Impact of Carbohydrate Quality on the Relationship Between Low-Carbohydrate Diet Patterns and Long-term Changes in Cardiometabolic Risk Factors: A Prospective Cohort Study

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by

Ghaida Aloraini, M.S.

Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy,
Tufts University, Boston, MA

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Thesis Committee

Paul F. Jacques, D.Sc. (Chair)

Nicola M. McKeown, Ph.D.

Alice H. Lichtenstein, D.Sc.

Sai Krupa Das, Ph.D.

DEDICATION

To my parents Fahad Aloraini & Foziah Alhabib

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Abstract

Background: Low Carbohydrate Diet (LCD) patterns have become increasingly popular over recent decades to control excess weight gain and, independent of weight loss, their favorable short-term (≤ 2 years) effects on other cardiometabolic risk factors. Yet, evidence from long-term studies of LCD patterns is unclear. This may be due to differences in the quality of carbohydrate foods, which may differentially influence cardiometabolic health.

Objectives: To examine the association between LCD patterns varying in carbohydrate quality and long-term changes in *(Aim 1)* waist circumference, fasting HDL and non-HDL cholesterol, triglyceride and glucose concentrations, blood pressure; and *(Aim 2)* biomarkers of inflammation and oxidative stress.

Methods: Data from the Framingham Heart Study Offspring cohort was used to address the aims of this dissertation. LCD patterns accounting for quality of carbohydrate sources were assessed by creating 2 LCD scores (LCDSs) reflecting higher intake of total fat and protein, and lower intake of (i) low-quality carbohydrate (high-quality LCDS, HQ-LCDS) and (ii) high-quality carbohydrate (low-quality LCDS, LQ-LCDS). The higher the score the more closely the participant followed the LCD pattern. In *Aim 1*, cardiometabolic risk factors; waist circumference, blood pressure, and HDL cholesterol, non-HDL cholesterol, triglyceride and fasting glucose concentrations, were standardized to annual changes and examined across quintiles of LCDSs using repeated measure mixed models adjusted for potential confounders in a prospective analysis of 3,294 participants over a median 16.4year follow-up period. In *Aim 2*, an inflammation and oxidative stress score was calculated by summing the standardized values of 9 circulating inflammatory biomarkers. Least-square means of changes in the inflammatory score across quintiles of LCDSs were estimated using multivariable linear regression models adjusted for potential confounders over a median 6.7 year follow up period among 2,225 participants.

Results: *Aim 1:* Annual gains in waist circumference (cm/y) increased across quintile categories for HQ-LCDS (mean ± SE in Q1: 0.58 ± 0.03, Q5: 0.69 ± 0.03; P_{trend}= 0.003), and LQ-LCDS (Q1: 0.57 ± 0.03, Q5: 0.74 ± 0.03; <0.001). A slowing in the annual increase in systolic blood pressure (mmHg/y) was observed across quintile categories for both HQ-LCDS (Q1: 0.16±0.07, Q5: 0.01±0.07; 0.03) and LQ-LCDS (Q1: 0.21 ± 0.07, Q5: -0.05 ± 0.07; 0.01). HQ-LCDS was positively associated with the annual increase in HDL cholesterol (mg/dL/y) (Q1: 0.51 ± 0.05, Q5: 0.67 ± 0.04; 0.006), and inversely associated with the annual decline in triglyceride concentrations (mg/dL/y) (Q1: -1.24 ± 0.23, Q5: -2.01 ± 0.22; <0.001). LQ-LCDS was positively associated with the annual increase in glucose concentrations (mg/dL/y) (Q1: 0.35 ± 0.05, Q5: 0.48 ± 0.05; 0.05). *Aim 2:* HQ-LCDS was inversely associated with change in the inflammation and oxidative stress score (Q1: 0.24 ± 0.16, Q5: -0.27 ± 0.16; 0.004), indicating that inflammation and oxidative stress increased in those in the lowest HQ-LCDS category while decreased in those in the highest category. No significant associations were observed for LQ-LCDS.

Conclusions: Our findings suggest that, over a long period of time, LCD patterns have mixed associations with cardiometabolic risk factors. Both LCD patterns were associated with an increase in waist circumference and favorable changes in blood pressure, independent of carbohydrate quality. By considering carbohydrate quality, LCD patterns based on lower intake of low-quality carbohydrates were associated with healthier lipid profiles and beneficial changes in inflammation and oxidative stress, supporting dietary guidance to consume diets rich in fruits, vegetables, legumes, and whole grains.

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Chapter 1. Introduction

1.1 Background and Significance

Cardiometabolic diseases, including heart disease, stroke, and type 2 diabetes (T2D), remain the leading causes of death and disability in the U.S. and worldwide (1,2). In addition to their impact on health, cardiometabolic diseases pose a substantial economic burden (2,3). Cardiometabolic risk factors such as abdominal obesity, dyslipidemia, hyperglycemia, hypertension, and low-grade systemic inflammation account for much of the early, subclinical expression of cardiovascular disease (CVD) in populations (4,5). Diet is an important, modifiable lifestyle behavior that strongly influences these cardiometabolic risk factors (6). A better understanding of dietary changes to manage and reduce cardiometabolic risk factors, and subsequently reducing the incidence of cardiometabolic diseases, is therefore relevant for both clinical practice and public health.

Many popular diet patterns with different macronutrient compositions have been widely promoted to support cardiometabolic health. One dietary pattern that has received considerable interest in recent decades, largely among those trying to lose weight, is the low-carbohydrate diet (LCD) pattern (7). There is no standard definition for LCD, and it typically refers to diet patterns with carbohydrate amount less than 45% of the total caloric intake, which is the lower limit of the Acceptable Macronutrients Distribution Range for healthy adults (8), and correspondingly higher intake of fat and/or protein to compensate for lower caloric intake from carbohydrates.

Evidence from randomized controlled trials (RCTs) ranging from a few days to two years reported that LCD patterns promoted weight loss (9–12) and improved other cardiometabolic risk factors, including fasting glucose concentrations and insulin resistance (13–15), dyslipidemia (9,10), high blood pressure (11,12), and systemic inflammation (16–18). Although evidence from RCTs is promising, it is limited by relatively short follow-up periods (ranging from a few days to 24 months), thus there is a gap in understanding the long-term effects of following an LCD pattern. Previous observational studies that examined the association between LCD patterns or lower total carbohydrate intake and intermediate risk factors for cardiometabolic diseases are cross-sectional in design and reported mixed results (19–33).

While no observational studies have prospectively examined the long-term relationship between lower carbohydrate intakes and cardiometabolic risk factors, evidence relating lower carbohydrate intake and T2D, CVD, and mortality is inconclusive (34–40). The inconsistency may arise, in part, from the many variations in the macronutrient composition of LCD patterns in terms of dietary carbohydrate quality, and types and sources of fat and protein consumed in place of the carbohydrates, as well as overall diet quality and the nature of the diet pattern (i.e., plant-based versus animal-based diet).

One key component of LCD pattern that has not been adequately examined yet is the quality of carbohydrates remaining in the diet. Dietary carbohydrates come from many sources that can differentially affect cardiometabolic risk factors. Consuming carbohydrates from low-quality food sources like refined grains, sweet-baked desserts, and added sugars, have been linked to adverse long-term cardiometabolic health and incidence of CVD and T2D (41–47). In contrast, carbohydrate consumption from high-quality food sources, such as whole grains, non-starchy vegetables, whole fruits, nuts and legumes, and correspondingly higher dietary fiber intake, has been favorably associated with health outcomes (41–45,48–50).

Because maintaining a low carbohydrate intake (i.e., <25 EI%) is challenging in free-living adults, low-carbohydrate diet scores (LCDSs) have been commonly applied by investigators in observational studies examining LCD patterns and health outcomes. LCDSs simultaneously capture lower carbohydrate intakes and higher fat and/or protein intakes as an overall dietary pattern, with a higher score reflecting greater adherence to the LCD pattern. Multiple LCDSs have been designed to capture different sources of protein and fat, and the quality of carbohydrates (34–37,39,40). However, none of the previous LCDSs consider the carbohydrates quality in LCD patterns, independent of types and sources of protein and fat.

To our knowledge, no previous study has prospectively explored the long-term (> 2 years) impact of carbohydrate quality among LCD patterns on changes in intermediate cardiometabolic risk factors.

1.2 Central Hypothesis and Specific Aims

The ***overall objective*** of the research described in this dissertation is to investigate the association between different LCD patterns varying in the quality of carbohydrate, and long-term changes in cardiometabolic risk factors. Our ***central hypothesis*** is that long-term adherence to an LCD pattern based on lower intake of low-quality carbohydrates and maintenance of high-quality carbohydrates is associated with more favorable measures of cardiometabolic health than an LCD pattern with lower intake of high-quality carbohydrates. To address this hypothesis, we utilized data from the National Heart, Lung, and Blood Institute Framingham Heart Study (FHS), which provides longitudinal data on cardiometabolic risk factors; demographic, anthropometric, lifestyle, and clinical characteristics; and dietary intake. To address the central hypothesis, the following specific aims were tested:

Specific Aim 1: To examine the longitudinal association between LCDSs varying in carbohydrate quality and changes in cardiometabolic risk factors, including waist circumference, systolic and diastolic blood pressure and fasting blood concentrations of HDL and non-HDL cholesterol, triglyceride and glucose, over up to 23 years of follow-up in the FHS Offspring cohort (FOS; exams 5-9, 1991-2014). The ***working hypothesis*** is that an LCDS that reflects a pattern of lower intake of low-quality carbohydrates and maintenance of high-quality carbohydrates is associated with reduced waist circumference, lower risk of high blood pressure, improvement in plasma lipid profile (increased fasting HDL cholesterol and reduced fasting non-HDL cholesterol and triglyceride levels) and reduced fasting serum glucose concentration over time.

Specific Aim 2: To assess the long-term association between LCDSs varying carbohydrate quality and changes in biomarkers of inflammation and oxidative stress including C-reactive protein, interleukin 6, monocyte chemoattractant protein 1, P-selectin, tumor necrosis factor receptor II, soluble intercellular adhesion molecule-1, osteoprotegerin, lipoprotein phospholipase A2 mass and activity and urinary isoprostanes indexed to urinary creatinine over up to 10 years of follow-up in the FOS cohort (exams 7 and 8, 1998-2008). The ***working hypothesis*** is that following an LCDS that represents a pattern of lower intake of low-quality carbohydrates sources and preservation of high-

quality carbohydrate is associated with reduced risk of low-grade chronic inflammation and oxidative stress over time.

1.3 Literature Review

The following is a summary of existing literature on low-carbohydrate diets, including RCTs that included LCD treatment arms and observational studies that used LCDSs or focused on total carbohydrate intake with substitution of carbohydrates with other macronutrients. We focused on the potential confounding of the low-carbohydrate diets by determinants of cardiometabolic risk, mainly the confounding by carbohydrate quality and overall diet quality, specifically sources of protein and fat.

1.3.1 Low-Carbohydrates Diet Patterns and Cardiometabolic Risk

As early as 1825 (51), and again in 1972, LCDs have been considered as a strategy for weight loss(52). More recently, there continues to be an interest in LCD approaches, particularly for prevention or management of T2D (53–55). A variety of popular LCD patterns have been widely promoted through the media for weight loss and improving cardiometabolic health, such as Keto, Atkins, South Beach, Zone, and Paleo diets, with carbohydrates being replaced with protein and/or fat intakes (7,67–70) (**Figure 1**).

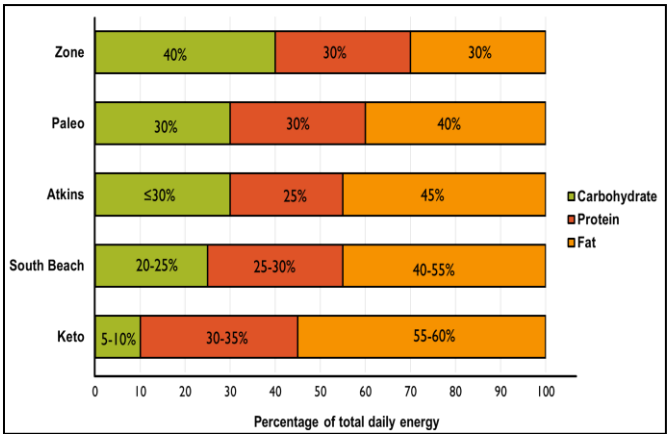

Figure 1. Macronutrients ratios for popular LCD patterns

While all LCD patterns include a reduction in the overall intake of carbohydrates, there is no clear consensus on the definition of an LCD. The definition is typically based on the percentage of total daily energy from carbohydrates and/or absolute carbohydrate

intake, but as seen in **Figure 1**, the upper range of carbohydrate intake can vary widely. For reference, the Acceptable Macronutrient Distribution Range for carbohydrate is 45% to 65% of calories from carbohydrates (8). In observational (19,34–39,55,56) and human intervention (9,11,57–66) studies, different degrees of carbohydrate restriction have been reported. For our summary of RCTs, we will classify LCDs as follows(9,11,51,52):

(1) Very low carbohydrate diet or ketogenic diet: < 10% of total daily energy (% EI) from carbohydrates or (20-50 gm/d for a reference 2000 kcal diet).

(2) Low carbohydrate diets: 10-25 % EI from carbohydrates or (50-125 gm/d for a reference for a reference 2000 kcal diet).

(3) Moderate-low carbohydrate diet: 26-44 %EI from carbohydrates or (126- 220 gm/d for a reference 2000 kcal diet).

In observational studies, LCD diet patterns were examined using two methods (1) LCDSs and/or (2) substitution method of total carbohydrate intake presented as gm/d or %EI with other macronutrients. Most of these studies compared lower intake of carbohydrates represented by the lowest category of the LCDSs or total carbohydrate intake with the highest category of carbohydrate intake. Using this approach, participants in the lowest category of LCDS or total carbohydrate intake are classified as consuming an LCD pattern. However, given that LCDs are not commonly consumed for extended periods of time in the general population, not all participants in the lowest LCD categories will meet the LCD definitions applied for RCTs and some may exceed 45 EI% for carbohydrate, which is the lower border of Acceptable Macronutrients Distribution Range.

Prospective cohort studies of the associations between LCDSs or lower total carbohydrate intake and cardiometabolic risk

While no prospective cohort studies have examined the association between LCD patterns and cardiometabolic risk factors, 17 prospective cohort studies examined the relationships between LCD patterns represented as LCDSs and different health outcomes including risk of CVD, T2D and all-cause and cause-specific mortality in adults (34–36,38–40,56–65). Halton and colleagues created an overall LCDS, capturing diets low in

total carbohydrates and high in total protein and fat, and applied this score to examine the association of LCD patterns on the risk of coronary heart disease (CHD) in one study and T2D in another study (35,66). Both studies used 20 years of follow-up data from 85,000 women in the Nurse's Health Study (NHS). Findings from these two studies showed no significant association between the overall LCDS and CHD or T2D. Plant- and animal-based LCDSs were also used in these studies, capturing diets low in total carbohydrates and high in plant protein and fat and diets low in total carbohydrates and high in animal protein and fat, respectively. While no significant associations were found between the animal-based LCD pattern and risk of CHD or T2D, there were significant inverse associations between plant-based LCDS and CHD and T2D risk. However, the nature of the plant-based LCDS may have resulted in confounding by overall diet and carbohydrates quality, as the study participants who consumed greater amounts of plant protein and fats in place of carbohydrates would likely have higher intakes of healthy plant-based oils and other nutrients found in plant foods, including fiber, in this LCD diet pattern.

Ten other prospective cohort studies adapted the LCDSs developed by Halton and colleagues (35) to examine the association between LCD patterns and T2D (36,38), arterial fibrillation (37), all-cause and cause-specific mortality in different populations (39,40,53,54,59,60,62). Evidence from these studies was inconsistent regarding the association between overall LCDS and cardiometabolic diseases or mortality outcomes. Two studies failed to show a significant association between overall LCDS and CVD mortality and/ or all-cause mortality (39,65), and the remainder suggested significant protective (38,40,56) or harmful associations between the overall LCDS and outcomes (36,62,63). Consistent beneficial associations were observed between plant-based LCD pattern and outcomes while consistent adverse associations were observed between animal-based LCD pattern and health outcomes. However, the association between LCD patterns and health outcomes cannot clearly be attributed to the lower carbohydrate in these studies because of the possible confounding by the sources of protein (i.e., animal vs. plant) and types of fats consumed in place of carbohydrates.

Five of the prospective cohort studies (58–61,68), which have explored the impact of long-term adherence to LCD patterns, have focused only on higher protein intake in

compensation of lower energy intake from carbohydrates, since many of popular LCD patterns encourage high protein intake, given the concern in Western countries that high fat diets should be avoided. A higher low carbohydrates/high protein diet score, reflecting higher adherence to a low carbohydrates/high protein diet, animal sources than among those whose protein consumption was significantly associated with higher CVD mortality in three studies (59,60,68) and total mortality in one study(60), while unrelated to mortality in another study (61). One limitation of these four studies was the lack of consideration of the protein sources. This confounding by protein sources was addressed in a subsequent study performed by Lagiou et al., that examined the association between low carbohydrates/high protein diet score and the incidence of CVDs and observed a positive association among participants, whose protein consumption was derived mainly from animal sources than among those whose protein consumption was mainly from plant sources (58) . However, this study did not capture the quality of carbohydrates remaining in the diet that may be differentially associated with CVDs.

Only two of the prospective observational study assessed carbohydrates quality in the association between LCDSs and mortality (39,40). In these studies, healthy and unhealthy LCDSs were created, where a higher healthy LCDS indicates lower intake of low-quality carbohydrates, and higher intakes of plant protein and unsaturated fatty acids, while the higher unhealthy LCDS indicates lower intake of high-quality carbohydrates, and higher intakes of animal protein and saturated fatty acids. Findings from these studies suggested a positive association between unhealthy LCD and mortality, and an inverse association between healthy LCD and mortality. While these scores are good markers of unhealthy and healthy diets, it is unclear what role the carbohydrates quality played in these association independent of the overall diet quality, and sources of dietary fat and protein.

Ten prospective cohort studies investigated the role of total carbohydrate intake as grams or %EI per day in relation to cardiometabolic disease (34,37,58,69–72) and CVD mortality (59,61,70). All observational analyses of carbohydrate intake that account for total energy involve macronutrient substitution, which traditionally have been referred to as substitution analysis below. In these studies, carbohydrate intake was substituted with

either a specific macronutrient (i.e., fat, protein, or alcohol) (37,58,59,66,71) or a non-specified mixture of macronutrients (59,61,69).

Non-specific substitution analysis:

Four studies have explored the association between carbohydrate quantity and CVD or CVD mortality by substituting total carbohydrates with a mixture of fat and protein in their analyses (59,61,69). Ho and colleagues found that those with lower carbohydrate intake had a lower risk of CVD when carbohydrate intake was substituted with a non-specified combination of fat and protein (69). In the other three studies, substitution of carbohydrates with a combination of fat and protein was not significantly associated with CVD mortality (59,61).

Specific substitution analysis:

Five studies substituted total carbohydrates for a specific macronutrient either protein, fat, or alcohol when examined the association between total carbohydrate intake and CVD, T2D, or CVD mortality (34,58,59,71). In one study, carbohydrates were substituted for fat, and they found a direct relationship between higher carbohydrate intake and increased risk of T2D (66). In other three studies, carbohydrate intake was substituted for protein instead of fat. Two of them observed that higher total carbohydrate intake was associated with increased risk of CVD (58), hemorrhagic stroke (71), while no significant association with CVD mortality in one study (59). Another study by Zhang et al. observed that people with a lower carbohydrate intake had a higher risk of incident atrial fibrillation (64). However, one limitation of this study was the substitution of carbohydrates with alcohol as total energy, protein, and fat, but not alcohol, were adjusted for in the statistical models. Increased alcohol consumption may contribute to high blood pressure (70), which may explain the increased risk of atrial fibrillation in this study.

Cross-sectional studies of the associations between LCDSs or lower total carbohydrate intake and cardiometabolic risk factors

Several cross-sectional studies examined the association between LCDSs or lower total carbohydrate intake and cardiometabolic risk factors in free-living adults (19,21–

23,25,33,73–75). The associations between LCDSs with total cholesterol, triglyceride, and lipoproteins were examined in seven studies (19,21–23,25,75,76). One study showed positive associations between higher overall LCDS and higher blood concentrations of HDL, LDL and total cholesterol, and triglyceride (23), where carbohydrate restriction was combined with higher fat, especially saturated fat and reduced fiber intake. Two other studies observed a positive association between both animal and plant LCDSs and higher HDL cholesterol concentration (21,75). Mixed results were reported between LCD patterns and insulin resistance or impaired fasting glucose (22,23,75). Two studies observed positive association between LCD patterns and insulin resistance, as determined by elevated insulin and blood glucose concentrations (22,23), where higher LCDSs were lower in total fiber and whole grain and/or higher in saturated to polyunsaturated fatty acids ratio, while another study observed negative association between LCDS and impaired fasting glucose (75). There was no evidence from the cross-sectional studies of associations between LCDS and risk of hypertension (19,21,22,76) or body weight or waist circumference or lower body mass index (BMI) or visceral fat level (19,21,22,25,74,76). Limited evidence suggests an association between LCDS and systematic inflammation as determined by lower galectin-3 and interleukin-1β concentrations (24), where higher a LCDS was characterized by lower refined grains intake and glycemic load and higher omega-3 to omega-6 polyunsaturated fatty acids ratio, monounsaturated fatty acids, fiber, and vegetable protein intake.

