Low-Carbohydrate Diets and Mortality in Older Chinese: A 15-Year Follow-Up of Guangzhou Biobank Cohort Study

Ce Sun

Sun Yat-sen University

Wei Sen Zhang

Guangzhou Twelfth People's Hospital

Chao Qiang Jiang

Guangzhou Twelfth People's Hospital

Ya Li Jin

Guangzhou Twelfth People's Hospital

Xue Qing Deng

Sun Yat-sen University

Jean Woo

The Chinese University of Hong Kong

Kar Keung Cheng

University of Birmingham

Tai Hing Lam

Guangzhou Twelfth People's Hospital

G Neil Thomas

University of Birmingham

Lin Xu (✉ xulin27@mail.sysu.edu.cn)

Sun Yat-sen University

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Abstract

Background: Studies on long-term effects of low-carbohydrate diet (LCD) on mortality accounting for quality and sources of carbohydrate are unclear. Hence, we examined the associations of LCDs with all-cause and cause-specific mortality in a population-based cohort study.

Methods: Prospective study using data from Guangzhou Biobank Cohort Study (GBCS). 20,206 participants (13.8% diabetes) aged 50+ years were recruited from 2003-2006 and followed up until 19 April 2021. Overall, vegetable-based, and meat-based LCD scores were calculated based on the percentage of energy as total and subtypes of carbohydrate, fat and protein. The main outcomes were all-cause, cancer and CVD mortality. Cox regression were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During 294,848 person-years of follow-up, 4,624 deaths occurred, including 3,661 and 963 deaths in participants without and with diabetes, respectively. In all participants, overall LCD score was not associated with all-cause and cause-specific mortality after multivariable adjustment. However, the adjusted HRs (95%CIs) of all-cause and CVD mortality for the highest, versus the lowest, quartiles of vegetable-based were 1.16 (1.05-1.27 $P_{\text{trend}} < 0.001$) and 1.39 (1.19-1.62 $P_{\text{trend}} < 0.001$), respectively. Meanwhile, we found that the adjusted HRs (95%CIs) of all-cause and CVD mortality for highest, versus lowest, quartile of meat-based LCD were 0.89 (0.81-0.97 $P_{\text{trend}} = 0.007$) and 0.81 (0.70-0.93 $P_{\text{trend}} = 0.02$), respectively. Similar associations were found in participants after excluding those with diabetes. In diabetic patients, there was no association between vegetable-based LCD or meat-based LCD scores and mortality. However, we found a positive association between the highest quartile of vegetable-based LCD score and CVD mortality comparing with the lowest quartile (HR 1.54, 95% CI, 1.11-2.14 $P_{\text{trend}} = 0.003$).

Conclusions: Vegetable-based LCD score was positively and meat-based LCD score was negatively associated with all-cause and CVD mortality. Inconsistencies in the literature on the health effect of LCD may reflect the importance of the geographical context and age-related nutrient composition of the diet.

Background

The primary source of energy from food worldwide is carbohydrate, providing over 50% of the daily energy intake, followed by sources from fat and plant and animal protein [1]. However, there are substantial differences in the proportion of macronutrient intakes between Asia and western countries [2, 3]. The traditional Chinese diet is characterized by a high intake of carbohydrate and vegetables as well as moderate intake of animal foods [4]. In a recent meta-analysis of predominantly western populations (6 of 7 studies) high carbohydrate intake was associated with higher risk of all-cause mortality and cardiovascular disease (CVD) [5]. Although low-carbohydrate diets (LCD) have been suggested to be useful in weight, blood pressure and glucose management in short-term randomized controlled trials [6, 7], studies on long-term health effects of LCD remain controversial [8], probably due to different levels and sources of baseline carbohydrate intake in diverse populations.

In addition to the quantity of carbohydrate, quality and source might also play a role in health outcomes [1, 9]. Carbohydrate from refined grains and added sugar was associated with higher risk of diabetes and CVD, whereas that from whole grains, non-starchy vegetables and fruits was associated with a lower risk [1, 10]. Likewise, high-quality carbohydrate (whole grains, non-starchy vegetables and fruits) or low-carbohydrate diets are recommended for patients with diabetes to manage glycemic index and glycemic load, although long-term compliance is low [11, 12]. Despite an increasing popularity of LCD diets, we searched PubMed using keywords of ("low carbohydrate diet" or "carbohydrate quality") and mortality up to September 17th, 2021, and found no population-based cohort studies reporting the association of LCDs with mortality by considering both quality and sources of carbohydrate in Asians and non-Asians.

We therefore conducted a prospective cohort study, using data from Guangzhou Biobank Cohort Study (GBCS), to investigate the associations of types of LCD with the risk of all-cause, cancer and CVD mortality in an older Chinese sample. Furthermore, we also examined whether the associations of types of LCD with the risk of all-cause, cancer and CVD mortality varied by diabetes status.

Methods

Study design and sample

The GBSC is a population-based cohort study in South China [13]. Briefly, GBSC is a 3-way collaboration among the Guangzhou Twelfth People's Hospital and the Universities of Hong Kong and Birmingham. All participants were recruited from a community social and welfare association, the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE) from 2003 to 2008. GHHARE is a large unofficial organization with ten branches throughout all districts of Guangzhou. Membership of this association is open to Guangzhou residents aged 50 years or older for a nominal, monthly fee of four CNY ($\approx$ 50 US cents). Baseline information was collected using computer-assisted face-to-face interview by trained nurses. Information of anthropometrics, blood pressure, fasting plasma glucose, lipids and inflammatory markers was collected following standard protocols. Reliability of the questionnaire was tested 6 months into recruitment by recalling 200 randomly selected participants for re-interview, and the results were satisfactory [13]. Ethics approval was granted by the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China. As the Food Frequency Questionnaire (FFQ) was shortened in phase 3 of baseline (2006-2008), participants from phase 3 were not included in the current analysis.

