Determinants of Indigenous Diet Quality and Their Association with Inflammation and Biological Age in the NHLBI Strong Heart Family Study

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2024

Committee:

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Program Authorized to Offer Degree:

Nutritional Sciences

University of Washington

Abstract

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Chronic, systemic, low-grade tissue inflammation is a major etiologic component of metabolic dysfunction that has been positively associated with biological age and chronic noncommunicable disease (NCD) risk. Chronic systemic inflammation, biological age, and NCD risk are influenced by a wide range of factors, including certain modifiable lifestyle factors such as diet quality. We examined whether diet quality, assessed using the 2010 Alternative Healthy Eating Index, was associated with inflammation (serum interleukin-6 and C-reactive protein) and biological age (leukocyte telomere length) in a sample of American Indian adults in the NHLBI Strong Heart Family Study, a population with disproportionately high rates of NCDs. This analysis found that better diet quality at baseline was associated with lower levels of CRP during an 8-year follow-up. This relationship appeared to be driven by increases in whole grain and legume consumption. The analysis also found poor diet quality among study participants overall. This finding was expanded upon in a review of the historical and social determinants of Indigenous diet quality and identified the concept of Indigenous Food Sovereignty as a direction for future community and policy efforts aiming to improve the health and wellbeing of Indigenous populations.

Introduction

Global rates of chronic noncommunicable diseases (NCDs) have drastically increased in recent decades.[1] This is the result of a combination of driving forces, including rapid unplanned urbanization, the globalization of unhealthy lifestyles, and population aging.[1] NCDs are responsible for 74% of all deaths worldwide, with four groups of diseases accounting for 80% of all premature deaths: cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes (including kidney disease deaths resulting from diabetes).[1,2] The burden of NCDs among adults of working age contributes to high healthcare costs, limited ability to work, and financial insecurity, thus perpetuating poverty and straining economic development.[2] However, some NCDs may be preventable by focusing on the mitigation of their metabolic risk factors including hypertension, hyperglycemia, hyperlipidemia, and excess visceral adipose tissue.[1] With this in mind, it is valuable to explore the biological processes that underlie metabolic dysfunction and can lead to risk factors for NCDs.

A major etiologic component of metabolic dysfunction is chronic, systemic, low-grade tissue inflammation, also known as metaflammation.[3,4] Inflammation is an innate immune response to actual or perceived bodily insults and is typically measured by two functionally linked biomarkers secreted in large amounts in the setting of inflammation: interleukin-6 (IL-6), a cytokine that regulates acute-phase protein synthesis in hepatocytes, and C-reactive protein (CRP), an acute-phase protein whose production in the liver is stimulated by IL-6.[5–7] CRP in particular is relatively easy and inexpensive to measure and, at high levels, has been associated with cardiovascular disease.[8] The inflammatory response is intertwined with the biochemical pathways that regulate metabolism, and the crosstalk between the two is described by the term immunometabolism.[3,5] Thus, levels of inflammation are impacted by a wide range of genetic, psychosocial, socioeconomic, environmental, and lifestyle factors that also influence the regulation of the metabolic and stress responses.[5] Inflammation resulting from these factors, as opposed to acute infections, manifests as a chronic state of low-grade activation of pro-inflammatory biochemical pathways.[5] A chronic, systemic, low-grade inflammatory state is a pathological feature of NCDs and appears to play a role in the development and progression of these diseases.[6,9]

Chronic systemic inflammation is also associated with biological age. Biological age refers to an individual's functional or physiological age, in contrast to a person's chronological age which refers only to the passage of time since birth.[10] Biological age can be measured by an individual's cellular telomere length, with peripheral blood leukocyte telomere length (LTL) being the marker commonly examined in cross-sectional and longitudinal analyses in humans.[11] Telomeres are regions of long, repeating sequences of DNA that cap the ends of chromosomes.[12–14] Their primary role is to maintain genomic stability by preventing the loss of base pairs during successive cellular divisions.[13–15] Telomeres become shorter with each somatic cellular division.[13,16] Over time, telomere length declines until a threshold is reached at which the cell can no longer divide, resulting in cellular senescence and eventually cell death.[12,14,16–18] For this reason, telomere length is thought to be a cellular marker of biological aging,[14–17] which is further supported by an inverse relationship between chronological age and telomere length.[15] Telomere length has also been inversely associated with risk of developing age-related NCDs and premature death, further supporting its use as a marker of biological age.[12,13,16,18] Biological aging has been positively associated with inflammation throughout the literature, and factors that increase inflammation have been associated

with shortened telomere length and vice versa.[13,17] In addition, several in vivo studies have reported associations between shorter telomeres and dysregulations in inflammatory markers.[16]
Chronic systemic inflammation, biological aging, and NCD risk are influenced by a wide variety of factors that also affect the regulation of metabolism and stress.[5] Genetics play a large role in determining NCD risk, accounting for approximately 25-40% of the variation in CRP levels between individuals and 70% of LTL variability.[16,19] The remaining differences between individuals are determined by external factors (including psychosocial, socioeconomic, environmental, and lifestyle factors), which tend to be influenced by an individual's social determinants of health (SDOH).[16] According to the WHO, the SDOH can be more important than healthcare or lifestyle choices for influencing health and may account for 30-55% of health outcomes.[20] The SDOH, however, have been inequitably determined by centuries of institutionalized racism, engendering significant health inequities for communities of color.[21] The "Weathering Hypothesis" proposed by Arline T. Geronimus in 1992 describes how accumulated exposure to stress, poverty, dangerous environments, and general social disadvantage accelerate body 'wear and tear' and biological aging.[22,23] This hypothesis has been supported using telomere length and measures of allostatic load.[23] The theory of allostatic load is described as the cumulative physiological burden of stress on the body's systems, owing to repeated adaptation to stressors.[22–24] Allostatic overload, then, is characterized by dysregulation of the body's physiological stress systems, chronic activation of inflammatory pathways, accelerated biological aging, and oxidative stress.[16,24] Further, the stress response is known to disrupt metabolic processes through the alteration of glucose metabolism, hormone action, mitochondrial adjustments, and increased deposition of visceral fat tissue.[25] Therefore, in the setting of chronic stress, defined by chronic activation of the stress response, these cumulative effects contribute to ongoing metabolic dysfunction and increased NCD risk.[25] In fact, large-scale epidemiological studies have shown allostatic load to be predictive of premature mortality and physical and cognitive decline.[24] Additionally, chronic stressors can modify gene expression and exert epigenetic effects that predispose subsequent generations to poorer health outcomes.[26,27] In these ways, allostatic load reflects differences in exposure to chronic stressors and their resulting contributions to downstream disparities in health outcomes.

An important population for which these associations can be explored is American Indians.[1]*
American Indian (AI) communities are characterized by significant socioeconomic and health inequities resulting from centuries of institutionalized oppression and historical injustices perpetuated by White settler-colonialism.[28] AI populations have disproportionately high rates of NCDs, infectious diseases, suicide, substance use, unintentional injury, interpersonal violence, and premature death compared to other racial and ethnic groups in the United States.[28–31] The SDOH for AI communities tend to include high rates of poverty, food insecurity, and unemployment, poor housing, inadequate education, and discrimination in the delivery of health services.[28,29,31] Additionally, research among AI populations have found high rates of trauma exposure, a category of extreme stress that can dysregulate the physiological stress system, chronically activate pro-inflammatory pathways, and accelerate biological aging.[16,24,32] This may relate to historical and intergenerational trauma, which an American Psychiatric Association Stress and Trauma toolkit says puts Indigenous peoples at higher risk for poor mental health.[33] Taken together, AI populations are at disproportionately higher risk for developing NCDs and generally having poorer health outcomes.

[1]* Many names are used to refer to the original inhabitants of North America. The participants in the SHFS prefer the term "American Indians." Thus, we will use this term throughout the paper when applicable in respect of their preference.

