [35–37]. The above evidence is concordant with our finding

that the plant-based LCD score was significantly inversely related to CRP, but usual and animal-based LCD scores were not related CRP.

In our cross-sectional study, we observed no relation of LCDs to LDLc, and TC. Data available from longitudinal studies may help to understand our findings: Sacks et al. [6] showed with 65 % carbohydrate—20 % fat diet, LDLc decreased by 6 % from baseline in 2 years; with 35 % carbohydrate—40 % fat diet, it decreased by 1 %. A meta-analysis by Hu et al. [2] showed that weighted mean changes in LDLc and TC with low fat diet were −6.0 and −10.1 mg/dL, respectively; −2.1 and −4.6 mg/dL, respectively, with LCD. These studies showed some reduction in LDLc and TC with LCD, but the effects were significantly less than those with low fat diets. Yancy et al. [21] reported LDLc and TC did not change with LCD, whereas Noakes et al. [22] showed LDLc increased significantly by 7 % on very LCD, without significant change in TC. Gögebakan et al. [23] also showed significant increase in LDLc and TC with low glycemic index diet. Thus, previous studies reported varying changes in LDLc, from decrease to increase, probably depending on compositions of LCD.

As to a cutoff carbohydrate intake for defining LCD, we came to our recommendation that it be set at no more than 50 % kcal, because we found significant increment in CRP at decile 6; significant decrement in HDLc at decile 8 of plant-based LCD score; mean intakes of carbohydrate in decile 6 and decile 8 of plant-based LCD score were 50.4, and 49.5 %, respectively.

Main strengths of the present study are: (1) its population-based samples; (2) standardized collection of high-quality nutrition and laboratory measures; and (3) use of multiple procedures for quality-control. The study was limited by its cross-sectional design. Findings may or may not be generalizable to other populations. Especially due to the cross-sectional nature of this study, its results must be interpreted cautiously in regard to cause–effect relationships. The observed putatively beneficial effect of LCD on HDLc needs to be interpreted with caution since HDLc has been reported to be a weaker predictor of CVD than LDLc and CRP [38]. However, in the Japanese general population, HDLc was found to be inversely associated with all-cause mortality in a cohort study [39]. Other limitations include the following: the effect-size underestimation due to limited reliability in nutrient measurement (regressiondilution bias), despite four standardized state-of-the-art measurements; limited generalizability to persons younger than 40 years and older than 59 years; measurement error in blood chemical variables due to only one blood sample collected; non-fasting blood sample used, possibly producing error in LDLc measurement; insulin not measured, thus interpretation is speculative related to the link from LCD, lower insulin concentration, and higher HDLc concentration. INTERMAP/INTERLIPID field work was from 1997 to 1999; thus, there is the need to consider whether the Japanese habitual diet changed since. Available data indicate that the Japanese diet has not changed much: according to the National Nutritional Survey in Japan, % kcal from protein, fat, and carbohydrate were 16.0, 26.3, and 57.7 % in 1998; 14.6, 26.2, and 59.2 % in 2012 [40, 41].

Conclusions

Usual, animal-based, and plant-based LCD scores were significantly positively related to non-fasting HDLc. The plant-based LCD score was significantly inversely related to CRP. The plant-based LCD score was related to greater PUFA and lesser SFA and dietary cholesterol intake in comparison with the other two LCD scores. These may have contributed to our finding that only the plant-based LCD score was significantly inversely related to CRP. Carbohydrate intake below 50 % of total energy with higher intakes of vegetable protein and MUFA + PUFA, and lower intakes of SFA may be favorable for reducing CMRF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Category limits (% kcal) for nutrients used in determining the LCD score INTERMAP/INTERLIPID Study, Japan