Assessment of LCD score

Information of diet was collected using a FFQ validated by Woo *et al* [14]. The LCD diet score was calculated as per the method described in a recent study by Shan *et al* [8]. Briefly, percentages of energy from carbohydrate, fat and protein for each participant were each calculated and used to rank the participants into 11 strata. For carbohydrate, participants in the lowest group received 10 points and those in the highest group received 0 points. The order of the strata for fat and protein was reversed. The scores of the three macronutrients were summed to create an overall LCD score, which ranged from 0 to 30. Two additional LCD scores were also created: (1) vegetable-based LCD scores were calculated according to the percentage of energy from high-quality carbohydrate, plant protein and unsaturated fat; (2) meat-based LCD scores were calculated according to the percentage of energy from low-quality carbohydrate, animal protein and saturated fat (Supplementary Table 1). Based on the Healthy Eating Index (HEI) 2015, high-quality carbohydrate was defined as carbohydrate from whole grains, whole fruits, legumes and non-starchy vegetables, and low-quality carbohydrate as carbohydrate from refined grains, added sugar, fruit juice, potato and other starchy vegetables[3]. As we found a significant interaction between LCDs and diabetes on all-cause mortality (P for interaction <0.001), we also conducted pre-specified analyses by diabetes status (Supplementary Table 2). Diabetes was defined by having a history of diabetes or fasting glucose ≥ 7.0 mmol/L at baseline.

Ascertainment of mortality

Details of the methods were described elsewhere, and information on the causes of death up to April 19, 2021 was obtained through record linkage with the Death Registry of the Guangzhou Center for Disease Control and Prevention (GCDC) [15]. Briefly, causes of death were coded by trained nosologists in each hospital according to the *International Classification of Diseases*, Tenth Revision (ICD-10). If death certificates were not issued by medical institutions, the causes of death were verified by GCDC as part of its quality assurance program by cross-checking past medical history and conducting a verbal autopsy. Moreover, we also conducted verbal autopsy meetings in the Guangzhou Twelfth

People's Hospital to further clarify the deaths of unclear causes. In the present study, the primary outcome was mortality from all causes, and the secondary outcome was mortality from cancer and CVD.

Potential confounders and mediators

As sex, age, socioeconomic factors (education, family income) [16], lifestyle factors (smoking, drinking and physical activity), body mass index (BMI) [17], and history of cancer and CVD were associated with both dietary pattern and mortality, these factors were considered as potential confounders and adjusted in the regression model. The potential mediators between LCD score and all-cause mortality risk included systolic blood pressure (SBP), fasting plasma-glucose (FPG) total cholesterol (TC) and self-rated health at baseline. Procedures for measuring these were reported previously [13].

Statistical analysis

Chi-square test and one-way analysis of variance (ANOVA) were used to compare baseline categorical and continuous variables by quartiles of LCD scores, respectively. Person-years of follow-up were assessed from the date of baseline enrollment to death or end of the present study on April 19, 2021, whichever came first. The LCD scores were categorized into quartiles. Multivariable Cox proportional hazards regression was used to calculate hazard ratio (HRs) and 95% confidence intervals (CI) of mortality associated with LCD score. Schoenfeld's residuals were used to test the proportional hazard assumption and no violations of the proportional hazard assumption were found. Model 1 was the crude model without any adjustment. In multivariable analyses, model 2 adjusted for sex and age, and model 3 additionally adjusted for education, family income, smoking, drinking, physical activity, BMI and history of cancer and CVD. Model 4 adjusted for determinants considered potential mediators, namely, SBP, FPG, TC and self-rated health. In addition, the non-linearity of the effect of LCD score on mortality risk was estimated by adding a quadratic term to the model with the quartiles of LCD scores as a continuous variable and the fitness of the models with and without the quadratic term was compared using the likelihood ratio (LR) test [18]. A non-significant *P*-value was interpreted as an indication of a linear effect of LCD score on mortality risk.

Furthermore, stratification analysis was done for the associations between diet score and all-cause mortality according to several potential effect modifiers at baseline. As many statistical tests were performed in subgroup analysis, we used the Bonferroni correction to account for multiple testing and the significance level was set at $P < 0.002$ ($0.05/8$ [subgroups] $\times 3$ [dietary scores]). To assess the extent to which baseline risk factors explained the associations of LCD score with mortality, the percentage of excess risk mediated (PERM) was calculated for the following four groups of explanatory variables: (1) SBP; (2) FPG; (3) TC; (4) self-rated health. For each risk-factor group, we calculated PERM as: $PERM = [HR(E+C) - HR(E+C+M)] / [HR(E+C) - 1] \times 100$, where E=exposure, C=covariates (sex, age, education, family income, smoking, drinking, BMI, physical activity, and history of cancer and CVD), M=explanatory variable being tested [19]. A crude model was first developed, then adjusted for age and sex and subsequently to address other potential confounders (education, family income, oil intake, smoking, drinking, physical activity, BMI, and history of cancer and CVD), and finally to examine for proposed mediators (systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health). To account for potential bias due to reverse causality, we conducted a sensitivity analysis excluding participants who died within the first three years of follow-up. Statistical analysis was done using Stata (STATA Corp LP, version 15). Two-sided *P*-values < 0.05 were considered as statistically significant.