Despite the predominance of health outcomes being determined by genetics and the SDOH, many public health efforts target individual lifestyle modifications as a means of improving health outcomes. Thus, this paper focuses on diet as a modifiable lifestyle factor that can improve health through its effects on the metabolic risk factors for NCDs. There is substantial evidence to suggest that foods, nutrients, and non-nutrient food components modulate both acute and chronic inflammation.[6] Global shifts in dietary patterns towards the modern Western diet have been linked to the dramatic rise in NCD incidence seen worldwide.[9] Research suggests that this rapid global increase in rates of NCDs may be partially attributable to the proinflammatory nature of the Western diet, which tends to be ultra-processed, energy-dense, nutrient-poor, and high in added sugars, saturated fatty acids, and trans fatty acids.[6,9,34] The pro-inflammatory effects of the Western diet are explained in part by the effects of oxidative/nitrosative stress,[35] with an emerging area of research focusing on the negative impacts on the human gut microbiome.[4] Diet plays a significant role in shaping the gut microbiome, with even short-term changes in diet inducing large, temporary alterations to the microbial community structure and activity.[36,37] Changes in the microbial community and their resulting metabolites alter the responsiveness of local immune cells and may disturb gut barrier integrity, allowing harmful microbial products to enter the bloodstream and induce systemic inflammation.[4]

Anti-inflammatory dietary patterns – as characterized by high consumption of omega-3 fatty acids, antioxidants, polyphenols, and fiber – have been associated with protective effects for inflammation, associated NCD risk, and biological aging.[9,13,17,34,35,38] Anti-inflammatory diet patterns align with the Alternative Healthy Eating Index (AHEI), which is based on foods and nutrients predictive of chronic disease risk.[39] The AHEI was developed by the Harvard University T.H. Chan School of Public Health as an alternative to the U.S. Department of Agriculture's (USDA) Healthy Eating Index (HEI), which measures adherence to the Dietary Guidelines for Americans.[39,40] High scores on the AHEI-2010 have been shown to be inversely associated with inflammation and NCD risk and are characterized by high consumption of fruits, vegetables, whole grains, nuts, legumes, and unsaturated fats, and low consumption of refined grains, added sugars, saturated and trans fatty acids, red and processed meats, sodium, and alcohol.[39–41] Taking together the AHEI's demonstrated inverse association with NCD risk and the links between chronic systemic inflammation, biological aging, and NCD risk, it is valuable to examine whether adherence to the AHEI is associated with decreased levels of inflammation and slowed biological aging.

We examined these relationships in an AI population using data from the Strong Heart Family Study. The Strong Heart Family Study (SHFS) is a longitudinal cohort study of the cardiovascular health of AIs from 12 tribal communities in Arizona, North Dakota, South Dakota, and Oklahoma. The study has been supported by the National Heart, Lung, and Blood Institute (NHLBI) since 1988 and is the largest epidemiologic study of an AI population to date.[42] The study was designed to characterize the metabolic and cardiovascular health profile of AIs, and data has been collected on a wide variety of risk factors for cardiovascular diseases over the past 30+ years, including markers of inflammation (IL-6, CRP) and biological age (LTL).[42] However, no one thus far has examined the associations between diet quality, inflammation, and biological age using this data. We used data collected from Phases IV (baseline) and V (follow-up) of the SHFS to examine these relationships, with the intent of using the results to inform policy and community efforts that benefit the health and wellbeing of AI communities.

Methods

Setting and Study Population

The SHFS, a family-based cohort study of risk factors for cardiovascular diseases, is an ongoing study that involves 12 tribal communities in Arizona, North Dakota, South Dakota, and Oklahoma.[42] The original sample included 2,756 participants from 94 families, all of whom completed two examinations over an 8-year period: 2001-2003 (baseline) and 2006-2009 (follow-up).[42] Both study exams included a personal interview, physical examination, medication review, laboratory work-up, and dietary assessment.[43] Details on the study methods and data collection instruments have been reported elsewhere.[44] Tribal communities were involved in all components of the study.[43] The institutional review board from each Indian Health Service region and all 12 tribal communities approved the study, and written informed consent was obtained from all participants at each exam. This research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.[43]

For this analysis, we included SHFS participants with available data on diet, markers of inflammation (IL-6, CRP), and biological age (LTL). Participants reporting extreme caloric intake (<600 or >6,000 kcal/day for females, <600 or >8,000 kcal/day for males) were excluded. We also excluded participants who were missing data for >10% of foods on the food frequency questionnaire and participants with missing values for the AHEI components. Participants missing values of IL-6, CRP, or LTL were also excluded. Following exclusions, the remaining sample to be analyzed totaled 2,076 participants. The numbers of participants included and excluded from analysis are shown in *Figure 1*.

Primary Exposure: Diet Quality assessed by Alternative Healthy Eating Index (AHEI) Scores

The primary exposure was diet quality assessed using the 2010 Alternative Healthy Eating Index (AHEI). The AHEI is a composite score that includes daily servings of fruits and vegetables, whole grains, nuts and legumes, n-3 long-chain polyunsaturated fatty acids, sugar-sweetened beverages and fruit juices, red and processed meats, trans fatty acids, sodium, and alcohol consumption.[39,40] The AHEI has consistently been shown to be predictive of chronic disease risk in diverse populations.[39,40] AHEI scores are measured on a scale of 0-110, with a score of 0 being complete nonadherence (highest NCD risk) and a score of 110 being perfect adherence to the index (lowest NCD risk).[40] AHEI scores were assigned to SHFS participants based on responses to a self-administered Block Food Frequency Questionnaire (FFQ) completed as part of the baseline and follow-up examinations. Participants received guidance on how to fill in the questionnaire during the exam.

The FFQ assessed average food intake over the past year and included questions on 119 food items. Food item categories included: vegetables; fruits; cold cereal; fat or oil in cooking; meats and main dishes; snacks; breads; beverages; vitamin, mineral, and botanical supplements, etc. The quantity of food consumed was assessed using frequency of consumption measures (i.e., “Never,” “A few times a year,” “Once per month,” “2-3 times per month,” “Once per week,” “2 times per week,” “5-6 times per week,” “Every day”) and portion sizes. Portion sizes were only required if the food was eaten more than once per week. Portion sizes were described by either natural portions (i.e., one apple, one candy bar, etc.) or standard volume and weight portions (i.e., 1 tbsp, ¼ cup, ½ cup, 1 cup, etc.). For the latter, participants were provided visuals to assist in identifying the standard portion consumed. The nutrient analysis of the

beverage section assumed standard sizes for glasses, bottles, cans, etc. The final page of the questionnaire asked about consumption of common Indigenous foods, including spam, menudo, pozole, guyvsava, and frybread. The FFQs were analyzed by Block Dietary Data Systems (Berkeley, CA) to calculate average daily energy and nutrient intake.

Primary Outcomes: Inflammation (IL-6, CRP) and Biological Age (LTL)

Inflammation (IL-6, CRP)

Inflammation was assessed by evaluating serum concentrations of IL-6 and CRP, two commonly assayed, functionally linked biomarkers that increase in concentration in the setting of inflammation.[5] The IL-6 assay was performed on the Bioplex 100 (Luminex, X-MAP) instrument for samples collected at the baseline exam only and had intra-assay and inter-assay coefficients of variation (CVs) of 3.51% and 4.48%, respectively.[43] Circulating concentrations of CRP were assessed using an immunoturbidimetric method (Vitros Chemistry Products, number 6801739, Ortho Clinical Diagnostics, Rochester, NY) for samples collected at the baseline and follow-up exams.[43] The sensitivity of the assay was 0.175 mg/L and the CV was less than 4.1%.[43]

Biological Age (LTL)