Points	Carbohydrate	Total protein	Total fat	Animal protein	SFA	Veg protein	MUFA + PUFA
0	63.7–78.6	10.0–13.1	9.3–18.5	2.6–5.9	1.8–4.4	4.0–5.6	5.4–11.3
1	60.6–63.6	13.2–14.0	18.6–20.3	6.0–6.8	4.5–5.0	5.7–6.0	11.4–12.5
2	58.8–60.5	14.1–14.6	20.4–22.0	6.9–7.4	5.1–5.5	6.1–6.4	12.6–13.5
3	57.3–58.7	14.7–15.0	22.1–23.3	7.5–7.9	5.6–5.9	6.5–6.7	13.6–14.3
4	55.5–57.2	15.1–15.6	23.4–24.4	8.0–8.4	6.0–6.3	6.8–6.9	14.4–15.0
5	53.9–55.4	15.7–16.0	24.5–25.5	8.5–8.9	6.4–6.7	7.0–7.2	15.1–15.6
6	52.3–53.8	16.1–16.6	25.6–26.5	9.0–9.5	6.8–7.1	7.3–7.4	15.7–16.4
7	50.1–52.2	16.7–17.1	26.6–27.7	9.6–10.2	7.2–7.5	7.5–7.7	16.5–17.3
8	47.3–50.0	17.2–17.9	27.8–29.3	10.3–10.9	7.6–8.0	7.8–8.1	17.4–18.3
9	44.2–47.2	18.0–19.1	29.4–31.6	11.0–12.1	8.1–9.0	8.2–8.6	18.4–19.7
10	29.3–44.1	19.2–26.2	31.7–42.6	12.2–18.2	9.1–12.9	8.7–11.5	19.8–26.7

LCD score was calculated by modifying the methods of Halton et al. [12]. Data are shown as a percentage of energy. Number of people in each cell is either 99 or 100. We divided the study participants into 11 strata of fat, of protein, and of carbohydrate intake, expressed as a percentage of energy. For fat and protein, participants in the highest stratum received 10 points for that macronutrient, down to participants in the lowest stratum, who received 0 points. For carbohydrate, the order of the strata was reversed. The points for each of the three macronutrients were then summed to create the overall diet score, which ranged from 0 to 30 (usual LCD score). We also created two additional LCD scores by modifying usual LCD score calculation. One was calculated according to the percentage of energy as carbohydrate, the percentage of energy as animal protein, and the percentage of energy as SFA (including plant SFA) (animal-based LCD score), and the other according to the percentage of energy as carbohydrate, the percentage of energy as vegetable protein, and the percentage of energy as MUFA plus PUFA (plant-based LCD score)

LCD low-carbohydrate diet, *SFA* saturated fatty acids, *Veg protein* vegetable protein, *MUFA* mono-unsaturated fatty acids, *PUFA* poly-unsaturated fatty acids

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Table 2

Characteristics of participants by quintile of usual, animal-based, and plant-based LCD score-INTERMAP/INTERLIPID Study, Japan

Variable	Usual LCD				Animal-based LCD			
	Quintile 1	Quintile 3	Quintile 5	Trend *P*	Quintile 1	Quintile 3	Quintile 5	Trend *P*
LCD score	0–8	14–17	22–30		0–8	14–17	22–30	
N (1097)	219	242	216		222	229	207	
Age (year)	*50.1 ± 5.7*	*49.4 ± 5.0*	*49.1 ± 5.0*	*0.040*	*50.4 ± 5.6*	*49.8 ± 5.0*	*48.6 ± 4.9*	*0.007*
Men (%)	52.5 %	46.3 %	49.5 %	0.702	47.8 %	45.9 %	49.3 %	0.501
BMI (kg/m^2)	*23.3 ± 2.7*	*23.5 ± 2.9*	*23.7 ± 3.0*	*0.039*	23.4 ± 2.6	23.3 ± 2.8	23.8 ± 3.0	0.054
LDLc (mg/dL)	121.1 ± 30.7	124.3 ± 29.9	117.7 ± 30.0	0.052	122.8 ± 31.1	123.1 ± 29.8	119.6 ± 29.4	0.067
HDLc (mg/dL)	*52.5 ± 12.9*	*58.0 ± 14.8*	*58.1 ± 14.9*	*<0.001*	*52.4 ± 12.8*	*58.1 ± 14.4*	*58.3 ± 15.2*	*<0.001*
TC (mg/dL)	196.3 ± 32.3	203.3 ± 31.1	200.4 ± 30.5	0.164	196.7 ± 33.4	201.3 ± 32.1	202.0 ± 30.4	0.110
UA (mg/dL)	5.0 ± 1.3	4.9 ± 1.4	5.1 ± 1.4	0.224	5.0 ± 1.4	4.9 ± 1.4	5.1 ± 1.3	0.120
CRP# (mg/L)	*0.33*	*0.30*	*0.28*	*0.044*	0.32	0.31	0.29	0.248
	(*0.19, 0.73*)	(*0.16, 0.56*)	(*0.15, 0.57*)		(0.16, 0.71)	(0.16, 0.58)	(0.15, 0.64)	
HbA1c (%)	4.6 ± 0.7	4.7 ± 0.6	4.7 ± 0.7	0.350	4.6 ± 0.6	4.6 ± 0.6	4.7 ± 0.7	0.076
Smoking (cigarettes/day)	*7.6 ± 12.0*	*5.3 ± 10.4*	*5.3 ± 10.0*	*0.039*	6.3 ± 11.4	5.1 ± 9.9	6.0 ± 11.1	0.434
PA score	*33.7 ± 8.6*	*32.0 ± 7.6*	*30.4 ± 5.5*	*<0.001*	*33.6 ± 8.2*	*32.1 ± 7.3*	*31.0 ± 7.1*	*<0.001*
Edu ≥ 16 year	*5.5* %	*8.3* %	*15.3* %	*<0.001*	*5.9* %	*3.9* %	*15.9* %	*<0.001*
		Plant-based LCD						
		Quintile 1		**Quintile 3**		**Quintile 5**		**Trend *P***
LCD score		0–10		14–16		20–29		
N (1097)		241		218		239		
Age (year)		*49.7 ± 5.6*		*49.1 ± 5.1*		*48.9 ± 5.3*		*0.022*
Men (%)		*57.7 %*		*52.3 %*		*45.6 %*		*0.010*
BMI (kg/m^2)		23.3 ± 2.9		23.5 ± 2.9		23.5 ± 2.9		0.457
LDLc (mg/dL)		122.2 ± 30.3		122.5 ± 28.8		121.0 ± 31.3		0.055
HDLc (mg/dL)		*53.5 ± 13.6*		*56.4 ± 14.5*		*59.1 ± 15.0*		*<0.001*
TC (mg/dL)		199.0 ± 31.9		200.8 ± 30.5		201.4 ± 32.8		0.649
UA (mg/dL)		5.1 ± 1.3		5.1 ± 1.4		4.9 ± 1.4		0.090

