Diet, Iq'mik Smokeless Tobacco Use and Cardiometabolic Risk among Yup'ik Alaska Native People living in Southwest Alaska

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Abstract

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Yup’ik Alaska Native people live in rural communities in Southwest Alaska. Many Yup’ik people retain aspects of their traditional lifestyle, including a subsistence diet and use of iq’mik smokeless tobacco. We aimed to characterize associations between these aspects of Yup’ik lifestyle and biomarkers of cardiometabolic (CM) status (e.g., lipids, blood pressure, glucose, adiposity). We conducted three analyses using Center for Alaska Native Health Research adult study participants. First, we tested the reproducibility and reliability of previously identified dietary patterns: “processed foods”; “fruits and vegetables”; and “subsistence foods”. We used confirmatory factor analysis to measure reproducibility and composite reliability (n=267) and intraclass correlation coefficients for test-retest reliability (n=113). Next, we characterized associations between dietary pattern quartiles and biomarkers of CM status using regression adjusted for confounders (n=637). Finally, we characterized the association between current iq’mik use and biomarkers of CM status using regression models adjusting for measures of Yup’ik lifestyle or adjusting for a propensity score (n=874). The results confirmed the dietary patterns based on acceptably correlated factor loadings for 17 of the 18 foods used in the analysis and model fit criteria were all above the 0.90 threshold. Composite and test-retest reliability were respectively 0.73 and 0.66 for “processed foods”, 0.72 and 0.54 for “fruits and vegetables”, and 0.56 and 0.34 for “subsistence foods”. Comparing participants in the fourth to first quartile for each dietary pattern, we identified significant associations between “processed foods” and log triglycerides (β=0.11); “fruits and vegetables” and diastolic blood pressure (DBP) (β=2.87) and HbA1c (β=-0.08); and “subsistence foods” and log triglycerides (β=-0.10) and DBP (β=-3.99). Current iq’mik use was significantly associated with log high-density lipoprotein cholesterol (β=0.05), log triglycerides (β=-0.07), HbA1c (β=-0.05), log fasting blood glucose (β=-0.02), log waist circumference (β=-0.04), and log body mass index (β=-0.04), using either adjustment method. Therefore, we confirmed the reproducibility and reliability of the dietary patterns, and found evidence that both diet and iq’mik use were associated with CM risk. The dietary associations align with results from previous studies, and can be used for future research and development of health interventions. However, the iq’mik findings are novel requiring further study.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. INTRODUCTION

The Yukon-Kuskokwim Delta in Southwest Alaska is home to about 25,000 people, of whom approximately 85% are Alaska Native.(1) Bethel, with a population of 7,000, is the regional hub for 58 remote communities, most with less than 500 residents (ranging from less than 100 to 1000).(2,3) Each community is a federally recognized tribe, with the exception of Bethel.(4) The Yukon-Kuskokwim Delta covers an area of approximately 75,000 square miles(5–7) and as the name implies is formed by the Yukon and Kuskokwim rivers.(6) The majority of communities in the region are located along one of these rivers that are important to the traditional lifestyle. These rivers, the delta, and the Bering Sea coastline, provide a rich habitat for wild berries, fish, birds, and land and sea mammals that make up the subsistence diet.(8) Given the geography, most communities are not connected by roads, so travel is predominantly by small plane, snow machine, or ice roads in the winter, and boat or four-wheeler in the summer.(2,3)

The majority of Alaska Native people living in the Yukon-Kuskokwim Delta region are of Yup’ik descent, representing the largest concentration of Yup’ik people in the world.(6,9) Yup’ik people are considered one of the most culturally and linguistically intact among Alaska Native groups.(3,7) Most Yup’ik people speak the Yup’ik language and many continue to participate in subsistence activities. Men hunt and fish while women process the meat and gather berries and wild greens,(8) activities that are important aspects of the Yup’ik culture.(7) Another activity strongly associated with a traditional Yup’ik lifestyle is the use of iq’mik, a traditional form of smokeless tobacco.(7) Iq’mik is not used for ceremonial or religious reasons, but is considered a social activity.(6,7) Based on qualitative interviews with Yup’ik women, keeping busy with subsistence activities, being physically active, eating subsistence foods, and transmitting cultural knowledge are considered key to healthy aging.(8) However, the Yup’ik lifestyle is changing, with greater access to an abundance of market-based foods and a more sedentary lifestyle.(3) The current Yup’ik diet consists of a mix of traditional foods and market-based foods, with approximately a quarter of the energy intake coming from traditional foods.(10)

Research from the 1960 and 1970s suggested a relatively low prevalence of cardiometabolic (CM) diseases (e.g., cardiovascular disease, diabetes mellitus) among indigenous arctic populations including Alaska Native people.(11–13) However between 1990 and 2009 Alaska Native people experienced 65% higher all-cause mortality relative to United States (US) whites.(14) Although cancer was the leading cause of death, CM diseases comprised a substantial proportion of the mortality among Alaska Native people.(14) In Alaska Native females, heart disease is the second leading cause of death, stroke is the fourth, and diabetes mellitus is the ninth.(14) In Alaska Native males, heart disease is the third leading cause of death, stroke is the sixth, and diabetes mellitus is the ninth.(14) Specifically in the Yukon-Kuskokwim Delta, between 2004 and 2007, the heart disease death rate was 192.9 per 100,000 in Alaska Native people, compared to 209.5 per 100,000 in US whites. Whereas the cerebrovascular death rate was 71.9 per 100,000 in Alaska Native people, compared to 46.1 per 100,000 in US whites.(15)

Although Alaska Native people experience disproportionally higher mortality, the majority of research conducted to date on CM risk has been in non-Alaska Native populations. Given both the burden of CM diseases(16,17) and paucity of CM disease research among Alaska Native people, there is a need for additional research. Lifestyle, cultural, environmental, and social determinants of health thought to alter CM disease risk in Alaska Native people include: physical activity; stress and coping styles; cultural identity; access to health services; socioeconomic status; depression; tobacco use;

alcohol consumption; and diet.(3,18,19) These characteristics are thought to contribute in part to CM disease through modification of lipid levels (e.g., low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG]), blood pressure (e.g., systolic [SBP] and diastolic [DBP]), blood glucose (e.g., fasting blood glucose [FBG], glycated hemoglobin [HbA1c]), and adiposity (e.g., waist circumference [WC] and body mass index [BMI]). Lipids,(20) blood pressure,(21) blood glucose,(22) and adiposity(23,24) have consistently been shown to be associated with CM disease risk and thus represent biomarkers of CM status. We are particularly interested in better characterizing Yup'ik lifestyle and how it is associated with biomarkers of CM status (and thus CM disease itself), because of the ongoing dietary and cultural transition occurring in Yup'ik communities. Acknowledging that the Yup'ik cultural transition to a more western or modern lifestyle will likely continue, there could be great benefit to identifying approaches to minimize its adverse health impacts (e.g., education on selecting healthy market foods(25)) based on research findings.

The Center for Alaska Native Health Research (CANHR) at the University of Alaska Fairbanks has been conducting longitudinal community-based participatory research with Yup'ik people living in the Yukon-Kuskokwim Delta since 2001.(3) CANHR aims to determine protective and risk factors for CM disease among Yup'ik people, including both genetic and environmental factors, with the goal of developing culturally appropriate interventions to prevent and reduce CM diseases.(3) To meet these aims, CANHR has been conducting recurring visits to 11 coastal and tundra communities in the Yukon-Kuskokwim Delta. Participating communities have received between two and eight research visits each depending on availability and funding. During these visits, a team of CANHR staff including the Principal Investigator, Community Engagement and Clinical Support Director (a cultural anthropologist and nurse), a technician, and a bilingual Yup'ik Cultural Consultant, spend between one and two weeks in each community collecting data.(3) A variety of data are collected including demographic, socioeconomic, lifestyle, food frequency, and physical measures and blood samples for biomarkers of CM status.

This dissertation uses CANHR data from these research visits to evaluate two lifestyle factors, diet and iq'mik smokeless tobacco use, in relation to biomarkers of CM status. We begin by characterizing the reproducibility and reliability of dietary patterns based on food frequency questionnaire data from a sample of Yup'ik people (chapter 2). Next, we present the associations between these dietary patterns and biomarkers of CM status (chapter 3). Finally, we present the association between iq'mik use and the same biomarkers of CM status (chapter 4). We conclude by summarizing and discussing the findings from these three studies (chapter 5).

CHAPTER 2. CHARACTERIZING THE REPRODUCIBILITY AND RELIABILITY OF DIETARY PATTERNS AMONG YUP'IK ALASKA NATIVE PEOPLE

This dissertation chapter is published in the British Journal of Nutrition.(26)

ABSTRACT

Food frequency questionnaire (FFQ) data can be used to characterize dietary patterns for diet-disease association studies. Among a sample of Yup'ik people from Southwest Alaska, we evaluated three previously defined dietary patterns: "subsistence foods" and market-based "processed foods" and "fruits and vegetables". We tested the reproducibility and reliability of the dietary patterns and tested associations of the patterns with dietary biomarkers and participant characteristics. We analyzed data from adult study participants who completed at least one FFQ with the Center for Alaska Native Health Research between September 2009 and May 2013. To test reproducibility we conducted a confirmatory factor analysis (CFA) of a hypothesized model using 18 foods to measure the dietary patterns (n=272). To test the reliability of the dietary patterns, we used CFA to measure the composite reliability (n=272) and intraclass correlation coefficients for test-retest reliability (n=113). Finally, to test associations we used linear regression (n=637). All CFA factor loadings, except one, indicated acceptable correlations between foods and dietary patterns (r > 0.40) and model fit criteria were greater than 0.90. Composite and test-retest reliability of dietary patterns were respectively 0.56 and 0.34 for subsistence foods, 0.73 and 0.66 for processed foods, and 0.72 and 0.54 for fruits and vegetables. In the multi-predictor analysis, dietary patterns were significantly associated with dietary biomarkers, community location, age, sex, and self-reported lifestyle. This analysis confirmed the reproducibility and reliability of the dietary patterns in this study population. These dietary patterns

can be used for future research and development of dietary interventions in this underserved population.

INTRODUCTION

The Yup'ik people of the Yukon-Kuskokwim Delta of Southwest Alaska are undergoing a transition affecting many aspects of their traditional lifestyle, including diet, which may influence health.(27–29) The traditional Yup'ik diet includes fish, marine mammals, wild birds, land mammals, and wild berries. The significant marine-based component to the diet includes high levels of eicosapentaenoic and docosahexaenoic acid (omega-3 polyunsaturated fatty acids). These omega-3 polyunsaturated fatty acids potentially have beneficial effects including reducing cardiovascular disease risk by lowering circulating triglycerides and inflammatory cytokines, and by increasing high-density lipoprotein cholesterol.(30,31) The current Yup'ik diet consists of a mix of traditional foods and market-based foods, with approximately a quarter of the energy intake coming from traditional foods.(10) Ongoing transition from the cardio-protective marine-based foods to more market-based foods may increase cardiometabolic disease in this population. Research to improve understanding of associations between diet and obesity, diabetes, and cardiovascular disease will require reliable methods to measure diet in Yup'ik people.

To better understand the diet of Yup'ik people, the Center for Alaska Native Health Research (CANHR) designed a semi-quantitative food frequency questionnaire (FFQ) specifically for Yup'ik people, based on the most frequently eaten foods.(32) A single FFQ captures data on the frequency of foods usually eaten over the previous 12 months, including foods consumed only seasonally. Because many traditional foods are only eaten when they are in season, seasonal consumption is needed to capture the complete diet.

There has been increasing interest in the use of FFQ data to describe dietary patterns for studies of diet and disease associations.(33,34) Dietary patterns are created from FFQ data by combining individual foods into measures that describe groupings of foods eaten by people, and thus may better measure overall diet of individuals because specific foods are not eaten in isolation.(34) However dietary patterns can be population specific,(34) such that it is important to identify dietary patterns in a specific study population of interest, such as the Yup’ik people.

We previously used exploratory factor analysis (FA) to identify three dietary patterns among a sample of 358 Yup’ik people living in the Yukon-Kuskokwim Delta.(32) The dietary patterns described a subsistence diet as well as two distinct market-based dietary patterns, that we named processed foods and fruits and vegetables.(32) These dietary patterns were associated with participant characteristics and also validated objectively measured biomarkers of diet, as well as aligning with findings from previous research.(10,35–37) Exploratory FA uses the underlying structure of the observed data from the sample of study participants to determine the dietary patterns, and thus could vary in different samples of study participants. As such, to facilitate use of the FFQ in future studies we sought to confirm the reproducibility of the dietary patterns using confirmatory FA, an approach that builds on the exploratory FA results.(34) Additionally, we sought to test the reliability of measurement of dietary patterns over a two to three year period. Reliability over this time period should not be significantly impacted by the ongoing nutritional transition since this transition involves population-level changes over multiple years.(27,38) Biomarkers of traditional and market food intake in the Yup'ik population(36) did not change significantly over a 10 year period. Other studies have found dietary patterns to be reliable,(39–42) however evaluation of the reproducibility of dietary patterns using confirmatory FA is less common.(41,43–46) To our knowledge, neither reproducibility nor reliability of dietary patterns have been reported for an Alaska Native population.

The purpose of this study was to test the reproducibility of the previously described dietary patterns in an independent sample of Yup'ik people using confirmatory FA methods and evaluate the reliability of the identified dietary patterns and specific foods collected with the FFQ. In addition, we sought to demonstrate the utility of the FFQ to determine dietary patterns by assessing associations of the dietary patterns with validated dietary biomarkers and study participant characteristics.

METHODS

STUDY SAMPLE

This dietary study was conducted among a Yup'ik study population living in Southwest Alaska, as previously described.(32) All data were collected as part of the University of Alaska Fairbanks CANHR studies, and detailed study recruitment methods are published elsewhere.(3,19) Briefly, CANHR conducts recurring research visits to 11 communities of the Yukon-Kuskokwim Delta. Within these communities, study participants are recruited using convenience sampling methods in which all individuals who self-identify as Alaska Native or who are married to an Alaska Native descendent, are greater than 14 years of age, and are non-pregnant, are eligible to participate.

For this analysis we restricted our sample to individuals that participated in CANHR studies between September 2009 and May 2013 and self-reported their ethnicity as Yup'ik. Due to the longitudinal nature of the study, participants could have completed more than one FFQ. We started with a sample of 770 individuals who completed 916 FFQs (Figure 1). We excluded FFQs that were completed when the study participant was <18 years of age, the FFQ was determined and recorded by the interviewer to be of poor quality, when the FFQ was missing data for analyzed foods, and when the FFQ values were considered unrealistic by study staff. After applying these exclusion criteria, 750 FFQs from 637 participants were available for analysis. In a previous analysis we evaluated FFQs from 358 study participants that completed their first eligible FFQ between September 2009 and August 2011 using exploratory FA.(32) The study participants that completed their first eligible FFQ between September 2011 and May 2013 comprise our "confirmatory FA" sub-sample of participants (n=272) (Figure 1). Our "test-retest" sub-sample of participants completed more than one eligible FFQ between September 2009 and May 2013 (n=113) (Figure 1). Finally our "association study" sample includes all CANHR study participants September 2009 to May 2013 with complete data on participant characteristics, utilizing the most recent FFQ for participants with >1 FFQ (n=637) (Figure 1).