Blood samples collected during the baseline examination were used to isolate peripheral blood leukocytes, from which genomic DNA was extracted. LTL was measured and assessed by E.B.'s laboratory (University of California, San Francisco, CA) using quantitative PCR.[45] LTL was measured as the ratio of telomeric product to single copy gene (T/S ratio) using a high-throughput telomere length assay system.[45] The T/S ratio reflects the average length of the telomeres based on the rationale that the longer the telomeres are in each sample, the more PCR product will be generated in PCR reactions using primers specific for the telomeric DNA.[45] Laboratory personnel conducting the assessments were blinded to the clinical characteristics of study participants.[45] Each sample was assessed three times and the mean LTL was used in statistical analysis.[45] 4.1% of samples were assessed twice for quality control.[45] Additional details of the laboratory methods and quality control procedures are described elsewhere.[45] The LTL of duplicate samples was high ($r = 0.95$) and the mean inter-assay and intra-assay CVs were 6.9% and 4.6%, respectively.[45]

Statistical Analysis

Generalized estimating equation (GEE) regression models with an independent working correlation and robust standard errors were used to examine associations of AHEI with IL-6 (cross-sectional), CRP (cross-sectional and longitudinal), and LTL (cross-sectional). We were unable to assess longitudinal associations of AHEI with IL-6 and LTL because this data was unavailable from the follow-up examination. GEE was used to address potential correlation within the data due to the family-based sampling of the study. IL-6 and CRP were assessed in their natural log forms to account for skewness in the data sets and will be referred to as ln(IL-6) and ln(CRP) in discussing the results, when applicable. All statistical analyses were conducted using STATA version 18.0.

Baseline characteristics of study participants were assessed categorically across quartiles of AHEI score, IL-6, CRP, and LTL. Covariates for the multivariate analysis were selected *a priori* based on available data and potential associations of the selected factors with diet quality, inflammation, and biological age. Model 1 (crude model) adjusted for basic participant characteristics: age, sex, and site. Model 2 (primary

model) additionally adjusted for education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day). Model 3 (exploratory model) additionally adjusted for anthropometric factors and preexisting metabolic risk factors or health conditions that may mediate or confound associations: waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD, and prevalent diabetes.

In sensitivity analyses, we examined potential interactions of AHEI scores with age, sex, and waist circumference on ln(IL-6),[46,47] ln(CRP),[46,47] and LTL[48–50] to determine if these factors modify associations of diet quality with inflammation and/or biological age. To assess interaction, we included an interaction term for each factor with diet quality (i.e., AHEI*age, AHEI*sex, AHEI*waist) in Model 2. Additionally, we ran exploratory analyses for individual food and nutrient components of AHEI (separately) with longitudinal ln(CRP) to further examine associations identified in the longitudinal analysis. All models were also re-run excluding participants with prevalent CVD and/or diabetes since these diseases may impact both diet quality and inflammation.

Results

Baseline Characteristics of Study Participants

The mean (SD) age of participants was 40.7 (16.9) years old, and 59.5% of the analytic cohort was female. In general, diet quality was low in the cohort with a median (IQR) of 39.8 (34.3, 45.7) out of a possible score of 110 (*Figure 2*). Baseline characteristics of study participants according to AHEI, IL-6, CRP, and LTL are shown in *Table 1* and *Tables 2A-C*. Participants with higher diet quality tended to be older and female; had higher systolic blood pressure, HDL cholesterol, triglycerides, fibrinogen; and had higher rates of prevalent diabetes, CVD, cancer, and CKD compared to those with poorer diet quality. As expected, participants with higher quality diets consumed less red and processed meat, saturated fat, and added sugar, and more fiber from grains, fruits, and vegetables compared to participants who reported poorer diet quality. Participants with higher levels of inflammation (IL-6 and CRP) were more likely to be older and female; had higher anthropometric measurements (BMI, waist circumference, body fat percentage), LDL cholesterol, and fibrinogen; and had higher rates of prevalent diabetes, CVD, cancer, and CKD compared to participants with lower levels of inflammation. Lastly, participants with the shortest telomeres (LTL) were older; had higher anthropometric measurements (BMI, waist circumference, body fat percentage), systolic blood pressure, LDL cholesterol, and triglycerides; and higher rates of diabetes, CVD, cancer, and CKD compared to participants with longer telomeres.

Cross-sectional Analyses

We did not observe associations of AHEI with ln(IL-6) (*Table 3A*), ln(CRP) (*Table 3B*), or LTL (*Table 3C*) in cross-sectional analyses. Additionally, there were no statistically significant interactions of age, sex, or waist circumference with AHEI on ln(IL-6) or LTL. We did observe interactions of AHEI with age on ln(CRP) ($P < 0.0001$) and AHEI with waist circumference on ln(CRP) ($P < 0.0001$). This finding suggests differences in the magnitude of association between AHEI and ln(CRP) based on levels of age and waist circumference.

Longitudinal Analysis

In prospective analyses, higher diet quality at baseline was associated with lower levels of ln(CRP) at follow-up (*Table 4*). In the primary model (Model 2), for every standard deviation increase in diet quality (9.02 points of AHEI score), there was a corresponding decrease in ln(CRP) of 0.054 ± standard error of 0.026 (*P = 0.038*). The association was not attenuated with further adjustment for anthropometric measures and preexisting health conditions (Model 3). Further, analyses that excluded participants with cardiovascular disease or diabetes at baseline produced similar findings. There was no evidence of interaction of diet quality with age, sex, or waist circumference on ln(CRP). To further our understanding of this result, we conducted exploratory analyses for the individual food and nutrient components of AHEI (separately) with longitudinal ln(CRP). Results are shown in *Table 5.* When the foods that comprise the AHEI were assessed individually, we observed statistically significant associations of whole grains and legumes with ln(CRP). In particular, higher intake of whole grains and legumes at baseline was associated with lower levels of ln(CRP) 8 years later.

Discussion

In this large study of AI adults, better diet quality at baseline was associated with lower levels of CRP during an 8-year follow-up. This relationship appeared to be driven by increases in whole grain and legume consumption. These results are supported by existing research on anti-inflammatory dietary patterns, which include foods high in fiber such as whole grains and legumes.[9,13,17,34,38] This finding may be explained by fiber's beneficial health effects on the gut microbiome since dietary fiber is a good source of "microbiota accessible carbohydrates" (MACs) or prebiotics.[36] However, research on the relationship between dietary patterns and the gut microbiome is still in its infancy. We did not observe associations of diet quality with IL-6 or LTL, likely owing in part to the cross-sectional nature of the data. It is also possible that the lack of association of diet quality with IL-6 or LTL is due to limited variability in diet quality within the cohort since most participants reported poor diet quality. In this discussion, we evaluate our results in the context of related research, compare the diet quality scores of AIs in the SHFS with those of other populations, examine the historical and social determinants of low diet quality among AI populations, and discuss the concept of Indigenous food sovereignty to provide direction for future policy and community efforts in this area.

Evaluating the Results in the Context of Related Research

There is much existing research examining the association between diet quality and concentrations of CRP. In an abbreviated review of the literature (*Table 6*), we identified seven papers that assessed these associations in large cohort studies or population-based surveys: Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS),[19] the Multiethnic Cohort (MEC) Study,[51] Hispanic Community Health Study/Study of Latinos (HCHS/SOL),[52] the Multiethnic Study of Atherosclerosis (MESA),[53] the National Health and Nutrition Examination Survey (NHANES),[8,54] and the Nurses' Health Study I (NHS I).[41] Generally, the studies had large sample sizes (n=57,356 cumulatively) and, taken together, evaluated individuals from a wide variety of ages, race and ethnicities, and locations across the United States. Despite this, these studies were cross-sectional in design, which inherently limits the strength of the results and prevents conclusions of causation. All studies found that improved diet quality (assessed using a variety of indices) was significantly associated with decreased concentrations of CRP. The consistency of this trend across the studies and large sample sizes is compelling, but it cannot be separated from their limitations. Moreover, the results of our study strengthen the existing body of

evidence through the use of longitudinal data within an underrepresented population. Still, more longitudinal research is needed to better assess the nature of these associations.