Results

Participant characteristics

Of 20,490 participants, 128 with potentially unreliable dietary intake (<800 or >4200 kcal/d in men, and <600 or >3500 kcal/d in women), 57 who were followed up for less than 1 year, and 99 lost to follow-up with unknown vital status were excluded (Supplementary Figure 1). A total of 20,206 participants [mean (SD) age=62.7 (6.7) years; 14,423 (71.4%) women] including 17,416 participants without diabetes [mean (SD) age=62.5 (6.7) years; 12,364 (71.0%) women] and 2,790 participants with diabetes [mean (SD) age=64.1 (6.2) years; 2,059 (73.8%) women] were included in the present analysis. During an average of 14.8 years (SD= 3.3) with 294,848 person-years of follow-up, 4,624 deaths occurred, including 1,534 from cancer, 1,783 from CVD and 1,307 from other causes.

Table 1 shows that compared with a low LCD score (Q1), high LCD score (Q4) was associated with being women, having a younger age, higher education level and family income, lower physical activity, never smoking and a current alcohol consumer (all $P<0.05$). However, the potential mediators, lower FPG and SBP level were found in those with higher overall LCD score ($P<0.001$). Similar results were found in meat-based LCD score though BMI was lower but with increased history of cancer and CVD. In contrast, those with a higher vegetable-based LCD score had lower education level, with a greater proportion of smokers and higher SBP and lower TC levels. Vegetable-based LCD score showed no association with sex, age, family income, drinking, BMI, and history of CVD. Participants without diabetes showed similar patterns as all participants (Supplementary Table 3). In contrast, participants with diabetes showed no association of overall LCD score with sex, age, smoking, drinking and FPG level, no association of vegetable-based LCD score with smoking, history of cancer and SBP level, no association of meat-based LCD score with age, BMI, history of CVD and FPG level but a negative association between meat-based LCD score and drinking (Supplementary Table 3).

Mortality and LCD score

Table 2 shows that in all participants, after adjusting for sex, age, education, family income, smoking, drinking, physical activity, BMI and history of cancer and CVD, overall LCD score showed no association with all-cause mortality. For vegetable-based LCD score, the adjusted HR (95% CI) of all-cause mortality for the 2nd, 3rd and 4th quartile, versus the 1st quartile (Q1), was 0.99 (0.91-1.07), 1.11 (1.02-1.21) and 1.16 (1.05-1.27) (P for trend<0.001 and P for non-linear=0.18), respectively. For meat-based LCD score, the adjusted HR (95% CI) of all-cause mortality for the Q2, Q3 and Q4, versus the Q1, was 0.89 (0.83-0.97), 0.90 (0.83-0.97) and 0.89 (0.81-0.97) (P for trend=0.007 and P for non-linear=0.06), respectively.

Table 3 shows no association between overall LCD score and all-cause mortality in participants with or without diabetes. In those without diabetes, the results on vegetable-based LCD and meat-based LCD score were generally similar with those from the total population. Comparing with the Q1 group, participants in Q4 of vegetable-based LCD score showed a higher risk of all-cause mortality (HR 1.10, 95% CI 1.01-1.23), whereas those with the highest quartile of meat-based LCD score showed a lower risk of all-cause mortality (HR 0.87, 95% CI 0.79-0.97). In participants with diabetes, no associations of vegetable-based LCD score and meat-based LCD score quartiles with all-cause mortality were found, although there was a linear trend between vegetable-based LCD score and all-cause mortality (P for trend=0.04).

Supplementary Table 4 shows no association of the overall LCD score with mortality of cancer, CVD and other causes. The vegetable-based LCD score was associated with higher risk of CVD mortality (Q1: reference, Q2: 1.18 (1.03-1.34), Q3: 1.36 (1.18-1.56) and Q4 1.39 (1.19-1.62), P for trend<0.001 and P for non-linear=0.15), whereas the higher meat-based LCD score quartiles were associated with lower risk of CVD mortality (Q1: reference, Q2: 0.84 (0.75-0.95), Q3: 0.82 (0.72-0.93) and Q4: 0.81 (0.70-0.93), P for trend=0.02 and P for non-linear=0.10). Supplementary Table 5 shows similar results in participants without diabetes. In participants with diabetes, no association of overall LCD score and meat-based LCD score with CVD mortality was found. However, we found a positive association between vegetable-based

LCD score quartiles and CVD mortality (Q1: reference, Q2: 1.21 (0.89-1.63), Q3: 1.59 (1.18-2.15), Q4: 1.54 (1.11-2.14), P for trend=0.003 and P for non-linear=0.25).

Figure 1 shows that the HR of all-cause mortality comparing Q4 to Q1 of vegetable-based LCD score was 1.16 (1.05-1.27) after adjustment for potential confounders. The HR decreased by 14% after adjusting for SBP, 27% after adjusting for FPG and 2% after adjusting for self-rated health, and increased by 3% after adjusting for TC. The overall attenuation after adjustment for mediators was 41%. Similar patterns were found for the association between vegetable-based LCD score and cause-specific mortality. FPG appeared to be the strongest mediator in vegetable-based LCD diet. For meat-based LCD, the HR of all-cause mortality was 0.89 (0.81-0.97) after adjustment for potential confounders, which increased by 10% after adjusting for SBP, 24% after adjusting for FPG and 1% after adjusting for self-rated health. FPG appeared to be the strongest mediator in meat-based LCD diet.

Figure 2 shows that in participants without diabetes, vegetable-based LCD score was associated with higher risk of mortality from all-cause mortality (HR comparing Q4 to Q1=1.10, 95% CI 1.01-1.23) and CVD (HR 1.26, 95% CI 1.06-1.51). After adjustment for mediators, the HRs of all-cause mortality became non-significant (HR 1.06, 95% CI 0.96-1.18). SBP appeared to be the strongest mediator (PERM=26% for all-cause mortality and 19% for CVD mortality). In participants with diabetes, no association of vegetable-based LCD score with all-cause mortality was found. However, we found that vegetable-based LCD score was associated with a higher risk of CVD mortality (adjusted HR 1.54, 95% CI, 1.11-2.13), for which TC appeared to be the strongest mediator (PERM=16%). Figure 3 shows that in participants without diabetes, meat-based LCD score was associated with lower risk of all-cause and CVD mortality, which was partly mediated by SBP (PERM=13% for all-cause and CVD mortality). No association of meat-based LCD score with cancer and other-cause mortality was found.