Nine cross-sectional studies have examined the association between total carbohydrate intake presented as gm/d or %EI and cardiometabolic risk factors (20,23,26,27,29–32,77). Consistent evidence suggested a significant association between higher total carbohydrate consumption and reduced HDL cholesterol concentration (26,27,29–31) . On the other hand, mixed results were observed regarding the association between total carbohydrate intake and weight as determined by BMI and/or waist circumference (20,29,31), concentrations of triglyceride (20,23,26,27,29–31), total (20,23,26,27,29–31) and LDL cholesterol (20,23,26,29,31), glucose (20,27,29–31)and insulin (23,29). These different findings may be due to the variation in carbohydrate quality in these studies and/ or the small sample size in many studies. There is limited evidence suggesting an association between higher intake of carbohydrates and greater

risk of T2D (31), metabolic syndrome (27,30), and hypertension (27); however, other studies have not confirmed these observations (20,31,77). Only one of these studies evaluated the association between total carbohydrate intake and hs-CRP, a marker of systemic inflammation, and no significant association was found (20).

Summary and limitations of previous observational studies

Many prospective cohort and cross-sectional studies examined the association between LCDSs or lower total carbohydrate intake and health outcomes, including risk of CVD, T2D, CVD mortality and all-cause mortality in adults. Evidence from prospective cohort studies linking higher plant-based LCDS, representing an LCD pattern lower in total carbohydrate intake and higher intake of protein and fat from plant sources, with lower risk of cardiometabolic diseases and mortality is fairly consistent. Likewise, prospective cohort studies that considered animal-based LCDS, representing an LCD pattern lower in total carbohydrate intake and higher intake of protein and fat from animal sources, consistently demonstrated that a higher LCDS was associated with higher risk of these health outcomes. However, these LCD patterns do not allow us to determine the specific role of carbohydrate or carbohydrate quality in modulating risk due to confounding by macronutrient and overall diet quality introduced in these scores.

Prospective evidence linking overall LCDS, reflecting an LCD pattern lower in total carbohydrate intake and higher in total fat and protein intake, and diet patterns where carbohydrate intake was substituted with fat, protein or alcohol or non-specified mixture of macronutrients are mixed. Only two prospective cohort studies assessed carbohydrate quality in the association between LCDSs and mortality. In these studies, healthy LCDSs, reflecting an LCD pattern lower in low-quality carbohydrate intake, and higher intakes of plant protein and unsaturated fatty acids, were inversely associated with mortality, and unhealthy LCDSs, reflecting an LCD pattern lower in high-quality carbohydrate intake, and higher intakes of animal protein and saturated fatty acids, were inversely associated with mortality. As with the LCDS evidence described above, the specific association between carbohydrate quality and mortality cannot be established because of the confounding inherent in the scores.

Evidence from cross-sectional studies reported consistent favorable association between lower LCDS and lower intake of total carbohydrates and HDL cholesterol concentration. On the other hand, they reported mixed results relating lower LCDS and lower intake of total carbohydrates and other cardiometabolic risk factors including, blood pressure, waist circumference, blood lipid profile, blood glucose and insulin concentrations.

In addition to the inherent confounding by diet quality in most of the LCDSs used in these studies, other limitations of studies both examining LCDSs and total carbohydrate intake include inadequate assessment of diet, such as using a single dietary assessment; cross-sectional design or short follow-up time for the cardiometabolic diseases outcomes, raising the concern of reverse causality; and small sample size of many of the cross-sectional studies.

Intervention Studies

The effect of LCD patterns on cardiometabolic risk factors has been examined in many RCTs ranging from few days to 24 months, and conducted on healthy adults, people with one or more metabolic syndrome risk factors and people with T2D. Below we summarized evidence from systematic reviews and meta-analyses of these RCTs (9–12,78–86) based on cardiometabolic risk markers and the degree of carbohydrate restriction. The classification of LCD based on the degree of carbohydrates restriction is as follows: (1) Low-Moderate Carbohydrate Diets (26-44 %EI); (2) Low Carbohydrates Diets (10-25 %EI); (3) Very Low-Carbohydrate Diet or ketogenic diet (<10 EI% or 20-50 g/d).

Body weight: Studies based on all degrees of LCD restriction have consistently resulted in greater weight loss compared to moderate carbohydrate diet (45-55 EI%) or high- carbohydrates/ low fat diets at 6 months, especially when diets were hypocaloric (9,10,83). However, results from longer-term RCTs (> 6 months to 2 years) are equivocal, with some studies reporting that weight reduction in LCDs is equivalent to that for higher carbohydrate content diets (9,83,84), partly because ketogenic diets were difficult to maintain for longer periods, while others reported a greater weight reduction in LCDs compared to higher carbohydrate diet groups (11,12,78,81,82).

Blood lipids: Compared to higher carbohydrate diets, all LCDs groups result in increases in total and LDL cholesterol concentrations with more pronounced increases in the very-low-carbohydrate diets (10–12,78,83). The low total carbohydrate intake in these studies was accompanied by high saturated fatty acids or low fiber intakes, which are key determinants of total and LDL cholesterol concentrations. Meta-analyses of RCTs with interventions up to 2 years consistently reported that HDL cholesterol concentration was significantly higher after LCD interventions compared to higher carbohydrate diet groups (9–12,78,79,81–83). Triglyceride concentrations were significantly lower in all LCDs groups compared to diet with higher carbohydrate contents (10–12,78,81–83). The studies that showed beneficial effects on triglyceride concentration also reported a higher in polyunsaturated fatty acid consumption. Evidence from these RCTs suggests that LCD may help improve blood HDL cholesterol and triglyceride concentrations independent of weight loss, based on studies that showed improvements in blood lipids during weight loss maintenance periods and studies that showed improvements in blood lipids with no significant difference in weight loss between the lower and higher carbohydrate diet interventions (87–95).

Glucose, hemoglobin A1c and insulin: There were no significant effects of any of the LCDs groups for fasting glucose, insulin and hemoglobin A1c (HbA1c) compared to higher carbohydrate content diets for people without T2D, although there were trends in favor of the low and very low carbohydrates diets for these outcomes (9). For those with T2D, there were no significant differences in blood glucose and insulin concentrations between any of the LCDs and higher carbohydrate diet groups (9,11,80). However, Low and very-low carbohydrate diets resulted in a greater reduction in HbA1c vs. moderate or high carbohydrates/ low fat diet in short-term studies ($\leq$ 6 months) (79,84–86). Evidence from these RCTs suggests that LCD may have more favorable effect on HbA1c than higher carbohydrate diets with similar weight reduction in people with T2D (93,96–98). At $\geq$ 6 months HbA1c was similar between the LCD and higher carbohydrate diet groups, except in one meta- analysis (86). Hintress et al., reported a significantly decreased HbA1c in the LCD group at one year (86). Although there were no significant differences

in HbA1c responses between LCDs and higher carbohydrate diets in most meta-analyses of RCTs at ≥ 6 months, LCDs resulted in a greater reduction in the use of diabetes medications compared to higher carbohydrate diets (9).

Blood Pressure: Conflicting results were reported regarding the effect of LCD diets blood pressure compared to higher carbohydrate diets(9). One meta-analysis concluded there was no significant difference in systolic blood pressure but found a significantly lower diastolic blood pressure for a very low carbohydrate diet compared to a high carbohydrate/low-fat diet (78). Other meta-analyses reported no significant difference between diet groups for either systolic or diastolic blood pressure (81,82,84).

Inflammation: The few systematic reviews and meta-analyses that examined the effect of LCDs on systemic inflammation reported no significant difference between very low carbohydrate diet and high carbohydrate/ low fat diets. However, in some cases, trends in favor of very low-carbohydrate diets for CRP were reported (78–80). Of two RCTs that examined the effect of a moderate low-carbohydrate diet on circulating inflammatory biomarkers, one observed no significant effect compared to a moderate carbohydrate diet (99), while a second study reported significant increases in adiponectin and decreases in intercellular adhesion molecule-1 concentrations compared to a high-carbohydrate/ low-fat diet (16).

In summary, adherence to an LCD resulted in greater weight loss and decrease in HbA1c concentration compared to higher carbohydrate diets in shorter-term studies ≤6 months. It also resulted in increases in HDL cholesterol, and decreases in triglyceride concentrations and diastolic blood pressure that were maintained beyond 6 months. These favorable effects on cardiometabolic risk factors may be independent of weight loss based on RCTs that showed improvements in cardiometabolic risk factors with similar weight reduction in LCDs and higher carbohydrate diets. Also, a greater increase in total and LDL cholesterol concentrations was observed in LCDs compared to high carbohydrate/ low fat diets. These increases could be attributed to lower fiber intakes, as well as the higher saturated fatty acid intakes that often accompany carbohydrate restriction. The mixed results regarding the cardiometabolic health effects of LCDs may

be due to limitations of these studies. One limitation is that the food sources of carbohydrates, glycemic index, and glycemic load of the intervention diets were not clearly described making it difficult to clearly interpret the findings. Additionally, the short duration of these studies does not provide insight into the long-term effect of LCDs.

1.3.2 Carbohydrate Quality and Cardiometabolic Risk

In the past couple of decades, interest has shifted from carbohydrates quantity to carbohydrate quality to obtain better cardiometabolic health. The current 2020-2025 Dietary Guidelines for Americans recommended limiting energy intake from added sugar to no more than 10% and consuming at least half of all grains as whole grains (100). According to data from National Health and Nutrition Examination Survey (NHANES) from 1999-2016, there have been modest, beneficial changes in the carbohydrate quality of American adults (101). Intake of low-quality carbohydrates sources decreased significantly from 45.1% to 41.8% of total energy, including a significant decline in added sugar from 16.4% to 14.4% of total energy, whereas that from high-quality carbohydrates increased modestly but significantly from 7.4% to 8.6% of total energy including a significant, but modest, increase in whole grain intake from 2% to 2.6% of total energy. However, these intakes of high- and low-quality carbohydrates are still not on par with recommendations, making this a public health concern (101).

Different dimensions and measures have been used to assess carbohydrates quality, including glycemic index, glycemic load, whole grains, total fiber intake, cereal fiber or added sugars and carbohydrate quality ratios such as ratio of carbohydrates to total fiber and ratio of carbohydrates to cereal fiber (45,102). Carbohydrates quality has been shown to be more strongly associated with CVD and T2D risk than total carbohydrate intake. For instance, while evidence of association between total carbohydrate consumption and risk of CHD was inconsistent (103), several studies on CVD risk have shown inverse association with carbohydrate sources or subtypes such as whole grains and dietary fibers (49,104–106), and positive associations with sugar-sweetened beverages and refined grains (44,107).

Several potential mechanisms explain how carbohydrate quality is associated with cardiometabolic risk. Diet patterns rich in dietary fiber have been shown to improve

glucose and insulin responses, increase satiety and reduce overall energy intake through slower digestion and absorptions of the dietary fiber (108). Soluble, viscous fiber, such as beta-glucan in whole grain oats have beneficial effects on blood lipids (109). Further, dietary fiber fermentation by the gut microbiota produces short-chain fatty acids that affect lipid and glucose metabolism and enhance satiety through the production of peripheral peptide tyrosine–tyrosine and glucagon-like peptide-1(110). In contrast, low-quality carbohydrates such as refined grains and added sugars result in more rapid and higher increase in blood glucose concentration (111). The low-quality carbohydrate food sources can also alter lipoprotein secretion and clearance, resulting in higher fasting triglyceride concentration (112,113). Moreover, the refining process of carbohydrates removes various essential nutrients, such as B vitamins, vitamin E, vitamin K, folate and minerals like magnesium, iron, potassium, calcium, and selenium present in whole grains (114). Although refined grains are federally mandated to have certain nutrients added back (thiamin, riboflavin, niacin, folate, and iron), refined grain products still lack essential nutrients like vitamin E, vitamin B6, magnesium, fiber, and potassium. As a result, they are unable to provide the same potential health advantages as whole grains, such as improved glucose metabolism, reduced inflammation, or lower blood pressure (115–117).

1.3.3 Gaps in the literature

There are two major gaps in the existing knowledge on the role of LCD patterns in modulating cardiometabolic risk factors. First, there are no prior long-term (> 2 years) studies that have examined the association between LCD patterns and intermediate risk factors for cardiometabolic disease. Second, no previous study has investigated the direct impact of carbohydrate quality in LCD patterns in relation to cardiometabolic risk factors. My thesis research aims to address both of these gaps and provide insight into the impact of carbohydrate quality in LCDs.

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Chapter 2. Impact of Carbohydrate Quality on the Association between Low-Carbohydrate Diet Scores and Longitudinal Changes of Cardiometabolic Risk Factors

Impact of Carbohydrate Quality on the Association between Low-Carbohydrate Diet Scores and Longitudinal Changes of Cardiometabolic Risk Factors

Ghaida F. Aloraini,[1,2] Nicola M. McKeown,[3] Gail T. Rogers,[1] Sai Krupa Das,[1,2] Alice H. Lichtenstein,[1,2] Paul F. Jacques[1,2]

Affiliations:

[1] USDA Human Nutrition Research Center on Aging, Tufts University, Boston MA

[2] Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA

[3] Sargent College, Boston University, Boston, MA

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Corresponding author:
Paul F Jacques
Jean Mayer USDA Human Nutrition Research Center at Tufts University
711 Washington Street
Boston, MA 02111
Email: paul.jacques@tufts.edu

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Abbreviations:

List of abbreviations and their definitions for all non-standard abbreviations

CMRF	cardiometabolic risk factor
DBP	Diastolic blood pressure
FHS	Framingham Heart Study
FOS	Framingham Offspring Study
HQ-LCDS	High-quality low-carbohydrate diet score
LCD	Low-carbohydrate diet
LCDS	Low-carbohydrate diet score
LQ-LCDS	Low-quality low-carbohydrate diet score
MET	Metabolic equivalent of task
PAI	Physical activity index
RCT	Randomized controlled trial
SBP	Systolic blood pressure
T-LCDS	Total low-carbohydrate diet score
WC	Waist circumference
%EI	Percentage of total daily energy

2.1 Abstract

(294 words)

Background: While low-carbohydrate diet (LCD) patterns have been promoted to improve cardiometabolic risk factors, evidence from long-term studies on the impact of carbohydrate quality in these diets remains equivocal.

Objective: To examine long-term associations among LCD patterns varying in carbohydrate quality and changes in cardiometabolic risk factors (waist circumference, fasting HDL and non-HDL cholesterol, triglyceride and glucose concentrations, and blood pressure).

Methods: Dietary intakes, health status and lifestyle data were collected in Framingham Offspring cohort participants (n=3294) approximately every 4 years over a median 16.4-year period. We assessed LCD patterns accounting for quality of carbohydrate sources using 2 LCD scores (LCDSs) reflecting higher intake of total fat and protein, and lower intake of (i) low-quality carbohydrate (high-quality LCDS, HQ-LCDS) and (ii) high-quality carbohydrate (low-quality LCDS, LQ-LCDS). Repeated measures regression analyses were used to examine associations between LCDSs and annualized change in cardiometabolic risk factors.

Results: Baseline median age was 55 years and 54% of participants were female. Annual gains in waist circumference (cm/y) increased across quintile categories (mean for Quintile 1, Quintile 5; P_{trend}) for HQ-LCDS (0.58, 0.69; 0.003), and LQ-LCDS (0.57, 0.74; <0.001). A slower annual increase in systolic blood pressure (mmHg/y) was observed across quintile categories for HQ-LCDS (0.16, 0.01; 0.03), and LQ-LCDS (0.21, -0.05; 0.01). Higher HQ-LCDS was associated with a greater annual increase in HDL cholesterol concentrations (mg/dL/y) (0.51, 0.67; 0.006) and greater annual decline in triglyceride concentrations (mg/dL/y) (-1.24, -2.01; <0.001). Higher LQ-LCDS was associated with a greater annual increase in glucose concentrations (mg/dL/y) (0.35, 0.48; 0.05).

Conclusions: Although both high- and low-quality LCD patterns were associated with greater increases in waist circumference, our overall findings support recommendations

on preserving high-quality carbohydrate in the context of a lower carbohydrate diet and replacing low-quality carbohydrate with more healthy energy sources.

Keywords: low-carbohydrate diet, carbohydrate quality, cardiovascular disease, waist circumference, fasting glucose, blood lipids, blood pressure, prospective cohort study.

2.2 Introduction

Significant advances have been made in preventing and treating cardiometabolic disorders; however, they remain the leading cause of death and disability in the United States, particularly in older adults (1). Cardiometabolic risk factors (CMRFs) such as elevated blood pressure and fasting glucose concentrations, dyslipidemia, and central adiposity are early warning signs of cardiovascular disease (CVD), and type 2 diabetes (2,3). In the United States, about 47 million people are living with one or more CMRFs (2), which highlights a need for interventions that focus on tackling these modifiable risk factors to reduce the burden of cardiometabolic disorders.

In this regard, low carbohydrate diet (LCD) patterns that favor relatively high intakes of fat and/or protein have received considerable interest in recent decades because of their potential beneficial effects on cardiometabolic health. Randomized controlled trials (RCTs) ranging from few days to 24 months reported such diets promoted weight loss (4–7) and improve CMRFs, including hyperglycemia and insulin resistance (8–10), dyslipidemia (4,5), hypertension (6,7), and systemic inflammation (11,12). Whether these improvements in CMRFs are primarily dependent on weight reduction or balance of macronutrients has yet to be determined. Although evidence from RCTs is promising, it is limited by the relatively short follow-up period, and thus offers little understanding of the long-term effects of LCD patterns. Additionally, the effect of the quality of the restricted carbohydrate and types of fat and/or protein consumed in their place is unclear. While no prior prospective cohort studies examined the association between lower carbohydrate intakes and CMRFs, evidence relating lower carbohydrate intakes to type 2 diabetes, CVD and mortality remains equivocal (13–17). The inconsistency may arise, in part, from the many variations in the macronutrient composition of LCD patterns and differences in overall diet quality, the nature of the diet pattern (i.e., plant-based versus animal-based diet), and the quality of carbohydrate remaining in the diet. Lower-quality carbohydrate diets, characterized by higher intakes of refined grains, sweet-baked desserts, and added sugars, have been linked to adverse long-term cardiometabolic health and incidence of CVD and type 2 diabetes (18–24). In contrast, high-quality carbohydrate diets, characterized by higher intakes of whole grains, non-starchy vegetables, whole fruits, nuts and legumes, and correspondingly higher dietary fiber, have

been favorably associated with health outcomes (18–22,25–27). Because of the differential health impacts of high- and low-quality carbohydrate sources, it is particularly important to consider carbohydrate quality when the absolute intake of carbohydrate is restricted.

Most of the previous observational studies that examined LCD patterns used dietary scores to simultaneously consider the lower intakes of carbohydrates and higher intakes of fat and/or protein as an overall diet. Halton et al., (13) created a simple summary score called the "low-carbohydrates diet score" (LCDS) to classify participants according to their relative amounts of dietary fat, protein, and carbohydrate. The highest score represents the highest intake of fat and protein and the lowest intake of carbohydrates, whereas the lowest score, represents the lowest intake of fat and protein and the highest intake of carbohydrate. Modified versions of the LCDS were subsequently created to capture different sources of protein and fat, and the quality of carbohydrates (14,28,29). However, none of the previous LCDSs consider the carbohydrates quality in LCD patterns, independent of types and sources of protein and fat.

To examine importance of carbohydrate quality in the relationship between LCD patterns and CMRFs, independent of sources of fat and protein, we used data from the Framingham Heart Study (FHS) to create two new LCDSs that represent lower intakes of either high-quality carbohydrates or low-quality carbohydrates, and higher intakes of total fat and protein. These scores were then used to determine their associations with changes in CMRFs, including waist circumference (WC), fasting HDL and non-HDL cholesterol, triglyceride and glucose concentrations, and systolic and diastolic blood pressures, during a median period of 16.4 years. We hypothesized that an LCDS that represents maintenance of high-quality carbohydrates in a lower carbohydrate diet is associated with more favorable measures of cardiometabolic health than an LCDS representing a pattern with lower intake of high-quality carbohydrates.

2.3 Methods

Study population:

This prospective cohort study is based on data collected from the FHS Offspring cohort. The FHS is a longitudinal, community-based observational study, that began in 1948, with the aim of exploring the risk factors associated with cardiovascular disease in residents of Framingham, Massachusetts (30). In 1971, the FHS recruited 5,124 offspring of the original cohort into the Framingham Offspring Study (FOS). Approximately every 4 years, this cohort completes a series of questionnaires, and undergo standardized medical examinations, including physical examination and laboratory tests (31).