We also sought to identify related research exploring potential associations between diet quality and IL-6 or LTL. Nettleton et al. evaluated 5,089 adults in the MESA study and found that both CRP and IL-6 concentrations were negatively associated with a researcher-defined "Comprehensive Healthy Dietary Pattern" score, though this study was also cross-sectional.[53] Results from a large prospective study (Whitehall II cohort) indicate that participants who maintained a high AHEI score (n=1736, 37.7%) or improved AHEI score over a 6-year follow-up (n=681, 14.8%) showed significantly lower mean levels of IL-6 than those who had consistently low AHEI scores (n=1594, 34.6%) during that time.[55] This study is more compelling due to its prospective design, however its generalizability is limited by its predominantly White study population (93.8% of participants).[55] For LTL, two papers analyzing longitudinal associations between diet quality and LTL in the PREDIMED-NAVARRA cohort study identified associations between improved diet quality (as measured by the DII and Mediterranean diet) and longer telomeres.[13,38] The present study did not find an association between diet quality and IL-6 or diet quality and LTL. This could be due to the cross-sectional nature of the data or the limited variability of diet quality within the cohort, which was mostly low.

Comparison of Diet Quality Across Diverse Populations

More than 75% of the participants in the SHFS scored below the 50% mark (an AHEI score of 55) in diet quality. To provide context for these results, it is useful to compare SHFS participant AHEI scores to those of other populations. Thus, we identified studies analyzing AHEI scores in large cohorts or population-based surveys: NHS I,[56] the Health Professionals Follow-Up Study (HPFS),[57] the MEC Study,[58] and NHANES.[59] Participant characteristics and results of these studies are reported in *Table 7.* Among these, the NHS I,[56] HPFS,[57] and MEC study[58] reported higher median or average AHEI scores for a larger proportion of participants when compared to the scores of SFHS participants. The scores in the NHS I, HPFS, and MEC studies also tended to have greater variation and a higher ceiling of maximum scores, while the low end of the scores were comparable to those of the SFHS participants. In contrast, the study using data from NHANES reported low adjusted-mean AHEI scores that were comparable to SHFS participants' Quartile 1 scores.[59] This sample was large, nationally representative, and stratified AHEI scores across various demographics, although not categorically.[59] The study also reported significantly higher AHEI scores for the high socioeconomic status (SES) group compared to the medium and low SES groups. From these studies, it appears that there are significant differences in diet quality between groups (particularly when stratifying by SES), but diet quality among American adults is poor overall.[59]

Exploring how SHFS participant diet quality scores compare to those of other populations provides useful context for understanding our results. However, the populations in these cohort studies (predominantly non-Indigenous and living in urban and suburban areas) have very different risk profiles from the SHFS participants who are Indigenous and living on rural reservations. Moreover, the challenges to health and wellbeing faced by SHFS participants and other AI communities are distinct from those of the general population. These unique barriers may be attributed to a history of systemic oppression that disrupted traditional Indigenous food ways and engendered present day inequities in diet quality, health, and wellbeing. Thus, in order to understand these health inequities, it is necessary to review the historical and social determinants that created them.

Framing the Results in Context: Historical & Social Determinants of Indigenous Diet Quality

For thousands of years, Native tribes in North America were sustained by complex food systems adapted to each tribe's unique ecology.[29,60] Native peoples cultivated communal knowledge and traditions for their land that promoted community health and were passed down over generations.[60] Beginning with the arrival of European settlers, Native food systems and practices became disrupted through the effects of "virgin soil" epidemics and forced displacement of self-governing tribes from their ancestral lands.[60,61] "Indian removal" became U.S. government policy in the 1800s and is recognized by modern scholars as state-sanctioned ethnic cleansing.[61] "Indian removal" was enacted through policies such as the systematic slaughter of the American bison to coerce the Plains tribes into submission through starvation; the Indian Removal Act of 1830 which forced the migration of tens of thousands of Native peoples from their homelands onto reservation land, which tended to have low arability; and the Dawes Act of 1887 that resulted in the transfer of 93 million acres of land out of American Indian control.[60] These atrocities of settler-colonialism had dramatic and transformative effects on the health and wellbeing of Native populations. As Robin Wall Kimmerer, botanist, author and member of the Citizen Potawatomi Nation, writes in *Braiding Sweetgrass*, "In the settler mind, land was property, real estate, capital or natural resources. But to our people, it was everything: identity, the connection to our ancestors, the home of our nonhuman kinfolk, our pharmacy, our library, the source of all that sustained us."[62]

The impact of these historical events is evident in AI communities in the present day, manifesting as historical and intergenerational trauma and inequities in health and socioeconomic outcomes.[30,33] As noted previously, the "Weathering Hypothesis" describes how accumulated exposure to stress (including trauma), poverty, dangerous environments, and general social disadvantage accelerate body 'wear and tear' and biological aging.[22,23] This contributes to allostatic overload, characterized by systemic dysregulation of the body's physiological stress systems, chronic activation of inflammatory pathways, accelerated biological aging, and oxidative stress.[16,24] For this reason, AI populations are at a disproportionately greater risk for poorer health outcomes, particularly when accounting for the epigenetic transfer of this risk to subsequent generations.[19]

As of 2021, nearly 1 in 4 AIs lived in poverty, more than twice the rate of White Americans.[29] Moreover, from 2010-2020, food insecurity among AIs was roughly double, at times triple, those of White Americans.[29] Food insecurity and poor diet quality among present-day AI communities, as observed in the results of this study, is directly linked to the historical disruption of traditional food systems, inability to cultivate unfamiliar and non-arable lands, and the replacement of traditional foods with government commodity food rations. Since the 1800s, the U.S. government has provided food commodities to tribal communities to prevent starvation on reservations and meet treaty and policy obligations.[29] Commodity rations consisted of non-Native foods that were low cost and shelf-stable, many of which were low quality, sometimes rancid, and nutritionally inadequate, including lard, wheat flour, canned meat, and canned fruits and vegetables high in sodium and sugar.[29] These foods contributed to the rise of diet-related NCDs among AI communities, which had previously been rare.[29] Today, food assistance for AI communities is provided through the USDA's Food Distribution Program on Indian Reservations (FDPIR). As of 2016, the FDPIR constituted the sole or primary food source for 37.7% of program participants.[29] Since 2002, the FDPIR has worked with tribal nations and other government entities to improve the nutritional quality of the distributions and include more Native food items.[29]

In spite of these improvements, access to fresh, healthy food remains an issue. Dr. Amanda Fretts, an author of this study and member of Mi'kmaq Eel Ground First Nation, notes that the rural nature of reservations makes it difficult for AIs to access fresh, healthful foods.[63] Compounding this issue, individuals in AI communities earn lower incomes but pay higher prices for basic food products.[29,64] A 2018 report by First Nations Development Institute found that, compared to the national average, consumers in Indian Country paid an additional 56 cents for a gallon of milk, 84 cents for a loaf of bread, 61 cents per pound of chicken, and 47 cents for a dozen eggs.[64] These structural issues present significant and ongoing barriers to achieving health and wellbeing in AI communities.

Direction for Future Policy and Community Efforts: Indigenous Food Sovereignty

The concept of food sovereignty was developed by an international peasants' movement known as La Via Campesina and was first introduced during the 1996 World Food Summit.[65] La Via Campesina defined food sovereignty as, "the right of all peoples to healthy and culturally appropriate food and the right to define their own food and agricultural systems."[30,65] The food sovereignty movement was positioned in opposition to neoliberal policies that increase dependence on the global industrial food system at the expense of human and planetary health.[30,65] According to Dr. Charlotte Coté, a professor of American Indian Studies at the University of Washington and member of the Tseshaht First Nation, the food sovereignty movement can be "Indigenized" by moving beyond rights-based discourse and emphasizing the cultural responsibilities and relationships Indigenous peoples have with their environment.[30] Thus, Indigenous food sovereignty is intrinsic to the Indigenous struggles for decolonization and self-determination.[30] In this way, Indigenous food sovereignty provides a framework for how we can support the health and wellbeing of AI communities.