This study was conducted according to the guidelines of the Declaration of Helsinki and all procedures involving study participants were approved by the University of Alaska Fairbanks Institutional Review Board and the Yukon-Kuskokwim Health Corporation Human Studies Committee. Written informed consent was obtained from participants prior to data collection.

DATA COLLECTION

Each study participant completed an in-person interview in English or Yup'ik during which the FFQ was administered, a fasting blood sample was collected, and demographic data were obtained. Red blood cells were isolated and samples prepared to obtain the $\delta^{15}N$ and $\delta^{13}C$ stable isotope ratios at the Alaska Stable Isotope Facility as previously described.(36,37) Among Yup'ik people, $\delta^{15}N$ is strongly correlated with traditional marine intake and $\delta^{13}C$ is strongly associated with corn-based market foods.(36) Collected demographic data included location of residence (i.e., coastal or inland community), age, sex, and cultural identification (i.e., self-reported adherence to “Kass’aq” [white] and Yup’ik lifestyle). The cultural identification questions were not mutually exclusive; for example, a participant could report “a lot” for adherence to both the Yup’ik and Kass’aq lifestyle.

Dietary data were collected using the CANHR FFQ designed specifically for Yup’ik people and included the 163 mostly commonly eaten foods based on nearly 2000 24-hour food recalls from Yup’ik people. The current version of the FFQ has been used since September 2009. Participants reported how frequently they typically consumed each food during the previous 12 months, and for traditional subsistence foods, it was further elicited if they ate the food seasonally or year-round. Frequency of consumption was measured on two nine-point scale groupings of frequency, one for foods and one for beverages. For both scales, the least frequent group was “never or less than once per month”; for foods the greatest frequency group was “two or more times per day” and for beverages the greatest frequency group was “six or more times per day”. Serving size was not collected in order to minimize study participant burden.

We converted frequency of consumption from the nine-point scale groups to a continuous scale of annual consumption by multiplying the reported frequency of consumption to a 365 day scale. For foods potentially eaten seasonally (i.e., seal and walrus soup, non-oily fish, wild greens, and bird soup), if the participant reported eating the food seasonally, the annual consumption was calculated as the product of the annual frequency and the proportion of the year that food was typically available (as determined by cultural experts from communities). Annual frequency for each food was then transformed to the natural log scale to improve the distribution. Foods eaten “never or less than once per month” were changed from an annual frequency of 0.0 to 0.01 for the natural log transformation.

STATISTICAL ANALYSIS

We used confirmatory FA to test the reproducibility of the dietary patterns (Analysis A); confirmatory FA and intraclass correlation coefficients (ICC) to test the reliability of dietary patterns (Analysis B); and Pearson correlations and linear regression to test associations of the dietary patterns with dietary biomarkers and participant characteristics (Analysis C). All analyses were conducted using SAS 9.3. Two-sided p-values <0.05 were considered statistically significant.

Reproducibility of dietary patterns (Analysis A)

FA is a data reduction method, using the correlations between observed variables (foods) to derive a smaller number of unobserved variables called factors or underlying constructs, and which we will refer to as the dietary patterns. Broadly, FA can either be categorized as exploratory or confirmatory. We previously used exploratory FA, which requires no *a priori* hypotheses about how the foods are correlated or the number of dietary patterns. In contrast, confirmatory FA requires an *a priori* hypothesis and tests a hypothesized model of directional relationships between foods and dietary patterns. We used the exploratory FA results as a basis for designing the hypothesized model to be tested using confirmatory FA. When conducting the exploratory FA we selected 22 foods from the FFQ, using a two-stage process described in detail elsewhere.(32) A list of foods used in the exploratory FA is provided in Appendix 1.

We tested a confirmatory FA model with same three underlying constructs as the exploratory FA: processed foods; fruits and vegetables; and subsistence foods.(32) For this analysis, we evaluated a "confirmatory FA" sub-sample (Figure 1). We hypothesized a model in which each dietary pattern was computed from the foods with highest exploratory FA standardized loadings for that construct. However, in our exploratory FA, seven of the 22 foods did not have high standardized loadings (>0.35) for any of the three constructs. Four of these seven foods with a standardized loading <0.35 loaded most highly on the fruits and vegetables dietary pattern, even though they were inconsistent with this dietary pattern (i.e., pudding and jello, dried salmon, wild game soup, and pancakes). As such, we *a priori* elected to exclude these foods from the confirmatory FA (Appendix 1). The three other foods with standardized loadings <0.35 each loaded most highly on the food group most consistent with the food item (i.e., canned tuna with processed foods, market berries in akutaq[1] with fruits and vegetables, and bird soup with subsistence foods) and thus we *a priori* decided to include these foods in our confirmatory analysis (Appendix 1).

Thus, for the confirmatory FA, a total of 18 food items were included in the hypothesized model. Specifically, we hypothesized that the following foods measured each of the following dietary patterns: 1) Processed foods included: salty snacks, sweetened cereals, pizza, sweetened drinks, hot dogs and lunch meat, fried chicken, and canned tuna; 2) Fruits and vegetables included: fresh citrus, potato salad, citrus juice, corn, green beans, green salad, and market berries in akutaq; and 3) Subsistence foods included: seal or walrus soup, non-oily fish, wild greens, and bird soup. In the model specifications the three dietary patterns were allowed to be correlated. Model fit was assessed based on goodness of fit criteria (relative amount of observed variance predicted); Bentler Comparative Fit Index and Bentler-Bonett Non-normed Fit Index (relative improvements in fit of the model compared

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[1] Traditional dessert typically made from a combination of berries, sugar, and fat (historically seal oil and now primarily Crisco vegetable shortening [Proctor and Gamble, Cincinnati, OH]).

to a null model corrected for number of parameters); and the Root Mean Squared Error Approximation (degree of discrepancy per degree of freedom).(47)

Reliability of dietary patterns (Analysis B)

We evaluated the reliability of the 18 individual foods included in the confirmatory FA and the dietary patterns using two complementary approaches, confirmatory FA(48) and test-retest.(49) The confirmatory FA approach measured internal consistency from a single FFQ for each participant, whereas the test-retest approach measured intra-individual variability from two FFQs administered two to three years apart to the same participant. Both measures of reliability were reported on a scale of 0 to 1, with greater values indicating better reliability than lower values.

Using confirmatory FA we calculated the indicator reliability for the individual foods and composite reliability for the dietary patterns in the “confirmatory FA” sub-sample of 272 participants (Figure 1). Factor composite reliability measures the correlation between the dietary pattern and each food hypothesized to measure the dietary pattern, and it is based on the squared standardized loadings and sum of the error variances.(50) Indicator reliability describes the percent of the variance in the food that is explained by the dietary pattern it measures and is calculated by squaring the standardized factor loadings for each food.(48)

We evaluated test-retest reliability among the 113 participants with >1 FFQ (i.e., “test-retest” sub-sample, Figure 1) using ICC,(49,51) which described the proportion of variance for each food between participants as compared to within a participant. As such, the higher the ICC, the less variation observed within the same participant. Using the test-retest sub-sample we also measured the reliability of a participant’s report of eating each of the seasonal foods year-round as compared to only in season. For this we measured reliability using the kappa statistic because seasonal consumption was characterized as yes or no.(49)

Association analyses (Analysis C)

In order to determine if the identified dietary patterns were associated with previously validated dietary biomarkers (i.e., stable isotope ratios) and demographic characteristics (e.g., age, sex) that have been reported to be associated with diet in this(10,35,36) and other indigenous arctic study populations,(27,52,53) we measured associations of dietary patterns with dietary biomarkers and participant characteristics. For this analysis, we used all 637 participants in our study, referred to as the "association sample" (Figure 1). Estimated dietary pattern scores indicate a participant's frequency of consumption of foods included in that dietary pattern relative to other study participants. The greater the dietary pattern score, the greater the frequency of consumption of the foods used to measure that dietary pattern. Scores were calculated as the average of the natural log transformed frequency of consumption for each food measuring the dietary pattern (formula provided in Appendix 2). Each food measuring the dietary pattern was equally weighted.(54) Although this differs from the method we used in our previous exploratory FA (scores were weighted by the factor loading of each food), we elected to use this method because the factors scores can be applied to new study participants without the need to calculate new factor loadings.(55) Dietary patterns scores were standardized with a mean of zero and standard deviation of one.

We measured Pearson correlations between each dietary pattern (based on the scores) and the dietary biomarkers δ^{15}N and δ^{13}C. We also tested associations between the dietary patterns and participant characteristics (i.e., community location, age, sex, and self-reported lifestyle) using simple linear regression. Age was modeled in years as a linear term and community location (inland or coastal) and sex as binary terms. We consolidated cultural identification measures (i.e., Kass'aq [white] and Yup'ik lifestyle) into those participants reporting "not at all" or "some" in one group and "a lot" in a second group because of a small number of participants in the "not at all" group. Finally, to test for independent associations we regressed the dietary pattern score against the participant characteristics (i.e., inland community, age, male sex, and a lot for Kass'aq and Yup'ik lifestyle) using a multi-predictor linear regression model for each dietary pattern.

RESULTS

SAMPLE CHARACTERISTICS

Participants were from six coastal and four inland communities. Overall the three different sub-samples used for this analysis were similar, with the test-retest sub-sample comprising slightly older participants and a greater proportion of women (Table 1).

Natural log transformation of food frequencies improved the normality (Table 2). However, after transformation, not all foods were normally distributed, with 22% and 56% of foods with skewness and kurtosis values greater than one respectively.

REPRODUCIBILITY (ANALYSIS A)

All confirmatory FA standardized factor loadings were >0.40, with the exception of sweetened cereals with a factor loading of 0.26 (Table 3). The dietary patterns were not necessarily mutually exclusive. We evaluated a number of model fit criteria to assess our measurement model. Goodness of fit, adjusted goodness of fit, Bentler Comparative Fit Index, and Bentler-Bonett Non-normed Index values were 0.93, 0.91, 0.92, and 0.91, respectively, all above the recommended threshold of

0.90.(47,48) Additionally, the Root Mean Squared Error Approximation of 0.04 was less than the recommended threshold of 0.05.(47) The confirmatory FA t-tests for all foods were >3.29 allowing us to reject the null hypothesis of factor loadings equal to zero ($P<0.01$).

RELIABILITY (ANALYSIS B)

Composite reliability, a measure of internal consistency, of dietary patterns was 0.73 for processed foods, 0.72 for fruits and vegetables, and 0.56 for subsistence foods (Table 4). In comparison, test-retest reliability, a measure of intra-individual variability, of dietary patterns was 0.66 for processed foods, 0.54 for fruits and vegetables, and 0.34 for subsistence foods (Table 4). For individual foods, indicator reliability, also a measure of internal consistency, ranged from 0.07 for sweetened cereals to 0.46 for pizza, and test-retest reliability from 0.11 for market berries in akutaq to 0.50 for sweetened drinks, with better reliability for market-based foods (Table 4). For seasonal foods, the reliability of reported consumption in season only, as compared to year-round, was 0.21 for seal or walrus soup, 0.19 for non-oily fish, 0.22 for wild greens, and 0.17 for bird soup.

ASSOCIATIONS (ANALYSIS C)

Calculated dietary pattern factor scores, a relative ranking across study participants of frequency of intake for foods, were approximately normally distributed (Appendix 3). The market-based factors, processed food and fruits and vegetables were correlated ($r=0.57$, $P<0.01$). The subsistence foods factor scores were weakly correlated with factor scores for processed foods ($r=0.10$, $P=0.01$) and fruits and vegetables ($r=0.19$, $P<0.01$).

Among the 628 participants with biomarker data, $\delta^{15}N$, a biomarker of marine-food intake, was significantly negatively correlated with the processed foods dietary pattern ($r=-0.43$, $P<0.01$) and fruits and vegetables (r=-0.18, P<0.01), and positively correlated with the subsistence food dietary pattern (r=0.29, P<0.01). Conversely, $\delta^{13}C$, a biomarker of corn-based foods, was positively correlated with the processed foods dietary pattern (r=0.29, P<0.01) and fruits and vegetables (r=0.13, P<0.01), but was not correlated with subsistence foods.

In single-predictor linear regression analyses, greater relative frequency of processed foods was significantly associated with living in an inland community, being of younger age, male sex, reporting “a lot” for Kass’aq (white) lifestyle and “not at all/some” for Yup’ik lifestyle (Table 5). All associations remained independently significant in the multi-predictor linear regression analysis except male sex and “not at all/some” for Yup’ik lifestyle. Similar associations were observed for the other market-based dietary pattern; greater relative frequency of fruit and vegetable consumption was significantly associated with living in an inland community and being of younger age (Table 5). In the multi-predictor linear regression analysis, community location and age remained independently associated with fruits and vegetables and sex became significant (significance was borderline based on single-predictor model). In contrast, greater relative frequency for the subsistence dietary pattern was associated with living in a coastal community, being of older age, reporting “not at all/some” for Kass’aq lifestyle, and “a lot” for Yup’ik lifestyle (Table 5). In the multi-predictor analysis, community location, and lifestyle characteristics remained independently associated.

DISCUSSION

We confirmed both the reproducibility and reliability of the processed foods, fruits and vegetables, and subsistence foods dietary patterns identified from FFQs in this Yup’ik study population. Moreover, the observed associations between dietary patterns and both participant characteristics and dietary biomarkers aligned with findings from our previous exploratory FA(32) as well as other studies in indigenous arctic populations using other measures of diet. (10,27,35,36,52,53) Taken together, these results demonstrate the utility of the FFQ to measure these dietary patterns in Yup'ik people for use in future research.

Measures of the confirmatory FA model fit were acceptable and the hypothesized relationships based on the exploratory FA were significant, suggesting that our model of the three dietary patterns identified from our previous exploratory FA analysis is consistent with the data in the new sample.