Dietary intake assessment began at the FOS fifth study exam (1991-1995). This study used data from the FOS 5th, 6th (1995 – 1998), 7th (1998–2001), 8th (2005–2008), and 9th exam (2011-2014) study examinations cycles. We defined the baseline exam as the first exam at which a participant had available data on dietary intake and covariates, with available data on CMRFs at that exam and a consecutive exam. We included subjects who attended at least 2 consecutive exams between the 5th and 9th exams and were free of diabetes at baseline (n=3,294). Of these participants, the 5th exam was baseline for 2,846, the 6th exam for 232, the 7th exam for 164, and the 8th exam for 52 **(Figure 1)**. The participants included in the final analyses contributed 10,047 observations based on exam intervals. The Institutional Review Board for Human Research at Boston University Medical Center approved all the FHS procedures and protocols. All participants provided written informed consent before study participation. The current project was reviewed and approved by the Tufts Health Sciences Institutional Review Board.

Dietary Assessment:

Dietary intakes were assessed using the Harvard semi-quantitative food frequency questionnaire (FFQ), designed to capture the habitual dietary intake over the past 12 months (32). The FFQs were mailed to the participants who were given instructions to complete them at home, and to bring them to their study exam appointment. Two different versions of FFQ were used to assess dietary intake in FHS. The first FFQ consists of a list of 126 items and was used in exams 5 through 8. This FFQ was then

modified and expanded to a list of 150 items in exam 9 of the FOS. The food list include standard serving sizes and a selection of nine frequency categories ranging from "never, or < 1 serving/ month" to "≥ 6 servings/day" (32). Dietary information was considered valid if reported energy intakes were >600 kcal/day for both men and women; < 4,000 kcal/day for women; and <4,200 kcal/day for men; and if ≥14 food items were left blank. Daily nutrient and energy intakes were calculated by multiplying the frequency of intake of each food item by the nutrient and energy content and summing across all food items. The reproducibility and validity of the FFQ has been evaluated for nutrients intakes for both men (32) and women (33) in other cohorts. The correlation coefficients between FFQ and multiple diet records for women and men, respectively, are 0.61 and 0.73 for total carbohydrate, 0.52 and 0.44 for protein, 0.54 and 0.67 for total fat. Additionally, the correlation coefficients are 0.68 for dietary fiber in men (32) and 0.56 for crude fiber in women(33).

We created two new LCDSs to examine LCD patterns while considering carbohydrate quality in these diets and maintaining the same fat and protein intakes to limit confounding by sources of fat and protein. Our scores are modified versions of the original Total LCDS (T-LCDS) developed by Halton and colleagues (13). Briefly, the T-LCDS was created using estimates of total carbohydrate, total fat, and total protein intakes. To calculate the score, the participants' intakes of each macronutrient, expressed as a percentage of energy intake, were divided into 11 approximately equal-sized categories. Participants with intakes in the lowest carbohydrate category were assigned a carbohydrate score of 10, while those in the highest category were assigned a score of 0. The scoring is the opposite for the protein and fat, with those in the highest category of intakes being assigned scores of 10 and those in the lowest category assigned scores of 0. The scores for each macronutrient were summed for a total score. A higher T-LCDS reflects participants who had a lower energy intake from total carbohydrates and higher energy intakes from total fat and total protein, with a range of 0 to 30.

In our scores, we accounted for intake from either high or low carbohydrate quality sources rather than scoring carbohydrate as a total. To assess the carbohydrate quality of all carbohydrate-containing foods in the FFQ, we applied a validated metric 10:1

carbohydrate: fiber ratio, defined as at least 1 gram of fiber per 10 grams of carbohydrate, with values ≤ 10 indicating high-quality carbohydrate sources (34). In creating the high-quality LCDS (HQ-LCDS), the percent energy intake from low-quality carbohydrates were scored, and participants with intakes in the lowest category of low-quality carbohydrate (2.8 – 24.4 %EI) were assigned a score of 10, while those in the highest category (44.4 – 78.2 %EI) were assigned a score of 0 **(Supplemental Table 1)**. A higher HQ-LCDS represents a diet pattern where individuals consume less low-quality carbohydrate and more fat and protein. For the low-quality LCDS (LQ-LCDS), high-quality carbohydrates were scored, and participants with intakes in the lowest category of high-quality carbohydrate (0.7 – 6.3 %EI) were assigned a score of 10 while those in the highest category (23.6 – 56.1 %EI) were assigned a score of 0. A higher LQ-LCDS represents a diet pattern where individuals consume less high-quality carbohydrate and more fat and protein.

Cardiometabolic Risk factors:

Cardiometabolic risk factors measured at the 5th through 9th examination cycles were included in these analyses: WC (cm); fasting HDL and non-HDL cholesterol, triglyceride, and glucose (mg/dL) concentrations; and systolic (SBP) and diastolic blood pressure (DBP) (mm Hg). WC was measured at the level of the umbilicus with the participant standing. Fasting blood samples (≥ 8 hours) were obtained. Plasma HDL cholesterol and triglyceride concentrations were measured using enzymatic/colorimetric procedures (Roche Cobas Analyzer c501, Roche Diagnostics). Non-HDL cholesterol concentrations were calculated as total cholesterol minus HDL cholesterol concentrations. Serum glucose concentration was measured using a hexokinase reagent kit (A-Gent glucose test; Abbot). Blood pressure was measured as an average of two readings for each participant in a sitting position after 5-minutes of rest using a random-zero sphygmomanometer. Because the time interval between exams differed between participants, we characterized changes in our outcomes as annualized changes by dividing the absolute change by the number of years between exams.

For outliers, we first excluded biologically implausible values. Next, we applied a Winsorization approach to outliers for the biologically plausible data by setting them to a

value of 0.5 above the 99th percentile + (3 x interquartile range), or 0.5 below the 1st percentile – (3 x interquartile range). Finally, we excluded observations with studentized residual that are beyond ± 3. Final sample size varied by outcome [WC, *n*= 3,251 (9,713 observations), HDL cholesterol, *n* = 3,223 (9,490); non-HDL cholesterol, *n*= 3,227 (9,493); triglyceride, *n* = 3,228 (9,469); glucose, *n*= 3,211 (9,426); SBP, *n*= 3,290 (10,020); and DBP, *n*= 3,294 (10,047)].

Covariates:

Potential confounders of the association between LCD patterns and cardiometabolic risk factors were considered as covariates in our analyses. These include age (years); sex (female, male); body mass index (BMI) (kg/m^2); menopausal status (menstruation ceased >1 year); lifestyle factors including current smoking status (smoking regularly within the year before the exam: yes, no), physical activity [measured by a physical activity index (PAI), a score based on the sum of sedentary, slight, moderate and vigorous activity expressed as metabolic equivalent of task (MET-hrs/d)] (35), alcohol intake (%energy/d), total energy intake (kcal/d); and pharmacological treatment (yes/no) for hypertension, dyslipidemia and hyperglycemia. In addition to adjustment for sex, we included age at the beginning of each exam interval and all other time varying covariates as an average over each exam interval. To minimize missing covariate data in our analyses, we imputed the following covariates: height, BMI and PAI. Height was imputed by bringing forward values from the previous exam, if previous exam value was not available, we brought backward values from the following exam. Missing BMI data was calculated by using the available weight and imputed height data. PAI was imputed by determining the median PAI score of the sample who had available PAI data, stratified by age, sex, BMI and perceived health status, and applying these medians to subjects with missing PAI data. Additionally, since PAI was not assessed in exam 6, exam 5 values were carried forward.

Statistical Analyses:

Repeated measures mixed models (SAS PROC MIXED) with unstructured covariance matrix were used to examine the association between the LCDSs and standardized annual changes in CMRFs. The LCDSs were averaged over each exam interval (i.e., an average

of 2 consecutive exams) and categorized using baseline quintile values. A test for linear trend across categories of LCDSs was applied by assigning the median value of LCDSs for each category and treating these as a continuous variable. The statistical model was adjusted for sex, baseline of exam interval, periodic baseline CMRF value and age, and average values of total energy, alcohol intake, physical activity, BMI (except for WC), menopausal status, smoking status and medications for hypertension, dyslipidemia, and hyperglycemia across the exam interval.

All statistical analyses were performed using SAS (version 9.4; SAS institute). All reported P values are 2 sided and statistical significance was set at $P < 0.05$. We did not correct for multiple testing since all the analyses were testing the common hypothesis that an LCDS that represents lower intake of low-quality carbohydrates is associated with more favorable measures of cardiometabolic health than a LCDS represents lower intake of high-quality carbohydrates. We also did not further adjust according to the number of individual outcome measures since these CMRFs are correlated and are considered collectively to increase the risk of CVD.

Secondary/Sensitivity Analyses:

We conducted several secondary analyses. First, we investigated the association between the T-LCDS and annual changes in CMRFs. Second, we assessed interactions between the quintiles of LCDSs with time categories identified by the exam interval, to examine if the patterns of change in the CMRFs across quintile categories of LCDSs differ by exam interval. Additionally, given that the association between LCDSs and CMRFs may depend on the underlying glycemic status of participants, we tested interactions between the quintile categories of LCDSs and impaired serum fasting glucose concentrations (normal: ≤ 99 mg/dL; impaired: ≥ 100 mg/dL). Further, we tested interactions between quintile categories of LCDSs and sex for WC and HDL cholesterol outcomes since sex differences may affect these outcomes. Interactions were evaluated by including cross-product terms in the mixed models and assessing the statistical significance of the interaction term at the 0.05 significance level. When significant interactions were detected, stratified analysis was performed.

We performed two sensitivity analyses to examine the consistency of the associations. First, we adjusted our main models for change in WC, because of the known associations between WC and the other CMRFs. Second, dairy foods, which are perceived to be a healthy source of carbohydrate but did not contain fiber (plain yogurt, skim milk and low-fat and reduced fat milk), did not meet the definition of high-quality carbohydrate sources using 10:1 carbohydrate to fiber ratio metric. Thus, as part of our sensitivity analyses, we included these foods as high-quality carbohydrates instead of low-quality carbohydrates.

2.4 Results

Participants characteristics:

A total of 10,047 observations from 3,294 participants who attended at least 2 consecutive exams were included in the present analysis. The median follow-up time was 16.4 y (interquartile range: 9.3 y, minimum: 1.2, maximum: 23.2). The median (25^{th} -75^{th} percentile) baseline age of participants was 55 y (48 y - 62 y), and 54.2% were females (**Table 1**). Participants, on average, were in the overweight category based on BMI (26.6 kg/m^2) and WC (92.7 cm), moderately physically active, and reported a low prevalence of smoking (18.2%). They had a high prevalence of hypertension (47%). Across increasing quintile categories of both HQ-LCDS and LQ-LCDS, participants were younger, more likely to be females, and less likely to take lipid-lowering medications. Compared to participants in the lowest quintile of LQ-LCDS, those in the highest quintile were more likely to be smokers, have hypertension and poorer diet quality.

The median intakes, expressed as a percent of energy, were 51.2% for total carbohydrate, with 12.4% from high-quality carbohydrate sources and 35.8% from low-quality carbohydrate sources. While approximately 25% of our study population had intakes below the Acceptable Macronutrient Distribution Range for carbohydrates (36), few participants consumed less than 25% of energy from carbohydrates **(Supplemental Figure 1).** Total carbohydrates were ~ 18%EI lower in the highest vs. the lowest quintile categories for both LCDSs. Low-quality carbohydrates were 17.6%EI lower in the highest quintile of HQ-LCDS compared to the lowest quintile, whereas high-quality carbohydrates were 12.5%EI lower in the highest quintile of LQ-LCDS compared to the

lowest quintile **(Table 1)**. The medians of the T-LCDS and LQ-LCDS were similar for women and men, whereas the median HQ-LCDS were higher in women than men **(Supplemental Table 2**). We observed annual increases in the mean WC, SBP, and fasting plasma HDL cholesterol and serum glucose concentrations during the follow-up period, and annual decreases in the mean DBP, non-HDL cholesterol, and triglyceride concentrations during follow-up (**Supplemental Table 3**). Total protein intake increased by 6.2%EI and 4.0%EI across quintiles categories of HQ-LCDS and LQ-LCDS, respectively. Total and saturated fat intake increased by 10.9%EI and 4.1%EI across quintiles categories of HQ-LCDS and 13.4%EI and 5.7%EI across quintiles categories of LQ-LCDS, respectively.

HQ-LCDS:

After adjustment for potential confounding factors, we observed a significant positive association between HQ-LCDS and annual change in WC, as well as a significant inverse association between HQ-LCDS and mean annual change in SBP, **(Table 2)**. Higher HQ-LCDS was also significantly associated with a greater mean annual increase in plasma HDL cholesterol and decrease in triglyceride concentrations. All associations remained statistically significant after further adjustment for change in WC (**Supplemental Table 5**). These associations also remained significant after including dairy foods that are perceived to be healthy but did not contain fiber in the high-quality carbohydrate category instead of low-quality carbohydrate category (**Supplemental Table 7**).

LQ-LCDS:

As with the HQ-LCDS, after accounting for potential confounders, we observed a significant positive association between LQ-LCDS and mean annual increase in WC, as well as a significant inverse association with mean annual increase in SPB **(Table 3)**. The associations with SBP remained significant after further adjustment for change in WC in the main models (**Supplemental Table 6**), and after including low-fat dairy foods in the high-quality carbohydrate category (**Supplemental Table 8**). Adherence to LQ-LCDS was positively associated with mean annual increase in fasting serum glucose concentration, which remained significant after further adjustment for change in WC.

However, this marginally significant association was modestly attenuated after including low-fat dairy foods in the high-quality carbohydrate category in sensitivity analyses suggesting that low-fat dairy, which unlike other high-quality carbohydrate sources, had no fiber, might be differentially related to change in glucose than the other high-quality carbohydrates.

Secondary Analyses:

After adjustment for potential confounders, there was a greater mean annual increase in WC in those in the highest quintile of T-LCDS compared to the lowest quintile, while a slower increase in SBP across quintile categories of T-LCDS with no change in the highest quintile (**Supplemental Table 4**). The association between SBP and T-LCDS remained significant after further adjustment for change in WC.

There were significant interactions between time (exam interval) and HQ-LCDS (P <0.001) and LQ-LCDS (P <0.05) for WC, as well as time and HQ-LCDS (P= 0.003) for fasting glucose concentrations, and time and LQ-LCDS for DBP (P= 0.03) **(Supplemental Table 9)**. After the data were stratified by time, the relationships between the scores and WC were consistent across time strata; those in the highest quintile of the scores had a greater mean increase in WC. The stratified analyses demonstrate the substantial decline in the annual change in WC with advancing age over the follow-up period. In the highest quintile of HQ-LCDS, compared to the lowest quintile, there was a greater mean increase in annual fasting serum glucose concentrations from exam 5 to 6 and exam 7 to 8. For DBP, there was a slower mean decrease from exam 6 to exam 7 in the highest quintile of LQ-LCDS compared to the lowest quintile.

We also observed significant interactions between HQ-LCDS and the presence of impaired fasting glucose in the glucose model (P= 0.008), and between LQ-LCDS and the presence of impaired fasting glucose in the non-HDL cholesterol model (P= 0.02) **(Supplemental Table 10)**. After the data were stratified by the presence of impaired fasting glucose concentration, no significant associations in either stratum were observed for either outcome measures. We also examined the potential effect modification of the HDL cholesterol and WC by sex, but we observed no significant interactions.

2.5 Discussion

In this large community-based, prospective cohort study among U.S. adults, low-carbohydrate diet scores had differential associations with CMRFs based on carbohydrate quality. We observed that a higher HQ-LCDS, representing a lower intake of low-quality carbohydrates with higher fat and protein**,** was associated with favorable changes in HDL cholesterol and triglyceride concentrations, whereas a higher LQ-LCDS, characterized by lower consumption of high-quality carbohydrates and the same higher fats and protein intake distributions as the HQ-LCDS, was associated with adverse changes in serum glucose concentration. Both HQ-LCDS and LQ-LCDS, were associated with a lower increase in SBP over the 23-y observational period (median follow-up of 16.4 y), but an increased annual gain in WC during this period. As far as we are aware, our analysis is the first to consider impact of low carb diets on changes in risk factors while accounting for carbohydrate quality.

Our results showing that both LCDSs were positively associated with a greater annual increase in WC were inconsistent with evidence from previous longer-term RCTs (> 6 months - 2 years). While some RCTs reported that weight reduction in LCDs was equivalent to that for high-carbohydrate/low-fat diets (4,5,37–39), others reported a greater weight reduction in low-carbohydrate diets compared to low-fat diets (40–45). The few RCTs that reported the effect of LCD interventions on abdominal adiposity (46) (47–49), which may be a stronger risk factor than BMI for CVD and metabolic disorders (50–52), demonstrated comparable or greater reductions for hypocaloric LCDs compared with isocaloric low-fat diets. While results of earlier cross-sectional observational studies on lower-carbohydrate diet patterns and WC have been inconsistent (53–57), our study is the first longitudinal study to examine the role of lower-carbohydrate diet patterns and change in WC. The basis of the larger increase in WC associated with higher LCDSs observed in our study is unclear, but our observations are consistent with three previous prospective cohort studies that observed that a higher total fat (58,59) or saturated fat intake (58–60) at the expense of carbohydrates was associated with higher WC (60) or body weight (58,59), even after accounting for cereal fiber, fruit and vegetable intakes in one of these studies (59). We observed that total and saturated fat intake was ≥44% and

50% higher among those in the highest quintile categories of the LCDSs compared to those in the lowest categories. Yet, due to the observational nature of these studies, the effect of the residual confounding cannot be ruled out, particularly by other characteristics of dietary patterns rich in sources of saturated fat.

A higher HQ-LCDS was associated with an increase in plasma HDL cholesterol concentration and a decrease in plasma triglyceride concentration over time. These results were consistent with meta-analyses of RCTs with interventions up to 2 years reporting that LCDs resulted in lower triglyceride and higher HDL cholesterol concentrations compared to low fat/high carbohydrate diet in adults with overweight and obesity (61–63). Evidence from these RCTs suggests that LCDs may help improve blood HDL cholesterol and triglyceride concentrations independent of weight loss, based on studies that showed improvements in blood lipids during weight loss maintenance periods and studies that showed improvements in blood lipids with no significant difference in weight loss between low and higher carbohydrate diet interventions (47,64–71). The lower consumption of low-quality carbohydrate between participants in the highest quintile category of HQ-LCDS compared with those in the lowest quintile category maybe responsible for the improved plasma concentrations of HDL cholesterol and triglyceride as no association with blood lipids was seen for the LQ-LCDS based on a comparable difference in total carbohydrate intake. Evidence from prospective cohort studies have shown that low-quality carbohydrates, such as refined grains and added sugars, are associated with adverse changes in lipoprotein concentrations (21,23,72), incident dyslipidemia (23) and risk of CVD (73,74) and CVD mortality (75,76).

A higher LQ-LCDS was associated with a greater increase in fasting serum glucose over time, perhaps a consequence of the lower fiber contents of the diet as higher dietary fiber intake is established as having beneficial effect on glycemic control (77,78). While previous systematic reviews and meta-analyses of RCTs reported no significant differences for fasting glucose, insulin and hemoglobin A1c (HbA1c) concentrations between lower and higher carbohydrate diet groups among people without type 2 diabetes (4,43,79), LCDs resulted in a greater reduction in HbA1c concentration compared to higher carbohydrate diets in short-term studies ($\leq$ 6 months) among those with type 2

diabetes (4,6,80). Evidence from these RCTs suggests that LCDs may have more favorable effect on HbA1c than higher carbohydrate diets with similar weight reduction in people with type 2 diabetes (81–84). However, none of the previous RCTs have specifically examined carbohydrate quality in the LCD intervention group. Earlier observational studies that examined the association between LCDSs and fasting blood glucose concentrations (54,55,85) or risk of type 2 diabetes reported mixed results (14,15,17), and none of these studies assess the role of carbohydrate quality within LCDSs.

We observed favorable associations between the LCDSs and SBP, independent of carbohydrate quality, but not DBP. While no RCTs have considered the effect of carbohydrate quality in LCDs on blood pressure, systematic reviews of RCTs with durations up to two years examined the impact of LCDs on blood pressure in adults who were overweight or obese with (61) or without (57–59) comorbidities. They reported inconsistent findings, with one showing no significant differences between LCDs and low-fat diets for SBP but a significant decrease in DBP for the low carbohydrate intervention (61), and others reporting no significant difference for either SBP or DBP (62,63,86). No longitudinal observational study examined the association between lower carbohydrate diet patterns and blood pressure, and of the cross-sectional studies (53–56,85,87,88) that examined this association, only one study found that a total carbohydrate intake was associated with a lower DBP (56). The beneficial link between lower carbohydrate diet patterns and blood pressure may be due to the increased protein intake in these diets. Based on observational data (89–95), it has been documented that higher dietary protein intake, especially from plant sources (89,92,95) is inversely associated with blood pressure.