One policy moving in this direction is the FDPIR's Self-Determination Demonstration Project. The aim of the project is to empower Tribal Nations to purchase foods through the FDPIR that align with their Native culture and traditions.[66] For example, a joint project with the Oneida Nation and Menominee Indian Tribe in Wisconsin used project funds to purchase locally procured meats, fish, wild rice, and apples from the Oneida Nation Farm and the Oneida Nation Apple Orchard.[66] Since 2021, the USDA has awarded millions of dollars to participating tribal nations and is currently in round 2 of project implementation.[67] More projects like this are needed to continue the advancement of Indigenous food sovereignty and the right of Indigenous peoples for self-determination. Janie Hipp, Director of the Indigenous Food and Agriculture Initiative at University of Arkansas School of Law, writes about Indian Country, "It is only by regaining our foods [that] we will be able to restore our health, our resilience as peoples and secure the stability and diversification within our own communities and local economies."[68]

Strengths and Limitations

This study has many strengths. This was a large study that examined data in an underrepresented population. The analysis used a detailed data set which included demographic, social, behavioral and clinical factors. Appropriate statistical measures were used across multiple models to control for potential confounding variables. Additionally, the FFQ administered to participants attempted to obtain the most accurate diet information possible and mitigate recall bias by including an Indigenous foods component and providing visuals to assist participants in recalling portion sizes. The FFQ also sought to capture detailed dietary information over the course of a year. This study is distinguished in its ability to evaluate

the prospective associations between diet quality and CRP, given that much of the existing research in this area within large cohort studies and population surveys is cross-sectional. Finally, this study attempted to humanize its participants by thoroughly evaluating the results within a historical and social context, with the intent of providing practical direction for policy efforts and future research.

There are several limitations to this study that should be considered. The SHFS is an observational study, which limits our ability to form conclusions regarding the causal nature of the relationships between diet quality, inflammation, and biological age. Cross-sectional analyses are also prone to the influence of confounding variables, despite our best efforts to control for them. Additionally, we were unable to assess longitudinal associations of diet quality with IL-6 and LTL because this data was unavailable from the follow-up examination. There is a need for more longitudinal data collection of IL-6 and LTL within AI populations in order to analyze these associations. We were able to assess the longitudinal associations of CRP with diet quality, but it was difficult to compare our results to those of other studies since we log-transformed our data to address skewness. Additionally, diet quality in this study was assessed using a self-reported FFQ. It is possible that some participants did not accurately recall the frequency or typical quantities of their food intake over the past year. Although the FFQ utilized in the SHFS has been shown to be validated and reliable in free-living populations, misclassification of diet quality is possible. Lastly, despite our best efforts to use the strongest and most recent data available to inform this paper, more research is needed to illuminate the complex mechanisms and relationships between diet quality, inflammation, biological age, chronic stress and trauma, and the social determinants of health.

Conclusion

In this paper, we explored the relationships of diet quality with inflammation and biological age for AI populations. We found that improvements in diet quality were significantly associated with decreases in inflammation over time, primarily driven by increases in whole grain and legume consumption. We also found that overall diet quality was low for SHFS participants and explored the underlying reasons for this through an investigation of the historical and social determinants of health inequities in AI populations. Lastly, we identified Indigenous food sovereignty as a guide for future policy initiatives to improve the health and wellbeing of Native peoples and communities.