Subgroup and sensitivity analyses

Supplementary Figures 2 to 7 show similar associations in most subgroups. After Bonferroni corrections for multiple testing, the association between vegetable-based LCD score and all-cause mortality appeared to be stronger in obese than non-obese participants (Supplementary Figure 3, P for interaction<0.001). Higher vegetable-based LCD score was associated with a higher risk of all-cause mortality (HR for Q4 versus quartile 1=1.55, 95% CI 1.18-2.04). Similar results were observed in participants without diabetes (Supplementary Figure 6, all P for interaction<0.001). Similar results were found after excluding deaths within the first three years of follow-up (Supplementary Table 6 and 7).

Discussion

Although after a long-term follow-up for nearly 15 years, no association of overall LCD score with risk of all-cause and cause-specific mortality was found in our study. In prespecified subgroup analyses, we found that vegetable-based LCD score was positively, whereas meat-based LCD score was negatively associated with all-cause and CVD mortality. Similar associations were observed for participants without diabetes. In participants with diabetes, a positive association of vegetable-based LCD score with risk of CVD mortality was found.

Comparison with previous studies

Most studies considered LCD based on animal-derived protein and fat sources as a risk factor of mortality, whereas LCD based on plant-derived protein and fat reduced mortality [5, 20, 21]. Furthermore, studies show that higher level of whole grain intake was associated with lower risk of all-cause mortality, whereas refined grain intake was associated with higher risk of all-cause mortality [22, 23]. This highlights that, a healthy LCD diet is not only dependent on the sources of macronutrients but also on the quality of them. A previous study using a new classification approach of LCD score found that participants with low low-quality refined carbohydrate, high unsaturated fat and plant protein intake had

lower all-cause and cancer mortality risk, whilst those with low high-quality unrefined carbohydrate and high saturated fat and animal protein intake had higher all-cause mortality risk [8]. Our results generally supported the intake of high-quality carbohydrate, and further showed that participants with low low-quality refined carbohydrate, high saturated fat and animal protein intake had lower all-cause and CVD mortality risk, and with low high-quality unrefined carbohydrate, high unsaturated fat and plant protein intake had higher mortality risk. The discrepancy might be due to the differential amount and sources of carbohydrate, fat and protein in the West and non-West settings.

The percentage of energy from carbohydrate, fat and protein in our study were similar with the China Health and Nutrition Survey (CHNS) [24]. Notably, the percentage of energy from carbohydrate (especially high-quality carbohydrate) in our study was higher than that reported in the US (total carbohydrate, 57.1% *versus* 50.5%; high-quality carbohydrate, 10.6% *versus* 8.6%, respectively), whereas the percentage of energy from animal protein and saturated fat intake was much lower than the US (animal protein, 7.4% *versus* 10.4%; saturated fat, 4.9% *versus* 11.9%, respectively) [3]. Moreover, compared with the US, total per capita consumption of meat in Asians was much lower (49.4kg/year *versus* 122.8kg/year), whereas the percentage of energy from fish/sea food consumption was higher (43.5% *versus* 26.0%) [25]. Some recent studies showed that fish/sea food consumption was associated with lower risk of all-cause and CVD mortality in Asians, but not in the US populations [26, 27]. Meta-analyses show that total mortality is in participants who have high intakes of both red and processed meat than in those with low meat intakes in western high-income countries (28). However, meat is good source of energy and a range of essential nutrients, including protein and micronutrients such as iron, zinc, and vitamin B12 for low-income countries. A previous study showed that Indian vegetarians had a more favorable cardiovascular risk profile than that of non-vegetarians [29]. Along with these findings, our results support the beneficial effects of moderate consumption of animal protein. In addition, the non-significant association between meat-based LCD and CVD mortality in diabetic patients could also be explained by the lower levels of fish consumption than those without diabetes [26]. Moreover, a recent meta-analysis also showed that substituting fish with red and processed meat was associated with increased risks of all-cause mortality in patients with type 2 diabetes [30]. Apart from differential amount of high-quality carbohydrate, saturated fat and animal protein intake, the discrepancies could also be at least partly explained by the low-quality carbohydrate, unsaturated fat and plant protein. Notably, comparing with the US, the percentage of energy from low-quality carbohydrate (46.4% *versus* 41.8%), due in part to the high white rice intake, and plant protein (8.5% *versus* 5.8%) intake was higher in our sample, whereas percentage of energy from unsaturated fat was lower (monounsaturated fatty acids, 8.6% *versus* 13.1%; polyunsaturated fatty acids, 6.3% *versus* 8.2%).

Regarding the results on vegetable-based LCD, our results were generally consistent with previous studies in Asia showing positive associations between plant-based diets consisting of a high intake of refined carbohydrates and the risk of metabolic syndrome and CVD [31, 32]. In our study, participants with higher vegetable LCD score had higher levels of unsaturated fat consumption and higher risks of all-cause and CVD mortality, which could be partly explained by the cooking method. In traditional Chinese cuisine, plant oil is often used for stir-frying, pan-frying and deep-frying and is heated to a high temperature [33]. High heat has been shown to cause partial hydrogenation of unsaturated plant oils to produce trans unsaturated fats. Studies have consistently shown trans unsaturated fats consumption to be associated with higher risk of all-cause and CHD mortality [34]. Moreover, as CVD is a leading cause of mortality in people with type 2 diabetes mellitus [35], the stronger positive association between vegetable-based LCD and CVD mortality in participants with diabetes in our study also warrants further attention.