Strengths and Limitations:

The strengths of the present study include the large sample size and prospective design of the FOS cohort with repeated measures of exposure, outcomes and covariates followed up for over 23 years. We were able to control for lifestyle and dietary factors that may confound the association between the LCDSs and cardiometabolic risk factors. We used two different scores to assess habitual lower carbohydrate diet patterns to

examine the relationship between carbohydrate quality and changes in cardiometabolic risk factors. Whereas prior studies using LCDSs have examined healthy and unhealthy dietary patterns in the context of lower carbohydrate diets for other health outcomes, it was not possible to examine the independent association between carbohydrate quality and health outcomes due to confounding by plant and animal sources of fat and protein that were inherent in these LCDSs. Rather, we chose to focus on the role of carbohydrate quality in lower carbohydrate diets in a manner that allowed us to isolate the association of carbohydrate quality on cardiometabolic risk factors independent of consumption sources of fat and protein. We achieved this by using the same protein and fat distributions for both our high- and low-carbohydrate quality LCD scores.

Despite these strengths, there were some limitations. First, we could not assess the associations with very low carbohydrate diet patterns as few individuals in our study population consumed less than 25% of energy from carbohydrates **(Supplemental Figure 1).** Second, the use of self-reported FFQs to estimate dietary intake may be subject to recall and social desirability biases that lead to potential misclassification of nutrient intake. However, FFQs provide good indication of relative intake and are appropriate for ranking individuals' intakes. Third, many of the observed differences in annual CMRFs changes across the quintile categories were modest, although some may still be relevant to cardiometabolic disease risk at the population level, particularly over time. For example, over a median of 16.4 years of follow-up, the difference in SBP annual increase in the highest LCDS category compared to the lowest category would result in an approximately 2.3 mm Hg lower SBP, a difference that would result in clinically significant reduction in heart failure, coronary heart disease and stroke events (96). Likewise, a 2.6 mg/dL difference in plasma HDL cholesterol concentrations based on the different annual increases between the highest and lowest quintile of HQ-LCDS would translate to 5% reduction in CVD mortality risk (97). The observed 2.3 cm greater WC between the highest and lowest LCDS quintiles would translate to an approximately 4.5% increase in CVD incidence (98). The observed 2.1 mg/dL difference in the increase in fasting glucose concentration between the highest and lowest quintiles of LQ-LCDS would translate into an approximate 18% increase in type 2 diabetes risk (99). Fourth, the generalizability of our results to non-white European racial and ethnic groups is limited

and as with all observational studies, we cannot rule out residual confounding. Fifth, although 10:1 carbohydrate to fiber ratio is a validated metric for carbohydrates quality, some carbohydrate rich foods that are considered as healthy but do not contain fiber, such as plain yogurt and low-fat dairy, fail to meet the definition of high-quality carbohydrates. To address this issue, we conducted a sensitivity analysis to include these healthy foods in the high-quality carbohydrates group and this did not change the conclusions.

2.6 Conclusions

The intent of this research was to isolate the long-term relationships between lower carbohydrate diets based on their carbohydrate quality and changes in cardiometabolic risk factors. Our results suggest that, over long follow-up periods, LCD patterns that consider carbohydrate quality independently of fat and protein sources have mixed and relatively modest associations with CMRFs. Specifically, LCD patterns, regardless of carbohydrate quality, were favorably associated with SBP, yet had an adverse association with abdominal adiposity. The associations with other CMRFs were dependent on the carbohydrate quality in the LCD patterns. LCD patterns that maintained high-quality carbohydrate intake while replacing low-quality carbohydrate sources with fat and protein were associated with beneficial changes in plasma HDL cholesterol and triglyceride concentrations, while LCD patterns that replaced high-quality carbohydrate sources with fat and protein was associated with harmful changes in serum glucose concentrations. Altogether, our findings support recommendations on preserving high-quality carbohydrates in the context of a lower carbohydrate diet and replacing low-quality carbohydrate with more healthy energy sources.

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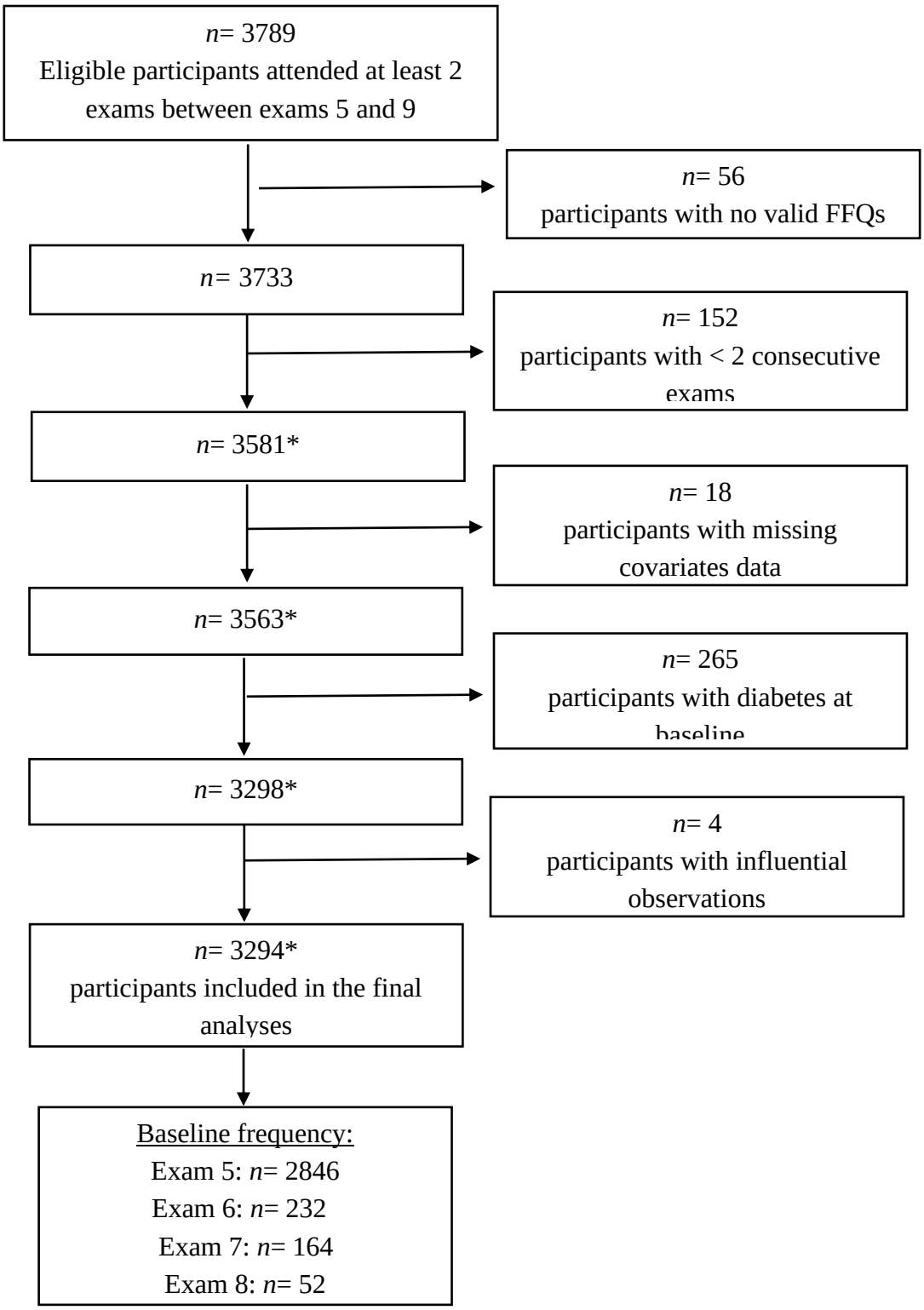


*These represent the maximum number of participants; the numbers are different based on the outcomes.

Figure 1. Flow chart for the selection of the Framingham Offspring cohort Study participants

Table 1. Baseline characteristics of study participants according to quintiles of HQ-LCDS and LQ-LCDS in the Framingham Offspring Study[1]

		HQ-LCDS		LQ-LCDS	
	Total	**Quintile 1**	**Quintile 5**	**Quintile 1**	**Quintile 5**
Median score (IQR) [2]	-	6 (4 - 7)	24 (23 - 26)	7 (5 - 8)	23 (22 - 25)
Characteristics [3]					
n	3294	649	603	605	619
Age, y	55 (48 - 62)	55 (47 - 62)	53 (47 - 61)	58 (50 - 65)	52 (46 - 60)
Female, n (%)	1786 (54.2)	289 (44.5)	373 (61.9)	311 (51.4)	330 (53.3)
Weight, kg	75.7 (64.4 - 87.1)	76.7 (65.3 - 86.2)	76.2 (64.9 - 89.4)	73.9 (63.5 - 84.8)	77.6 (66.7 - 92.5)
BMI, kg/m^2	26.6 (23.8 - 29.6)	26.2 (23.6 - 28.8)	27.3 (23.8 - 30.9)	25.9 (23.5 - 28.7)	27.7 (24.5 - 31.2)
WC, cm	92.7 (82.6 - 101.6)	92.7 (83.8 - 101)	93.3 (81.3 - 104.1)	91.4 (81.9 - 100.3)	94.6 (83.8 - 104.8)
HDL cholesterol, mg/dL	49 (40 - 60)	47 (39 - 58)	50 (41 - 62)	48 (40 - 60)	48 (39 - 59)
Non-HDL cholesterol, mg/dL	152 (126 - 177)	156 (128 - 182)	149 (123 - 171)	157 (129 - 182)	151 (123.5 - 177)
Triglyceride, mg/dL	115 (83 - 166)	124 (86 - 182)	107 (76 - 155)	119 (83 - 172)	110 (79 - 166)
Glucose, mg/dL	94 (89 - 101)	94 (89 - 101)	95 (88 - 101)	94 (89 - 102)	96 (89 - 102)
SBP, mm Hg	124 (112 - 136)	125 (115 - 136)	122 (111 - 135)	125 (114 - 139)	122 (112 - 135)

DBP, mm Hg	74 (68 - 81)	74 (69 - 81)	75 (68 - 81)	74 (67 - 81)	75 (68 - 81)
PAI, MET-hr/d	33.6 (30.6 - 37)	33.7 (30.9 - 37.6)	33.8 (30.6 - 37.1)	33.4 (30.8 - 36.8)	33.6 (30.6 - 37)
Current smoker, n (%)	601 (18.2)	140 (21.6)	114 (18.8)	68 (11.3)	147 (23.7)
Hypertension, n (%)	1549 (47)	299 (46.1)	284 (47.1)	268 (44.3)	308 (49.8)
Blood pressure medication n (%)	587 (17.8)	118 (18.2)	118 (19.6)	117 (19.4)	114 (18.5)
Lipid lowering medication, n (%)	246 (7.5)	70 (10.8)	38 (6.3)	69 (11.4)	39 (6.2)
Dietary intake [4]					
DGAI score	60.4 (52.2 - 68.6)	58.4 (50.4 - 66.1)	58.8 (50.3 - 66.3)	67 (59.9 - 73.7)	51.4 (45 - 58)
Total energy, kcal	1796 (1410 - 2240)	1960 (1563 - 2377)	1667 (1326 - 2122)	1832 (1438 -2213)	1751 (1380 -2171)
Total carbohydrate, %EI	51.2 (45.3 - 56.6)	59.7 (55.6 - 63.3)	42.1 (38.3 - 46.4)	60.9 (57.1 - 64.4)	42.6 (39 - 46.3)
Total fat, %EI	29.9 (25.7 - 34.1)	24.9 (21.4 - 27.8)	35.8 (32.7 - 38.8)	23.3 (20.2 - 25.9)	36.7 (34 - 39.3)
Total protein, %EI	16.6 (14.6 - 18.8)	13.6 (12.2 - 15)	19.8 (18.3 - 21.7)	14.8 (13.1 - 16.4)	18.8 (17.1 - 20.9)
Alcohol, %EI	1.5 (0 - 5.5)	1.7 (0 - 6)	1.2 (0 - 4.6)	1.9 (0.3 - 6.1)	0.9 (0 - 4.1)
HQ-carbohydrate, %EI	12.4 (8.1 - 17.7)	11.2 (7 - 16.7)	12.7 (8.5 - 17)	20.2 (15.9 - 25.6)	7.7 (5.8 - 10.1)
LQ-carbohydrate, %EI	35.8 (30.7 - 41.2)	45.5 (41.2 - 49.7)	27.9 (24.5 - 30.9)	37.3 (31.8 - 42.8)	33.2 (28.4 - 37.7)
Total Fiber, gm	17 (12.5 - 22.2)	17.1 (12.7 - 23.1)	15.3 (11.1 - 20.6)	22.1 (16.8 - 28.1)	12.8 (9.9 - 17)

SFA, %EI	10.3 (8.5 - 12.1)	8.3 (6.9 - 9.8)	12.4 (10.8 - 13.9)	7.4 (6.4 - 8.7)	13.1 (11.7 - 14.7)
PUFA, %EI	5.6 (4.7 - 6.7)	4.8 (4 - 5.7)	6.6 (5.6 - 7.7)	4.9 (4.1 - 5.7)	6.4 (5.5 - 7.4)
MUFA, %EI	11 (9.3 - 12.7)	9.1 (7.8 - 10.4)	13.2 (11.9 - 14.6)	8.4 (7.2 - 9.5)	13.7 (12.6 - 14.9)

[1] Values are medians (and interquartile ranges: 25th to 75th percentile) or frequency (and percentages). BP, blood pressure; DBP, diastolic blood pressure; DGAI, dietary guidelines adherence index; %EI, percent of total daily energy; HDL-C, high density lipoprotein cholesterol; LCDS, low-carbohydrate diet pattern scores; HQ-LCDS, high-quality low-carbohydrate diet pattern score; IQR, interquartile range; LQ-LCDS, low-quality low-carbohydrate diet pattern score; MET, Metabolic equivalent task; MUFA, monounsaturated fatty acids; SBP, systolic blood pressure; SFA, saturated fatty acids; PAI, physical activity index; PUFA, polyunsaturated fatty acids; WC, waist circumference.

[2] Adjusted for age and sex and total energy.

[3] Adjusted for age and sex.

[4] All dietary intake variables were adjusted for age, sex and total energy, except total energy variable which was adjusted for age and sex only.

Table 2. Annual change in cardiometabolic risk factors across quintiles of HQ-LCDS in the Framingham Offspring Study at exams 5 to 9 [1]

HQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	6	11	15	18.5	23.5	
Range	0 - 8	8.5 - 13	13.5 - 16	16.5 - 21	21.5 - 30	
WC, n (observations)	1404	2519	1809	2585	1394	
Annual change, cm [3]	0.58 ± 0.03	0.63 ± 0.02	0.62 ± 0.03	0.67 ± 0.02	0.69 ± 0.03	0.003
HDL cholesterol, n (observations)	1346	2449	1766	2543	1384	
Annual change, mg/dL	0.51 ± 0.05	0.54 ± 0.03	0.65 ± 0.04	0.59 ± 0.03	0.67 ± 0.04	0.006
Non-HDL cholesterol, n (observations)	1342	2450	1765	2543	1393	
Annual change, mg/dL	-1.58 ± 0.14	-1.57 ± 0.1	-1.85 ± 0.12	-1.62 ± 0.1	-1.64 ± 0.14	0.67
Triglyceride, n (observations)	1336	2445	1760	2541	1387	
Annual change, mg/dL	-1.24 ± 0.23	-1.15 ± 0.17	-1.79 ± 0.2	-1.78 ± 0.17	-2.01 ± 0.22	<0.001
Glucose, n (observations)	1347	2437	1752	2531	1359	

Annual change, mg/dL	0.34 ± 0.05	0.37 ± 0.04	0.36 ± 0.04	0.42 ± 0.03	0.41 ± 0.05	0.14
SBP, n (observations)	1462	2573	1861	2668	1455	
Annual change, mm Hg	0.16 ± 0.07	0.11 ± 0.06	0.15 ± 0.06	-0.01 ± 0.05	0.01 ± 0.07	0.03
DBP, n (observations)	1468	2581	1862	2673	1463	
Annual change, mm Hg	-0.22 ± 0.04	-0.17 ± 0.03	-0.19 ± 0.04	-0.24 ± 0.03	-0.18 ± 0.04	0.81

[1] Values are means ± SE. DBP, diastolic blood pressure; HDL, high density lipoprotein; HQ-LCDS, high-quality low-carbohydrate diet pattern score; SBP, systolic blood pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for systolic and diastolic blood pressure) (yes/ no).

Table 3. Annual change in cardiometabolic risk factors across quintiles of LQ-LCDS in the Framingham Offspring Study at exams 5 to 9 [1]

LQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	7	11.5	15	18	22.5	
Range	0 - 9	9.5 - 13	13.5 - 16	16.5 - 20	20.5 - 30	
WC, n (observations)	1377	2420	2049	2302	1565	
Annual change, cm [3]	0.57 ± 0.03	0.61 ± 0.02	0.62 ± 0.03	0.67 ± 0.02	0.74 ± 0.03	<0.001
HDL cholesterol, n (observations)	1343	2344	2003	2267	1533	
Annual change, mg/dL	0.56 ± 0.05	0.61 ± 0.03	0.57 ± 0.04	0.59 ± 0.04	0.60 ± 0.04	0.69
Non-HDL cholesterol, n (observations)	1338	2348	1996	2279	1531	
Annual change, mg/dL	-1.71 ± 0.14	-1.67 ± 0.11	-1.75 ± 0.12	-1.55 ± 0.11	-1.59 ± 0.13	0.37
Triglycerides, n (observations)	1329	2353	1995	2267	1524	
Annual change, mg/dL	-1.97 ± 0.23	-1.57 ± 0.17	-1.46 ± 0.19	-1.45 ± 0.18	-1.56 ± 0.21	0.20
Glucose, n (observations)	1337	2336	1991	2248	1513	
Annual change, mg/dL	0.35 ± 0.05	0.37 ± 0.04	0.34 ± 0.04	0.39 ± 0.04	0.48 ± 0.05	0.05

SBP, n (observations)	1427	2496	2090	2394	1613	
Annual change, mm Hg	0.21 ± 0.07	0.11 ± 0.06	0.09 ± 0.06	0.05 ± 0.06	-0.05 ± 0.07	0.01
DBP, n (observations)	1441	2494	2109	2390	1612	
Annual change, mm Hg	-0.20 ± 0.04	-0.20 ± 0.03	-0.23 ± 0.03	-0.20 ± 0.03	-0.19 ± 0.04	0.86

[1] Values are means ± SE. DBP, Diastolic Blood Pressure; HDL, High Density Lipoprotein; LQ-LCDS, low-quality low-carbohydrate diet pattern score; SBP, Systolic Blood Pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (continuous) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for systolic and diastolic blood pressure)(yes/ no).