The foods measuring the market-based dietary patterns had higher factor loadings than the foods measuring the subsistence foods dietary pattern, an indication that we are better able to measure the market-based dietary patterns. However, only one of the 18 foods (sweetened cereals) did not appear to be a good measure of the dietary pattern it was hypothesized to measure based on the exploratory factor analysis. Finally, the dietary patterns we identified align well with other studies of dietary patterns in Alaska Native people and relatively well with an American Indian population and other global populations. Four dietary patterns were identified among Inupiat Eskimos, the “traditional” dietary pattern with similar foods to our subsistence foods pattern, a “purchased healthy” dietary pattern which was similar to our fruits and vegetables dietary pattern, and the “western” and “beverages and sweets” dietary patterns which together were similar to our processed foods dietary pattern.(56) Similarly a study of American Indians identified four dietary patterns, “western”, “traditional”, “healthy”, and “unhealthy”.(57) The “western” and “unhealthy” dietary pattern foods were similar to those included in our processed foods dietary pattern; the “healthy” pattern included foods in our fruits and vegetables dietary pattern but also included fish which was included in our subsistence foods pattern; and finally the “traditional” dietary pattern which included dry beans, Mexican foods, stews, etc. likely captured similar lifestyle aspects as our subsistence pattern but did not include any overlap in foods.(57) More broadly the “prudent” and the “western” diet are commonly reported in the literature(58); of these our fruits and vegetables dietary pattern somewhat aligns with the prudent and our processed food pattern with the western diet. The INTERHEART study of acute myocardial infarction in 52 countries similarly found a dietary pattern comparable to the “prudent” and “western” dietary pattern, but also identified a distinct “oriental” dietary pattern.(59) In this Yup’ik population, our processed foods and fruits and vegetables dietary patterns are consistent with dietary patterns found in other populations, but the subsistence dietary pattern is unique to Alaska Native people.

Overall composite and test-retest reliability of dietary patterns from this FFQ were sufficient to be useful for future research in this population. Our two to three year test-retest reliability, particularly for the market-based dietary patterns (0.66 for processed foods and 0.54 for fruits and vegetables), was not dissimilar from the 0.63 to 0.73 range in reliability reported in studies of one year reliability.(39,42) In our study, composite reliability was more similar across the three dietary patterns and higher than the test-retest reliability, while test-retest reliability varied across the three dietary patterns. Test-retest reliability was greatest for processed foods, followed by fruits and vegetables, and finally subsistence foods. There are a number of possible reasons for this discrepancy. By evaluating test-retest reliability using FFQs administered two to three years apart, we measured the reliability of diet pattern analysis over the longer term; however in such analyses it is difficult to differentiate measurement error from true changes in diet. For example, the availability of fruits and vegetables in the market might be a result of seasonality and the difficulty of stocking perishable foods, while subsistence food availability can depend on environmental factors such as fish runs, migration patterns, ice pack, weather, and regulatory restrictions.(60) In contrast, the availability of processed foods such as snacks and cereals is likely to be more consistent throughout the year. It is also possible that the lower test-retest reliability for the subsistence foods could be a result of greater error in measurement of seasonally consumed foods. That is, when participants reported subsistence foods intake, they were asked whether the food was eaten year-round or only in season, a distinction that may have been too coarse or too confusing to participants to accurately capture intake. For example, a participant might preserve food to be eaten year-round, but the food did not last the full year. The challenge of measuring if foods were eaten year-round or only in season was further highlighted by the weak test-retest reliability for the seasonal consumption question (ranging from 0.17 to 0.22).

Indicator reliability for foods was similar, irrespective of the dietary pattern that the food measured. This is an indication that the strength of the various foods measuring each of the dietary patterns were similar, and thus that the foods measuring a particular dietary pattern were not substantially better at measuring that dietary pattern. In contrast, test-retest reliability was generally better for foods measuring the market-based dietary patterns, particularly processed foods, as compared to those foods measuring the subsistence food dietary pattern. Reasons for the lower test-retest reliability, particularly for subsistence foods, are probably similar to those influencing the dietary patterns as described above.

We observed a correlation between usual diet over the previous 12 months based on dietary patterns and diet over the previous two to three months, as measured by the stable isotope biomarkers. The nitrogen isotope ratio ($\delta^{15}N$), a validated biomarker of traditional marine food intake(36,37) was correlated with the subsistence food dietary pattern, but the correlation was weaker than expected based on previous studies.(36) This is likely because widely-consumed traditional marine foods, such as salmon, have a large effect on $\delta^{15}N$, but are not included in the subsistence food dietary pattern. Salmon was not included in our subsistence food dietary pattern because it did not load highly when we conducted the two-stage exploratory factor analysis.(32) This is likely because the entire population so frequently eats salmon that it does not differentiate individual dietary consumption. The weaker correlation between the subsistence dietary pattern and $\delta^{15}N$ could also be the result of the error in measuring the subsistence foods with the FFQ as described above. The carbon isotope ratio ($\delta^{13}C$) was correlated with the processed foods dietary pattern and was elevated in many of the same foods (market meats, sweetened beverages, and corn-based cereals).

Use of objective biomarkers and the dietary patterns together could be valuable because dietary patterns can capture a more complete picture of the diet whereas biomarkers are more objective. Moreover, FFQs and stable isotope biomarkers measure diet over different time periods and are subject to different types of measurement error (e.g., recall bias versus laboratory error). The observed correlations between the validated stable isotope biomarkers and our dietary patterns provided us further confidence in the dietary patterns. However, in this study population no comparable biomarker of fruit and vegetable intake is available, so the fruit and vegetable dietary pattern is currently our best measure of this component of the diet. This highlights one of the advantages of the FFQ, that it measures a variety of foods for which biomarkers are not currently available. Depending on the research question of interest, it would be possible in this study population to reduce participant burden by either using a FFQ targeted specifically to fruit and vegetable intake or a FFQ collecting only the 18 foods used to measure the dietary patterns. However such an approach would not allow for measuring the diversity of the Yup’ik diet. If such a change were made to study protocols, additional studies should be conducted to ensure that the modified FFQ captured the same data as the full FFQ, e.g., to capture accurate intake of market berries in akutaq is it necessary to also ask about wild berries in akutaq.

The associations we observed between dietary patterns and demographic characteristics aligned well with other studies among indigenous arctic populations, including Yup'ik people. For example, a number of other studies reported an association between older age and greater consumption of traditional or subsistence foods.(10,27,35,36,52,53) We further observed an association between greater frequency of consumption of subsistence foods and living in a coastal community, an association observed in a Yup'ik population using both 24-hour food recalls and isotopic biomarkers.(10,36) The association between sex and subsistence food intake is inconsistent across studies in arctic indigenous populations,(27,36,52) however our finding of no association between sex and subsistence food frequency of consumption aligns with another study of Yup'ik people.(10) The observed associations between dietary patterns and participant characteristics using the full cohort were similar to those based on our exploratory FA study sample.(32) The majority of observed differences were significant associations that were not significant in our smaller exploratory FA sample, specifically the associations of: processed foods with community location and sex; fruits and vegetables with age and sex; and subsistence foods with Kass'aq lifestyle. The consistency of associations between diet and demographic characteristics from our study and other studies in arctic indigenous populations as well as our previous exploratory FA analysis(32) further strengthens our confidence that we are capturing actual dietary patterns among Yup'ik people with this FFQ.

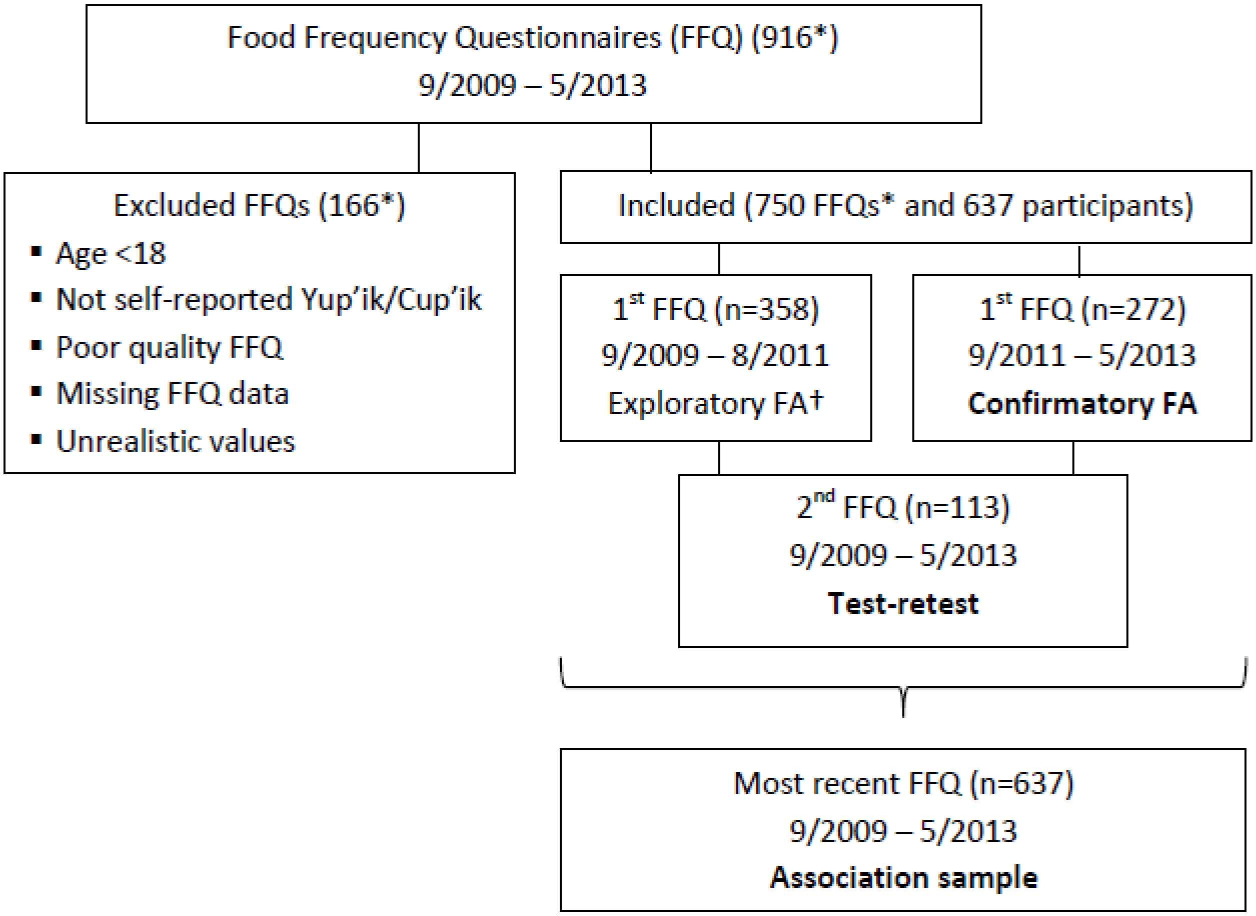
Strengths of this study include the use of FFQ data consistently collected since 2009 in a longitudinal cohort of Yup'ik study participants from inland and coastal communities. As such, we were able to rigorously test the dietary patterns we previously identified with exploratory FA in a new, but similar, study sample using confirmatory FA. Furthermore, we were able to compare the dietary patterns with validated objectively measured biomarkers of diet. This study was also subject to limitations. Data collection involved convenience sampling, potentially limiting generalizability. Participants living in the same households were not excluded, and diet may be correlated among these individuals, potentially impacting factor loadings. Although our study sample size was limited, the confirmatory factor analysis included more than five participants for each parameter being estimated as recommended.(50) Further, the test-retest analysis had an adequate sample to measure the ICC with a two-sided alpha of 0.05 and power of 0.80 assuming an ICC of 0.60 and a minimally acceptable ICC of 0.40.(49) The FFQ used in the analysis has not been validated due to the challenge of obtaining a gold standard to compare against. Twenty-four hour food recalls, frequently used for validation studies are expensive and logistically challenging to obtain in this population during all seasons because of the inaccessibility and remoteness of communities. In addition, the FFQ we used did not capture serving size so that it is not possible to determine percent energy for food groups or specific nutrients. In our association analysis we compared 30 associations – these should be cautiously interpreted due to the potential for inflated type one errors. Finally, all food frequency data were collected using the same FFQ, and thus there is potential for systematic error violating the confirmatory FA assumption of no correlated errors between foods.

In conclusion, we confirmed the reproducibility and reliability of the three dietary patterns in this Yup'ik study population using FFQ data. Measures of model fit were acceptable and structural relationships were significant, suggesting that our hypothesized confirmatory factor analysis model of dietary patterns fit this new sample of Yup'ik people. Reliability, both composite and test-retest, was acceptable, an indication that the dietary patterns were stable over a multi-year period. Therefore, these dietary patterns will be useful for current pharmacogenetic and cardiometabolic research as well as future research and development of dietary interventions in this underserved population.

TABLES AND FIGURES

FIGURE 1

Numbers of Food Frequency Questionnaires (FFQ) collected, numbers of participants, and dates of data collection for each of the three analyses: Confirmatory Factor Analysis (FA); Test-retest; and Association study.



**The number of FFQs is greater than the number of study participants since some participants completed >1 FFQ. These values are numbers of FFQs, not participants, participants are indicated using (n=) notation.*

†Published elsewhere(32) *(note: exclusion criteria differ slightly from current analysis)*

TABLE 1

Characteristics of Yup'ik study participants included in confirmatory factor analysis, test-retest reliability analysis, and full cohort association analysis, by community location.

	All communities	Coastal communities	Inland communities
Confirmatory Factor Analysis (September 2011-May 2013)			
Sample size	272	176	96
Median age in years (25th-75th)	33.0 (22.0-51.5)	29.0 (21.0-50.5)	34.5 (23.0-52.0)
Sex (% male)	52.9	52.8	53.1
Kass'aq (white) lifestyle (%)*			
Missing	0.4	0.6	0.0
Not at all/some	81.3	84.1	76.0
A lot	18.4	15.3	24.0
Yup'ik lifestyle (%)*			
Missing	0.7	0.6	1.0
Not at all/some	45.6	47.2	42.7
A lot	53.7	52.3	56.3
Test-retest (September 2009 - May 2013)			
Sample size	113	83	30
Median age in years at FFQ1 (25th-75th)	43.0 (29.0-58.0)	43.0 (26.0-62.0)	45.0 (33.0-52.0)
Median age in years at FFQ2 (25th-75th)	45.0 (32.0-60.0)	45.0 (28.0-64.0)	47.0 (35.0-54.0)
Sex (% male)	38.9	37.4	43.3
Kass'aq (white) lifestyle (%)*			
Missing	0.0	0.0	0.0
Not at all/some	82.3	80.7	86.7
A lot	17.7	19.3	13.3
Yup'ik lifestyle (%)*			
Missing	0.9	1.2	0.0
Not at all/some	44.3	43.4	46.7
A lot	54.9	55.4	53.3
Association Study (September 2009 - May 2013)			
Sample size	637	389	248
Median age in years (25th-75th)	37.0 (23.0-54.0)	37.0 (23.0-54.0)	38.0 (23.5-54.0)
Sex (% male)	46.2	46.0	46.4
Kass'aq (white) lifestyle (%)*			
Missing	0.3	0.3	0.4
Not at all/some	82.4	81.2	84.3
A lot	17.3	18.5	15.3
Yup'ik lifestyle (%)*			
Missing	0.6	0.8	0.4
Not at all/some	45.5	47.3	42.7
A lot	53.9	51.9	56.9

* self-reported

TABLE 2

Mean, median, 25th percentile (%tile), and 75th percentile (%tile) of the untransformed and natural log transformed annual frequency of consumption for each of the 18 foods included in the confirmatory factor analysis (n=272), Yup'ik study participants, September 2009 – May 2013.