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Appendix

Figure 1: Inclusion and Exclusion of Participants From Analysis

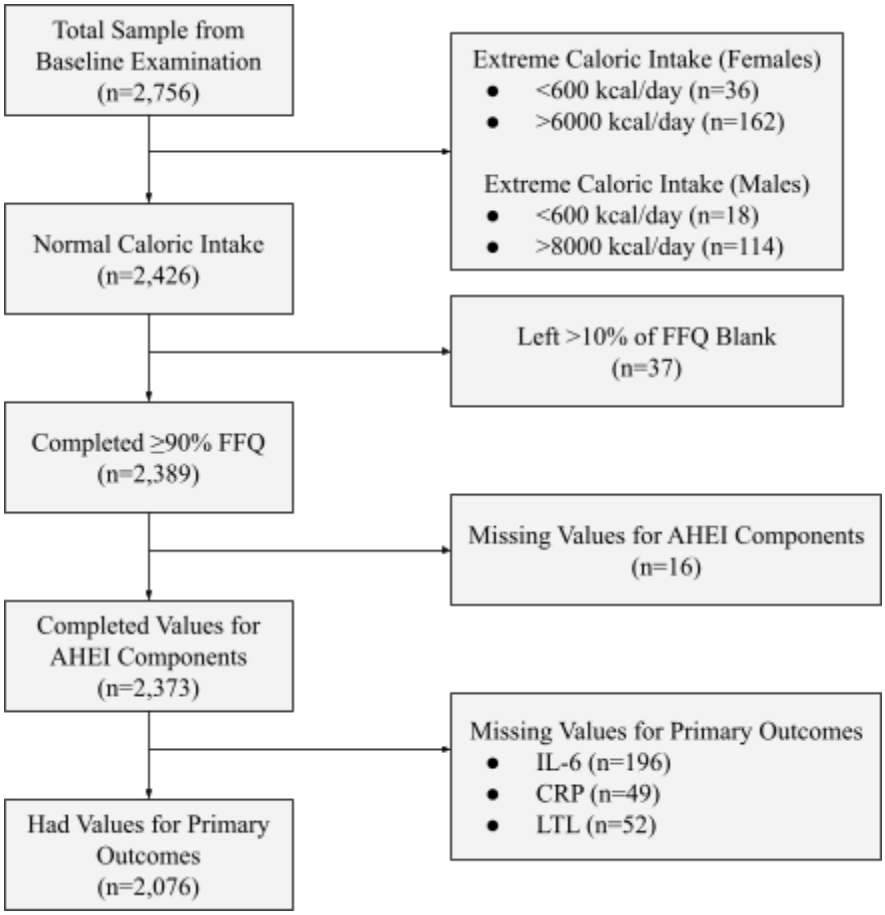

Figure 2. Distribution of Continuous Participant AHEI-2010 Scores

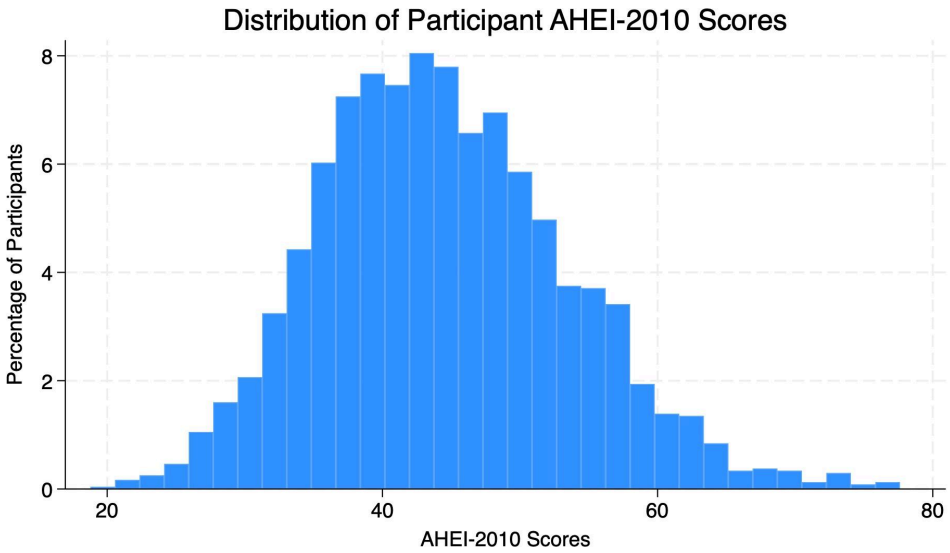

Table 1. Baseline Characteristics of SHFS Participants According to Quartile of Diet Quality (AHEI) (n=2373)[1]				
Quartile **Median AHEI Score (IQR)**	**Q1** **34.6 (31.8, 36.5)**	**Q2** **41.0 (39.6, 42.5)**	**Q3** **46.8 (45.2, 48.5)**	**Q4** **55.3 (52.3, 59.0)**
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age, years	34.1 (14.7)	40.3 (17.0)	41.8 (16.3)	46.6 (17.1)
Sex, % F	54.4	59.0	61.6	63.1
Education, years	11.8 (2.1)	12.2 (2.3)	12.4 (2.3)	12.7 (2.3)
Smoking, % current	39.9	35.2	37.7	31.4
Alcohol consumption, % current	61.4	54.1	59.9	55.6
BMI, kg/m^2	30.6 (7.8)	31.4 (7.2)	31.2 (7.2)	31.9 (7.3)
Waist circumference, cm	100.1 (18.5)	102.5 (17.2)	102.4 (17.6)	103.7 (19.1)
Body fat, %	34.9 (10.3)	36.3 (10.3)	36.4 (9.9)	36.6 (9.5)
Systolic blood pressure, mm Hg	120.0 (14.7)	123.0 (16.7)	124.1 (16.7)	125.2 (17.4)
HDL cholesterol, mg/dL	51.0 (14.0)	51.1 (13.5)	51.9 (14.6)	52.5 (15.9)
LDL cholesterol, mg/dL	97.8 (31.4)	102.0 (30.3)	100.7 (30.0)	99.1 (29.8)
Triglycerides, mg/dL	146.0 (90.3)	159.4 (112.7)	176.6 (244.0)	181.4 (223.1)
Fibrinogen, mg/dL	372.1 (86.4)	381.2 (82.4)	382.1 (90.0)	384.3 (92.3)
Prevalent diabetes, %	11.4	17.7	22.8	23.9
Prevalent CVD, %	2.4	4.7	3.5	6.6
Prevalent cancer, %	2.5	3.2	6.2	5.7
Prevalent CKD[2], %	3.4	6.5	7.3	9.0

Activity, steps per day	6232.6 (4025.7)	5910.5 (3945.1)	5485.6 (3403.4)	5753.5 (4340.0)
Total calories, kcal/day	2461.4 (1121.6)	2291.5 (1204.4)	2347.3 (1370.2)	2651.8 (1585.1)
Saturated fat, % calories	11.7 (2.2)	11.6 (2.4)	11.6 (2.1)	11.2 (2.1)
Protein, % calories	12.6 (2.9)	12.7 (2.8)	13.0 (2.8)	13.8 (3.0)
Processed meat, grams/1000 calories	17.9 (11.1)	14.4 (10.4)	12.5 (8.2)	10.3 (7.9)
Unprocessed red meat, grams/1000 calories	27.0 (18.4)	24.3 (17.3)	23.3 (17.3)	19.6 (14.7)
Fiber from grains, grams/1000 calories	3.1 (1.3)	3.3 (1.4)	3.6 (1.6)	4.2 (2.1)
Fruits & vegetables, servings/day	2.7 (1.5)	3.1 (1.9)	3.8 (2.3)	5.2 (3.3)
Added sugars, teaspoon equivalents/day	27.0 (16.2)	22.9 (16.6)	20.8 (15.1)	19.8 (15.7)

[1]characteristics described as mean (SD), else %; Abbreviations: SHFS, Strong Heart Family Study; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; CKD, chronic kidney disease
[2]prevalent CKD includes stage 3 and above

Table 2A. Baseline Characteristics of SHFS Participants According to Quartile of Interleukin-6 (IL-6) (n=2,177)[1]

Quartile **Median IL-6 (IQR)**	**Q1** **0.81 (0.45, 1.15)**	**Q2** **2.34 (1.98, 2.83)**	**Q3** **4.66 (3.93, 5.5)**	**Q4** **12.52 (8.67, 26.04)**
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age, years	39.1 (16.4)	40.5 (16.7)	41.0 (17.1)	42.5 (17.7)
Sex, % F	55.3	58.3	60.4	63.1
Education, years	12.2 (2.3)	12.3 (2.3)	12.2 (2.3)	12.3 (2.3)
Smoking, % current	36.1	36.4	35.7	35.3
Alcohol consumption, % current	59.5	58.3	58.0	55.1
BMI, kg/m^2	29.7 (6.5)	31.0 (6.5)	32.4 (7.9)	32.6 (8.3)
Waist circumference, cm	98.7 (17.0)	101.8 (16.0)	104.6 (18.3)	105.1 (20.5)
Body fat, %	33.9 (9.1)	36.0 (9.9)	37.2 (10.5)	37.5 (10.4)
Systolic blood pressure, mm Hg	122.2 (16.8)	123.5 (16.0)	123.9 (16.8)	123.9 (16.5)
HDL cholesterol, mg/dL	52.8 (15.7)	51.4 (13.7)	51.1 (13.8)	50.5 (14.2)
LDL cholesterol, mg/dL	102.9 (30.9)	98.8 (29.6)	100.1 (31.6)	97.5 (29.9)
Triglycerides, mg/dL	161.1 (129.2)	166.0 (147.0)	181.3 (298.9)	160.2 (108.3)
Fibrinogen, mg/dL	354.6 (74.8)	375.8 (82.7)	391.1 (89.1)	399.7 (99.1)
Prevalent diabetes, %	15.8	19.0	21.3	21.3
Prevalent CVD, %	2.2	5.1	5.2	5.7
Prevalent cancer, %	3.5	4.4	4.2	5.5
Prevalent CKD[2], %	3.8	5.2	7.4	10.8
Activity, steps per day	6407.7 (4328.6)	5906.4 (4061.3)	5628.5 (3864.0)	5250.0 (3385.5)

Total calories, kcal/day	2462.9 (1369.1)	2386.0 (1291.4)	2452.5 (1334.6)	2419.1 (1352.5)
Saturated fat, % calories	11.5 (2.2)	11.4 (2.3)	11.6 (2.2)	11.6 (2.2)
Protein, % calories	13.0 (2.9)	12.9 (3.0)	13.0 (2.8)	12.8 (2.8)
Processed meat, grams/1000 calories	13.9 (10.0)	14.1 (11.3)	13.8 (9.2)	13.8 (9.2)
Unprocessed red meat, grams/1000 calories	23.4 (16.5)	23.4 (16.8)	23.9 (16.9)	23.8 (18.1)
Fiber from grains, grams/1000 calories	3.5 (1.6)	3.5 (1.7)	3.6 (1.8)	3.6 (1.5)
Fruits & vegetables, servings/day	3.7 (2.4)	3.8 (2.9)	3.8 (2.6)	3.6 (2.3)
Added sugars, teaspoon equivalents/day	23.0 (16.2)	22.4 (15.6)	22.3 (16.5)	22.4 (15.8)

[1]characteristics described as mean (SD), else %; Abbreviations: SHFS, Strong Heart Family Study; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; CKD, chronic kidney disease
[2]prevalent CKD includes stage 3 and above

Table 2B. Baseline Characteristics of Study Participants According to Quartile of C-Reactive Protein (CRP) (n=2,324)[1]