Supplemental Materials

Supplemental Table 1. Macronutrients Ranges in Low-Carbohydrate Diet Scores

Points	Total Carbohydrate Intake	High-Quality Carbohydrate Intake	Low-Quality Carbohydrate Intake	Total Protein Intake	Total Fat Intake
			percentage of energy		
0	60.2 - 82.4	23.6 – 56.1	44.4 - 78.2	6.7 - 13.5	9.3 - 22.9
1	56.9- 60.1	20.2 - 23.5	40.9 - 44.3	13.6 - 14.6	23.0 - 25.4
2	54.6 - 56.8	17.9 - 20.1	38.5 - 40.8	14.7 - 15.4	25.5 - 27.3
3	52.6 - 54.5	16.0 - 17.8	36.7 - 38.4	15.5 - 16.1	27.4 - 28.7
4	51.0 - 52.5	14.4 - 15.9	35.0 - 36.6	16.2 - 16.8	28.8 - 30.2
5	49.3 - 50.9	12.9 - 14.3	33.5 - 34.9	16.9 - 17.4	30.3 - 31.5
6	47.4 - 49.2	11.5 - 12.8	31.8 - 33.4	17.5 - 18.1	31.6 - 32.8
7	45.4 - 47.3	10.0 - 11.4	30.0 - 31.7	18.2 - 18.8	32.9 - 34.3
8	42.8 - 45.3	8.5 - 9.9	27.7 - 29.9	18.9 - 19.7	34.4 - 36.1
9	39.3 - 42.7	6.4 - 8.4	24.5 - 27.6	19.8 - 21.1	36.2 - 38.6
10	8.2 - 39.2	0.7 - 6.3	2.8 - 24.4	21.2 - 40.8	38.7 - 63.8

Supplemental Table 2. Baseline characteristics in participants of the Framingham Offspring Cohort Study [1]

	Total	Males	Females
Characteristics [2]			
n	3294	1508	1786
Age, y	55 (48-62)	55(48-62)	54(47-62)
Weight, kg	75.7 (64.4 - 87.1)	84.4 (77.1 - 94.1)	66.2 (59.4 - 75.7)
BMI, kg/m2	26.6 (23.8 - 29.6)	27.5 (25.3 - 30.1)	25.5 (22.8 - 29.1)
WC, cm	92.7 (82.6 - 101.6)	97.8 (91.4 - 104.1)	85.1 (76.2 - 96.5)
HDL cholesterol, mg/dL	49 (40 - 60)	42 (35 - 50)	56 (46 - 67)
Non-HDL cholesterol, mg/dL	152 (126 - 177)	157 (134 - 180)	147 (122 - 175)
Triglyceride, mg/dL	115 (83 - 166)	125 (86 - 184)	110 (80 - 154)
Glucose, mg/dL	94 (89 - 101)	97 (92 - 103)	92 (87 - 99)
SBP, mm Hg	124 (112 - 136)	126 (116 - 137)	121 (109 - 136)
DBP, mm Hg	74 (68 - 81)	76.5 (70 - 83)	72 (66 - 79)
PAI score, MET-hr/d	33.6 (30.6 - 37)	34.2 (31.2 - 38.5)	32.5 (30.3 - 36.3)
Current smoker n (%)	601 (18.2)	270 (17.9)	331 (18.5)
Hypertension n (%)	1549 (47)	811 (53.8)	738 (41.3)
Blood pressure medication n (%)	587 (17.8)	292 (19.4)	295 (16.5)
Lipid lowering medication n (%)	246 (7.5)	144 (9.6)	102 (5.7)
Postmenopausal n (%)	1186 (36)	-	1186 (66.4)
Dietary intake [3]			

DGAI score	60.4 (52.1 - 68.6)	56.6 (48.6 - 64.2)	63.5 (55.5 - 71)
T- LCDS	15 (10 - 20)	15 (9 - 20)	15 (10 - 20)
HQ-LCDS	15 (10 - 20)	14 (9 - 19)	16 (11 - 21)
LQ-LCDS	15 (11 - 19)	15 (10 - 19)	15 (11 - 19)
Total energy, kcal	1796 (1410 - 2240)	1963 (1524 - 2405)	1681 (1343 - 2075)
Total carbohydrate, %EI	51.2 (45.3 - 56.6)	50 (44.2 - 56)	51.8 (46.3 - 57)
Total fat, %EI	29.9 (25.7 - 34.1)	30.1 (25.8 - 34.4)	29.7 (25.6 - 33.9)
Total protein, %EI	16.6 (14.6 - 18.8)	15.8 (13.9 - 17.9)	17.4 (15.3 - 19.5)
Alcohol, %EI	1.5 (0 - 5.5)	2.9 (0.4 - 8.2)	0.9 (0 - 3.7)
HQ-carbohydrate, %EI	12.4 (8.1 - 17.7)	11 (7.2 - 15.9)	13.8 (9.4 - 18.8)
LQ-carbohydrate, %EI	35.8 (30.7 - 41.2)	36.5 (31.4 - 41.8)	35.2 (30.1 - 40.7)
Total fiber, gm	17 (12.5 - 22.2)	17 (12.5 - 22.2)	16.9 (12.5 - 22.2)
SFA, %EI	10.3 (8.5 - 12.1)	10.4 (8.5 - 12.2)	10.1 (8.4 - 12)
PUFA, %EI	5.6 (4.7 - 6.7)	5.5 (4.6 - 6.5)	5.7 (4.7 - 6.8)
MUFA, %EI	11 (9.3 - 12.7)	11.2 (9.5 - 13)	10.8 (9.2 - 12.5)

[1] Values are medians (and interquartile ranges: 25th to 75th percentile) or frequency (and percentages). DBP, diastolic blood pressure; DGAI, dietary guidelines adherence index; %EI, percent of total daily energy; HDL, high density lipoprotein; LCDS, low-carbohydrate diet pattern scores; HQ-LCDS, high-quality low-carbohydrate dietary pattern score; LQ-LCDS, low-quality low-carbohydrate diet pattern score; MET, Metabolic equivalent task; MUFA, monounsaturated fatty acids; SBP, systolic blood pressure; PAI, physical activity index; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; WC, waist circumference.

[2] Adjusted for age and sex.

[3] All dietary intake variables were adjusted for age, sex and total energy, except total energy variable was adjusted for age and sex only.

Supplemental Table 3. Annual change in cardiometabolic risk factors in the Framingham Offspring Study at exams 5 to 9[1]

WC, cm	0.64 ± 0.01
HDL cholesterol, mg/dL	0.60 ± 0.02
Non-HDL cholesterol, mg/dL	-1.64 ± 0.06
Triglyceride, mg/dL	-1.41 ± 0.11
Glucose, mg/dL	0.48 ± 0.02
SBP, mm Hg	0.10 ± 0.03
DBP, mm Hg	-0.21 ± 0.02

[1] Values are means ± SEs adjusted for exam interval, periodic baseline cardiometabolic risk factor value (continuous, periodic baseline age (continuous), sex (male/ female), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol), and hypertension (for systolic and diastolic blood pressure) (yes/ no).

DBP, diastolic blood pressure; HDL cholesterol, high density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.

Supplemental Table 4. Annual change in cardiometabolic risk factors across quintiles of T-LCDS in the Framingham Offspring Study at exams 5 to 9 [1]

T-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	6	10.5	14.5	18.5	24	
Range	0 - 8	8.5 - 12	12.5 - 16	16.5 - 21	21.5 - 30	
Annual Δ WC cm, n (observations)	1533	1866	2327	2388	1599	
Model 1 [3]	0.58 ± 0.03	0.60 ± 0.03	0.66 ± 0.02	0.64 ± 0.02	0.72 ± 0.03	<0.001
Annual Δ HDL cholesterol mg/dL, n (observations)	1484	1817	2257	2352	1581	
Model 1	0.50 ± 0.04	0.61 ± 0.04	0.57 ± 0.04	0.63 ± 0.04	0.61 ± 0.04	0.08
Model 2 [4]	0.51 ± 0.04	0.61 ± 0.04	0.57 ± 0.04	0.61 ± 0.03	0.61 ± 0.04	0.11
Annual Δ Non-HDL cholesterol mg/dL, n (observations)	1477	1813	2269	2351	1583	
Model 1	-1.64 ± 0.13	-1.64 ± 0.12	-1.69 ± 0.11	-1.66 ± 0.11	-1.60 ± 0.13	0.90
Model 2	-1.61 ± 0.13	-1.61 ± 0.12	-1.65 ± 0.11	-1.59 ± 0.1	-1.58 ± 0.13	0.81
Annual Δ Triglyceride mg/dL, n (observations)	1472	1815	2264	2343	1576	
Model 1	-1.43 ± 0.22	-1.69 ± 0.2	-1.24 ± 0.18	-1.75 ± 0.18	-1.83 ± 0.21	0.16
Model 2	-1.40 ± 0.22	-1.67 ± 0.19	-1.17 ± 0.18	-1.65 ± 0.17	-1.77 ± 0.2	0.23

Annual Δ Glucose mg/dL, n (observations)	1475	1814	2242	2344	1551	
Model 1	0.33 ± 0.05	0.38 ± 0.04	0.36 ± 0.04	0.41 ± 0.04	0.44 ± 0.04	0.06
Model 2	0.34 ± 0.05	0.39 ± 0.04	0.37 ± 0.04	0.42 ± 0.04	0.45 ± 0.04	0.06
Annual Δ SBP mm Hg, n (observations)	1591	1909	2402	2456	1662	
Model 1	0.12 ± 0.07	0.21 ± 0.06	0.13 ± 0.06	-0.03 ± 0.06	-0.02 ± 0.07	0.01
Model 2	0.15 ± 0.07	0.25 ± 0.06	0.14 ± 0.06	0.00 ± 0.06	0.01 ± 0.07	0.009
Annual Δ DBP mm Hg, n (observations)	1599	1919	2404	2464	1662	
Model 1	-0.21 ± 0.04	-0.17 ± 0.04	-0.17 ± 0.03	-0.26 ± 0.03	-0.19 ± 0.04	0.64
Model 2	-0.20 ± 0.04	-0.15 ± 0.04	-0.16 ± 0.03	-0.24 ± 0.03	-0.17 ± 0.04	0.71

[1] Values are means ± SE. DBP, Diastolic Blood Pressure; HDL, High Density Lipoprotein; LCDS, low-carbohydrate diet pattern score; SBP, Systolic Blood Pressure; T-LCDS, total low-carbohydrate diet pattern; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Model 1 adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for systolic and diastolic blood pressure) (yes/ no).

[4] Model 2 adjusted for model 1 covariates + change in waist circumference (continuous).

Supplemental Table 5. Annual change in cardiometabolic risk factors after further adjustment for change in waist circumference across quintiles of HQ-LCDS in the Framingham Offspring Study at exams 5 to 9 [1]

HQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
HDL cholesterol, n (observations)						
Annual change, mg/dL [3]	0.51 ± 0.04	0.53 ± 0.03	0.64 ± 0.04	0.58 ± 0.03	0.67 ± 0.04	0.008
Non-HDL cholesterol, n (observations)						
Annual change, mg/dL	-1.57 ± 0.14	-1.52 ± 0.1	-1.82 ± 0.12	-1.58 ± 0.1	-1.60 ± 0.13	0.72
Triglyceride, n (observations)						
Annual change, mg/dL	-1.20 ± 0.22	-1.09 ± 0.17	-1.75 ± 0.2	-1.72 ± 0.17	-1.94 ± 0.22	<0.001
Glucose, n (observations)						
Annual change, mg/dL	0.36 ± 0.05	0.38 ± 0.04	0.37 ± 0.04	0.44 ± 0.03	0.42 ± 0.05	0.16
SBP, n (observations)						
Annual change, mm Hg	0.21 ± 0.07	0.14 ± 0.06	0.17 ± 0.06	0.01 ± 0.05	0.02 ± 0.07	0.02
DBP, n (observations)						
Annual change, mm Hg	-0.20 ± 0.04	-0.16 ± 0.03	-0.16 ± 0.04	-0.23 ± 0.03	-0.17 ± 0.04	0.74

[1] Values are means ± SE. DBP, diastolic blood pressure; HDL, high density lipoprotein; HQ-LCDS, high-quality low-carbohydrate diet pattern score; SBP, systolic blood pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for SBP and DBP)(yes/ no) + change in waist circumference (continuous)

Supplemental Table 6. Annual change in cardiometabolic risk factors after further adjustment for change in waist circumference across quintiles of LQ-LCDS in the Framingham Offspring Study at exams 5 to 9 [1]

LQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
HDL cholesterol, n (observations)						
Annual change, mg/dL [3]	0.56 ± 0.05	0.61 ± 0.03	0.56 ± 0.04	0.57 ± 0.04	0.60 ± 0.04	0.77
Non-HDL cholesterol, n (observations)						
Annual change, mg/dL	-1.66 ± 0.14	-1.66 ± 0.1	-1.7 ± 0.11	-1.48 ± 0.11	-1.56 ± 0.13	0.33
Triglycerides, n (observations)						
Annual change, mg/dL	-1.91 ± 0.23	-1.56 ± 0.17	-1.39 ± 0.19	-1.33 ± 0.18	-1.55 ± 0.21	0.17
Glucose, n (observations)						
Annual change, mg/dL	0.36 ± 0.05	0.38 ± 0.04	0.35 ± 0.04	0.40 ± 0.04	0.49 ± 0.04	0.05
SBP, n (observations)						
Annual change, mm Hg	0.24 ± 0.08	0.13 ± 0.06	0.11 ± 0.06	0.08 ± 0.06	-0.01 ± 0.07	0.02
DBP, n (observations)						
Annual change, mm Hg	-0.18 ± 0.04	-0.19 ± 0.03	-0.20 ± 0.03	-0.18 ± 0.03	-0.17 ± 0.04	0.86

[1] Values are means ± SE. DBP, diastolic blood pressure; HDL, high density lipoprotein; LQ-LCDS, Low-quality low-carbohydrate diet pattern score; SBP, systolic blood pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for SBP and DBP)(yes/ no) + change in waist circumference (continuous)

Supplemental Table 7. Annual change in cardiometabolic risk factors across quintiles of HQ-LCDS 2 in the Framingham Offspring Study at exams 5 to 9 [1]

HQ-LCDS 2	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	6	11	15	18.5	23.5	
Range	0 - 8	8.5 - 13	13.5 - 16	16.5 - 21	21.5 - 30	
WC, n (observations)	1393	2499	1833	2594	1392	
Annual change, cm [3]	0.59 ± 0.03	0.63 ± 0.02	0.61 ± 0.03	0.66 ± 0.02	0.7 ± 0.03	0.005
HDL cholesterol, n (observations)	1337	2419	2368	1979	1385	
Annual change, mg/dL	0.48 ± 0.05	0.57 ± 0.03	0.61 ± 0.04	0.61 ± 0.04	0.65 ± 0.04	0.008
Non-HDL cholesterol, n (observations)	1334	2420	2363	1981	1395	
Annual change, mg/dL	-1.48 ± 0.14	-1.66 ± 0.11	-1.66 ± 0.11	-1.72 ± 0.12	-1.67 ± 0.13	0.35
Triglyceride, n (observations)	1323	2421	2356	1979	1390	
Annual change, mg/dL	-1.17 ± 0.23	-1.18 ± 0.17	-1.63 ± 0.18	-2.02 ± 0.19	-1.94 ± 0.22	<0.001
Glucose, n (observations)	1336	2409	1782	2536	1363	
Annual change, mg/dL	0.34 ± 0.05	0.36 ± 0.04	0.36 ± 0.04	0.43 ± 0.04	0.43 ± 0.05	0.07

SBP, n (observations)	1442	2561	1885	2675	1456	
Annual change, mm Hg	0.2 ± 0.07	0.12 ± 0.06	0.15 ± 0.06	-0.03 ± 0.05	-0.02 ± 0.07	0.004
DBP, n (observations)	1447	2568	1888	2680	1464	
Annual change, mm Hg	-0.20 ± 0.04	-0.18 ± 0.03	-0.18 ± 0.04	-0.23 ± 0.03	-0.21 ± 0.04	0.46

[1] Values are means ± SE. DBP, diastolic blood pressure; HDL, high density lipoprotein; HQ-LCDS2, high-quality low-carbohydrate diet pattern score (a second version where plain yogurt, low and reduced-fat and skim milk included in high-quality carbohydrate group); SBP, systolic blood pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for systolic and diastolic blood pressure) (yes/ no).

Supplemental Table 8. Annual change in cardiometabolic risk factors across quintiles of LQ-LCDS 2 in the Framingham Offspring Study at exams 5 to 9 [1]

LQ-LCDS 2	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	7	11.5	15	18	22.5	
Range	0 - 9	9.5 - 13	13.5 - 16	16.5 - 20	20.5 - 30	
WC, n (observations)	1377	2377	2102	2299	1558	
Annual change, cm [3]	0.56 ± 0.03	0.60 ± 0.02	0.63 ± 0.03	0.67 ± 0.02	0.74 ± 0.03	<0.001
HDL cholesterol, n (observations)	1341	2311	2063	2247	1528	
Annual change, mg/dL	0.57 ± 0.05	0.63 ± 0.04	0.54 ± 0.04	0.58 ± 0.04	0.61 ± 0.04	0.97
Non-HDL cholesterol, n (observations)	1340	2306	2069	2251	1526	
Annual change, mg/dL	-1.78 ± 0.14	-1.69 ± 0.11	-1.68 ± 0.11	-1.62 ± 0.11	-1.49 ± 0.13	0.12
Triglycerides, n (observations)	1328	2316	2064	2241	1519	
Annual change, mg/dL	-2.1 ± 0.23	-1.51 ± 0.17	-1.44 ± 0.19	-1.36 ± 0.18	-1.71 ± 0.21	0.22
Glucose, n (observations)	1337	2299	2056	2224	1509	
Annual change, mg/dL	0.35 ± 0.05	0.38 ± 0.04	0.33 ± 0.04	0.41 ± 0.04	0.45 ± 0.05	0.11

SBP, n (observations)	1427	2445	2165	2381	1602	
Annual change, mm Hg	0.19 ± 0.07	0.07 ± 0.06	0.13 ± 0.06	0.06 ± 0.06	-0.03 ± 0.07	0.04
DBP, n (observations)	1440	2448	2181	2377	1600	
Annual change, mm Hg	-0.18 ± 0.04	-0.25 ± 0.03	-0.18 ± 0.03	-0.2 ± 0.03	-0.19 ± 0.04	0.79

[1] Values are means ± SE. DBP, Diastolic Blood Pressure; HDL, High Density Lipoprotein; LQ-LCDS2, low-quality low-carbohydrate diet pattern (a second version where plain yogurt, low and reduced-fat and skim milk included in high-quality carbohydrate group score); SBP, Systolic Blood Pressure; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (continuous) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for systolic and diastolic blood pressure)(yes/ no).

Supplemental Table 9. Annual Change in cardiometabolic risk factors across quintiles of high and low-quality LCDS in the Framingham Offspring Study at exams 5 to 9, stratified by baseline of exam-interval [1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
HQ-LCDS						
WC cm, n (observations)						
All	1404	2519	1809	2585	1394	
exam 5	426	693	526	740	402	
exam 6	381	675	490	690	366	
exam 7	317	650	425	623	339	
exam 8	280	501	368	532	287	
Annual Δ WC cm						
exam 5	1.15 ± 0.08	1.04 ± 0.06	1.16 ± 0.07	1.32 ± 0.06	1.54 ± 0.08	<0.001
exam 6	0.72 ± 0.09	0.95 ± 0.07	0.66 ± 0.08	0.91 ± 0.07	0.75 ± 0.09	0.99
exam 7	0.20 ± 0.05	0.30 ± 0.04	0.34 ± 0.04	0.35 ± 0.04	0.44 ± 0.05	0.001
exam 8	0.14 ± 0.06	0.16 ± 0.04	0.11 ± 0.05	0.13 ± 0.04	0.09 ± 0.06	0.49

Glucose mg/dL, n (observations)						
All	1347	2437	1752	2531	1359	
exam 5	412	674	515	734	389	
exam 6	366	660	477	678	357	
exam 7	306	621	406	610	338	
exam 8	263	482	354	509	275	
Annual Δ Glucose mg/dL						
exam 5	0.53 ± 0.10	0.60 ± 0.08	0.51 ± 0.09	0.82 ± 0.07	1.05 ± 0.10	<0.001
exam 6	0.33 ± 0.15	0.44 ± 0.11	0.66 ± 0.13	0.47 ± 0.11	0.26 ± 0.15	0.90
exam 7	0.59 ± 0.08	0.55 ± 0.06	0.72 ± 0.07	0.73 ± 0.06	0.84 ± 0.08	0.002
exam 8	-0.44 ± 0.10	-0.21 ± 0.07	-0.37 ± 0.08	-0.23 ± 0.07	-0.46 ± 0.10	0.85
LQ-LCDS						
WC cm, n (observations)						
All	1377	2420	2049	2302	1565	

exam 5	429	631	569	679	479	
exam 6	383	645	544	613	418	
exam 7	306	624	500	545	379	
exam 8	259	520	436	465	289	
Annual Δ WC, cm						
exam 5	0.93 ± 0.08	1.12 ± 0.06	1.19 ± 0.07	1.38 ± 0.06	1.45 ± 0.07	<0.001
exam 6	0.66 ± 0.09	0.81 ± 0.07	0.91 ± 0.08	0.85 ± 0.07	0.86 ± 0.09	0.13
exam 7	0.34 ± 0.05	0.25 ± 0.04	0.28 ± 0.04	0.38 ± 0.04	0.44 ± 0.05	0.02
exam 8	0.12 ± 0.06	0.15 ± 0.04	0.08 ± 0.05	0.1 ± 0.05	0.24 ± 0.06	0.36
DBP mm Hg, n (observations)						
All	1441	2494	2109	2390	1612	
exam 5	434	643	576	686	483	
exam 6	402	661	566	645	436	
exam 7	327	642	510	569	392	

exam 8	278	548	457	490	301	
Annual Δ DBP mm Hg						
exam 5	0.28 ± 0.09	0.26 ± 0.07	0.23 ± 0.08	0.28 ± 0.07	0.34 ± 0.09	0.57
exam 6	-0.89 ± 0.14	-0.68 ± 0.11	-0.35 ± 0.11	-0.54 ± 0.11	-0.52 ± 0.13	0.04
exam 7	0.04 ± 0.07	-0.09 ± 0.05	-0.21 ± 0.06	-0.09 ± 0.05	-0.07 ± 0.06	0.36
exam 8	-0.45 ± 0.08	-0.45 ± 0.06	-0.44 ± 0.06	-0.49 ± 0.06	-0.53 ± 0.08	0.42

[1] Values are means ± SE. DBP, diastolic blood pressure; LCDS, low-carbohydrate dietary pattern score; HQ-LCDS, high-carbohydrates low-carbohydrate dietary pattern score; LQ-LCDS, low-quality low-carbohydrate dietary pattern score; WC, waist circumference.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (except for WC, continuous), total energy (continuous), alcohol intake (continuous) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for triglyceride, HDL- and non-HDL cholesterol) , and hypertension (for SBP and DBP)(yes/ no).