	Untransformed values				Natural log transformed values			
Foods	Mean	Median	25th %tile	75th %tile	Mean	Median	25th %tile	75th %tile
Processed foods								
Salty snacks	60.52	30.00	12.00	104.35	1.88	3.40	2.48	4.65
Sweetened cereals	46.92	12.00	0.00	52.18	0.51	2.48	-4.61	3.95
Pizza	29.13	12.00	0.00	30.00	0.50	2.48	-4.61	3.40
Sweetened drinks	257.68	78.27	24.00	365.00	3.23	4.36	3.18	5.90
Hot dogs and lunch meat	36.66	12.00	0.00	30.00	1.31	2.48	-4.61	3.40
Fried chicken	21.29	12.00	0.00	30.00	0.47	2.48	-4.61	3.40
Canned tuna	10.00	0.00	0.00	12.00	-1.81	-4.61	-4.61	2.48
Fruits and vegetables								
Fresh citrus	35.02	12.00	0.00	30.00	1.35	2.48	-4.61	3.40
Potato salad	13.01	0.00	0.00	12.00	-1.06	-4.61	-4.61	2.48
Citrus juice	61.36	24.00	0.00	78.27	0.31	3.18	-4.61	4.36
Corn	67.11	30.00	12.00	104.35	2.48	3.40	2.48	4.65
Green beans	45.23	30.00	0.00	52.18	1.46	3.40	-4.61	3.95
Green salad	13.12	0.00	0.00	12.00	-2.00	-4.61	-4.61	2.48
Market berries in akutaq†	18.64	12.00	0.00	12.00	-0.54	2.48	-4.61	2.48
Subsistence foods								
Seal or walrus soup‡	25.56	12.00	0.00	30.00	0.98	2.48	-4.61	3.40
Non-oily fish (not dried)‡	19.38	3.96	0.00	14.61	-0.13	1.38	-4.61	2.67
Wild greens‡	7.46	0.00	0.00	5.10	-1.58	-4.61	-4.61	1.63
Bird soup‡	38.96	26.09	7.50	45.65	1.88	3.26	2.01	3.82

† Traditional dessert commonly made with berries, Crisco, sugar and sometimes fish

‡ Seasonal food items

TABLE 3

Confirmatory factor analysis standardized factor loadings for foods used to estimate dietary patterns (n=272), Yup'ik study participants, September 2011 – May 2013.

Foods	Processed foods	Fruits and vegetables	Subsistence foods
Salty snacks	0.64	0	0
Sweetened cereals	0.26	0	0
Pizza	0.68	0	0
Sweetened drinks	0.57	0	0
Hot dogs and lunch meat	0.56	0	0
Fried chicken	0.47	0	0
Canned tuna	0.45	0	0
Fresh citrus	0	0.53	0
Potato salad	0	0.60	0
Citrus juice	0	0.53	0
Corn	0	0.55	0
Green beans	0	0.55	0
Green salad	0	0.44	0
Market berries in akutaq*	0	0.43	0
Seal or walrus soup†	0	0	0.57
Non-oily fish (not dried)†	0	0	0.45
Wild greens†	0	0	0.48
Bird soup†	0	0	0.47

* Traditional dessert commonly made with berries, Crisco, sugar and sometimes fish

† Seasonal food items

TABLE 4

Reliability of dietary patterns and foods used to estimate dietary patterns, Yup'ik study participants. Composite reliability of dietary patterns and indicator reliability of foods based on confirmatory factor analysis (n=272), September 2011 – May 2013. Test-retest reliability of dietary patterns and foods measured using intraclass correlation coefficients (n=113), September 2009 – May 2013.

Dietary patterns Foods	Confirmatory Factor (n=272)	Test-retest† (n=113)
Processed foods	0.73	0.66
Salty snacks	0.41	0.40
Sweetened cereals	0.07	0.41
Pizza	0.46	0.46
Sweetened drinks	0.32	0.50
Hot dogs and lunch meat	0.32	0.33
Fried chicken	0.23	0.25
Canned tuna	0.20	0.45
Fruits and vegetables	0.72	0.54
Fresh citrus	0.28	0.36
Potato salad	0.36	0.41
Citrus juice	0.28	0.34
Corn	0.31	0.33
Green beans	0.30	0.31
Green salad	0.20	0.32
Market berries in akutaq‡	0.18	0.11
Subsistence foods	0.56	0.34
Seal or walrus soup£	0.33	0.25
Non-oily fish (not dried)£	0.20	0.24
Wild greens£	0.23	0.22
Bird soup£	0.22	0.32

* Composite reliability of dietary patterns (i.e., internal consistency of foods measuring the dietary pattern) and indicator reliability of foods (i.e., the percent of the variance in the food explained by the dietary pattern)

† Values are intraclass correlation coefficients

‡ Traditional dessert commonly made with berries, Crisco, sugar and sometimes fish

£ Seasonal food items

TABLE 5

Associations between natural log transformed dietary pattern scores and Yup'ik study participant characteristics, single-predictor models include only the participant characteristic and multi-predictor models are adjusted for the other study participant characteristics (n=637), Yup'ik study participants, September 2009 – May 2013.

	Processed foods				Fruits and vegetables				Subsistence foods			
	Single-predictor		Multi-predictor (R^2=0.31)		Single-predictor		Multi-predictor (R^2=0.08)		Single-predictor		Multi-predictor (R^2=0.14)	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Inland community	0.29	<0.01	0.31	<0.01	0.34	<0.01	0.35	<0.01	-0.53	<0.01	-0.56	<0.01
Age (1 year)	-0.90	<0.01	-0.03	<0.01	-0.34	<0.01	-0.01	<0.01	0.18	0.02	0.00	0.98
Male sex	0.17	0.03	0.10	0.12	-0.15	0.05	-0.18	0.02	0.04	0.58	0.04	0.55
A lot for Kass'aq lifestyle[*]	0.58	<0.01	0.36	<0.01	0.17	0.11	0.12	0.23	-0.32	<0.01	-0.25	0.01
A lot for Yup'ik lifestyle[†]	-0.43	<0.01	-0.09	0.22	-0.02	0.80	0.12	0.13	0.49	<0.01	0.49	<0.01

[*] n=635 due to missing data

[†] n=633 due to missing data

CHAPTER 3. ASSOCIATIONS BETWEEN DIET AND CARDIOMETABOLIC RISK AMONG YUP'IK ALASKA NATIVE PEOPLE USING FOOD FREQUENCY QUESTIONNAIRE DIETARY PATTERNS

ABSTRACT

In previous analyses, we identified three dietary patterns from food frequency questionnaire data among a sample of Yup'ik Alaska Native people living in Southwest Alaska: a "subsistence foods" dietary pattern and two market-based dietary patterns "processed foods" and "fruits and vegetables". In this analysis, we aimed to characterize the association between the dietary patterns and biomarkers of cardiometabolic (CM) status (lipids, blood pressure, glucose, adiposity). We used linear regression to estimate the mean of each biomarker of CM status comparing participants in the highest (4th) to the lowest (1st) quartile of each dietary pattern. Models were adjusted for age, sex, past smoking, current smoking, and physical activity and accounted for clustering at the community-level using multilevel models. The sample of 637 Yup'ik participants had a mean age of 40 years, 54% were women, and nearly equal proportions of current, past and never smokers. Mean log triglyceride levels were significantly higher among participants in the 4th compared to the 1st quartile of the processed foods dietary pattern (β=0.11). Mean HbA1c percent was significantly lower (β=-0.08) and mean diastolic blood pressure (DBP) mm Hg was significantly higher (β=2.87) among participants in the 4th compared to the 1st quartile of the fruits and vegetables dietary pattern. Finally, mean log triglyceride levels and mean DBP mm Hg were significantly lower among participants in the 4th

compared to the 1st quartile of the subsistence foods dietary pattern (β=-0.10 and β=-3.99 respectively). We found increased CM risk, as reflected by increased triglycerides, associated with eating a greater frequency of processed foods, and reduced CM risk, as reflected by lower triglycerides and DBP, associated with eating a greater frequency of subsistence foods. These findings support efforts that encourage a diet high in subsistence foods as a way to reduce further CM disease**.**

INTRODUCTION

American Indian and Alaska Native people have long suffered from health disparities,(14) and these health disparities continue despite efforts to reduce them. Between 1990 and 2009, all-cause mortality was 65% higher in Alaska Native people relative to United States (US) whites.(14) Cardiovascular and metabolic diseases are substantial contributors to this increased mortality in Alaska Native people.(14) Among Alaska Native females, heart disease is the second leading cause of death, stroke is the fourth, and diabetes mellitus is the ninth.(14) In Alaska Native males, heart disease is the third leading cause of death, stroke is the sixth, and diabetes mellitus is the ninth.(14) A number of lifestyle factors including physical activity, stress, depression, smoking, alcohol consumption, and diet may contribute to cardiometabolic (CM) disease risk in Alaska Native people.(18)

Many indigenous populations, including Alaska Native people, are undergoing nutritional transitions, characterized by the substitution of traditional foods for market-based processed foods.(38,61) The traditional diet of some Alaska Native people, including Yup'ik people residing in remote communities in the Yukon-Kuskokwim Delta of Southwest Alaska, is abundant in marine mammals and fish that include high levels of eicosapentaenoic and docosahexaenoic acid (omega-3 polyunsaturated fatty acids). Omega-3 polyunsaturated fatty acids may have beneficial effects in preventing cardiovascular disease risk by lowering circulating triglycerides and inflammatory markers and increasing high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I.(30,31,62) Thus, this nutritional transition in Yup'ik people could have adverse effects in terms of obesity, diabetes, and cardiovascular disease,(10,27,28,35,63) potentially further amplifying current health disparities.

Additional research is warranted to better understand the relationships between diet and CM disease risk in Yup'ik people. In this analysis, we use dietary patterns previously identified from a food frequency questionnaire (FFQ) in a sample of Yup'ik people to characterize associations between diet and biomarkers of CM status.

METHODS

STUDY SAMPLE

This project took place as part of the University of Alaska Fairbanks Center for Alaska Native Health Research (CANHR) studies for which detailed study recruitment methods have been published elsewhere.(3,19) In brief, CANHR conducts recurring cross-sectional research in 11 of the 58 remote Yup'ik communities in the Yukon-Kuskokwim Delta region of Southwest Alaska.(32) At each research visit, enrolled study participants completed an in-person interview in English or Yup'ik during which demographic data were obtained and a FFQ was interviewer-administered. In addition, fasting blood samples were collected, physical measures were taken, and participants were fitted with an Actiheart monitoring device that recorded movement and heart rate.

Our sample included 637 individuals who participated in CANHR studies between September 2009 and May 2013 (the period during which the same FFQ version was used), were greater than 18 years of age, were not pregnant, who self-reported their ethnicity as Yup'ik, and had complete data required to determine the dietary patterns, as describe below. For individuals who had participated in more than one research visit, we used the data from their most recent visit with both FFQ and activity data available for analysis.

Informed consent was obtained from participants prior to data collection. This study was approved by the University of Alaska Fairbanks Institutional Review Board, the Yukon-Kuskokwim Health Corporation Human Studies Committee, and the University of Washington Institutional Review Board.

DATA COLLECTION

Diet

Dietary data were collected using a Yup'ik specific FFQ developed by CANHR researchers and local community research assistants. The FFQ included 163 of the mostly commonly eaten foods. Participants reported how frequently they typically consumed each food during the previous 12 months. For traditional subsistence foods it was further elicited whether they ate the food seasonally or year-round. Frequency of consumption was measured on nine-point scale groupings of frequency, with one for foods and one for beverages. For both scales, the least frequent group was "never or less than once per month"; for foods the greatest frequency group was “two or more times per day” and for beverages the greatest frequency group was “six or more times per day.” Serving size was not collected in order to reduce participant burden.

Briefly, three dietary patterns were identified using a two-stage exploratory factor analysis(32) and then reproduced using a confirmatory factor analysis.(26) The resulting dietary patterns included two market-based dietary patterns, a “processed foods” pattern and a “fruits and vegetables” pattern, as well as a “subsistence foods” dietary pattern that captured traditional diet. The “processed foods” dietary pattern was measured using the following foods from the FFQ: salty snacks, sweetened cereals, pizza, sweetened drinks, hot dogs and lunch meat, fried chicken, and canned tuna; the “fruits and vegetables” dietary pattern was measured using fresh citrus, potato salad, citrus juice, corn, green beans, green salad, and market berries in akutaq (Eskimo ice cream); and finally the “subsistence foods” dietary pattern included seal or walrus soup, non-oily fish, wild greens, and bird soup (Appendix 4).

Dietary pattern scores were estimated as the average of the natural log transformed frequency of consumption for each food measuring the dietary pattern.(26) Each study participant received a score for each of the three dietary patterns. The greater the dietary pattern score, the greater the frequency of consumption of the foods used to measure that dietary pattern. Dietary pattern scores were grouped into quartiles in which the first or lowest quartile represented the lowest frequency of consumption for that dietary pattern and the fourth or highest quartile represented the highest frequency of consumption of foods used to measure that dietary pattern.

Biomarkers of cardiometabolic status

Biomarkers of CM status were collected from study participants by trained observers and included fasting blood samples for lipid determinations (low-density lipoprotein cholesterol [LDL-C], HDL-C, triglycerides [TG]), fasting blood glucose (FBG) levels, and glycated hemoglobin (HbA1c), as described below. Measurements of systolic (SBP) and diastolic (DBP) blood pressure and waist circumference (WC) were obtained by physical exam.

Participants were asked to fast for eight to twelve hours prior to providing blood samples. Lipid concentrations were measured with the Poly-Chem System Chemistry Analyzer (Polymedco Inc, Cortlandt Manor, NY) in the Nutritional Assessment Laboratory at the University of California Davis. FBG was measured with a Cholestech LDX analyzer and HbA1c was measured using the Bayer HbA1c DCA 2000+ analyzer.

Blood pressure was obtained while the participant was sitting quietly with their arm resting comfortably on a flat surface between heart and waist level using the OMRON HEM907 automated blood pressure cuff. After a five-minute resting period, three measures were taken with a one-minute interval between each. The mean of the last two measures was used for analysis, unless the final measure was not available in which case the mean of the first two measures was used.

WC was measured twice using a Gulick II 150 cm anthropometric tape attached with a tension-meter. The WC measure was taken directly on the skin at a level immediately below the lowest lateral portion of the rib cage while the participant was standing. If the two WC measures differed by more than two centimeters, then a third measure was taken and the final measure was the average of the two closest measures. We selected WC for this analysis because a study in Yup'ik people found that of the obesity-related measures (e.g., WC, body mass index [BMI], waist-to-hip ratio), WC was consistently better correlated with obesity-related risk factors.(64)

Covariates

At the same visit when diet and biomarkers of CM status were obtained, data on potential confounding factors were also collected. Specifically self-reported age, sex, smoking, and medication use for lowering lipids, for controlling diabetes, and for controlling hypertension were obtained. In addition, study participants wore an Actiheart combined heart rate/movement monitoring device for four-consecutive days. We used the average total counts per day measure to ascertain physical activity levels, as counts per day was found to be the best measure of physical activity energy expenditure in free-living Yup'ik people (unpublished data).