Regarding the null association between the overall LCD and mortality, our results were consistent with some [8, 36] but not all [20, 37] previous studies. For example, a recent study in Japan showed a U-shape association between overall LCD score and all-cause mortality [37]. The authors suggested that sources of food might have modified the association [37]. Another study in the US showed a positive association between overall LCD and all-cause mortality

[20]. The differences in the results could be partly due to the substantial variation in carbohydrate consumption across different populations (i.e., about 60% of the overall energy was from carbohydrate in Asians vs. 50.5% in the US) [2, 3]. Higher carbohydrate consumption could lead to greater glycemic burden, and a subsequently higher risk of insulin resistance and vascular complications [38-40], which warrants further research in populations with high carbohydrate intake.

Strengths and limitations

Strengths of our study included the large sample size, long duration of follow-up and comprehensive adjustment for potential confounders. There were some limitations in the present study. Firstly, changes in dietary patterns were not assessed during follow-up. However, our previous study found that the dietary patterns of our sample were relatively stable [41, 42]. Secondly, residual confounding could not be fully ruled out, although we adjusted for a wide range of potential confounding factors reported in previous literature. Thirdly, our results may not be directly applicable to younger or western populations. Fourthly, the null association in the subgroup of participants with diabetes could be due to the relatively small sample size. Although a recent meta-analysis showed that patients adhering to an LCD for six months may experience remission of diabetes without adverse consequences [43], further studies on the health effects related to long-term and types of LCD patterns in diabetic patients are warranted.

In conclusion, we found that vegetable-based LCD score was positively, whereas meat-based LCD score was negatively associated with all-cause mortality. Inconsistencies in the literature on the health effect of LCD may reflect the importance of the geographical context and age-related nutrient composition of the diet.

List Of Abbreviations

CI, confidence interval; CVD, cardiovascular disease; GBCS, Guangzhou Biobank Cohort Study; GCDC, Guangzhou Center for Disease Control and Prevention; GHHARE, Guangzhou Health and Happiness Association for the Respectable Elder; HEI, Healthy Eating Index; HR, hazard ratio; LCD, low-carbohydrate diet; PERM, percentage of excess risk mediated

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China. The informed consent was given by all participants to data collection and individual follow-up.

Consent for publication

Not Applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Author contributions

CS, LX, THL, CQJ, WSZ, YLJ, GNT, JW and KKC have substantial contributions to conception and design, acquisition of funding, data and interpretation of data; CS and LX analyzed the data, CS, LX, THL and CQJ drafted the article, THL, LX and CQJ revised it critically for important intellectual content, and all authors contributed to final approval of the paper.

Acknowledgements

Not Applicable

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Tables

Table 1 Baseline characteristics by quartiles of low-carbohydrate-diet score in 20,206 participants recruited in 2003-2008 ^a

Characteristic	Overall low-carbohydrate -diet score		P-value	Vegetable-based low-carbohydrate-diet score		P-value	Meat-based low-carbohydrate-diet score		P-value
	Quartile 1	Quartile 4		Quartile 1	Quartile 4		Quartile 1	Quartile 4	
Number of participants	5,100	4,936		5,278	3,775		5,163	4,418	
Age, mean (SD), year	63.5 (6.5)	62.1 (6.8)	0.04	62.7 (6.7)	62.8 (6.6)	0.70	63.4 (6.6)	62.0 (6.8)	0.02
Sex			<0.001			0.56			<0.001
Women	1,696 (33.3)	3,707 (75.1)		3,740 (70.9)	2,677 (70.9)		3,398 (65.8)	3,432 (77.7)	
Men	3,404 (66.7)	1,229 (24.9)		1,538 (29.1)	1,098 (29.1)		1,765 (34.2)	986 (22.3)	
Education level			<0.001			<0.001			<0.001
Less than primary school	2,678 (52.5)	1,988 (40.3)		2,231 (42.3)	1,878 (49.8)		2,826 (54.8)	1,619 (36.6)	
Middle school	2,009 (39.4)	2,445 (49.5)		2,463 (46.7)	1,609 (42.6)		2,003 (38.8)	2,305 (52.2)	
College or above	413 (8.1)	503 (10.2)		584 (11.0)	288 (7.6)		330 (6.4)	493 (11.2)	
Family income, RMB/year			<0.001			0.21			<0.001
<20,000	1,261 (24.7)	820 (16.6)		992 (18.8)	764 (20.2)		1,297 (25.2)	688 (15.6)	
20,000-30,000	986 (19.3)	935 (18.9)		1,062 (20.1)	756 (20.0)		1,004 (19.5)	839 (19.0)	
30,000-50,000	781 (15.3)	1,063 (21.5)		979 (18.6)	689 (18.3)		812 (15.7)	943 (21.4)	
≥ 50,000	473 (9.3)	902 (18.3)		768 (14.5)	550 (14.6)		443 (8.6)	880 (20.0)	
Do not know	1,599 (31.4)	1,216 (24.7)		1,474 (28.0)	1,016 (26.9)		1,598 (31.0)	1,060 (24.0)	
BMI, mean (SD), kg/m²	23.8 (3.3)	23.7 (3.3)	0.71	23.7 (3.2)	23.8 (3.3)	0.63	23.9 (3.3)	23.7 (3.3)	0.02
Physical activity			<0.001			<0.001			<0.001
Low	305 (6.0)	479 (9.7)		285 (5.4)	498 (13.2)		378 (7.4)	397 (9.0)	
Moderate	2,113 (41.4)	2,630 (53.3)		2,416 (45.8)	1,808 (47.9)		2,155 (41.7)	2,347 (53.1)	
High	2,682	1,827		2,577	1,469		2,630	1,674	