Supplemental Table 10. Annual Change in cardiometabolic risk factors across quantiles of high and low-quality LCDS in the Framingham Offspring Study at exams 5 to 9, stratified by presence of impaired fasting glucose status [1]

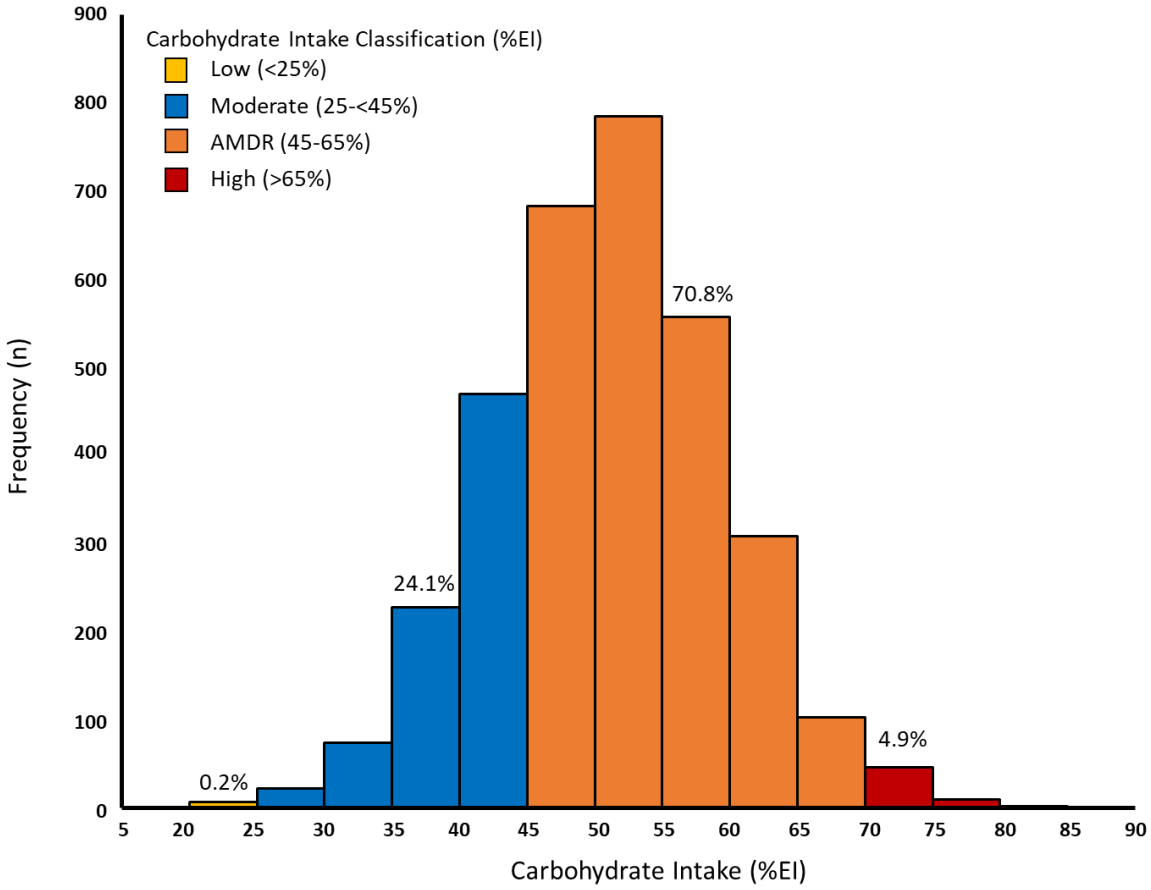
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
HQ-LCDS						
Glucose mg/dL, n (observations)						
Normal fasting glucose	862	1537	1105	1547	824	
Impaired fasting glucose	485	900	647	984	535	
Annual Δ Glucose mg/dL						
Normal fasting glucose	0.71 ± 0.06	0.72 ± 0.05	0.67 ± 0.06	0.72 ± 0.05	0.71 ± 0.06	0.99
Impaired fasting glucose	-0.3 ± 0.11	-0.17 ± 0.08	-0.07 ± 0.09	-0.09 ± 0.08	-0.10 ± 0.11	0.16
LQ-LCDS						
Non-HDL cholesterol mg/dL, n (observations)						
Normal fasting glucose	874	1473	1254	1355	875	
Impaired fasting glucose	462	871	741	920	653	
Annual Δ Non-HDL cholesterol mg/dL						

Normal fasting glucose	-1.27 ± 0.23	-1.4 ± 0.17	-0.94 ± 0.19	-1 ± 0.18	-0.98 ± 0.23	0.13
Impaired fasting glucose	-2.63 ± 0.31	-2.17 ± 0.22	-2.95 ± 0.24	-2.43 ± 0.21	-2.55 ± 0.26	0.84

[1] Values are means ± SE. HDL, High-density lipoprotein; HQ-LCDS, high- carbohydrates low-carbohydrate dietary pattern score; LQ-LCDS, low-quality low-carbohydrate dietary pattern score.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for baseline of exam interval (exam5, exam 6, exam7, exam8), periodic baseline cardiometabolic risk value (continuous), periodic baseline age (continuous), sex (male/ female), BMI (continuous), total energy (continuous), alcohol intake (continuous) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), medication use for hyperglycemia (for fasting glucose), dyslipidemia (for non-HDL cholesterol) (yes/ no).



Supplemental Figure 1. Baseline carbohydrate intake distribution based on percent energy.

Chapter 3. Low Carbohydrate Diet Patterns that Retain High Quality Carbohydrates are Associated with Beneficial Long-term Changes in Systemic Markers of Inflammation in the Framingham Offspring Cohort

Low Carbohydrate Diet Patterns that Retain High Quality Carbohydrates are Associated with Beneficial Long-term Changes in Systemic Markers of Inflammation in the Framingham Offspring Cohort

Ghaida F. Aloraini,[1,2] Nicola M. McKeown,[3] Gail T. Rogers,[1] Sai Krupa Das,[1,2] Alice H. Lichtenstein,[1,2] Paul F. Jacques[1,2]

Affiliations:

[1] USDA Human Nutrition Research Center on Aging, Tufts University, Boston MA

[2] Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA

[3] Sargent College, Boston University, Boston, MA

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Corresponding author:
Paul F Jacques
Jean Mayer USDA Human Nutrition Research Center at Tufts University
711 Washington Street
Boston, MA 02111
Email: paul.jacques@tufts.edu

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Abbreviations:

List of abbreviations and their definitions for all non-standard abbreviations

FHS	Framingham Heart Study
HQ-LCDS	High-quality low-carbohydrate diet score
LCD	Low-carbohydrate diet
LCDS	Low-carbohydrate diet score
LQ-LCDS	Low-quality low-carbohydrate diet score
MCP	Monocyte chemoattractant protein
MET	Metabolic equivalent of task
NSAID	Nonsteroidal anti-inflammatory drug
OPG	Osteoprotegerin
PAI	Physical activity index
T-LCDS	Total low-carbohydrate diet score
%EI	Percentage of total daily energy

3.1 Abstract

(300 words)

Background: Low Carbohydrate Diet (LCD) patterns have been studied as a potential strategy to reduce chronic inflammation. Evidence remains equivocal, potentially due to differences in the quality of carbohydrate sources among LCD patterns.

Objectives: To prospectively examine the associations between LCD patterns varying in carbohydrate quality, and changes in biomarkers of inflammation and oxidative stress.

Methods: We used data from the Framingham Offspring Study, exams 7 and 8 [1998-2008; n = 2225; mean ± SD baseline age: 60.1 ± 8.9 y]. Dietary intakes, health, and lifestyle data were collected at each exam over a median 6.7-y follow-up period. We assessed LCD patterns accounting for quality of carbohydrate sources using 2 LCD scores (LCDSs) reflecting higher intake of total fat and protein, and lower intake of (i) low-quality carbohydrate (high-quality LCDS, HQ-LCDS) and (ii) high-quality carbohydrate (low-quality LCDS, LQ-LCDS). An inflammation and oxidative stress score was calculated by summing the standardized values of 9 inflammatory biomarkers. Least-square means of changes in the inflammatory scores across quintile categories of LCDSs were estimated using multivariable linear regression models, adjusted for potential confounders.

Results: HQ-LCDS was inversely associated with change in the inflammation and oxidative stress score (mean ± SE in Q1: 0.24 ± 0.16, Q5: -0.27 ± 0.16; P_{trend}= 0.004), indicating that inflammation and oxidative stress increased in those in the lowest HQ-LCDS category and decreased in those in the highest category. HQ-LCDS was also inversely associated with changes in intercellular adhesion molecule-1 (Q1: 0.18 ± 0.01, Q5: 0.13 ± 0.01 log-ng/mL; P_{trend}= 0.003) and lipoprotein phospholipase A2 activity (Q1: 0.01 ± 0.01, Q5: -0.03 ± 0.01 log-nmol/mL/min; P_{trend}= 0.001). No significant associations were observed for LQ-LCDS.

Conclusions: LCD patterns that replaced low-quality carbohydrate sources with fat and protein were inversely associated with inflammation and oxidative stress scores, which may result in reduced chronic disease risk.

Keywords: low-carbohydrate diet, carbohydrate quality, chronic inflammation, oxidative stress, cytokines, C-reactive protein, aging, Framingham Heart Study.

3.2 Introduction

Chronic low-grade inflammation, characterized by elevated concentrations of inflammatory markers in the systemic circulation, plays a pivotal role in the development of many chronic diseases, such as obesity (1), type 2 diabetes (2), cardiovascular disease (3), neurodegenerative diseases (4), and some cancers (5), particularly in older adults. Low Carbohydrate Diet (LCD) patterns have been studied as a potential strategy to modulate inflammatory activity and reduce risk of metabolic dysfunction and chronic disease (6–11). However, the evidence remains equivocal. Prior observational studies have been cross-sectional, and focused on a limited number of inflammatory biomarkers (10,11). Intervention studies have had relatively short follow-up periods (ranging from few weeks to 12 months), hence, cannot assess the long-term association between LCD patterns and changes in systemic inflammation biomarkers (12–18). Frequently, the quality of dietary carbohydrates was not assessed.

Dietary carbohydrates come from many sources that can differentially affect chronic low-grade inflammation process(19–21). High-quality carbohydrate diets, characterized by higher intakes of whole grains, non-starchy vegetables, whole fruits, nuts and legumes, and correspondingly higher dietary fiber, are associated with lower circulating concentrations of serum C-reaction protein (CRP) and other biomarkers of inflammation (20–23). Conversely, lower-quality carbohydrate diets, characterized by higher intakes of refined grains, sugar sweetened beverages, sweet-baked desserts, and other sweet snacks, promote chronic low-grade inflammation (19–24).

Low-carbohydrates diet scores (LCDSs), applied in most of the previous observational studies that examined LCD patterns and health outcome measures, simultaneously factor together lower carbohydrate intakes and higher fat and/or protein intakes (25–30). Multiple LCDSs have been created that captured the different sources of protein and fat, in addition to the quality of carbohydrates. Yet, to our knowledge, no previous study considered LCDSs that considered carbohydrate quality independently from protein or fact quality or used LCDSs to examine the relationship between lower carbohydrate diets and biomarkers of inflammation and oxidative stress.

The objective of the present study was to prospectively assess long-term associations between LCDSs reflecting high-quality carbohydrates or low-quality carbohydrates, in combination with higher total fat and protein, and changes in circulating and urinary biomarkers of inflammation and oxidative stress, among community dwelling participants of the Framingham Heart Study (FHS) Offspring cohort. We hypothesized that an LCDS that represents maintenance of high-quality carbohydrates in a lower carbohydrate diet is associated with less inflammation and oxidative stress than an LCDS representing a pattern with lower intake of high-quality carbohydrates.

3.3 Methods

Study population:

This prospective study used data from the National Heart, Lung, and Blood Institute (NHLBI) FHS Offspring cohort. The FHS is a long-term ongoing cohort study, initiated in 1948, with the aim of exploring cardiovascular disease (CVD) risk factors in residents of Framingham, Massachusetts, USA (31). In 1971, 5,124 offspring of the FHS original cohort and their spouses were recruited into the Offspring cohort. Approximately every 4 years, this cohort undergoes a standard medical examination, consisting of laboratory and anthropometric assessments, as well as dietary intake assessment. It is also continuously monitored for various cardiometabolic disorders including CVD, diabetes and hypertension (32). Data from the seventh (1998–2001, n= 3539) and eighth (2005–2008, n= 3021) examination cycles were used for the analyses. Of the 3539 participants who attended exam 7, which is the baseline of our study, we excluded from the present analysis those who did not attend follow-up exam 8 (n= 670) or had missing or invalid dietary data (n=275), non-fasting plasma outcome measures (n=144), or missing inflammation biomarkers measures (n= 225). Therefore, 2225 participants were included in the primary longitudinal analysis **(Figure 1)**. All participants provided written informed consent before study participation. The Institutional Review Board for Human Research at Boston University Medical Center approved all the FHS data-collection protocols. The current study protocol was approved by the Tufts Health Sciences Institutional Review Board.

Assessment of LCDS:

The Harvard semi-quantitative food frequency questionnaire (FFQ) was used to assess dietary intake at both examinations (33). The FFQ was designed to capture the habitual dietary intake over the past 12 months and included a list of 126 items with standard serving sizes and 9 frequency categories ranging from "never, or < 1 serving/ month" to "≥ 6 servings/day". Invalid dietary data was defined as a total energy intake <600 kcal/d for both males and females, or ≥4000 kcal/d for females or ≥4200 kcal/d for males, or those which had ≥12 blank items. Daily nutrient and energy intakes were computed by multiplying the frequency of intake of each food item by the nutrient and energy content and summing across all food items. The validity and reliability of the FFQ has been evaluated for both men (33) and women(34)in other cohorts. The correlation coefficients between FFQ and multiple diet records for females and males, respectively, are 0.61 and 0.73 for total carbohydrate, 0.52 and 0.44 for protein, 0.54 and 0.67 for fat. The validity of the FFQ was evaluated for dietary fiber in men with correlation coefficient of 0.68 (33), and for crude fiber in women with correlation coefficient of 0.56 (34).

To examine the carbohydrate quality in LCD patterns, we created two LCDSs. Our scores are modified versions of the original Total LCDS (T-LCDS) developed by Halton et al.(26), which was created using estimates of total carbohydrate, total fat, and total protein intakes. To compute the score, the participants were divided into 11 approximately equal-sized categories each of fat, protein and carbohydrate intakes, expressed as percentage of energy. For carbohydrate intake, participants in the lowest category were assigned a score of 10, while those in the highest category were assigned a score of 0. The scoring is the opposite for the protein and fat, with those in the highest category of intakes assigned scores of 10 and those in the lowest category assigned scores of 0. The scores for each of the three macronutrients were summed for a total score. A higher T-LCDS reflects participants who had a lower energy intake from total carbohydrates and higher energy intakes from total fat and total protein, with a range of 0 to 30. Therefore, the higher the score, the more closely the participants follow an LCD pattern.

To create our scores, we first characterize the carbohydrate quality of all carbohydrate-containing food items in the FFQ using a validated metric (10: 1 carbohydrate: fiber), defined as ≥ 1 gram of fiber per 10 grams of carbohydrate. This ratio is based on the ratio of carbohydrate-to-fiber in whole wheat (35). In creating the high-quality LCDS (HQ-LCDS), the percent of energy intake from low-quality carbohydrates were scored, and participants with intakes in the lowest category were assigned a score of 10, and those in the highest category were assigned a score of 0. A higher HQ-LCDS reflects a diet pattern where participants consume less low-quality carbohydrate and more total fat and protein. For the low-quality LCDS (LQ-LCDS), high-quality carbohydrates were scored, with participants in the lowest intake category were assigned a score of 10, and those in the highest category were assigned a score of 0. A higher LQ-LCDS reflects a diet pattern where individuals consume less high-quality carbohydrate and more total fat and protein. To allow us to examine the association of carbohydrate quality and inflammation independent of differences types of fatty acids or sources of protein, our scores were based on total fat and protein intake.

Inflammation and oxidative stress outcomes:

We used nine biomarkers of inflammation and oxidative stress that were measured at the at the 7th and 8th examination cycles. Fasting blood samples were collected and stored at −80°C. Serum C-reactive protein (CRP) was measured with a highly sensitive assay. The following biomarkers were measured in duplicate by using commercially available enzyme-linked immunosorbent assay kits: serum interleukin-6 (IL-6), serum monocyte chemoattractant protein 1 (MCP-1), plasma P-selectin, plasma tumor necrosis factor receptor II (TNFRII), serum-soluble intercellular adhesion molecule 1 (ICAM-1), plasma osteoprotegerin (OPG), plasma lipoprotein phospholipase A2 (LPL-A2) mass and activity (36), and urinary isoprostanes indexed to urinary creatinine (37). Values of the individual biomarkers were log transformed prior to statistical analysis, except for the creation of the inflammation and oxidative stress score, described below.

The inflammation and oxidative stress score was created as the sum of the standardized rank values of nine biomarkers available at both examinations 7 and 8 (i.e., CRP, IL-6, MCP-1, P-selectin, TNFRII, ICAM-1, LPL-A2 mass, LPL-A2 activity, and

OPG), adapted from a score previously described in the Framingham Offspring study (38). Given the number of missing observations for urinary isoprostanes at examination 7, these were excluded from the score. Higher values of the inflammation and oxidative stress score indicate higher inflammation and oxidative stress and a positive change in this score represents an increase in inflammation and oxidative stress.

We applied a Winsorization approach to outliers of the change in outcomes by setting them to a value of 0.5 above the 95^{th} percentile + (2 x interquartile range), or 0.5 below the 5^{th} percentile – (2 x interquartile range).

Covariates:

Several potential confounders of the relationship between LCD patterns and chronic inflammation were included as covariates in our analyses. These include included age (years), sex (female, male), body mass index (BMI) (kg/m^2), menopausal status (menstruation ceased >1 year), current smoking status (yes, no), physical activity [measured by a physical activity index (PAI), a score based on the sum of sedentary, slight, moderate and vigorous activity expressed as metabolic equivalent of task (MET-hrs/d)] (39), alcohol intake (%energy/d), total energy intake (kcal/d), history of CVD (yes, no), nonsteroidal anti-inflammatory drug (NSAID) use (any, none), and pharmacological treatment (yes/no) for hypertension, dyslipidemia and hyperglycemia. To minimize missing covariates data, we imputed the following covariates: height, BMI and PAI. Height was imputed by bringing forward values from the previous examination, if previous exam value was not available, we brought backward values from the following examination. Missing BMI data was calculated by using the available weight and imputed height data. PAI was imputed by determining the median PAI score of the sample who had available PAI data, stratified by age, sex, BMI and perceived health status, and applying these medians to individuals with missing PAI data.

Statistical Analyses:

The LCDSs were averaged across examinations 7 and 8 to account for long-term intake and divided into quintile categories. Our primary outcome was the change in inflammation and oxidative stress score. Secondary outcomes included changes in the

logged values of the individual biomarkers. Change in each outcome was calculated as the value at examination 8 minus the value at examination 7. Our primary analysis estimated associations between HQ-LCDS, and LQ-LCDS, and the change in the inflammation and oxidative stress score. Secondary analyses included the following: 1) assessing associations between HQ-LCDS, and LQ-LCDS against changes in logged values of the individual biomarkers; 2) assessing T-LCDS against changes in the inflammation and oxidative stress score and logged values of the individual biomarkers.

We used multiple linear regression models (SAS PROC GLM) to estimate least-square means of the change in the outcome in each quintile category of protein intake adjusted for age, sex, alcohol intake, energy intake, smoking status, BMI, PAI, menopausal status, and the baseline (examination 7) value of the outcome (model 1); NSAID and corticosteroids use, history of cardiovascular disease, and treatment for hypertension, hyperglycemia, or dyslipidemia (model 2). P-trend across quintile categories of LCDSs was assessed by assigning the median value in each quintile category and treating it as a continuous variable in regression models.

We conducted a sensitivity analysis excluding observations with studentized residuals beyond ± 2. As these findings were consistent with the results that included these observations, we did not present the sensitivity analysis.

All statistical analyses were performed using SAS (version 9.4; SAS institute). All reported P values are 2 sided and statistical significance was set at a nominal α level of 0.05.

3.4 Results

The median follow-up time was 6.7 y (interquartile range: 0.7 y, minimum: 3.7 y, maximum: 8.6 y). At baseline, the median (25^{th} -75^{th} percentile) age of participants was 59 y (53y – 67y), 56% were female, mean BMI was 27.3 kg/m^2 **(Table 1)**. Participants in the highest quintile categories of both HQ-LCDS and LQ-LCDS, were more likely to be females, smokers, have higher BMI, and treated for diabetes, and less likely to be treated for dyslipidemia compared to the lowest quintile categories. Across increasing quintile categories of LQ-LCDS, participants had poorer diet quality as indicated by lower DGAI

scores, while across increasing quintile categories of HQ-LCDS, participants had similar DGAI scores.