STATISTICAL ANALYSIS

To improve the distribution of the biomarkers of CM status, we log transformed HDL-C, TG, FBG, and WC. Participant biomarkers of CM status more than four standard deviations from the mean were excluded from analyses: LDL-C (n=1), log TG (n=1), SBP (n=1), HbA1c (n=1), and log FBG (n=2). Furthermore, study participants taking a medication to treat a specific biomarker of CM status were excluded from all analyses of that risk factor. That is, participants taking cholesterol lowering medication were excluded from the LDL-C, HDL-C, and TG analyses (n=41), participants taking hypertension medication were excluded from SBP and DBP analyses (n=102), and participants taking diabetes medication were excluded from the HbA1c and FBG analyses (n=6). Participants who were not fasting were excluded from the LDL-C, HDL-C, TG, and FBG analyses (n=11). Thus, sample sizes varied for the analyses of the risk factors. Sample sizes also varied due to missing data for each measure as indicated in the tables. All analyses were performed using SAS and Stata. P-values < 0.05 were considered statistically significant.

To characterize the association between dietary patterns and biomarkers of CM status we used multilevel linear regression to estimate the mean of each biomarker of CM status among participants in the lowest quartile (first) compared to the other quartiles, with the second, third, and fourth quartiles included in the model as binary terms. The lowest (first) quartile was treated as the reference group. For ease of interpretation we report the differences between the first and fourth quartiles as the primary analysis. We also tested for trend by including the dietary pattern quartile in the model as a grouped-linear term. Potential confounding factors were adjusted for and clustering at the community level was accounted for by fitting a random intercept model using maximum likelihood.(65) The random intercept was for each of the 10 communities included in the analysis.

We adjusted for sex, past smoking, current smoking, age, and physical activity counts per day. Sex, past smoking, and current smoking were modeled as binary variables. Cigarette smoking was included as “past” and “current” (anyone smoking within previous year), with the reference group as “never” to represent the different risk among current versus previous smokers.(66,67) Age was modeled as a spline with two knots(65) and physical activity counts per day was log transformed to improve normality, and was included in the model as a centered linear term.

RESULTS

The characteristics of study participants are shown in Table 6. They ranged in age from 18 to 93 years, with a mean age of 39.9 years. Men comprised 46.2% of the participants. The majority of participants had smoked, with 31.1% reporting past smoking and 35.2% reporting current smoking. Mean counts per day of physical activity were 49.8 per 1000 counts per day, ranging from a low of 3.2 to a high of 181.0 per 1000 counts per day. There was large within community variation and small between community variation for each dietary pattern (Appendix 5).

LIPIDS

Neither LDL-C nor log HDL-C was significantly associated with any of the dietary patterns. Log TG was significantly associated with the processed foods and subsistence foods dietary patterns. Mean TG levels were 12% (β=0.11, P=0.046) higher among participants in the fourth compared to the first quartile of processed foods (Table 7), with an increasing trend at greater dietary pattern quartiles (P=0.031) (Table 7, Figure 2). In addition, mean log TG were inversely associated with the subsistence food dietary pattern, with mean log TG 10% lower among participants in the fourth compared to first quartile (β=-0.10, P=0.049) (Table 7).

BLOOD PRESSURE

Mean SBP was not significantly associated with any of the dietary patterns (Table 7). Mean DBP was 2.87 mm Hg higher among participants in the fourth compared to first quartile of the fruits and vegetables dietary pattern (β=2.87, P=0.014). In addition mean DBP was inversely associated with the subsistence food dietary pattern, with mean DBP 3.99 mm Hg lower among participants in the fourth compared to first quartile (β=-3.99, P<0.001, P-trend<0.001) (Table 7, Figure 3).

BLOOD GLUCOSE

Mean HbA1c was inversely associated with the fruits and vegetables dietary pattern, with a 0.08% lower HbA1c among participants in the fourth compared to the first quartile (β=-0.08, P=0.013, P-trend=0.007) (Table 7, Figure 4). FBG was not significantly associated with any of the three dietary patterns (Table 7).

ADIPOSITY

No significant associations were observed between any of the dietary patterns and mean log WC (Table 7).

DISCUSSION

Dietary patterns derived from FFQ data are associated with CM disease risk in this sample of Yup'ik people. Specifically, we found evidence of increased CM risk related to the processed foods dietary pattern based on the higher TG measures (a risk factor for CM disease) and reduced CM risk related to the subsistence foods dietary pattern based on the lower TG and DBP (measures of reduced risk for CM disease). The association between the fruits and vegetables dietary pattern and CM disease risk was less clear in this population given the conflicting associations: reduced CM risk based on lower HbA1c levels but increased risk based on higher DBP.

The 12% lower TG measure in the lowest compared to the highest quartile of the processed foods dietary pattern is similar to the magnitude of change in TG measures observed among statin users.(68) This association is consistent with findings from a study using a biomarker of market food intake(69) in Yup'ik people but differs from market-based dietary patterns determined from FFQ data among Inupiat people.(56) The processed foods dietary pattern includes many of the same foods that are captured with the δ^{13}C biomarker, which is elevated in market foods based on corn, corn-fed meats, or sugar cane and thus strongly associated with total market food intake.(69) Nash et al., identified a positive association between δ^{13}C and TG and no association between δ^{13}C and HbA1c, FBG, and WC, all consistent with our findings from the same Yup'ik study population.(69) However δ^{13}C was also reported to be negatively associated with LDL-C, HDL-C and positively associated with SBP and DBP,(69) associations not observed in our study. Using FFQ data Eilat-Adiar et al., identified 2 dietary patterns in Inupiat people that share similarities with our processed foods dietary pattern, a "beverages and sweets" pattern and "western foods" pattern.(56) Neither the "beverages and sweets" pattern nor the "western foods" dietary pattern was significantly associated with HDL-C, TG, or SBP.(56) The "beverages and sweets" dietary pattern was found to be positively associated with LDL-C,(56) an association in the opposite direction than was found by Nash et al. using the δ^{13}C biomarker.(69)

To our knowledge, there is only one other study that reported biomarkers of CM status associations with fruits and vegetables in an Alaska Native population. Eilat-Adiar et al.,(56) used FFQ data to identify a "healthy purchased" dietary pattern which includes fruits and vegetables, however this dietary pattern was not associated with LDL-C, HDL-C, TG, or SBP. In comparison, our fruits and vegetables dietary pattern suggested a possible positive association with DBP and a negative association with HbA1c. The inverse association with HbA1c is consistent with studies in other populations, in which dietary patterns favoring fruits and vegetables were found to be beneficial(70) for diabetes prevention. Although the inverse association between HbA1c and the fruits and vegetables dietary pattern was significant, the 0.08% difference in HbA1c between the highest and lowest quartile is likely not a clinically meaningful difference. Metformin, a medication used to treat high glucose, lowers HbA1c by approximately 0.9% among non-insulin-dependent diabetes mellitus patients.(71) The higher DBP in the fourth compared to first quartile of the fruit and vegetable dietary pattern was not as we expected. The reason for this association is not clear. The types of fruits and vegetables available in these remote communities are typically canned rather than fresh, which may provide a partial explanation. It could also be due to the correlation between our processed foods and fruits and vegetables dietary patterns.(26) People buying fruits and vegetables are shopping in stores, where they might also be buying processed foods, which we found to be associated with increased TG levels.

A number of other studies have characterized the association between traditional foods and CM risk in indigenous circumpolar populations. These studies have consistently found traditional foods to be positively associated with LDL-C, HDL-C, and FBG and negatively associated with TG and SBP.(56,62,72,73) Of these associations, we only observed the inverse TG association, but we also observed a negative association between a traditional or subsistence diet and DBP. The 3.99 mm Hg difference in DBP between the first and fourth quartile is comparable to the reduction in DBP expected for a person with a baseline DBP of 90 to 95 mm Hg taking one hypertensive drug at half standard dose.(74) This reduction in DBP is associated with approximately a 14% reduction in coronary heart disease risk and 17% reduction in stroke risk.(74) The association between a traditional diet and DBP was first identified in the same Yup'ik study population by O'Brien et al. using the $\delta^{15}N$ biomarker elevated in traditional marine foods, and is consistent with findings from non-indigenous populations based on fish oil intake.(62) However O'Brien et al. also found $\delta^{15}N$ to be positively associated with LDL-C and HDL-C and inversely associated with TG and SBP.(62) In the same study population, and we only found the inverse association with TG, possibly because of the different composition of our subsistence food dietary pattern. The $\delta^{15}N$ biomarkers is specific to marine-based foods and our subsistence foods dietary pattern includes wild greens and bird soup, items not high in $\delta^{15}N$. Alternatively, it could be a result of using FFQ data, subject to measurement error, to define our dietary patterns.(75,76)

In our analysis the differences in dietary pattern factors scores, and thus dietary pattern quartiles, could be the result of substituting foods (e.g., substituting more processed foods for less subsistence foods) or it could be the result of eating more food overall (e.g., eating greater amounts of both processed foods and subsistence foods). As the FFQ did not capture serving size, it was challenging to account for the latter possibility of participants in the highest dietary pattern quartiles eating more food. To better differentiate between substitution of foods and overall eating more food, we conducted a sensitivity analysis using the same model with the addition of a summary measure of the annual frequency of consumption of the 18 foods used to determine the dietary patterns as a covariate. This model may better measure substitution of foods, as it allows for the comparison of changes in frequency of consumption for each dietary pattern among people eating overall similar frequencies of foods. To our knowledge this approach has not been previously reported. With one exception (a positive association between SBP and the fruit and vegetable dietary pattern), we found no meaningful differences in the associations observed between dietary patterns and biomarkers of CM status with the summary measure included (data not shown) compared to those associations observed and reported in the results without the summary measures. This indicates that our findings are likely not strongly influenced by those individuals who eat more overall.

Strengths of this study include the use of the same FFQ since 2009, variability in dietary patterns between individuals, within community variation in dietary patterns, and the use of reproducible and reliable dietary patterns. Our findings generally align with the findings from other indigenous circumpolar populations, however, we found fewer significant associations particularly when compared with the studies using biomarkers to measure diet.(62,69) This may be due to measurement error in the dietary patterns. It is possible that there is too much measurement error in dietary patterns derived from FFQ data, resulting in an attenuation of results, for us to detect significant associations in our relatively small sample. Studies of FFQ dietary patterns and CM risk in other populations have included thousands of subjects and even the smaller Eilat-Adar study in an Alaska Native population has a sample nearly twice the size of our study.(56) Other limitations include our inability to assess temporality due to the cross-sectional nature of the data, the potential lack of generalizability given the convenience sampling method employed, the exclusion of participants taking medications for CM diseases, and potential bias due to unmeasured confounding because alcohol use data was not collected. We also acknowledge the potential issue of multiple comparisons but elected not to report a more conservative P-value given the exploratory nature of our research. However, using a conservative Bonferroni P-value (<0.001) the inverse associations between DBP and the subsistence food dietary pattern remained statistically significant.

Overall we found associations between increased CM risk, as reflected by increased mean TG, associated with eating a greater frequency of processed foods, and reduced CM risk, as reflected by lower mean TG and DBP, associated with eating a greater frequency of subsistence foods. The association between the fruits and vegetable dietary pattern and CM risk was less clear, and will require further investigation. These findings align with other research and support efforts to further encourage a diet high in traditional subsistence foods as a way to further reduce CM disease related health disparities in this underserved population.

TABLES AND FIGURES

TABLE 6

Participant characteristics and biomarkers of cardiometabolic status, Yup'ik study participants, September 2009 - May 2013

	n	Overall
Participant characteristics		
Age in years, mean (range)	637	39.9 (18-93)
Male sex, %	637	46.2
Never smoker, %	637	33.7
Past smoker, %	637	31.1
Current smoker, %	637	35.2
Physical activity per 1000 counts a day, mean (range)	595	49.8 (3.2-181.0)
Biomarkers of cardiometabolic status		
LDL-C (mg/dL), mean (range)*	577	125.4 (51.5-250.2)
HDL-C (mg/dL), mean (range)†‡	578	63.0 (30.5-136.0)
TG (mg/dL), mean (range)†*	577	83.5 (27.0-393.0)
SBP (mm Hg), mean (range)£	534	115.8 (79.5-162.5)
DBP (mm Hg), mean (range)§	535	67.7 (37.0-98.0)
HbA1c (%), mean (range)ll	630	5.6 (4.3-6.9)
FBG (mg/dL), mean (range)†#	619	91.5 (58.0-139.0)
WC (cm), mean (range)†**	635	89.1 (58.9-144.2)

Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, and WC = waist circumference.

* excludes participants with missing data (n=7), who were not fasting when the sample was taken (n=11), who self-reported taking lipid lowering medications (n=41), and who had a measure >4 standard deviations from the mean (n=1)

†values presented here are not log transformed for ease of interpretation, but were log transformed for the analysis

‡ excludes participants with missing data (n=7), who were not fasting when the sample was taken (n=11), and who self-reported taking lipid lowering medications (n=41)

£ excludes participants who self-reported taking hypertension medication (n=102) and who had a measure >4 standard deviations from the mean (n=1)

§ excludes participants who self-reported taking hypertension medication (n=102)

ll excludes participants who self-reported taking diabetes medication (n=6) and who had a measure >4 standard deviations from the mean (n=1)

excludes participants who were not fasting when the sample was taken (n=10),who self-reported taking diabetes medication (n=6) and who had a measure >4 standard deviations from the mean (n=2)

** excludes participants with missing measures (n=2)

TABLE 7

Associations between dietary pattern quartile (only 4th quartile reported) and biomarkers of cardiometabolic status, using multilevel analysis accounting for community and adjusted for covariates† (n=637), Yup'ik study participants, Sept 2009 - May 2013

	Processed Foods			Fruits and Vegetables			Subsistence Foods		
	β	*P*	*P-trend*	β	*P*	*P-trend*	β	*P*	*P-trend*
Biomarkers of cardiometabolic status	4th v. 1st (ref) quartile		All 4 quartiles	4th v. 1st (ref) quartile		All 4 quartiles	4th v. 1st (ref) quartile		All 4 quartiles
Lipids									
LDL-C (mg/dL) (n=530)	-4.65	0.25	0.24	0.92	0.80	0.89	3.34	0.37	0.21
Log HDL-C (n=531)	-0.01	0.69	0.65	-0.03	0.36	0.49	0.04	0.16	0.10
Log TG (n=530)	0.11	0.046	0.031	0.07	0.17	0.05	-0.10	0.049	0.06
Blood pressure									
SBP (mm Hg) (n=492)	-0.50	0.75	0.96	2.37	0.10	0.27	-1.05	0.47	0.26
DBP (mm Hg) (n=493)	-0.78	0.56	0.60	2.87	0.014	0.06	-3.99	<0.001	<0.001
Blood glucose									
HbA1c (%) (n=577)	-0.03	0.43	0.28	-0.08	0.013	0.007	0.04	0.21	0.35
Log FBG (n=567)	0.00	0.85	0.84	-0.01	0.64	0.52	0.01	0.58	0.71
Adiposity									
Log WC (n=583)	0.03	0.15	0.23	0.02	0.15	0.17	0.02	0.32	0.64

Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, and WC = waist circumference.