Variable	Usual LCD				Animal-based LCD			
	Quintile 1	Quintile 3	Quintile 5	Trend *P*	Quintile 1	Quintile 3	Quintile 5	Trend *P*
CRP# (mg/L)		*0.34*		*0.32*		*0.28*		*0.003*
		(*0.18, 0.77*)		(*0.15, 0.67*)		(*0.15, 0.54*)		
HbA1c (%)		4.6 ± 0.5		4.6 ± 0.6		4.7 ± 0.7		0.651
Smoking (cigarettes/day)		*8.2 ± 12.2*		*6.6 ± 11.0*		*4.7 ± 9.8*		*<0.001*
PA score		*33.5 ± 8.7*		*32.5 ± 7.3*		*31.1 ± 5.9*		*<0.001*
Edu ≥ 16 year		*6.6 %*		*8.7 %*		*12.3 %*		*0.007*

Values by quintile of three types of LCD score are mean ± SD, percent, or #median (25th and 75th percentile) (only quintile 1, 3, 5 values are shown). Trend *P* values are for the relationship between the variables listed on the left and quintile of the diet score, obtained by the Mantel–Haenzel Chi-square test or the “contrast” option for linear regression analysis, shown

Italic values indicate statistical significance at the 5 % level

LCD low-carbohydrate diet, *BMI* body mass index (kg/m^2), *LDLc* serum low-density lipoprotein cholesterol concentration (mg/dL), *HDLc* serum high-density lipoprotein cholesterol concentration (mg/dL), *TC* total cholesterol concentration (mg/dL), *UA* uric acid (mg/dL), *CRP* C-reactive protein (mg/L), *HbA1c* hemoglobin A1c (%), *Smoking* smoking (cigarettes/d), *PA score* the Framingham Study physical activity index score, *Edu* education

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Table 3

Nutrient characteristics of participants by quintile of the three types of LCD score INTERMAP/INTERLIPID Study, Japan