The median dietary intakes, expressed as percentage of energy, were 50% for total carbohydrate with 13% for high-quality carbohydrates sources and 34% for low-quality carbohydrate sources. Median total carbohydrate intake was lower by approximately 19% in the highest quintile categories of both HQ-LCDS and LQ-LCDS compared to the lowest quintile categories. Median intake from low-quality carbohydrates were lower by 17% in the highest quintile category of HQ-LCDS compared to the lowest quintile category, whereas median intake from high-quality carbohydrates were lower by 13% in the highest quintile category of LQ-LCDS compared to the lowest quintile category. Median intake from low-quality carbohydrates was lower by 13% in the highest quintile category (29%EI) of T-LCDS compared to the lowest quintile category (41%EI), and median intake from high-quality carbohydrates were lower by 7% in the highest quintile category (11%EI) of T-LCDS compared to the lowest quintile category (18%EI). Baseline concentrations of inflammation biomarker by HQ-LCDS and LQ-LCDS quintile categories are presented in **Supplemental Table 1.**

HQ-LCDS was inversely associated with the change in the inflammation and oxidative stress score (mean $\pm$ SE in Q1: 0.24 ± 0.16, Q5: -0.27 ± 0.16; P_{trend}= 0.004), after adjusting for age, sex, BMI, smoking status, menopausal status, alcohol and total energy intake, and the baseline inflammation score **(Table 2)**. The results indicate that inflammation and oxidative stress increased in those with the lowest HQ-LCDS while it decreased in those with the highest HQ-LCDS. This association remained significant in the fully adjusted model. In secondary analyses, we observed a significant association between the T- LCDS and inflammation and oxidative stress score, but it weaker than we observed for HQ-LCDS (Table 2). Secondary analyses, examining the associations between HQ-LCDS and changes in logged values of individual biomarkers indicated that HQ-LCDS was inversely associations with ICAM-1 (P_{trend}= 0.003) and LPL-A2 activity (P_{trend}= 0.001), but not the other markers of inflammation and oxidative stress **(Supplemental Table 2)**. These findings suggest that inflammation was reduced in those whose diets were most consistent with LCD pattern that included high-quality

carbohydrates during follow-up whereas inflammation increased among those who consumed higher amounts of carbohydrate.

No significant associations were identified between LQ-LCDS and change in the inflammation and oxidative stress score **(Table 2)**. In a secondary analysis, significant inverse associations were observed between LQ-LCDS and change in the logged value of LPL-A2 mass (P_{trend}= 0.03) in the fully adjusted model **(Supplemental Table 3)**.

We also observed a statistically significant inverse association between T-LCDS and change in inflammation and oxidative stress score (Q1: 0.11 ± 0.16, Q5: -0.28 ± 0.16; P_{trend}= 0.04) after adjusting for age, sex, BMI, smoking status, menopausal status, alcohol and total energy intake and the baseline inflammation score **(Table 2),** which was similar to, although more modest than, that observed for HQ-LCDS. This association remained significant in the fully adjusted model. We also found statistically significant inverse associations between T-LCDS and logged ICAM-1 (P_{trend}= 0.02), and logged LPL-A2 activity (P_{trend}= 0.02) in the fully adjusted models **(Supplemental Table 4)**.

3.5 Discussion

In this longitudinal study, we found that consumption of an LCD pattern that retained high-quality carbohydrates was associated with favorable changes in the inflammation and oxidative stress score. Specifically, we observed the strongest inverse association between the HQ-LCDS, for which a higher score represented a lower intake of low-quality carbohydrate, and changes in inflammation and oxidative stress, while we observed no significant association between the LQ-LCDS, for which a higher score represents a lower intake of high-quality carbohydrate, and changes in inflammation and oxidative stress in spite of the fact that total carbohydrate intake was similar among those with the highest HQ-LCDS and LQ-LCDS scores. The similar association observed for T-LCDS and HQ-LCDS is likely due to the similar intakes of low-quality carbohydrates among those who scored high on both of these scores, a consequence of the fact that the majority of carbohydrates in the participants diets were low-quality.

Overall, our findings suggest that consumption of less low-quality carbohydrate is associated with less inflammation and oxidative stress. These findings are important

considering the increasing popularity of LCDs and the large number of people adopting these diets for perceived health benefits (40).

The favorable associations between lower intake of carbohydrate from low-quality food sources extend the previous evidence on the pro-inflammatory effects of low-quality carbohydrates. There is evidence that added sugars available in refined carbohydrates, sugar-sweetened beverages, dairy desserts may affect the inflammatory status (41,42). Major global contributors to free added sugars have been demonstrated to be sugar-sweetened beverages (43), which have been associated with higher concentrations of inflammatory biomarkers in cross-sectional, observational studies (44–51) and few randomized controlled clinical trials (52–55).

Some cross-sectional studies reported positive associations between either higher dietary glycemic index (GI, a ranking of carbohydrate foods by their glycemic potency) (56,57), glycemic load (GL, defined as the mathematical product of the GI and carbohydrate content) (58), or both (59,60) and higher concentrations of CRP. On the other hand, findings from a systematic review of randomized controlled trials on the effect of GI and GL on inflammatory biomarkers showed no significant effect of low GI or GL diets on CRP, TNF-α, leptin or IL-6 concentrations compared with the control diet (higher in GI or GL) (61).

Several possible mechanisms could be involved in the association between low-quality carbohydrates food sources with chronic inflammation. First, low-quality carbohydrates have a high GI that results in higher and more rapid increase in blood glucose concentration. In vitro, studies have shown that glucose can cause oxidation of membrane lipids, proteins, lipoproteins, and DNA and activate inflammation (62). Additionally, lower-quality carbohydrates food sources lack dietary fibers, which are crucial for maintaining a healthy digestive system and play an important role in modulating inflammation. In fact, it has been suggested that a diet rich in fiber can decrease the systemic inflammatory response by improving the intestinal barrier function and modulating the intestinal microbiota (63). This is because dietary fiber is essential for the formation of short-chain fatty acids, which are thought to play a key role in neuro-immune-endocrine regulation (63). Moreover, the refining process of carbohydrates

removes various essential nutrients, such as B vitamins, vitamin E, and minerals like magnesium and zinc, present in whole grains. These nutrients exert anti-inflammatory effects and are involved in supporting the immune response (64). Moreover, high consumption of added sugars can represent a substantial source of endogenous advanced glycation end products. Advanced glycation end products are compounds formed when sugars react with proteins or fats in a process known as glycation. These compounds have been linked to increased inflammation and oxidative stress (65).

We found similar beneficial associations between HQ-LCDS and T-LCDS with changes in inflammation and oxidative stress. This is likely because most of carbohydrate intake in our cohort is from low-quality carbohydrate sources which is similar to the findings from a recent nationally representative data from National Health and Nutrition Examination Survey, where mean energy intake from total carbohydrate was 51%, 42% of which is from low-quality carbohydrates sources, while 9% was from high-quality carbohydrate sources (66). However, the associations between LCDS and beneficial changes in inflammation and oxidative stress score is attenuated in T-LCDS compared to HQ-LCDS, partially because in T-LCDS both high-quality and low-quality carbohydrates intakes were lower.

The beneficial associations found between HQ-LCDS and T-LCDS with the change in inflammation/ oxidation score could be also due to higher dietary protein intake. In a previous study using data from Framingham offspring cohort, higher dietary protein intake, particularly from plant sources was associated with favorable changes in inflammation/ oxidative stress as assessed by the overall inflammation and oxidative stress score (38). However, the protein distribution in all of the LCD scores was identical, so this is unlikely to be responsible of any observed beneficial association as no association was observed with the LQ-LCDS.

Likewise, the higher LCDSs also reflected higher intake of total fats, including higher polyunsaturated fatty acids, in our population. While omega-3 fatty acids have been associated with lower concentrations of inflammatory biomarkers including CRP, interleukins IL-1 and IL-6, prostaglandin and cytokines in many observational and intervention studies (67–76), and the role of omeg-6 fatty acids and their interactions with

omega-3 fatty acids in modulating inflammatory process is complex and still not properly understood (77), the increase in different fatty acids was identical in all of the scores so, as with protein, it is unlikely that the increase in fatty acids is responsible for the beneficial association with inflammation and oxidative stress biomarkers, since no association was observed with the LQ-LCDS.

A major strength of the present study is the large, well-characterized cohort followed for an average of 7 years with repeated measures of exposures and outcomes from which changes in circulating and urinary biomarkers of inflammation and oxidative stress could be derived. Additionally, in our analyses, we used a combination of nine inflammation and oxidative stress biomarkers that are commonly used in observational and intervention studies; they are widely linked to chronic diseases and their risk factors, as well as aging process; and diet has been shown to be associated with their concentrations (78,79). Moreover, our focus was on the impact of carbohydrate quality in lower carbohydrate diet patterns and changes in inflammation and oxidative stress biomarkers. While there are no previous studies of LCDS and inflammation and oxidative stress, other studies using LCDSs have assessed healthy and unhealthy diet patterns in the context of lower carbohydrate diets to cardiometabolic risk factors by simultaneously considering fat quality and protein sources and carbohydrate quality. However, we chose to focus on the role of carbohydrate quality in lower carbohydrate diets and limit confounding by creating scores that did not link the quality of carbohydrates to plant and animal sources of fat and protein.

On the other hand, our study had some limitations. First, the use of self-reported FFQs to assess participants' dietary intake may be limited by recall and social desirability biases that lead to potential misclassification of nutrient intake. However, FFQs provide good estimates of relative intake and are appropriate for ranking individuals' intakes. Second, we could not examine the associations with very low carbohydrate diet patterns as few individuals in our study population consumed less than 25% of energy from carbohydrates. Third, we did not adjust for overall diet quality in our models because of the high correlation between the quality of carbohydrates and diet quality, which may lead to over adjustment bias. Fourth, although we addressed confounding in several ways,

residual confounding by unmeasured dietary or other lifestyle factors may also affect our results. Finally, the generalizability of our conclusions may be limited, as the Framingham Offspring cohort are predominantly Caucasian Americans.

3.6 Conclusions

The findings of our study suggested that long-term adherence to LCD patterns, particularly one that includes a lower intake of low-quality carbohydrate but maintains high quality carbohydrates, is associated with lower risk of chronic inflammation and oxidative stress, which may result in a reduced chronic diseases risk in aging populations. This lends support to recommendations on preserving high-quality carbohydrates in the diet and replacing low-quality carbohydrates with more healthy energy sources.

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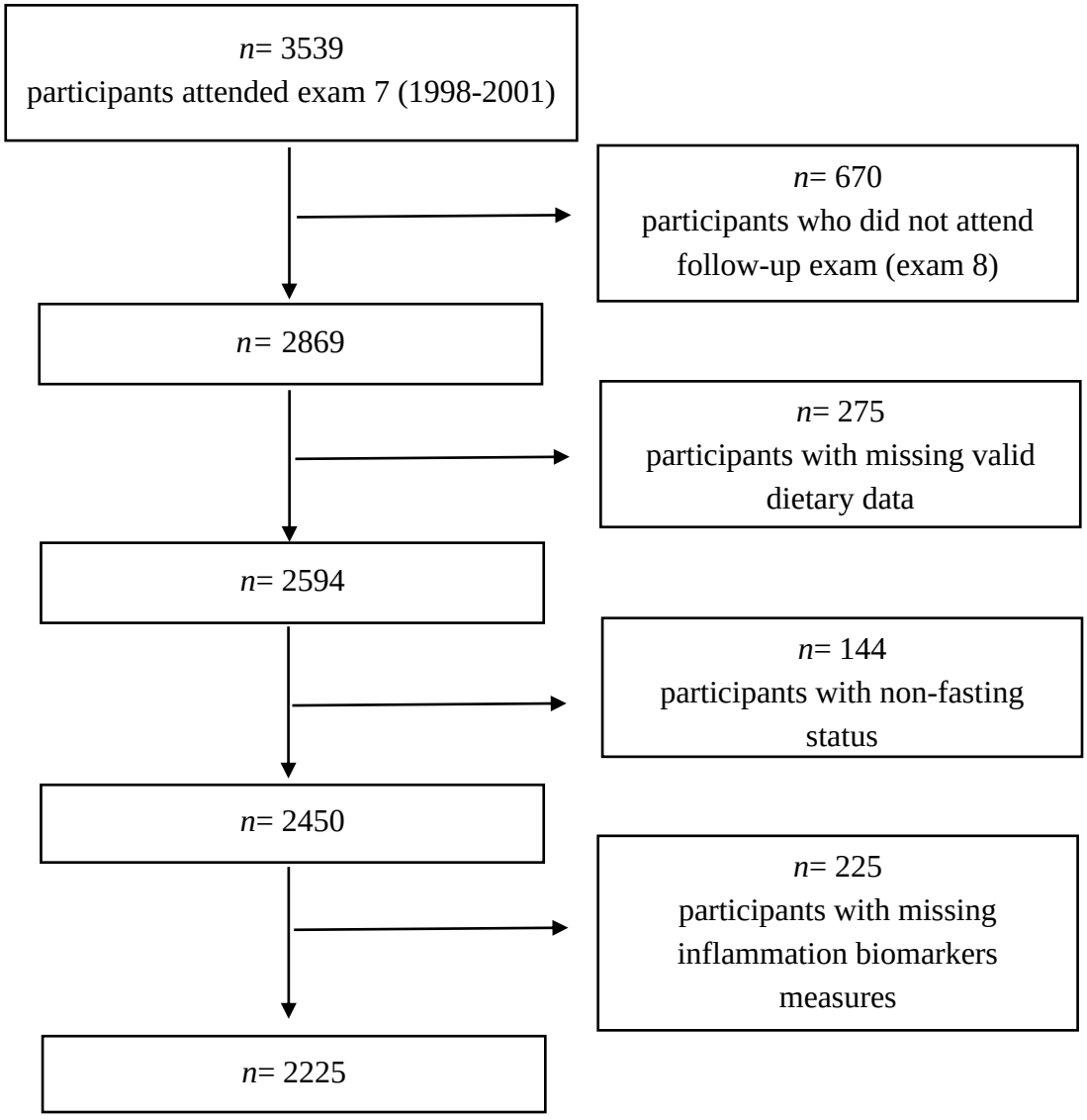

Figure 1. Flowchart for selection of study participants.

Table 1. Baseline characteristics by quintiles of HQ-LCDS and LQ-LCDS in 2225 participants of the Framingham Offspring Study at exam 7 [1]

		HQ-LCDS		LQ-LCDS	
	Total	**Quintile 1**	**Quintile 5**	**Quintile 1**	**Quintile 5**
Median score (IQR) [2]	-	6 (4 - 7)	24 (23 - 27)	7 (5 - 8)	23 (22 - 25)
Characteristics [3]					
n	2225	417	437	406	437
Age, y	59 (53 - 67)	60 (53 - 67)	60 (54 - 67)	62 (56 - 68)	57 (52 - 65)
Female, n (%)	1232 (55.4)	204 (48.9)	275 (62.9)	217 (53.4)	239 (54.7)
BMI, kg/m^2	27.3 (24.4 - 30.5)	26.5 (23.6 - 29.2)	27.8 (24.8 - 31.7)	26.3 (23.6 - 29)	28.3 (25.2 - 32.2)
PAI, MET-hr/d	36.8 (34.1 - 40)	36.4 (33.8 - 39.3)	36.8 (33.8 - 40.2)	36.8 (34.1 - 40.2)	36.9 (34.4 - 40.2)
Current smoker, n (%)	246 (11.1)	43 (10.2)	54 (12.3)	33 (8.1)	64 (14.7)
NSAID and corticosteroid use, n (%)	604 (27.1)	114 (27.4)	123 (28.2)	101 (24.8)	121 (27.7)
Hypertension treatment, n (%)	677 (30.4)	122 (29.3)	128 (29.2)	135 (33.3)	146 (33.4)
Dyslipidemia treatment, n (%)	428 (19.2)	102 (24.3)	76 (17.4)	93 (22.9)	77 (17.6)
Hyperglycemia treatment, n (%)	116 (5.2)	7 (1.7)	54 (12.2)	14 (3.5)	28 (6.5)

History of CVD, n (%)	228 (10.2)	55 (13.1)	51 (11.7)	52 (12.8)	51 (11.7)
Dietary intake [4]					
DGAI score	61.6 (52.7 - 69.6)	60 (52.5 - 67.3)	58.9 (51.3 - 67.3)	68.2 (62.6 - 74.7)	51.9 (45.1 - 58.6)
Total energy, kcal	1764 (1403 - 2173)	1852 (1475 -2230)	1633 (1343 -2026)	1719 (1396 -2101)	1716 (1351 -2160)
Total carbohydrate, %EI	50.1 (44.4 - 55.5)	58.8 (54.5 - 63.5)	41.6 (37.6 - 45.4)	60.2 (56.6 - 64)	41.7 (37.8 - 44.6)
Total fat, %EI	30.7 (26.2 - 35)	24.7 (21.4 - 28.2)	36.8 (33.5 - 39.6)	23.2 (20.9 - 26.2)	37.3 (34.7 - 40.6)
Total protein, %EI	17.2 (15.2 - 19.4)	14.3 (12.7 - 15.8)	20.5 (18.7 - 22.4)	15.6 (14 - 17)	19.6 (17.5 - 21.7)
Alcohol, %EI	1.6 (0 - 5.4)	2.1 (0 - 6.9)	0.9 (0 - 4.3)	1.6 (0 - 5.7)	1.1 (0 - 4.1)
HQ-carbohydrate, %EI	13 (8.7 - 18.7)	11.5 (7.5 - 17.9)	13.1 (9.1 - 17.9)	21.5 (16.9 - 26.7)	8.1 (6.1 - 10.9)
LQ-carbohydrate, %EI	34.1 (29.1 - 39.3)	43.4 (39.6 - 48.5)	26.4 (22.6 - 29.3)	36.4 (30.9 - 41.1)	31.4 (27 - 35.7)
Total Fiber, gm	17.3 (13.1 - 22.4)	17.2 (12.9 – 22.7)	15.6 (11.8 – 20.7)	21.9 (16.3 – 27)	13.2 (10.1 – 17.6)
SFA, %EI	10.6 (8.8 - 12.5)	8.6 (7.1 - 9.8)	12.8 (11.1 - 14.4)	7.7 (6.6 - 8.9)	13.2 (11.9 - 14.9)
PUFA, %EI	11.2 (9.4 - 13)	9 (7.5 - 10.5)	13.6 (12.2 - 15.1)	8.3 (7.2 - 9.5)	13.9 (12.8 - 15.4)
MUFA, %EI	5.6 (4.7 - 6.7)	4.7 (4 - 5.6)	6.7 (5.7 - 7.7)	4.8 (4 - 5.6)	6.4 (5.5 - 7.6)

[1] Values are medians (and interquartile ranges: 25th to 75th percentile) or frequency (and percentages). CVD, cardiovascular disease; DGAI, dietary guidelines adherence index; %EI, percent of total daily energy; LCDS, low-carbohydrate diet pattern scores; HQ-LCDS, high-quality low-carbohydrate diet pattern score; IQR, interquartile range; LQ-LCDS, low-quality low-carbohydrate diet pattern score; MET, Metabolic

equivalent task; MUFA, monounsaturated fatty acids; NSAID, nonsteroidal anti-inflammatory drug; SFA, saturated fatty acids; PAI, physical activity index; PUFA, polyunsaturated fatty acids;

[2] Adjusted for age and sex and total energy.

[3] Adjusted for age and sex.

[4] All dietary intake variables were adjusted for age, sex and total energy, except total energy variable which was adjusted for age and sex only.

Table 2. Adjusted least-square means of change in inflammation and oxidative stress score across quintiles of LCDSs in the Framingham Offspring Study [1]

LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
HQ-LCDS, n	438	444	468	412	463	
Median (Range)	7.5 (0 - 9.5)	11.5 (10 – 13)	15 (13.5 - 16.5)	18.5 (17 – 20)	23 (20.5 – 30)	
Model 1 [3]	0.24 ± 0.16	0.35 ± 0.16	-0.19 ± 0.15	-0.11 ± 0.16	-0.27 ± 0.16	0.004
Model 2 [4]	0.30 ± 0.16	0.36 ± 0.16	-0.17 ± 0.15	-0.15 ± 0.16	-0.32 ± 0.16	<0.001
LQ-LCDS, n	464	391	471	462	437	
Median (Range)	8.5 (1 - 10.5)	12 (11 – 13)	15 (13.5 – 16)	18 (16.5 - 19.5)	22 (20 – 30)	
Model 1	0.00 ± 0.16	-0.16 ± 0.17	0.01 ± 0.15	0.19 ± 0.15	-0.07 ± 0.16	0.73
Model 2	0.05 ± 0.16	-0.13 ± 0.17	-0.03 ± 0.15	0.18 ± 0.15	-0.10 ± 0.16	0.93
T-LCDS, n	459	424	474	416	452	
Median (Range)	7 (0 - 9.5)	11.5 (10 – 13)	15 (13.5 - 16.5)	18.5 (17 - 20.5)	23.5 (21 – 30)	
Model 1	0.11 ± 0.16	0.22 ± 0.16	0.00 ± 0.15	-0.03 ± 0.16	-0.28 ± 0.16	0.04
Model 2	0.17 ± 0.16	0.23 ± 0.16	0.00 ± 0.15	-0.04 ± 0.16	-0.35 ± 0.16	0.01

[1] Values are least-square adjusted means ± SE. HQ-LCDS, high-quality low-carbohydrate diet pattern score; LQ-LCDS, low-quality low-carbohydrate diet pattern score; T-LCDS, Total low-carbohydrate diet pattern score.

[2] $P < 0.05$ considered significant.

[3] Model 1 adjusted for age (continuous), sex (male/ female), BMI (continuous), total energy (continuous), alcohol intake (%EI/day), physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), baseline inflammation score value (continuous).