β and p-values for the 2nd and 3rd quartile not reported.

† Adjusted for age, sex, current smoking, past smoking, and physical activity counts per day.

FIGURE 2

Difference in mean log triglyceride (TG) levels in each processed foods dietary pattern quartile compared to the 1st quartile, with 95% confidence intervals (n=637), Yup'ik study participants, Sept 2009 - May 2013

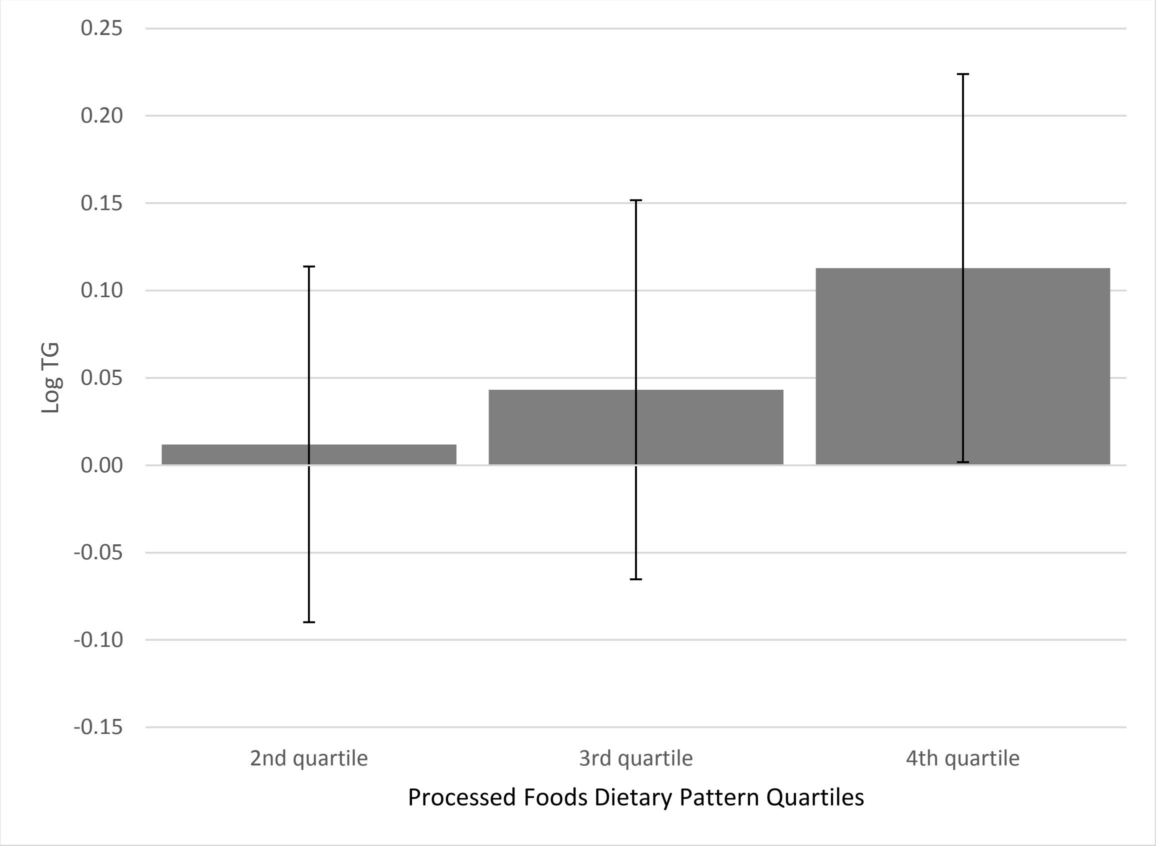


FIGURE 3

Difference in mean diastolic blood pressure (DBP) mm Hg in each subsistence foods dietary pattern quartile compared to the 1st quartile, with 95% confidence intervals (n=637), Yup'ik study participants, Sept 2009 - May 2013

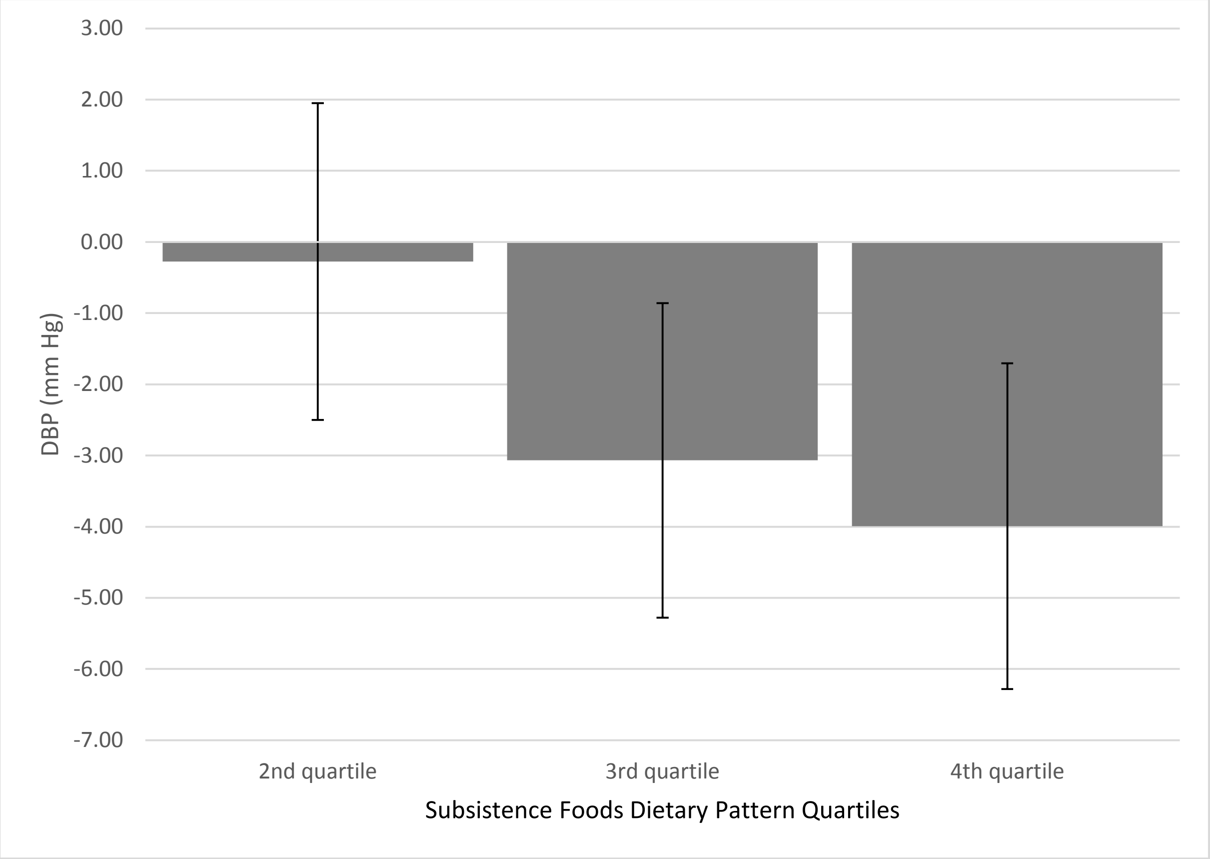
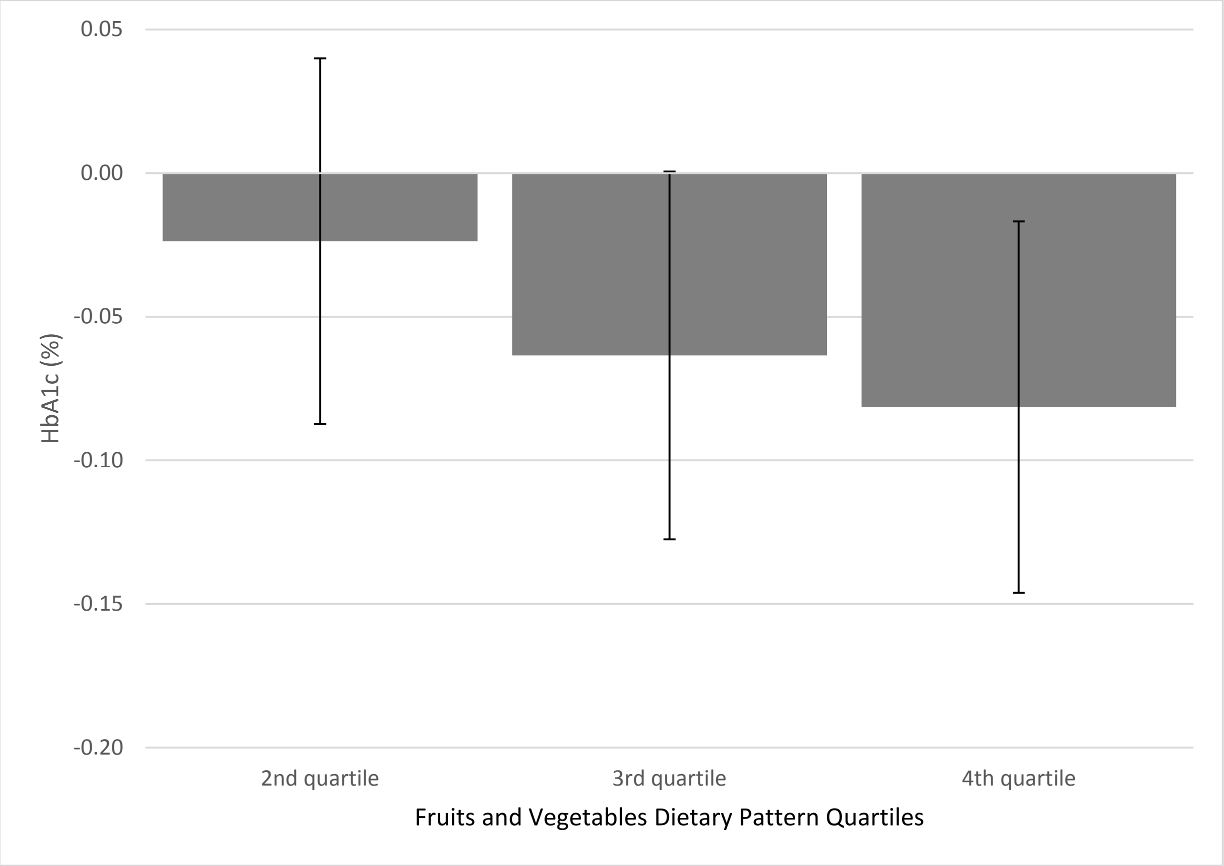


FIGURE 4

Difference in mean HbA1c % in each fruit and vegetable dietary pattern quartile compared to the 1st quartile, with 95% confidence intervals (n=637), Yup'ik study participants, Sept 2009 - May 2013



CHAPTER 4. ASSOCIATION BETWEEN IQ'MIK SMOKELESS TOBACCO USE AND CARDIOMETABOLIC RISK AMONG YUP'IK ALASKA NATIVE PEOPLE

ABSTRACT

The traditional lifestyle of Yup'ik Alaska Native people, including a diet abundant in marine-based foods and daily physical activity, may be cardio-protective. However iq'mik, a traditional form of smokeless tobacco used by >50% of Yup'ik adults, could increase cardiometabolic (CM) risk. Our objective was to characterize the associations between iq'mik use and biomarkers of CM status (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG], systolic blood pressure [SBP], diastolic blood pressure [DBP], glycated hemoglobin [HbA1c], fasting blood glucose [FBG], waist circumference [WC], and body mass index [BMI]). We assessed these associations using data from a cross-sectional sample of Yup'ik adults (n=874). Current iq'mik use, demographic, and lifestyle data were collected through interviews. Fasting blood samples were collected to measure LDL-C, HDL-C, TG, HbA1c, and FBG. SBP, DBP, WC, and BMI were obtained by physical exam. We characterized the association between current iq'mik use and continuous biomarkers of CM status using multiple approaches, including adjustment for measures of Yup'ik lifestyle and a propensity score representing the conditional probability of using iq'mik. Based on either adjustment method, current iq'mik use was significantly associated with at least 5% higher log HDL-C, 7% lower TG, 0.05% lower HbA1c, 2% lower FBG, 4% lower WC, and 4% lower BMI. Although the composition of iq'mik is different from other smokeless tobacco products, we are not aware of any studies

that have found smokeless tobacco to be inversely associated with CM disease risk. Additional research is needed to replicate these findings and explore physiologic mechanisms and/or additional potential confounders.