	(52.6)	(37.0)	(48.8)	(38.9)	(50.9)	(37.9)
Smoking	<0.001		<0.001		<0.001	
Never	3,944 (77.4)	4,045 (82.0)	4,301 (81.5)	2,890 (76.6)	3,915 (75.9)	3,731 (84.5)
Ever	581 (11.4)	393 (7.9)	532 (10.1)	380 (10.0)	600 (11.6)	327 (7.4)
Current	575 (11.3)	498 (10.1)	445 (8.4)	506 (13.4)	648 (12.5)	360 (8.1)

Table 1 Baseline characteristics by quartiles of low-carbohydrate-diet score in 20,206 participants recruited in 2003-2008 ^a (continued)

Characteristic	Overall low-carbohydrate -diet score		<i>P</i> -value	Vegetable-based low-carbohydrate-diet score		<i>P</i> -value	Meat-based low-carbohydrate-diet score		<i>P</i> -value
	Quartile 1	Quartile 4		Quartile 1	Quartile 4		Quartile 1	Quartile 4	
Drinking			0.001			0.24			0.004
Never	4,139 (81.4)	3,919 (79.5)		4,170 (79.2)	3,052 (81.0)		4,164 (80.8)	3,547 (80.5)	
Ever	138 (2.6)	102 (2.0)		116 (2.0)	84 (2.1)		130 (2.4)	86 (1.8)	
Current	823 (16.1)	915 (18.5)		991 (18.7)	639 (16.9)		869 (16.8)	785 (17.7)	
Dietary intake, mean (SD)									
Total energy, kcal/d	1,853 (520)	1,730 (502)	0.003	1,817 (530)	1,783 (488)	<0.001	1,835 (506)	1,781.0 (520)	<0.001
Total carbohydrate, % of total energy intake	67.6 (4.7)	46.5 (5.4)	<0.001	60.9 (8.0)	52.2 (8.7)	<0.001	65.9 (6.1)	48.0 (7.4)	<0.001
<i>High-quality carbohydrate</i>	10.1 (7.3)	10.0 (6.1)	<0.001	15.1 (7.2)	5.6 (3.8)	<0.001	7.4 (4.4)	13.8 (8.5)	<0.001
<i>Low-quality carbohydrate</i>	57.4 (8.7)	36.4 (7.1)	<0.001	45.8 (10.2)	46.5 (9.7)	<0.001	58.4 (6.6)	34.0 (6.9)	<0.001
Total protein, % of total energy intake	14.2 (1.9)	18.0 (2.8)	<0.001	16.5 (2.9)	15.3 (3.1)	<0.001	14.0 (2.0)	18.3 (2.8)	<0.001
<i>Animal protein</i>	5.2 (1.8)	10.1 (2.9)	<0.001	8.1 (3.1)	6.8 (2.8)	<0.001	5.1 (1.7)	10.1 (2.9)	<0.001
<i>Plant protein</i>	9.0 (1.3)	7.9 (1.8)	<0.001	8.4 (1.6)	8.5 (1.8)	<0.001	8.9 (1.3)	8.2 (2.0)	<0.001
Total fat, % of total energy intake	12.9 (5.6)	26.1 (7.2)	<0.001	14.5 (6.0)	26.1 (7.8)	<0.001	13.2 (6.0)	26.6 (7.3)	<0.001
<i>Saturated fat</i>	3.4 (1.5)	6.2 (1.7)	<0.001	4.3 (1.8)	5.6 (1.8)	<0.001	3.0 (1.0)	7.0 (1.5)	<0.001
<i>Monounsaturated fat</i>	5.6 (2.5)	11.4 (3.4)	<0.001	6.2 (2.7)	11.4 (3.7)	<0.001	5.8 (2.7)	11.4 (3.7)	<0.001
<i>Polyunsaturated fat</i>	3.9 (2.4)	8.5 (3.5)	<0.001	4.0 (2.5)	9.2 (3.7)	<0.001	4.4 (2.8)	8.2 (3.7)	<0.001
History of CVD	2,058 (40.8)	2,052 (42.1)	0.20	2,171 (41.7)	1,581 (42.4)	0.70	2,013 (39.4)	1,908 (43.7)	<0.001
History of cancer	98 (1.9)	108 (2.2)	0.63	136 (2.6)	57 (1.5)	0.005	98 (1.9)	104 (2.4)	0.004
Fasting plasma-glucose, mmol/L	5.9 (1.6)	5.7 (1.9)	<0.001	5.9 (1.6)	5.7 (2.0)	<0.001	5.8 (1.7)	5.8 (1.9)	<0.001

Systolic blood pressure, mmHg	133.4 (22.4)	130.1 (22.2)	<0.001	130.3 (22.2)	132.6 (22.3)	<0.001	133.4 (22.4)	129.6 (22.2)	<0.001
Total cholesterol, mmol/L	3.7 (1.0)	3.7 (0.9)	0.51	3.7 (1.0)	3.6 (1.0)	<0.001	3.7 (1.0)	3.7 (1.0)	0.90

Abbreviations: BMI, body mass index; CVD, Cerebrovascular disease; SD, Standard Deviation;

^a Data are presented as number (percentage) of study participants unless otherwise indicated.

Note: one dollar almost equals to 7 RMB.