[4] Model 2 adjusted for model 1 covariates + history of cardiovascular disease (yes, no), non-steroidal anti-inflammatory drugs and corticosteroids use (yes, no), medication use for hyperglycemia, dyslipidemia , and hypertension (yes, no).

Supplemental Materials

Supplemental Table 1. Baseline concentrations of inflammation and oxidative stress biomarkers and inflammation score in 2225 participants of the Framingham Offspring Study at exam 7 [1]

Biomarker	Total	HQ-LCDS		LQ-LCDS	
		Quintile 1	Quintile 5	Quintile 1	Quintile 5
CRP, mg/L	2.1 (1 - 4.9)	1.9 (0.9 - 4.7)	2.1 (1 - 5.5)	1.8 (0.9 - 4.3)	2.3 (1 - 5.1)
IL-6, pg/mL	2.5 (1.7 - 4)	2.6 (1.7 - 4.1)	2.6 (1.8 - 4.1)	2.3 (1.7 - 3.7)	2.5 (1.7 - 3.9)
MCP-1, pg/mL	310 (252 - 379.2)	323 (268 - 388.6)	315 (254 - 391)	312 (251 - 376)	308 (250 - 386)
P-selectin, ng/mL	36.0 (28.1 - 45)	35.5 (28.2 - 45.4)	35.9 (27.7 - 45.1)	34.9 (27.8 - 43.9)	36.5 (29.3 - 45.3)
TNFRII, pg/mL	1935 (1646 -2318)	1970 (1662 - 2406)	1917 (1591 - 2327)	1970 (1675 -2427)	1914 (1595 -2288)
ICAM-1, ng/mL	238 (208 - 279)	243 (210 - 281)	236 (209 - 278)	238 (207 - 276)	237 (204 - 280)
LPL-A2 mass, ng/mL	286 (229 - 356)	293 (230 - 364)	287 (233 - 353)	278 (224 - 354)	289 (239 - 366)
LPL-A2 activity, nmol/mL/min	140 (118 - 164)	143 (121 - 167)	137 (116 - 165)	140 (116 - 162)	144 (118 - 169)
OPG, pmol/L	5.3 (4.4 - 6.2)	5.2 (4.4 - 6.1)	5.5 (4.5 - 6.6)	5.4 (4.6 - 6.5)	5.1 (4.3 - 6.2)
Corrected isoprostanes, ng/mmol	129 (88 - 187)	133 (86 - 196)	132 (90 - 195)	119 (81 - 173)	133 (95 - 191)
Inflammation and oxidative stress score	-0.1 (-3.2 - 3.0)	0.2 (-2.7 - 3.3)	0.0 (-3.5 - 3.1)	-0.5 (-3.2 - 2.7)	0.2 (-3.5 - 3.3)

[1] Values are medians (and interquartile ranges: 25th to 75th percentile) adjusted for age and sex. CRP, C-reactive protein; ICAM-1, soluble intracellular adhesion molecule 1; IL-6, interleukin 6; LPL-A2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1 (also known as CCL, chemokine [C-C motif] ligand); OPG, osteoprotegerin; TNFRII, tumor necrosis factor receptor II.

Supplemental Table 2. Adjusted least square means of change in individual biomarkers of inflammation or oxidative stress across quintiles of HQ-LCDS in the Framingham Offspring Study [1]

HQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	7.5	11.5	15	18.5	23	
Range	0 - 9.5	10 - 13	13.5 - 16.5	17 - 20	20.5 - 30	
Δ CRP, mg/L [3]	-0.24[4] ± 0.04	-0.28 ± 0.04	-0.32 ± 0.04	-0.31 ± 0.04	-0.32 ± 0.04	0.19
Δ IL-6, pg/mL	-0.34 ± 0.03	-0.34 ± 0.03	-0.37 ± 0.03	-0.33 ± 0.03	-0.38 ± 0.03	0.35
Δ MCP-1, pg/mL	0.19 ± 0.01	0.21 ± 0.01	0.19 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.15
Δ P-selectin, ng/mL	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.16
Δ TNFR II, pg/mL	0.24 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.37
Δ ICAM-1, ng/mL	0.18 ± 0.01	0.19 ± 0.01	0.15 ± 0.01	0.17 ± 0.01	0.13 ± 0.01	0.003
Δ LPL-A2 mass, ng/mL	-0.36 ± 0.01	-0.35 ± 0.01	-0.38 ± 0.01	-0.39 ± 0.01	-0.37 ± 0.01	0.24
Δ LPL-A2 activity, nmol/mL/min	0.01 ± 0.01	-0.01 ± 0.01	-0.03 ± 0.01	-0.04 ± 0.01	-0.03 ± 0.01	0.001
Δ OPG, pmol/L	-0.09 ± 0.01	-0.09 ± 0.01	-0.10 ± 0.01	-0.10 ± 0.01	-0.11 ± 0.01	0.07
Δ Corrected isoprostanes, ng/mmol [5]	-0.05 ± 0.03	0.00 ± 0.03	0.04 ± 0.03	-0.06 ± 0.03	0.00 ± 0.03	0.66

[1] Values are least-square adjusted means ± SE of the outcome, which is computed as the change in log value of the biomarker, modeled as exam 8 log value minus exam 7 log value. A higher value of the outcome indicates a larger change

(increase) in inflammation, whereas a lower value indicates a smaller change (increase if positive, decrease if negative), and therefore less inflammation. CRP, C-reactive protein; HQ-LCDS, high-quality low-carbohydrate diet pattern score; ICAM-1, soluble intracellular adhesion molecule 1; IL-6, interleukin 6; LPL-A2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1 (also known as CCL, chemokine [C-C motif] ligand); . OPG, osteoprotegerin; TNFRII, tumor necrosis factor receptor II.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for age (continuous), sex (male/ female), BMI (continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), baseline value of the outcome (continuous), history of cardiovascular disease (yes, no), non-steroidal anti-inflammatory drugs and corticosteroids use (yes, no), medication use for hyperglycemia, dyslipidemia , and hypertension (yes, no).

[4] The antilog of the mean difference of the log transformed values represent relative change (ratio) between the exam 8 and exam 7 values.

[5] N= 1825 for urinary creatinine-corrected urinary isoprostanes.

Supplemental Table 3. Adjusted least square means of change in individual biomarkers of inflammation or oxidative stress across quintiles of LQ-LCDS in the Framingham Offspring Study [1]

LQ-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	8.5	12	15	18	22	
Range	1 - 10.5	11 - 13	13.5 - 16	16.5 - 19.5	20 - 30	
Δ CRP, mg/L [3]	-0.26[4] ± 0.04	-0.31 ± 0.04	-0.31 ± 0.04	-0.32 ± 0.04	-0.27 ± 0.04	0.81
Δ IL-6, pg/mL	-0.34 ± 0.03	-0.37 ± 0.03	-0.37 ± 0.03	-0.33 ± 0.03	-0.36 ± 0.03	0.81
Δ MCP-1, pg/mL	0.18 ± 0.01	0.16 ± 0.01	0.20 ± 0.01	0.21 ± 0.01	0.19 ± 0.01	0.05
Δ P-selectin, ng/mL	0.11 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.12 ± 0.01	0.09 ± 0.01	0.47
Δ TNFR II, pg/mL	0.25 ± 0.01	0.22 ± 0.01	0.23 ± 0.01	0.23 ± 0.01	0.22 ± 0.01	0.21
Δ ICAM-1, ng/mL	0.19 ± 0.01	0.16 ± 0.01	0.14 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.17
Δ LPL-A2 mass, ng/mL	-0.39 ± 0.01	-0.38 ± 0.01	-0.36 ± 0.01	-0.36 ± 0.01	-0.36 ± 0.01	0.03
Δ LPL-A2 activity, nmol/mL/min	-0.03 ± 0.01	-0.01 ± 0.01	-0.03 ± 0.01	-0.02 ± 0.01	-0.03 ± 0.01	0.81
Δ OPG, pmol/L	-0.10 ± 0.01	-0.09 ± 0.01	-0.10 ± 0.01	-0.09 ± 0.01	-0.11 ± 0.01	0.51
Δ Corrected isoprostanes, ng/mmol [5]	-0.02 ± 0.03	-0.08 ± 0.03	0.01 ± 0.03	0.06 ± 0.03	-0.05 ± 0.03	0.53

[1] Values are least-square adjusted means ± SE of the outcome, which is computed as the change in log value of the biomarker, modeled as exam 8 log value minus exam 7 log value. A higher value of the outcome indicates a larger change (increase) in inflammation, whereas a lower value indicates a smaller change (increase if positive, decrease if negative), and therefore less inflammation. CRP, C-reactive protein; ICAM-1, soluble intracellular adhesion molecule 1; IL-6, interleukin 6; LPL-A2, lipoprotein-associated phospholipase A2; LQ-LCDS, low-quality low-carbohydrate diet pattern score; MCP-1, monocyte chemoattractant protein 1 (also known as CCL, chemokine [C-C motif] ligand); OPG, osteoprotegerin; TNFRII, tumor necrosis factor receptor II.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for age (continuous), sex (male/ female), BMI (continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), baseline value of the outcome (continuous), history of cardiovascular disease (yes, no), non-steroidal anti-inflammatory drugs and corticosteroids use (yes, no), medication use for hyperglycemia, dyslipidemia , and hypertension (yes, no).

[4] The antilog of the mean difference of the log transformed values represent relative change (ratio) between the exam 8 and exam 7 values.

[5] N= 1825 for urinary creatinine-corrected urinary isoprostanes.

Supplemental Table 4. Adjusted least-square means of change in inflammation scores and individual biomarkers across quintiles of T-LCDS in the Framingham Offspring Study [1]

T-LCDS	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend [2]
Median	7	11.5	15	18.5	23.5	
Range	0 - 9.5	10 - 13	13.5 - 16.5	17 - 20.5	21 - 30	
Δ CRP, mg/L [3]	-0.25[4] ± 0.04	-0.28 ± 0.04	-0.32 ± 0.04	-0.30 ± 0.04	-0.32 ± 0.04	0.22
Δ IL-6, pg/mL	-0.33 ± 0.03	-0.34 ± 0.03	-0.39 ± 0.03	-0.33 ± 0.03	-0.38 ± 0.03	0.28
Δ MCP-1, pg/mL	0.18 ± 0.01	0.20 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.18 ± 0.01	0.52
Δ P-selectin, ng/mL	0.12 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.19
Δ TNFR II, pg/mL	0.25 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.22 ± 0.01	0.22 ± 0.01	0.09
Δ ICAM-1, ng/mL	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.02
Δ LPL-A2 mass, ng/mL	-0.38 ± 0.01	-0.37 ± 0.01	-0.36 ± 0.01	-0.37 ± 0.01	-0.37 ± 0.01	0.82
Δ LPL-A2 activity, nmol/mL/min	-0.01 ± 0.01	-0.01 ± 0.01	-0.02 ± 0.01	-0.04 ± 0.01	-0.03 ± 0.01	0.02
Δ OPG, pmol/L	-0.10 ± 0.01	-0.10 ± 0.01	-0.09 ± 0.01	-0.10 ± 0.01	-0.12 ± 0.01	0.22
Δ Corrected isoprostanes, ng/mmol [5]	-0.04 ± 0.03	-0.01 ± 0.03	0.00 ± 0.03	0.03 ± 0.03	-0.04 ± 0.03	0.74

[1] Values are least-square adjusted means ± SE. CRP, C-reactive protein; ICAM-1, soluble intracellular adhesion molecule 1; IL-6, interleukin 6; LPL-A2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1 (also

known as CCL, chemokine [C-C motif] ligand); OPG, osteoprotegerin; T-LCDS, Total low-carbohydrate diet pattern score; TNFRII, tumor necrosis factor receptor II.

[2] $P < 0.05$ considered significant.

[3] Models adjusted for age (continuous), sex (male/ female), BMI (continuous), total energy (continuous), alcohol intake (%EI/day) , physical activity index (continuous), current smoker (yes/ no), menopausal status (yes/no periods had stopped for ≥1 y), baseline value of the outcome (continuous), history of cardiovascular disease (yes, no), non-steroidal anti-inflammatory drugs and corticosteroids use (yes, no), medication use for hyperglycemia, dyslipidemia , and hypertension (yes, no).

[4] The antilog of the mean difference of the log transformed values represent relative change (ratio) between the exam 8 and exam 7 values.

[5] N= 1825 for urinary creatinine-corrected urinary isoprostanes.

Chapter 4. Summary and Conclusions

4.1 Summary of Findings

The overall objective of this dissertation was to further our understanding of the role of carbohydrate quality in low-carbohydrate diet (LCD) patterns in relation to cardiometabolic health. This was achieved by examining long-term associations between two LCD scores (LCDSs) that represent lower intakes of either high-quality or low-quality carbohydrates, and higher intakes of total fat and protein in the context of an LCD pattern and changes in cardiometabolic risk factors. The central hypothesis was that an LCD pattern that reflects a lower intake of low-quality carbohydrates is more favorably associated with measures of cardiometabolic health than an LCD pattern representing a lower intake of high-quality carbohydrates. We tested our hypothesis by analyzing Framingham Heart Study offspring cohort data in two analyses using LCDSs to characterize the LCD diet patterns in relation to changes in (1) waist circumference (WC), blood pressure, blood lipid profiles, and serum glucose and (2) biomarkers of inflammation and oxidative stress. The results demonstrate that for most cardiometabolic risk factors, the LCDSs had differential associations based on carbohydrate quality, with lower intake of low-quality carbohydrate sources being associated with improved blood lipid profiles and reduced inflammation and oxidative stress markers over time, while lower intake of high-quality carbohydrates was associated with increased fasting serum glucose concentrations.

In the first analysis (Chapter 2), the associations between two LCDSs in which higher scores represent an LCD pattern with either lower intake of either high-quality or low-quality carbohydrate and higher intake of total fat and protein with long-term changes in WC, fasting HDL and non-HDL cholesterol, triglyceride, and glucose concentrations, and blood pressure were investigated in a cohort of middle-aged to older adults. As far as we know, our analysis is the first to consider the impact of LCD patterns on changes in intermediate risk factors while accounting for carbohydrate quality. A larger high quality (HQ)-LCDS value, indicating a lower intake of low-quality carbohydrates, was associated with increased plasma HDL cholesterol and decreased triglyceride concentrations, while a higher low quality (LQ)-LCDS value, indicating an

LCD pattern in which participants had lower consumption of high-quality carbohydrates with higher consumption of fats and protein, was associated with an increased serum glucose concentration. Over a median follow-up of 16.4 years both LCDSs were associated with a decrease in systolic blood pressure but an increase in WC.

In the second analysis (Chapter 3), we used data from the same cohort to examine the association between the aforementioned LCDSs and changes in circulating biomarkers of inflammation and oxidative stress, including inflammation and oxidative stress scores and individual biomarkers over a median follow up of 6.7 years. To our knowledge, this is the first study to examine the association between LCD patterns varying in carbohydrate quality in relation to changes in inflammation and oxidative stress biomarkers. Our analysis found that long-term adherence to LCD patterns, particularly an LCDS representing lower intake of low-quality carbohydrates, was associated with decreased inflammation and oxidative stress scores. Although total carbohydrate intake was similar among those with the highest HQ-LCDS and LQ-LCDS, we observed a strong inverse association between the HQ-LCDS for which a higher score represented a lower intake of low-quality carbohydrate, but not LQ-LCDS for which a higher score represented a lower intake of high-quality carbohydrate, and changes in inflammation and oxidative stress scores. These findings suggest that lower consumption of low-quality carbohydrates foods is associated with less inflammation and oxidative stress.

Taken together, the observations from our two analyses largely support our hypothesis for the beneficial role of lower intake of low-quality carbohydrates. HQ-LCDS was beneficially associated with changes in plasma HDL cholesterol and triglyceride concentrations, and biomarkers of inflammation and oxidative stress while LQ-LCDS was not. In addition, LQ-LCDS was adversely associated with serum glucose concentrations. These findings strongly support recommendations for preserving high-quality carbohydrates and reducing intake of low-quality carbohydrates in a moderate LCD pattern and replacing the latter with more healthy energy sources.

4.2 Public Health Implications

cardiovascular disease (CVD) is the leading cause of mortality globally. Lifestyle modifications, particularly diet, can have a significant impact on bringing these rates down (1). Therefore, global strategies to improve diet quality should be a global health priority. Increases in waist circumference, fasting glucose, triglycerides concentrations, blood pressure and low-grade inflammation, and decreases in HDL-cholesterol concentrations are associated with increase CVD risk, and together are referred to as the metabolic syndrome (2). Even modest improvements in these risk factors can reduce the population-level CVD risk. For example, a 2.6 mg/dL increase in plasma HDL cholesterol concentrations between the highest and lowest quintile of HQ-LCDS seen in our analysis would translate to a potential 5% reduction in CVD mortality (3).

The role of diet as a significant modifiable risk factor for cardiometabolic diseases is well established (4). By identifying dietary modifications that can help prevent or delay the development of cardiometabolic diseases, we could substantially reduce the burden of these diseases and improve quality of life. Findings from this research suggest that the benefits of LCD patterns on cardiometabolic health may be attributed to carbohydrate quality within the diet pattern. A lower intake of high-quality carbohydrates, including whole grains, whole fruits, legumes, and non-starchy vegetables, in the context of a moderate LCD pattern was associated with adverse changes in fasting serum glucose concentration. On the other hand, lower intakes of low-quality carbohydrates, including refined grains, sweet-baked desserts, sugar-sweetened beverages, and dairy desserts, as part of a moderate LCD pattern had beneficial associations with changes in cardiometabolic risk factors and thereby help reducing the burden of cardiometabolic diseases.

The current 2020-2025 Dietary Guidelines for Americans recommended limiting energy intake from added sugar to no more than 10% and consuming at least half of all grains as whole grains (5). According to data from National Health and Nutrition Examination Survey (NHANES) from 1999-2016, there have been modest improvements in American adults' dietary carbohydrate quality. Intake of low-quality carbohydrates

decreased significantly from 45.1 %EI to 41.8 %EI, including a significant decline in energy from added sugar (16.4 %EI to 14.4 %EI), while a modest increase in energy from high quality carbohydrates was observed (7.4 %EI to 8.6 %EI) (6). However, Americans are still not meeting recommended intakes of important sources of high-quality carbohydrates, such as vegetables (5), fruits (5) and whole grains (5,7), and are consuming far too many refined grains (5,6) and added sugars (6). Our findings suggest that a decrease in the mean intake of low-quality carbohydrates (from 45.5 %EI in the lowest HQ-LCDS quintile category to 27.9 %EI in the highest category) could translate to clinically important cardiometabolic health benefits, as noted above for HDL cholesterol, while a decrease in the mean intake of high-quality carbohydrates (from 20.2 %EI in the lowest LQ-LCDS quintile category to 7.7 %EI in the highest category) led to 2.1 mg/dL increase in fasting glucose over 16.4 years that would translate into an approximately 18% increase in type 2 diabetes (T2D) (8). This support recommendations from the American Diabetes Association and American Heart Association to maintain high-quality carbohydrates and decrease low-quality carbohydrate in moderate LCD patterns to reduce risk of T2D and CVD (9,10).

5.3 Limitations and Future Directions

Although this dissertation addresses important gaps in the existing literature on the relationship between LCD patterns and cardiometabolic risk factors through the utilization of the prospective nature over a long follow-up time of the FHS, there are some limitations to this work that future research could address. One limitation is that we could not assess the associations with very low carbohydrate diet patterns as few individuals in our study population consumed less than 25% of energy from carbohydrates. The mean carbohydrate intake in the lowest quintile categories for both LCDSs was approximately 42 %EI and thus, these findings reflect a moderate low carbohydrate diet pattern. To address this limitation, large-scale, long-term randomized controlled trials on the effect of LCDs on changes in cardiometabolic risk factors would be needed. Second, the use of self-reported food frequency questionnaires (FFQs) to

estimate dietary intake may be subject to recall and social desirability biases that lead to potential misclassification of nutrient intake. However, FFQs provide good indication of relative intake and are appropriate for ranking individuals' intakes. To address this limitation, newer phone apps and other technology may make it more feasible for using diet records and diet recalls in large prospective cohort studies, allowing for more accurate assessment of dietary intake. Third, our characterization of carbohydrate quality using the total carbohydrate to dietary fiber ratio is one of many currently in use. While our approach has been validated (11), standardizing a valid definition of carbohydrate quality would be an important advance for future research on LCD patterns and carbohydrate quality. Finally, participants of the Framingham Offspring cohort are predominantly Caucasian Americans, which may limit the generalizability of our findings.

4.4 Conclusions

This dissertation fills several gaps in the current knowledge base on LCD patterns. First, long-term changes in cardiometabolic risk factors, rather than hard outcomes, were not previously investigated in relation to LCD patterns. Similarly, no prospective cohort data on the relation of LCD patterns with changes in biomarkers of inflammation and oxidative stress have been reported, and no studies consider carbohydrate quality in these dietary patterns independently of fat quality and protein sources. Our findings support that an LCD pattern based on a lower intake of low-quality carbohydrates and preservation of high-quality carbohydrates helps in the maintenance of cardiometabolic health over time.

4.5 References

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