INTRODUCTION

Between 1990 and 2009, all-cause mortality was 65% higher in Alaska Native people relative to United States (US) whites, with cardiovascular and metabolic diseases comprising a substantial burden of the mortality.(14) Several lifestyle factors including physical activity, stress, depression, alcohol consumption, diet, and tobacco use may contribute to cardiometabolic (CM) disease risk in Alaska Native people.(18)

Yup'ik Alaska Native people primarily reside in 58 remote communities in the Yukon-Kuskokwim Delta region of Southwest Alaska where many maintain features of their traditional lifestyle. Aspects of their traditional lifestyle, including a diet abundant in marine mammals and fish and regular physical activity associated with hunting, fishing and preparing subsistence foods, are believed to be cardio-protective.(2,30,31,62) However, some characteristics of their traditional lifestyle may increase CM risk. Smokeless tobacco use is an important component of Yup'ik culture and an indication of enculturation because its use is related to speaking the Yup'ik language, consuming more traditional foods and medicines, and self-reported identification with a Yup'ik lifestyle.(7,77)

Iq'mik, a type of homemade smokeless tobacco, has been commonly used by Yup'ik people for at least 150 years.(7) Iq'mik has a unique composition; it is prepared by mixing a tree fungus ash (*Phellinus igniarius*) or willow ash with fire-cured tobacco leaves.(78,79) Tree fungus can be gathered locally or purchased in local stores.(5,9,78) Iq’mik is typically made by mixing the tobacco and ash together by pre-chewing in the mouth and then storing for subsequent use.(5,7,9,78) The addition of ash to the tobacco raises the pH of the tobacco, increasing the amount of both free (unionized) nicotine available for absorption(78–81) as well as the available levels of carcinogens.(82,83) A study comparing exposure to nicotine by different forms of tobacco in Alaska Native people found nicotine exposure to be highest in iq’mik users.(82) However, because iq’mik preparation is not standardized, estimates of pH and nicotine levels are inconsistent.(5) Use of iq’mik is considered a social activity strongly associated with a traditional lifestyle, and it is not used for ceremonial or religious reasons.(6,7) Among Yup’ik people in the Yukon-Kuskokwim Delta region of Southwest Alaska, iq’mik use often begins at a young age (e.g., among teething children)(5,79,84) and by 18 years of age approximately 80% of youth in a Yup’ik sample had tried smokeless tobacco (including iq’mik).(9) Iq’mik use is ubiquitous in Yup’ik communities, with more than 50% of adults chewing.(5,7) Women chew more than men, and iq’mik use during pregnancy is common because it is thought to be healthier than cigarette smoking.(5,84) In fact, there are few perceived health risks associated with iq’mik use, in part because it is considered “natural”.(5,7,9,78,80)

Smokeless tobacco products are available in a variety of forms including commercial chew, such as Copenhagen for example, common to the US, and snus, a moist powder tobacco most commonly used in Sweden.(79) The association between these forms of smokeless tobacco and biomarkers of CM status (e.g., lipids, blood pressure, glucose, adiposity) and CM disease (e.g., heart disease, myocardial infarction, stroke) has been studied in non-Alaska Native populations.(67,85,86) These studies, primarily in Sweden and the US, have reported inconsistent associations between smokeless tobacco use and CM risk.(87–89) One of two recent meta-analyses reported no association between snus and heart disease or stroke.(90) In comparison, a different meta-analysis of 11 studies found ever-use of smokeless tobacco to be significantly associated with an increased risk of fatal myocardial infarction (relative risk = 1.1) and fatal stroke (relative risk = 1.4).(86)(86)(Boffetta and Straif 2009)86)

(Boffetta and Straif) A case-control study of data from >27,000 participants in 52 countries reported chewing tobacco (including a variety of forms) to be associated with increased risk of non-fatal myocardial infarction (odds ratio = 2.2).(67) One study found snus use associated with the metabolic syndrome (odds ratio = 1.6 among the highest dose group).(91) In two studies of snus use and type two diabetes, one found a significant association (odds ratio = 2.7)(92) and the other did not.(93) To our knowledge there are no studies of the association between iq'mik smokeless tobacco use and CM risk.

With a rate of nearly three times as many users of smokeless tobacco among Alaska Native people as the general US population,(84,94) and the high prevalence of iq'mik use among Yup'ik people, additional research is needed. Specifically, we set out to characterize the association between iq'mik use and measures of CM disease risk to guide future development of health messaging and interventions. This association is particularly interesting because of the unique composition of iq'mik compared to other forms of smokeless tobacco.

METHODS

STUDY SAMPLE

All data were collected as part of the University of Alaska Fairbanks Center for Alaska Native Health Research (CANHR) studies, for which detailed study recruitment methods have been published elsewhere.(3,19) In brief, CANHR conducts recurring cross-sectional research in 11 Yup'ik communities in the Yukon-Kuskokwim Delta region of Southwest Alaska.(32) Study participants within these communities were recruited using convenience sampling methods.(3,19) All individuals who self-identified as Alaska Native or who were married to an Alaska Native descendent, were greater than 14 years of age, and were non-pregnant, were invited to participate in the research.(3,19) For this analysis we included study participants enrolled between October 2007 and May 2013, who self-reported their ethnicity as Yup'ik, and who were 18 years of age or older. For individuals who had participated in more than one research visit, we used the data from their most recent visit with complete data for analysis.

Informed consent was obtained from participants prior to data collection. This study was approved by the University of Alaska Fairbanks Institutional Review Board, the Yukon-Kuskokwim Health Corporation Human Studies Committee, and the University of Washington Institutional Review Board.

DATA COLLECTION

At each visit, enrolled study participants completed an in-person interview in English or Yup'ik, provided a blood sample, underwent a physical examination, and wore a 4-day heart rate monitor.

In-person Interviews

During the interviews participants self-reported demographic, socio-economic, and lifestyle information including age, sex, educational level, if they ran out of utility and / or food money before the end of the month, number of people in their household, if they spoke Yup'ik, if Yup'ik was the primary language spoken at home, and cultural identification (i.e., self-reported adherence to "Kass'aq" [white] and Yup'ik lifestyle). The cultural identification questions were measured as separate variables, but were not mutually exclusive; for example, a participant could report "a lot" for adherence to both the Yup'ik and Kass'aq (white) lifestyle. They also self-reported tobacco use, providing dose and duration information for current or past use of iq'mik, commercial chew, and cigarettes. Finally, they reported use of medications to treat CM risk (for lowering lipids, glucose, and blood pressure).

Blood Samples

Participants were asked to fast for 8-12 hours prior to providing blood samples. Lipid concentrations (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG]) were measured with the Poly-Chem System Chemistry Analyzer (Polymedco Inc, Cortlandt Manor, NY) in the Nutritional Assessment Laboratory at the University of California Davis. Fasting blood glucose (FBG) was measured with a Cholestech LDX analyzer and glycated hemoglobin (HbA1c) was measured using the Bayer HbA1c DCA 2000+ analyzer.

Red blood cells were prepared and assessed for measuring the nitrogen stable isotope ratio at the Alaska Stable Isotope Facility as previously described.(37) The nitrogen isotope ratio

($\delta^{15}N$) is elevated in traditional marine foods, such that red blood cell $\delta^{15}N$ is strongly correlated with traditional marine food intake(36) and intake of the omega-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid.(37) By convention and for ease of interpretation, isotope ratios are presented as delta values in “permil” relative to international standards : $\delta^{15}N = [(R_{sample} - R_{standard})/(R_{standard})] \cdot 1000‰$, R is the ratio of heavy to light isotope, and the standards are atmospheric nitrogen.

Physical exam

Systolic (SBP) and diastolic (DBP) blood pressure were obtained while the participant was sitting quietly with his or her arm resting comfortably on a flat surface between heart and waist level using an OMRON HEM907 automated blood pressure cuff. After a five minute resting period, three measures were taken with a one-minute interval between each. The mean of the last two blood pressure measures was used for analysis, unless the final measure was not available in which case the mean of the first 2 measures was used.

WC was measured twice using a Gulick II 150 cm anthropometric tape attached with a tension-meter. The WC measure was taken directly on the skin at a level immediately below the lowest lateral portion of the rib cage while the participant was standing. If the two WC measures differed by more than two cm then a third measure was taken, and the final measure was the average of the two closest measures. Height was measured in inches to the nearest 1/8 inch (without shoes). Weight (in pounds) was measured using a TANITA TBF-300A impedance analyzer while the participant was wearing a light gown. Height and weight were used to calculate BMI using the formula kg/m^2.

Finally, study participants were fit with an Actiheart combined heart rate/movement monitoring device that they wore for four consecutive days.

STATISTICAL ANALYSIS

Iq'mik use was categorized as current use or past/never use. Biomarkers of CM status were analyzed as continuous measures. To improve the distribution of the biomarkers of CM status, we natural log transformed HDL-C, TG, FBG, WC, and BMI. All analyses were performed using SAS and Stata. P-values < 0.05 were considered statistically significant.

We excluded 18 participants who reported commercial chew use, in order to specifically characterize the association between iq'mik use and CM risk, resulting in a sample of 874 participants. Study participants taking cholesterol medication were excluded from the LDL-C, HDL-C, and TG analyses (n=58), participants taking hypertension medication were excluded from SBP and DBP analyses (n=129), and participants taking diabetes medication were excluded from the FBG and HbA1c analyses (n=8). Participants who were not fasting were excluded from the LDL-C, HDL-C, TG, and FBG analyses (n=13). Furthermore, biomarkers of CM status more than four standard deviations from the mean were excluded from analyses; LDL-C (n=1), log TG (n=1), SBP (n=2), HbA1c (n=1), and log FBG (n=4). Thus, sample sizes varied for the analyses of the risk factors. In addition, sample sizes varied due to missing data for each measure.

We modeled the association between iq'mik use and biomarkers of CM status accounting for clustering at the community level by fitting a random intercept model using maximum likelihood.(65) The random intercept was for each of the 11 communities included in the analysis. We modeled the association using three different sets of covariates. We modeled the association adjusting for age and sex first. This model represents the association between iq'mik use and biomarkers of CM status, not taking into consideration the traditional Yup'ik lifestyle. Given the strong association between iq'mik use and living a more traditional Yup'ik lifestyle,(7) we used two different modeling approaches to adjust for confounding, as described in detail below. In one approach, we included a number of covariates measuring aspects of the traditional Yup'ik lifestyle in the model, referred to as the "lifestyle covariate adjusted" model. Using another approach we modeled the association adjusting for a continuous propensity score representing the conditional probability of currently using iq'mik, referred to as the "propensity score adjusted" model.

The lifestyle covariate adjustment model included current iq'mik use and potential confounders as covariates in the linear regression model.(65) Specifically, we adjusted for gender, more than five people in the household, cigarette smoking, Yup'ik as the primary language spoken at home, identified a lot with Yup'ik lifestyle, and identified a lot with Kass'aq (white) lifestyle as binary variables and age, $\delta^{15}N$, and counts per day of physical activity as continuous variables (centered by subtracting the mean). Cigarette smoking was included as past and current (anyone smoking within previous year), with the reference group as never smoking used in order to characterize the differences in risk among current versus pervious smokers.(66,67) Using all of the same variables as in the lifestyle covariate adjustment model, we ran an additional model that included an interaction between the binary variables current iq'mik use and current cigarette smoking to estimate the association between iq'mik use and biomarkers of CM status among non-smokers and current smokers.

The propensity score adjustment model included current iq’mik use and a continuous propensity score measure (centered around the mean) in the linear regression model.(65) The propensity score can be interpreted as the likelihood that the participant would use iq’mik based on a number of lifestyle, socio-economic, and demographic characteristics associated with biomarkers of CM status.(95) The inclusion of the propensity score measure in the model allows for comparing participants using iq’mik to those not using iq’mik balanced on observed covariates, reducing bias and increasing precision.(95,96) For each participant, a propensity score was estimated using logistic regression with iq’mik current use as the outcome and 11 covariates. We selected the 11 covariates based on their association with the biomarkers of CM status in our study using univariate analyses.(97) All covariates associated with the biomarkers of CM status were included in a non-parsimonious logistic regression model (that is, we did not use an algorithmic method to determine what variables to retain in our model). The following covariates were selected: age (spline), sex, smoking status (current including within the previous year or past relative to never), more than five people in the household, speaks the Yup’ik language, high school or greater education, ran out of utility money always or almost always, ran out of food money always or almost always, $\delta^{15}N$, and physical activity counts per day. We excluded six participants with propensity scores below 0.20 so that there was adequate overlap in propensity score distributions between current iq’mik users and past/never users (Appendix 6). These participants were also excluded from the other models for consistency of interpretation.

RESULTS

Participants ranged in age from 18 to 95, with a mean age of 39 (Table 8). Females comprised 54% of the sample (Table 8). Fifty-three percent of participants self-reported identifying a lot with the Yup'ik lifestyle and 18% identifying a lot with the Kass'aq (white) lifestyle (Table 8). Iq'mik was currently used by two-thirds of study participants, was previously used by 11% of participants, and never used by 23% (Table 8 and Figure 5). Initiation of iq'mik use ranged from as young as one to as old as 69 (older participants were primarily participants who quit smoking), with 14 years of age being the mean age participants started chewing (Table 8). Participants chewed the equivalent of 4 times a day for an average of 33 years (Table 8). Thirty-eight percent of participants currently smoked, of which 54% also used iq'mik (Table 8 and Figure 5), and 29% previously smoked, and 34% never smoked. Participants initiated smoking at an average age of 17 years and smoked an average of 4 pack-years (Table 8).

Twenty percent of participants used both iq'mik and cigarettes, 46% used iq'mik but not cigarettes, 18% used cigarettes but not iq'mik, and 16% used neither type of tobacco (Table 9). Participant characteristics differed within strata of iq'mik use and cigarette smoking as reported in Table 9. Among both smokers and non-smokers iq'mik users were generally younger (29 v. 34 and 43 v. 48, respectively), and among non-smokers more iq'mik users were female (66% v. 57%), lived in households with more than 5 members (53% v. 40%), and spoke Yup'ik as the primarily language at home (80% v. 64%).

In the age- and sex- adjusted association model, current iq'mik use was significantly positively associated with log HDL-C (β=0.05, P=0.02) and inversely associated with log TG (β= -

0.10, P<0.01), log FBG (β= -0.02, P=0.01), and log WC (β= -0.03, P<0.01) (Table 10, Model A). After adjusting for confounding using lifestyle covariate adjustments, current iq'mik use was significantly inversely associated with HbA1c (β= -0.05, P=0.04) and log BMI (β= -0.04, P=0.01), and remained associated with log HDL-C (β=0.05, P=0.02), log TG (β= -0.07, P=0.04), log FBG (β= -0.02, P=0.01), and log WC (β= -0.04, P<0.01) (Table 10, Model B). In the model adjusting for confounding using the propensity score approach, current iq'mik use was also positively associated with HDL-C (β=0.05, P=0.02) and inversely associated with log FBG (β= -0.02, P<0.01), log WC (β= -0.04, P<0.01), and log BMI (β= -0.04, P=0.03) (Table 10, Model C). Specifically, based on either the lifestyle covariate or propensity score model, current iq'mik use was associated with at least 5% higher HDL-C, 7% lower TG, 0.05% lower HbA1c, 2% lower FBG, 4% lower WC, and 4% lower BMI.

In the covariate adjusted model with an interaction term for current iq'mik use and current smoking, significant associations were found for iq'mik use among non-smokers but no significant associations were observed among smokers (Table 11). That is, among current non-smokers, current iq'mik use was associated with 8.37 mg/dL lower LDL-C (β= -8.37, P=0.02), 8% higher HDL-C (β=0.08, P<0.01), 10% lower TG (β=-0.10, P=0.03), 4.20 mm Hg lower SBP (β=-4.20, P<0.01), 2.85 mm Hg lower DBP (β=-2.85, P=0.01), 0.07% lower HbA1c (β=-0.07, P=0.03), 3% lower FBG (β=-0.03, P<0.01), 5% lower WC (β=-0.05, P<0.01), and 7% lower BMI (β=-0.07, P<0.01).

DISCUSSION

Iq'mik use differed by demographic and lifestyle characteristics, with iq'mik users generally being female, living in households with more people, speaking Yup'ik as primary language at home, identifying a lot with the Yup'ik lifestyle, and identifying less with the Kass'aq lifestyle. We found that among this sample of Yup'ik people, even after adjustment for confounding, current use of iq'mik smokeless tobacco was associated with higher HDL-C and lower TG, HbA1c, FBG, WC, and BMI. However, HbA1c and TG were not significantly associated with current iq'mik use in the propensity score model, although point estimates were similar. These associations, as well as those showing lower LDL-C, SBP and DBP, were also observed among non-smokers.