Table 2 Association of low-carbohydrate-diet (LCD) score with all-cause mortality

Characteristic	Quartiles of LCD scores				<i>P</i> for trend	<i>P</i> for non-linear
	1	2	3	4		
Overall LCD score ^a						
Median score (IQR)	6 (4, 8)	13 (11, 14)	18 (17, 19)	24 (22, 26)		
Person-years of follow-up	74,195	77,724	71,289	71,640		
Mortality rate (per 1000 person-years)	182.1	156.3	140.1	147.8		
Crude HR (95% CI)	1.00	0.87 (0.80-0.94) [*]	0.79 (0.72-0.85) ^{**}	0.83 (0.77-0.90) ^{**}	<0.001	0.07
Adjusted HR (95% CI) ^d	1.00	0.92 (0.85-0.99) [*]	0.89 (0.82-0.96) [*]	0.96 (0.88-1.04)	0.17	0.008
Adjusted HR (95% CI) ^e	1.00	0.95 (0.87-1.02)	0.92 (0.85-1.02)	0.99 (0.91-1.08)	0.73	0.04
Adjusted HR (95% CI) ^f	1.00	0.95 (0.88-1.03)	0.92 (0.84-1.00)	0.97 (0.89-1.06)	0.38	0.08
Vegetable-based LCD score ^b						
Median score (IQR)	11 (9, 12)	14 (13, 15)	17 (16, 18)	20 (19, 21)		
Person-years of follow-up	77,358	85,584	77,518	54,388		
Mortality rate (per 1000 person-years)	151.0	148.2	161.8	171.7		
Crude HR (95% CI)	1.00	0.98 (0.91-1.07)	1.08 (1.00-1.17) [*]	1.16 (1.06-1.26) ^{**}	<0.001	0.15
Adjusted HR (95% CI) ^d	1.00	0.99 (0.91-1.07)	1.12 (1.04-1.22) ^{**}	1.18 (1.09-1.29) ^{**}	<0.001	0.23
Adjusted HR (95% CI) ^e	1.00	0.99 (0.91-1.07)	1.11 (1.02-1.21) [*]	1.16 (1.05-1.27) [*]	<0.001	0.18
Adjusted HR (95% CI) ^f	1.00	0.98 (0.90-1.06)	1.09 (1.00-1.18)	1.09 (0.99-1.20)	0.01	0.20
Meat-based LCD score ^c						
Median score (IQR)	6 (3, 8)	13 (11, 14)	19 (17, 20)	24 (23, 27)		
Person-years of follow-up	74,816	75,838	79,936	64,259		
Mortality rate (per 1000 person-years)	186.9	155.7	143.2	140.1		
Crude HR (95% CI)	1.00	0.84 (0.77-0.90) ^{***}	0.78 (0.72-0.84) ^{***}	0.77 (0.71-0.84) ^{***}	<0.001	0.15
Adjusted HR (95% CI) ^d	1.00	0.89 (0.82-0.96) ^{**}	0.87 (0.80-0.94) ^{**}	0.88 (0.81-0.96) ^{**}	0.001	0.12

Adjusted HR (95% CI) ^e	1.00	0.89 (0.83-0.97) ^{**}	0.90 (0.83-0.97) ^{**}	0.89 (0.81-0.97) ^{**}	0.007	0.06
Adjusted HR (95% CI) ^f	1.00	0.89 (0.82-0.97) ^{**}	0.91 (0.84-0.98) [*]	0.91 (0.83-0.99) [*]	0.01	0.07

Abbreviations: IQR, Interquartile Range

^a Low carbohydrate, high total fat, and high protein intake

^b Low high-quality carbohydrate, high unsaturated fat, and high plant protein intake

^c Low low-quality carbohydrate, high saturated fat, and high animal protein intake

^d Adjusted for sex and age

^e Additionally adjusted for education, family income, smoking, drinking, physical activity, BMI and history of cancer and CVD.

^f Additionally adjusted for systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health at baseline.

*: 0.05; **: 0.01; ***: 0.001

Table 3 Association of low-carbohydrate-diet (LCD) score with all-cause mortality in participants without and with diabetes

Characteristic	Quartiles of LCD scores				<i>P</i> for trend	<i>P</i> for non-linear
	1	2	3	4		
Participants without diabetes						
Overall LCD score ^a						
Median score (IQR)	6 (4, 8)	13 (11, 14)	18 (17, 19)	24 (22, 26)		
Person-years of follow-up	66,071	68,119	61,773	59,855		
Mortality rate (per 1000 person-years)	171.0	147.1	124.2	127.3		
Crude HR (95% CI)	1.00	0.87 (0.80-0.95) [*]	0.74 (0.68-0.81) [*]	0.76 (0.70-0.84) [*]	<0.001	0.12
Adjusted HR (95% CI) ^d	1.00	0.92 (0.85-1.00)	0.86 (0.78-0.94) [*]	0.90 (0.82-0.99) [*]	0.005	0.06
Adjusted HR (95% CI) ^e	1.00	0.94 (0.86-1.03)	0.88 (0.80-0.98) [*]	0.92 (0.83-1.01)	0.03	0.19
Adjusted HR (95% CI) ^f	1.00	0.96 (0.87-1.04)	0.90 (0.81-0.99) [*]	0.93 (0.84-1.03)	0.08	0.25
Vegetable-based LCD score ^b						
Median score (IQR)	11 (9, 12)	14 (13, 15)	17 (16, 18)	20 (19, 21)		
Person-years of follow-up	68,770	74,652	66,646	45,749		
Mortality rate (per 1000 person-years)	140.5	135.3	146.7	154.5		
Crude HR (95% CI)	1.00	0.97 (0.89-1.06)	1.06 (0.97-1.15)	1.12 (1.02-1.23) [*]	0.008	0.15
Adjusted HR (95% CI) ^d	1.00	0.97 (0.89-1.06)	1.09 (0.99-1.19)	1.15 (1.04-1.26) [*]	0.001	0.16
Adjusted HR (95% CI) ^e	1.00	0.97 (0.88-1.06)	1.06 (0.97-1.17)	1.10 (1.01-1.23) [*]	0.02	0.26
Adjusted HR (95% CI) ^f	1.00	0.96 (0.88-1.05)	1.04 (0.95-1.15)	1.06 (0.96-1.18)	0.12	0.30
Meat-based LCD score ^c						
Median score (IQR)	6 (3, 8)	13 (11, 14)	19 (17, 20)	24 (23, 26)		
Person-years of follow-up	66,057	66,297	69,618	53,845		
Mortality rate (per 1000 person-years)	175.9	145.3	128.0	119.8		
Crude HR (95% CI)	1.00	0.83 (0.76-0.90) ^{**}	0.74 (0.68-0.81) ^{***}	0.70 (0.63-0.77) ^{***}	<0.001	0.06