Quartile **Median CRP (IQR)**	**Q1** **0.73 (0.4, 1.06)**	**Q2** **2.41 (1.9, 2.98)**	**Q3** **5.07 (4.32, 6.29)**	**Q4** **12.94 (10.2, 18.8)**
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, years	33.5 (16.5)	42.0 (17.4)	43.0 (16.0)	44.1 (15.2)
Sex, % F	49.1	52.0	65.2	72.9
Education, years	12.0 (2.4)	12.3 (2.3)	12.5 (2.2)	12.3 (2.2)
Smoking, % current	34.4	35.5	38.2	35.7
Alcohol consumption, % current	61.7	58.0	57.3	54.7
BMI, kg/m^2	26.6 (5.6)	30.2 (5.6)	32.8 (6.2)	35.5 (8.6)
Waist circumference, cm	90.5 (14.7)	100.4 (14.2)	106.3 (15.7)	111.4 (20.3)
Body fat, %	29.7 (9.2)	34.2 (8.4)	38.7 (8.5)	41.8 (9.6)
Systolic blood pressure, mm Hg	118.9 (15.6)	123.3 (17.4)	125.0 (15.8)	125.2 (16.4)
HDL cholesterol, mg/dL	54.5 (15.6)	50.6 (13.8)	50.6 (14.4)	51.0 (13.8)
LDL cholesterol, mg/dL	94.2 (30.1)	103.2 (30.5)	102.2 (30.1)	99.6 (30.0)
Triglycerides, mg/dL	144.8 (254.7)	166.2 (120.7)	187.9 (210.8)	165.5 (89.5)
Fibrinogen, mg/dL	317.5 (61.8)	363.5 (72.4)	388.6 (69.1)	446.6 (90.1)
Prevalent diabetes, %	7.9	16.3	22.8	28.3
Prevalent CVD, %	2.1	4.3	5.0	6.0
Prevalent cancer, %	2.6	4.0	5.0	6.0
Prevalent CKD[2], %	3.5	8.1	8.5	6.6
Activity, steps per day	7096.9 (4248.1)	6374.3 (4059.6)	5279.4 (3449.6)	4606.2 (3501.2)
Total calories, kcal/day	2504.2 (1443.3)	2389.2 (1329.9)	2489.4 (1307.6)	2383.2 (1273.1)

Saturated fat, % calories	11.5 (2.2)	11.6 (2.3)	11.6 (2.2)	11.6 (2.1)
Protein, % calories	12.9 (2.9)	13.1 (3.0)	13.1 (2.8)	13.0 (2.8)
Processed meat, grams/1000 calories	13.7 (10.3)	13.6 (9.3)	14.6 (10.9)	14.1 (9.5)
Unprocessed red meat, grams/1000 calories	23.4 (16.4)	24.3 (18.0)	24.3 (18.0)	23.2 (16.6)
Fiber from grains, grams/1000 calories	3.3 (1.4)	3.6 (1.7)	3.6 (1.6)	3.6 (1.8)
Fruits & vegetables, servings/day	3.6 (2.7)	3.7 (2.7)	3.8 (2.5)	3.7 (2.3)
Added sugars, teaspoon equivalents/day	24.0 (16.7)	22.1 (16.1)	22.5 (16.5)	21.7 (15.0)

[1]characteristics described as mean (SD), else %; Abbreviations: SHFS, Strong Heart Family Study; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; CKD, chronic kidney disease
[2]prevalent CKD includes stage 3 and above

Table 2C. Baseline Characteristics of SHFS Participants According to Quartile of Leukocyte Telomere Length (LTL) (n=2,321)[1]

Quartile **Median LTL (IQR)**	**Q1** **0.73 (0.63, 0.80)**	**Q2** **0.92 (0.89, 0.96)**	**Q3** **1.05 (1.02, 1.09)**	**Q4** **1.24 (1.18, 1.35)**
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age, years	48.2 (15.9)	44.2 (16.3)	38.4 (16.0)	32.2 (14.9)
Sex, % F	58.7	61.4	59.1	59.5
Education, years	12.4 (2.3)	12.4 (2.3)	12.3 (2.2)	12.0 (2.2)
Smoking, % current	33.4	36.1	38.1	36.7
Alcohol consumption, % current	52.5	54.5	57.9	65.5
BMI, kg/m^2	32.2 (7.4)	31.8 (7.6)	31.2 (7.2)	30.0 (7.3)
Waist circumference, cm	105.9 (19.0)	103.6 (17.7)	101.4 (18.0)	98.1 (17.3)
Body fat, %	36.7 (9.8)	36.8 (9.8)	35.7 (9.9)	35.1 (10.6)
Systolic blood pressure, mm Hg	125.0 (17.4)	124.6 (17.1)	123.5 (16.4)	119.5 (14.5)
HDL cholesterol, mg/dL	52.1 (14.8)	51.9 (14.6)	50.6 (14.4)	51.9 (14.4)
LDL cholesterol, mg/dL	100.3 (31.3)	101.9 (30.2)	101.6 (31.2)	95.6 (28.5)
Triglycerides, mg/dL	180.3 (241.8)	172.7 (133.3)	163.2 (145.6)	147.6 (186.2)
Fibrinogen, mg/dL	383.5 (92.2)	386.5 (91.8)	381.0 (81.8)	369.0 (84.4)
Prevalent diabetes, %	28.4	23.7	14.2	9.5
Prevalent CVD, %	7.2	4.8	3.3	2.2
Prevalent cancer, %	5.9	6.0	4.0	2.2
Prevalent CKD[2], %	10.7	7.9	4.7	3.1
Activity, steps per day	5202.8 (3888.8)	5544.8 (3824.7)	6120.3 (3822.9)	6563.3 (4176.2)
Total calories, kcal/day	2345.0 (1301.7)	2318.4 (1266.8)	2541.8 (1351.4)	2546.2 (1419.3)
Saturated fat, % calories	11.7 (2.3)	11.5 (2.1)	11.6 (2.2)	11.5 (2.2)
Protein, % calories	12.9 (2.9)	13.2 (2.9)	13.0 (2.8)	12.9 (3.0)

Processed meat, grams/1000 calories	13.5 (9.3)	14.1 (9.7)	14.4 (10.9)	13.9 (10.1)
Unprocessed red meat, grams/1000 calories	23.2 (17.6)	24.6 (17.9)	23.2 (16.1)	24.2 (17.4)
Fiber from grains, grams/1000 calories	3.6 (1.8)	3.6 (1.5)	3.5 (1.7)	3.4 (1.5)
Fruits & vegetables, servings/day	3.7 (2.4)	3.5 (2.3)	3.9 (2.9)	3.6 (2.5)
Added sugars, teaspoon equivalents/day	21.0 (16.4)	20.8 (14.1)	24.3 (16.4)	24.4 (17.3)

[1]characteristics described as mean (SD), else %; Abbreviations: SHFS, Strong Heart Family Study; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; CKD, chronic kidney disease
[2]prevalent CKD includes stage 3 and above

Table 3A. Cross-sectional Association of AHEI Score with the natural log of IL-6, assessed continuously.[1]

	Per SD Increase in AHEI Score (9.02)	
	β ± SE	*P*
Model 1[2]	-0.025 ± 0.031[JN1]	0.413
Model 2[3]	-0.028 ± 0.033	0.396
Model 3[4]	-0.032 ± 0.033	0.333

[1] Data were analyzed with the use of generalized estimating equations. AHEI, alternative healthy eating index; IL-6, interleukin-6.
[2] Crude model; Adjusted for age, sex, and site.
[3] Primary model; Adjusted in addition for education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day).
[4] Exploratory model; Adjusted in addition for waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD and diabetes.

Sensitivity Analysis
Assessed for potential interactions with age, sex, and/or waist circumference:

- No interactions with age, sex, or waist circumference.

Excluded participants with prevalent CVD and diabetes:

- No change in significance of association.

Table 3B. Cross-sectional Association of AHEI Score with the natural log of CRP, assessed continuously.[1]

	Per SD Increase in AHEI Score (9.02)	
	β ± SE	*P*
Model 1[2]	0.024 ± 0.025	0.330
Model 2[3]	0.034 ± 0.026	0.190

Model 3[4]	0.033 ± 0.024	0.171

[1] Data were analyzed with the use of generalized estimating equations. AHEI, alternative healthy eating index; CRP, C-reactive protein.
[2] Crude model; Adjusted for age, sex, and site.
[3] Primary model; Adjusted in addition for education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day).
[4] Exploratory model; Adjusted in addition for waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD and diabetes.

Sensitivity Analysis
Assessed for potential interactions with age, sex, and/or waist circumference:
- Interaction for AHEI score and age (P<0.000).
- Interaction for AHEI score and waist circumference (P<0.000).

Excluded participants with prevalent CVD and diabetes:
- No change in significance of association.