Variable	Usual LCD				Animal-based LCD			
	Quintile 1	Quintile 3	Quintile 5	Trend *P*	Quintile 1	Quintile 3	Quintile 5	Trend *P*
LCD score range	0–8	14–17	22–30		0–8	14–17	22–30	
Energy (kcal)	2012 ± 449	2047 ± 435	2043 ± 465	0.167	*1969 ± 437*	*2028 ± 401*	*2085 ± 486*	*0.003*
Alcohol (% kcal)	*3.0 ± 4.3*	*5.4 ± 7.3*	*4.7 ± 5.8*	*<0.001*	*2.5 ± 3.9*	*4.8 ± 6.6*	*5.5 ± 6.4*	*<0.001*
Keys score	*25.2 ± 5.4*	*30.0 ± 5.2*	*34.8 ± 6.1*	*<0.001*	*23.7 ± 4.5*	*29.7 ± 4.1*	*36.7 ± 5.5*	*<0.001*
Prot (% kcal)	*14.0 ± 1.4*	*15.7 ± 1.9*	*18.2 ± 1.9*	*<0.001*	*14.3 ± 1.6*	*16.0 ± 2.0*	*18.0 ± 2.1*	*<0.001*
Fat (% kcal)	*19.9 ± 3.4*	*25.5 ± 3.7*	*29.9 ± 3.6*	*<0.001*	*20.2 ± 3.6*	*25.3 ± 3.7*	*29.6 ± 4.0*	*<0.001*
SFA (% kcal)	*5.2 ± 1.3*	*6.8 ± 1.6*	*8.03 ± 1.65*	*<0.001*	*4.91 ± 1.02*	*6.65 ± 1.21*	*8.38 ± 1.56*	*<0.001*
MFA (% kcal)	*7.0 ± 1.5*	*9.3 ± 1.8*	*11.0 ± 1.8*	*<0.001*	*7.06 ± 1.52*	*9.13 ± 1.76*	*10.84 ± 1.89*	*<0.001*
PUFA (% kcal)	*5.3 ± 1.2*	*6.5 ± 1.3*	*7.4 ± 1.4*	*<0.001*	*5.80 ± 1.42*	*6.60 ± 1.39*	*6.88 ± 1.41*	*<0.001*
n-3 PUFA (% kcal)	*1.1 ± 0.3*	*1.4 ± 0.3*	*1.6 ± 0.4*	*<0.001*	*1.15 ± 0.32*	*1.34 ± 0.33*	*1.54 ± 0.41*	*<0.001*
n-6 PUFA (% kcal)	*4.3 ± 1.1*	*5.1 ± 1.2*	*5.8 ± 1.3*	*<0.001*	*4.63 ± 1.24*	*5.23 ± 1.23*	*5.31 ± 1.29*	*<0.001*
Trans FA (% kcal)	*0.4 ± 0.3*	*0.5 ± 0.3*	*0.5 ± 0.3*	*<0.001*	*0.31 ± 0.21*	*0.47 ± 0.31*	*0.53 ± 0.27*	*<0.001*
Total carb (% kcal)	*63.1 ± 4.2*	*53.4 ± 5.1*	*47.1 ± 4.8*	*<0.001*	*62.9 ± 4.1*	*53.8 ± 4.8*	*46.9 ± 5.1*	*<0.001*
Sugar (% kcal)	*19.9 ± 5.9*	*19.0 ± 4.6*	*17.3 ± 3.5*	*<0.001*	*19.4 ± 5.4*	*19.1 ± 4.5*	*17.7 ± 3.8*	*<0.001*
Starch (% kcal)	*43.1 ± 6.6*	*34.4 ± 5.5*	*29.8 ± 5.1*	*<0.001*	*43.5 ± 6.0*	*34.7 ± 5.2*	*29.2 ± 4.9*	*<0.001*
Dietary chol (mg/1000 kcal)	*154.5 ± 55.3*	*190.9 ± 56.8*	*242.7 ± 66.6*	*<0.001*	*153.1 ± 53.7*	*194.6 ± 59.2*	*246.5 ± 65.9*	*<0.001*

	Plant-based LCD			
	Quintile 1	Quintile 3	Quintile 5	Trend *P*
LCD score range	0–10	14–16	20–29	
Energy (kcal)	2066 ± 461	2114 ± 517	2028 ± 425	0.612
Alcohol (% kcal)	4.5 ± 6.3	5.9 ± 7.4	3.8 ± 4.9	0.131
Keys score	*27.9 ± 6.1*	*30.4 ± 6.2*	*31.2 ± 6.5*	*<0.001*
Prot (% kcal)	*14.8 ± 2.1*	*15.9 ± 2.1*	*16.9 ± 2.2*	*<0.001*
Fat (% kcal)	*19.9 ± 3.7*	*25.0 ± 3.2*	*29.8 ± 3.6*	*<0.001*
SFA (% kcal)	*5.5 ± 1.6*	*6.7 ± 1.6*	*7.6 ± 1.6*	*<0.001*
MFA (% kcal)	*7.0 ± 1.5*	*9.0 ± 1.5*	*10.9 ± 1.8*	*<0.001*