Adjusted HR (95% CI) ^d	1.00	0.89 (0.81-0.97) *	0.84 (0.77-0.92) **	0.83 (0.75-0.91) **	<0.001	0.13
Adjusted HR (95% CI) ^e	1.00	0.91 (0.83-0.99) *	0.89 (0.82-0.98) *	0.87 (0.79-0.97) **	0.006	0.28
Adjusted HR (95% CI) ^f	1.00	0.91 (0.83-0.99) *	0.91 (0.83-1.00) *	0.90 (0.82-1.00) *	0.02	0.26

Table 3 Association of low-carbohydrate-diet (LCD) score with all-cause mortality in participants without and with diabetes (continued)

Characteristic	Quartiles of LCD scores				<i>P</i> for trend	<i>P</i> for non-linear
	1	2	3	4		
Participants with diabetes						
Overall LCD score ^a						
Median score (IQR)	6 (3, 8)	13 (11, 14)	18 (17, 19)	24 (22, 26)		
Person-years of follow-up	8,124	9,605	9,516	11,784		
Mortality rate (per 1000 person-years)	272.0	221.8	243.8	252.0		
Crude HR (95% CI)	1.00	0.81 (0.67-0.98)	0.91 (0.76-1.09)	0.94 (0.79-1.12)	0.97	0.06
Adjusted HR (95% CI) ^d	1.00	0.87 (0.72-1.05)	0.93 (0.78-1.12)	1.00 (0.84-1.19)	0.68	0.11
Adjusted HR (95% CI) ^e	1.00	0.91 (0.75-1.10)	0.95 (0.78-1.16)	1.09 (0.90-1.31)	0.26	0.09
Adjusted HR (95% CI) ^f	1.00	0.90 (0.74-1.09)	0.96 (0.79-1.17)	1.06 (0.88-1.28)	0.34	0.14
Vegetable-based LCD score ^b						
Median score (IQR)	11 (9, 12)	14 (13, 15)	17 (16, 18)	20 (19, 21)		
Person-years of follow-up	8,587	10,932	10,872	8,639		
Mortality rate (per 1000 person-years)	235.2	236.0	253.9	262.8		
Crude HR (95% CI)	1.00	1.00 (0.84-1.21)	1.10 (0.92-1.32)	1.15 (0.95-1.39)	0.08	0.78
Adjusted HR (95% CI) ^d	1.00	1.02 (0.85-1.22)	1.20 (1.00-1.44)	1.20 (1.00-1.45)	0.02	0.86
Adjusted HR (95% CI) ^e	1.00	1.03 (0.86-1.25)	1.21 (1.00-1.47)	1.18 (0.95-1.45)	0.04	0.46
Adjusted HR (95% CI) ^f	1.00	1.04 (0.86-1.26)	1.26 (1.00-1.53)	1.21 (0.98-1.49)	0.03	0.31
Meat-based LCD score ^c						
Median score (IQR)	6 (3, 8)	13 (11, 14)	18 (17, 20)	24 (23, 27)		
Person-years of follow-up	8,758	9,541	10,318	10,413		
Mortality rate (per 1000 person-years)	269.5	228.5	246.2	244.9		
Crude HR (95% CI)	1.00	0.85 (0.70-1.02)	0.93 (0.78-1.11)	0.93 (0.78-1.11)	0.66	0.21
Adjusted HR (95% CI) ^d	1.00	0.85 (0.71-1.03)	0.91 (0.76-1.09)	0.94 (0.79-1.12)	0.70	0.16
Adjusted HR (95% CI) ^e	1.00	0.87 (0.72-	0.94 (0.78-	0.99 (0.82-	0.85	0.16

		1.04)	1.13)	1.19)		
Adjusted HR (95% CI) ^f	1.00	0.82 (0.67-1.00)	0.94 (0.78-1.13)	0.97 (0.80-1.17)	0.82	0.10

Abbreviations: IQR, Interquartile Range

^a Low carbohydrate, high total fat, and high protein intake

^b Low high-quality carbohydrate, high unsaturated fat, and high plant protein intake

^c Low low-quality carbohydrate, high saturated fat, and high animal protein intake

^d: Adjusted for sex and age

^e: Additionally adjusted for education, family income, smoking, drinking, physical activity, BMI, and history of cancer and CVD.

^f Additionally adjusted for systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health at baseline.

*: 0.05; **: 0.01; ***: 0.001

Figures

Figure 1

Associations between LCD score (Q4 versus Q1) and all-cause mortality, and proportions of the associations attributable to systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health in all-participants (A: vegetable-based LCD score; B: meat-based LCD score)

Figure 2

Associations between vegetable-based LCD score (Q4 versus Q1) and mortality, and proportions of the associations attributable to systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health (A: participants without diabetes; B: participants with diabetes)

Figure 3

Associations between meat-based LCD score (Q4 versus Q1) and mortality, and proportions of the associations attributable to systolic blood pressure, fasting plasma-glucose, total cholesterol and self-rated health (A: participants without diabetes; B: participants with diabetes)

Supplementary Files

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- [supplementaryfile.docx](#)