Table 3C. Cross-sectional Association of AHEI Score with LTL, assessed continuously.[1]

	Per SD Increase in AHEI Score (9.02)	
	β ± SE	*P*
Model 1[2]	-0.001 ± 0.005	0.797
Model 2[3]	-0.0006 ± 0.005	0.913
Model 3[4]	-0.0001 ± 0.005	0.984

[1] Data were analyzed with the use of generalized estimating equations. AHEI, alternative healthy eating index; LTL, leukocyte telomere length.
[2] Crude model; Adjusted for age, sex, and site.
[3] Primary model; Adjusted in addition for education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day).
[4] Exploratory model; Adjusted in addition for waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD and diabetes.

Sensitivity Analysis
Assessed for potential interactions with age, sex, and/or waist circumference:
- No interactions with age, sex, or waist circumference.

Excluded participants with prevalent CVD and diabetes:
- No change in significance of association.

Table 4. Longitudinal Association of AHEI Score with the natural log of CRP, assessed continuously.[1]

	Per SD Increase in AHEI Score (9.02)	
	β ± SE	*P*
Model 1[2]	-0.050 ± 0.024	0.041*
Model 2[3]	-0.054 ± 0.026	0.038*

Model 3[4]	-0.051 ± 0.025	0.043*

[1] Data were analyzed with the use of generalized estimating equations. AHEI, alternative healthy eating index; LTL, leukocyte telomere length.
[2] Crude model; Adjusted for age, sex, and site.
[3] Primary model; Adjusted in addition for education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day).
[4] Exploratory model; Adjusted in addition for waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD and diabetes.

**P* value is significant ($P < 0.05$).

Table 5. Longitudinal Association of Foods and Nutrients Comprising AHEI Score with the natural log of CRP, assessed continuously.[1, 2, 3]

AHEI Component	β ± SE	*P*
Vegetables	-0.011 ± 0.026	0.675
Fruit	-0.008 ± 0.026	0.755
Whole Grains	-0.054 ± 0.024	0.028*
Sugar-Sweetened Beverages	-0.014 ± 0.022	0.526
Legumes	-0.047 ± 0.022	0.032*
Meat	-0.002 ± 0.021	0.934
Trans Fats	-0.020 ± 0.020	0.306
Omega-3 Fatty Acids	-0.003 ± 0.024	0.901
Polyunsaturated Fats	-0.006 ± 0.023	0.804
Sodium	0.010 ± 0.019	0.616
Alcohol	-0.007 ± 0.029	0.803

[1] Data were analyzed using model 3; adjusted for age, sex, site, education (years), smoking (never, former, current), and pedometer-determined ambulatory activity (steps per day), waist circumference (cm), systolic blood pressure (mm Hg), LDL cholesterol (mg/dL), prevalent CVD and diabetes.
[2] Data were analyzed with the use of generalized estimating equations. AHEI, alternative healthy eating index; CRP, C-reactive protein.
[3]All participants were included in the analysis.

**P* value is significant ($P < 0.05$).

Table 6. Comparison of Results with Other Studies Evaluating Diet Quality and CRP Levels

Paper	**Study Characteristics**	**Participant Characteristics**	**Results**

Kuczmarski et al., 2013[19]	Cohort: Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) Cross-sectional study Data collection: 2004-2009 Location: Baltimore, MD	n=2,017 Ages: 30-64 y 43.7% Male 56.3% Female 42.3% White 57.7% Black Low-income, urban population	A 10% increase in micronutrient quality was associated with a 4% decrease in CRP levels.
Guillermo et al., 2019[51]	Cohort: The Multiethnic Cohort (MEC) Study Cross-sectional study Data collection: 2013-2016 Locations: Hawaii, California	n=1,806 Mean age = 69.2 y 49.6% Male 50.4% Female 22.4% White 16.4% Black 16.3% Native Hawaiian 23.9% Japanese American 21.0% Latino	Across ethnic groups, higher diet quality was positively associated with 13-23% lower levels of chronic inflammation (CRP).
Mattei et al., 2018[52]	Cohort: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Cross-sectional study Data collection: 2008-2011 Locations: Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA	n=14,623 Ages: 18-74 y 60% were ≥45 y Males and Females 100% Hispanic/Latino	The likelihood of having high-risk CRP concentrations (defined as ≥10 mg/L) was 23% lower for every 10 units of AHEI score increase ($p<0.0001$).
Nettleton et al., 2008[53]	Cohort: Multi-Ethnic Study of Atherosclerosis (MESA) Cross-sectional study Data collection:	n=5,089 Ages: 45-84 y 47.2% Male 52.8% Female 43.1% White	CRP and IL-6 levels were negatively associated with a researcher-defined “Comprehensive Healthy Dietary Pattern” score.

	2000-2002 Locations: Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; St Paul, MN	24.1% Black 20.3% Hispanic 12.5% Chinese	
Nicklas et al., 2012[54]	Cohort: National Health and Nutrition Examination Survey (NHANES) Cross-sectional study Data collection: 2001-2008 Location: National	n=18,988 Ages: ≥19 y 49% Male 51% Female 72% White 11% Black 12% Hispanic 5% Other	With increasing diet quality (HEI), there was a significant linear decrease in CRP (P = 0.0016).
Ford et al., 2004[8]	Cohort: National Health and Nutrition Examination Survey (NHANES) Cross-sectional study Data from 1988-1994 Location: National	n=13,811 Ages ≥20 y 48.4% Male 51.6% Female 77% White	HEI score was inversely associated with CRP concentration, but only among women. Among the HEI components, only the score for grains was inversely associated with CRP concentration.
Fargnoli et al., 2008[41]	Cohort: Nurses' Health Study I (NHS I) Cross-sectional study Dietary data collected from 1984-1990 Blood samples collected between 1989-1990 Location: National	n=1,022 100% Female Mean age ± SD across quintiles of AHEI score ranged from 54.9 ± 7.0 y to 58.5 ± 6.7 y.	AHEI score was inversely associated with plasma CRP. Women in the 5th quintile of AHEI score (n=387, AHEI score of 49-72) had 41% lower median CRP concentrations.

Table 7. Comparison of Diet Quality Results Across Large Cohort Studies

Paper	Study Characteristics	Participant Characteristics	AHEI-2010 Scores
Hagan et al., 2016[56]	Cohort: Nurses' Health Study I (NHS I) Data collection: 1992 Location: National	n=54,762 100% Female	Median scores in quintiles Q1: 39.9 Q2: 46.8 Q3: 51.9 Q4: 57.3 Q5: 65.2
Gu et al., 2022[57]	Cohort: Health Professionals Follow-Up Study (HPFS) Data collection: 2004 Location: National	n=44,525 100% Male ~90% White	Mean ± SD in quintiles Q1: 39.2 ± 4.2 Q3: 53.5 ± 1.6 Q5: 68.4 ± 4.7
Park et al., 2020[58]	Cohort: Multiethnic Cohort Study (MECS) Baseline data collection: 1993-1996 Follow-up data collection: 2003-2007 Locations: Hawaii, California	n=63,255 42.7% Male 57.3% Female <u>Race/Ethnicity</u> 10.6% Black 7.6% Native Hawaiian 34.5% Japanese American 19.2% Latino 28.1% White	Mean ± SD from baseline to 10-year follow up <u>Men</u> Baseline: 64.5 ± 9.9 Follow-up: 67.1 ± 10.4 <u>Women</u> Baseline: 65.7 ± 9.3 Follow-up: 67.9 ± 9.9
Wang et al., 2014[59]	Cohort: National Health and Examination Survey (NHANES) Baseline data collection: 1999-2000 Follow-up data collection: 2009-2010 Location: National	n=29,124 48.0% Male 52.0% Female Ages: 20-85 years Nationally representative sample	Adjusted mean (95% CI) from baseline to 10-year follow up <u>Men</u> Baseline: 34.0 (32.8 - 35.2) Follow-up: 35.7 (34.9 - 36.6) <u>Women</u> Baseline: 36.5 (35.5 - 37.5) Follow-up: 39.0 (38.3 - 39.8)