Variable	Usual LCD				Animal-based LCD			
	Quintile 1	Quintile 3	Quintile 5	Trend *P*	Quintile 1	Quintile 3	Quintile 5	Trend *P*
PUFA (% kcal)		*4.9 ± 1.0*		*6.3 ± 0.9*		*8.0 ± 1.2*		*<0.001*
n-3 PUFA (% kcal)		*1.1 ± 0.3*		*1.4 ± 0.3*		*1.6 ± 0.4*		*<0.001*
n-6 PUFA (% kcal)		*3.8 ± 0.9*		*4.9 ± 0.9*		*6.3 ± 1.1*		*<0.001*
Trans FA (% kcal)		*0.4 ± 0.2*		*0.4 ± 0.3*		*0.5 ± 0.3*		*<0.001*
Total carb (% kcal)		*60.7 ± 6.4*		*53.1 ± 6.9*		*49.5 ± 4.7*		*<0.001*
Sugar (% kcal)		*20.4 ± 6.1*		*18.4 ± 4.6*		*17.2 ± 3.5*		*<0.001*
Starch (% kcal)		*40.3 ± 8.1*		*34.8 ± 7.0*		*32.3 ± 5.0*		*<0.001*
Dietary chol (mg/1000 kcal)		*177.5 ± 65.1*		*199.5 ± 62.5*		*210.4 ± 69.3*		*<0.001*

Values by quintile of three types of LCD score are mean ± SD (only quintile 1, 3, 5 values are shown). All values are in % kcal, except for dietary cholesterol in mg/1000 kcal. Trend *P* values are for the relationship between the variables listed on the left and quintile of the diet score, obtained by the "contrast" option for linear regression analysis, shown

Italic values indicate statistical significance at the 5 % level

Energy dietary energy (kcal/d), *Alcohol* alcohol intake (% kcal), *Total prot* total protein (% kcal), *SFA* saturated fatty acids, *MFA* mono-unsaturated fatty acids, *PUFA* polyunsaturated fatty acids, *Total carb* total carbohydrate, *Dietary chol* dietary cholesterol

Table 4

Relations of three LCD scores to CMRF-INTERLIPID Study, Japan

Outcome variables	**Log CRP**	**HDLc**	**LDLc**	**TC**	**UA**	**HbA1c**
Usual LCD score						
Model 1						
β	−0.008 ± 0.005	*0.905 ± 0.146*	−0.547 ± 0.310	0.511 ± 0.329	0.010 ± 0.011	0.004 ± 0.006
P	0.079	*<0.001*	0.078	0.121	0.385	0.524
Model 2						
β	−0.005 ± 0.005	*0.731 ± 0.144*	−0.359 ± 0.315	0.496 ± 0.336	0.002 ± 0.012	0.004 ± 0.006
P	0.240	*<0.001*	0.255	0.141	0.864	0.499
Animal-based LCD score						
Model 1						
β	−0.006 ± 0.005	*0.940 ± 0.148*	−0.452 ± 0.316	*0.669 ± 0.335*	0.009 ± 0.012	0.007 ± 0.006
P	0.232	*<0.001*	0.153	*0.046*	0.456	0.248
Model 2						
β	−0.003 ± 0.005	*0.702 ± 0.148*	−0.206 ± 0.324	0.634 ± 0.345	−0.002 ± 0.012	0.007 ± 0.007
P	0.502	*<0.001*	0.525	0.067	0.900	0.307
Plant-based LCD score						
Model 1						
β	*−0.013 ± 0.004*	*0.678 ± 0.142*	−0.474 ± 0.300	0.031 ± 0.319	−0.004 ± 0.011	−0.002 ± 0.006
P	*0.003*	*<0.001*	0.114	0.922	0.709	0.754
Model 2						
β	*−0.010 ± 0.004*	*0.648 ± 0.148*	−0.405 ± 0.303	0.066 ± 0.323	−0.008 ± 0.011	−0.00002 ± 0.006
P	*0.018*	*<0.001*	0.181	0.838	0.483	0.997

Coefficients (*β*) ± standard errors, and *P* values from multiple linear regression models used to examine relations of deciles of the three LCD scores to CMRF are shown. Model 1 included site, age, sex, and BMI; Model 2, Model 1 variables + smoking (cigarettes/day), and alcohol intake (% kcal), the Framingham physical activity score, and years of education (≤9, 10–12, 13–15, ≥16 year; ≤9 year as reference)

Italic values indicate statistical significance at the 5 % level

LCD low-carbohydrate diet, *CMRF* cardiometabolic risk factors, *BMI* body mass index, *LDLc* serum low-density lipoprotein cholesterol concentration, *HDLc* serum high-density lipoprotein cholesterol concentration, *TC* serum total cholesterol concentration, *UA* serum uric acid concentration, *CRP* C-reactive protein, *HbA1c* hemoglobin A1c