We analyzed the association between iq'mik use and biomarkers of CM status among smokers and non-smokers, because of the well-established association between cigarette smoking and cardiovascular disease.(79,98) We found that many of the associations of iq'mik with biomarkers of CM status observed in our overall analysis were only seen in non-smokers. That is, we observed no significant associations between current iq'mik use and biomarkers of CM status among current smokers. The lack of association between iq'mik use and biomarkers of CM status among smokers could be due to the smaller sample size or because the risk associated with smoking(79,98,99) is so much stronger than that of iq'mik use that it dwarfs the contribution of iq'mik use.

Findings from other studies of smokeless tobacco have either found no significant association between smokeless tobacco use and CM risk/disease or that smokeless tobacco increases CM risk/disease.(79,86,90) These studies were typically restricted to non-smokers. Inconsistent findings across studies could be due in part to the variety of smokeless tobacco products used globally with differing manufacturing processes and additives.(79) For example, snus studies from Sweden indicate increased risk of fatal myocardial infarction and the INTERHEART study that included a variety of smokeless tobacco products indicated increased risk for acute myocardial infarction.(79) In comparison commercial chew studies from the US are equivocal.(79) Although iq'mik is different from any of the other smokeless tobacco products studied, we are not aware of any studies that have found smokeless tobacco to be inversely associated with CM disease risk.

Although the causal mechanism is unknown, it is possible that there is some property of iq'mik (e.g., chemical component) that is protective for CM risk. A qualitative study based on focus groups mentioned the possibility of iq'mik use in treatment for medical problems.(5) However, chemical analyses of iq'mik have found it to contain high levels of nicotine along with known carcinogens. Smokeless tobacco has been found to be associated with increased risk of oral cancers.(100) Thus, refuting the perception that iq'mik is less hazardous due to the "natural" ingredients.(79,83,101) Yet, among the studies that found smokeless tobacco use was associated with increased CM risk, the mechanisms by which smokeless tobacco was hypothesized to modify CM risk were not clear, but authors suggested that toxins in the tobacco itself could be associated with CM disease.(67)

Another possibility is that the observed associations could be due to residual confounding resulting from our inability to adequately adjust for Yup'ik lifestyle.(7) For example, a subsistence diet is an important aspect of the Yup'ik traditional lifestyle that has been shown to be associated with reduced CM risk.(2,62) In both the covariate lifestyle and propensity score models we adjusted for $\delta^{15}N$, a dietary biomarker of elevated traditional marine foods high in polyunsaturated fatty acids. However there may be other aspects of the traditional diet not captured in $\delta^{15}N$. To address this, we conducted a sensitivity analysis among a subset (~75% of initial sample) of participants with food frequency questionnaire (FFQ) data. We adjusted for a traditional subsistence food dietary pattern based on frequency of consumption of seal and walrus soup, non-oily fish, wild greens, and bird soup.(26,32) In the subset analysis, the estimates for TG, FBG, WC, and BMI were slightly attenuated and no longer statistically significant when we adjusted for this subsistence food dietary pattern (data not reported). It is also possible that people living a more traditional lifestyle consumed less sugary beverages. To evaluate this we created a measure of sugar-sweetened beverages based on FFQ data. We again found slightly attenuated estimates and no longer statistically significant differences for HDL-C, TG, FBG, WC, and BMI (data not reported). We further adjusted for $\delta^{13}C$ (elevated in market foods based on corn, corn-fed meats, or sugar cane) to create a measure of sugar intake as previously reported(69,102) and found a slight attenuation in the TG estimate and a p-value >0.05. Although the samples sizes are smaller, these sensitivity analyses suggest the potential for residual confounding. Moreover, although our dataset included a rich set of covariates, we were not able to adjust for alcohol use or allostatic load, both of which could be confounders.(2) In addition, there could be unmeasured confounders such as those related to social determinants of health (e.g., social support networks).

Alternatively, an explanation combining these ideas is the possibility that iq'mik use is associated with other aspects of Yup'ik lifestyle that are cardio-protective, and that iq'mik is used more by people enculturated in their Yup'ik lifestyle. As Wolsko and colleagues stated, "enculturation has been characterized as part of a healthy lifestyle that buffers the harmful effects of stress and enables one to engage in healthier behaviors."(7) Moreover, Yup'ik people report enculturation and practicing the traditional Yup'ik lifestyle is at the core of wellness and health.(103) As such, the use of iq'mik could be protective because its use is one aspect leading to being more enculturated in the Yup'ik lifestyle and through this, lead to improved health. Similarly, Boden-Albala et al., reported that bicultural identification reduces the effects of other deleterious risk factors for high blood pressure.(104)

Strengths of this study include detailed exposure and covariate measures collected consistently for all study participants. The availability of a rich set of covariates related to participant characteristics, socio-economic status, cigarette smoking, and Yup'ik lifestyle provided us an opportunity to adjust for many potential confounders. However as described above, there are a number of additional potential confounding factors (e.g., alcohol use, allostatic load, social determinants of health such as social support networks) that were not measured. Other limitations of this study include the potential for reverse causation given the cross-sectional nature of the data (e.g., people with elevated biomarkers of CM status quit using iq'mik), the potential lack of generalizability given the convenience sampling method employed and the exclusion of participants taking medications for CM diseases. We also acknowledge the potential for type one error given the multiple comparisons. Furthermore, these associations should not be over interpreted as data are based on biomarkers of CM status rather than disease outcomes.

Although iq'mik is different from other smokeless tobacco products, we are not aware of any studies that have found smokeless tobacco to be inversely associated with CM disease risk. Additional research is needed to replicate these findings, identify potential unmeasured confounders, and explore possible physiologic mechanisms. Given the high prevalence of iq'mik use in Yup'ik people and the CM disease burden, it would be of value to characterize the association between smokeless tobacco and CM disease risk for the development of health messaging and interventions.

TABLES AND FIGURES

FIGURE 5

Prevalence of iq'mik use overall and by cigarette smoking use, Yup'ik study participants (n=874), October 2007 - May 2013

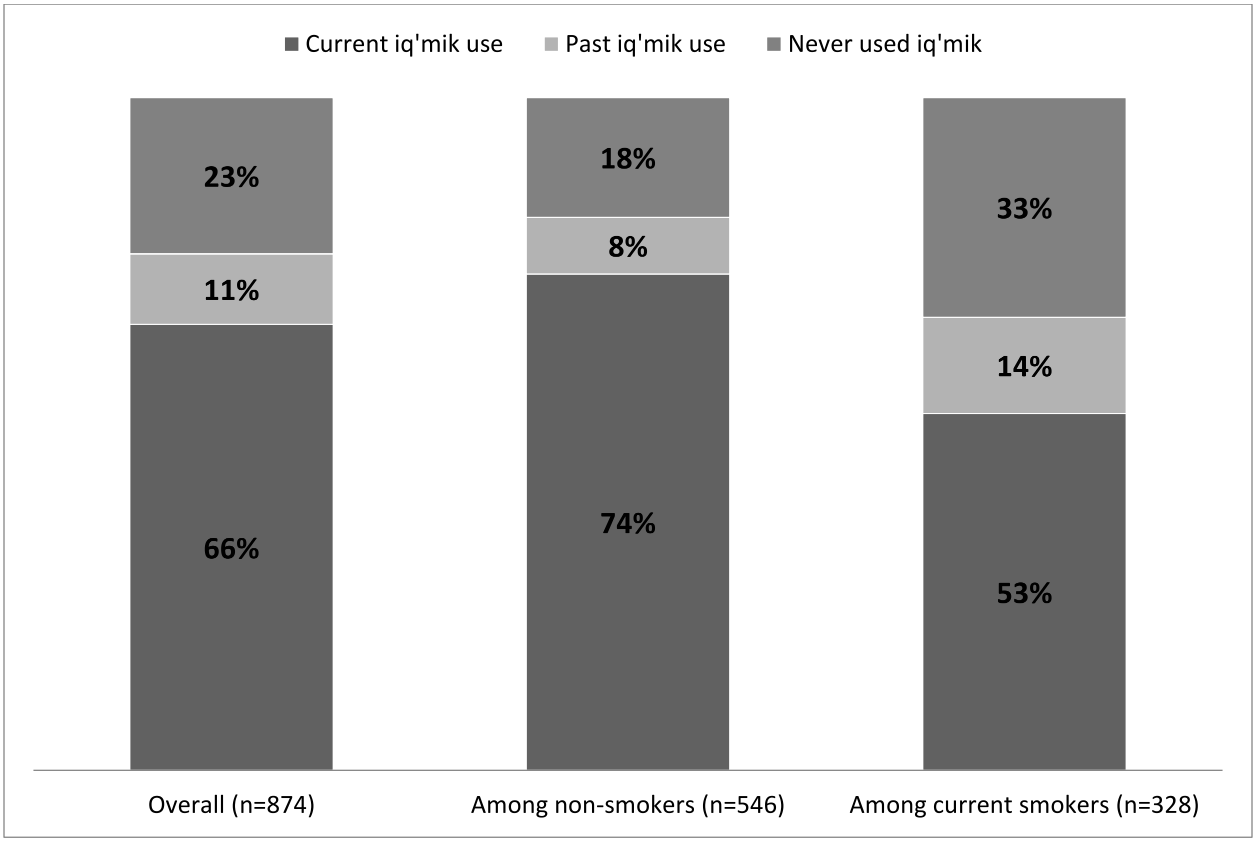


TABLE 8

Participant characteristics, tobacco use, and biomarkers of cardiometabolic (CM) status, Yup'ik study participants (n=874), October 2007 - May 2013.

	n	Overall
Participant characteristics		
Age, mean (range)	874	39 (18 - 95)
Female, %	874	53.5
>5 household members, %	874	50.8
Identify a lot with Yup'ik lifestyle, %	870	53.0
Identify a lot with Kass'aq (white) lifestyle, %	870	17.6
Yup'ik as the primary language spoken at home, %	874	70.5
Red blood cell δ^{15}N, mean (range)	872	8.9 (6.1 - 14.5)
Physical activity per 1000 counts a day, mean (range)	810	49.7 (3.2 - 214.8)
Iq'mik use		
% current iq'mik use	874	66.0
% past iq'mik use	874	10.6
% never iq'mik use	874	23.3
Current users		
Age started in years, mean (range)	577	14 (1 - 69)
Years of chewing 4x a day, mean (range)	576	33 (<1 - 323)
Cigarette smoking		
% current smoker	874	37.5
% past smoker	874	28.4
% never smoked	874	34.1
Current smokers		
Age started in years, mean (range)	328	17 (4 - 59)
Pack-years, mean (range)	328	4 (<1 - 54)
Biomarkers of CM status		
LDL-C (mg/dL), mean (range)	798	127.0 (51.5 - 263.0)
HDL-C (mg/dL), mean (range)*	799	62.6 (30.5 - 136.0)
TG (mg/dL), mean (range)*	799	84.1 (27.0 - 429.0)
SBP (mm Hg), mean (range)	743	115.7 (79.5 - 166.0)
DBP (mm Hg), mean (range)	745	67.6 (37.0 - 104.5)
HbA1c (%), mean (range)	748	5.6 (4.3 - 6.9)
FBG (mg/dL), mean (range)*	853	91.8 (56.0 - 244.0)
WC (cm), mean (range)*	866	89.4 (58.9 - 152.3)
BMI (kg/m^2), mean (range)*	873	27.2 (16.2 - 55.9)

Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, WC = waist circumference, and BMI = body mass index.

* values presented here are not log transformed for ease of interpretation, but were log transformed for the analysis

TABLE 9

Participant characteristics by current use of iq'mik and current use of cigarettes, Yup'ik study participants (n=874), October 2007 - May 2013.

	Current cigarette smoking			
	Non-smoker		Smoker	
Participant characteristics	Past/Never iq'mik user (n=143)	Current iq'mik user (n=403)	Past/Never iq'mik users (n=154)	Current iq'mik user (n=174)
Age, mean (range)	48 (18 - 95)	43 (18 - 83)	34 (18 - 77)	29 (18 - 75)
Female, %	57	66	36	37
>5 household members, %	40	53	50	55
Identify a lot with Yup'ik lifestyle, %	55	62	38	45
Identify a lot with Kass'aq (white) lifestyle, %	18	13	26	20
Yup'ik as the primary language spoken at home, %	64	80	57	66
Red blood cell $\delta^{15}N$, mean (range)	9.2 (6.4 - 14.5)	9.3 (6.7 - 13.2)	8.3 (6.1 - 12.6)	8.3 (6.1 - 11.6)
Physical activity per 1000 counts a day, mean (range)	44.7 (4.4-181.0)	45.5 (3.2 - 172.9)	56.5 (4.5 - 162.6)	57.3 (14.4 - 214.8)

TABLE 10

Association between current iq'mik use and biomarkers of cardiometabolic (CM) status, based on multilevel modeling accounting for community: A) adjusted for age and sex, B) adjusted for demographics and measures of Yup'ik lifestyle†, and C) adjusted for a propensity score of iq'mik use‡. Yup'ik study participants (n=868), October 2007 - May 2013.

Biomarker of CM status	A) Age- and sex- adjusted		B) Lifestyle covariate adjusted†		C) Propensity score adjusted‡	
	β	P	β	P	β	P
LDL-C (mg/dL)	-2.21	0.36	-3.03	0.25	-1.34	0.65
Log HDL-C (mg/dL)	**0.05**	**0.02**	**0.05**	**0.02**	**0.05**	**0.02**
Log TG (mg/dL)	**-0.10**	**0.002**	**-0.07**	**0.04**	-0.07	0.07
SBP (mm Hg)	-1.37	0.14	-1.77	0.08	-1.33	0.23
DBP (mm Hg)	-1.33	0.08	-1.16	0.15	-0.99	0.24
HbA1c (%)	-0.03	0.13	**-0.05**	**0.04**	-0.05	0.09
Log FBG (mg/dL)	**-0.02**	**0.01**	**-0.02**	**0.01**	**-0.02**	**0.004**
Log WC (cm)	**-0.03**	**0.007**	**-0.04**	**0.002**	**-0.04**	**0.004**
Log BMI (kg/m^2)	-0.03	0.06	**-0.04**	**0.01**	**-0.04**	**0.03**

Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, WC = waist circumference, and BMI = body mass index.

Bold indicates p-value <0.05

† Adjusted for male sex, >5 members of the household, past smoker, current smoker, Yup'ik primary language spoken in home, identifies a lot with Yup'ik lifestyle, identifies a lot with white lifestyle, and the centered linear terms: age, red blood cell δ^{15}N, and log counts per day of physical activity.

‡ Adjusted for propensity score as linear term. Propensity score predictors included: male sex, past smoker, current smoker, >5 members of the household, speaks Yup'ik language, high school or greater education, ran out of utility money always or mostly, ran out of food money always or mostly, and the linear terms age (spline), red blood cell δ15N, and log counts per day of physical activity.

TABLE 11

Association between current iq’mik use and biomarkers of cardiometabolic (CM) risk by cigarette smoking status†, Yup'ik study participants (n=868), October 2007 - May 2013.

	Current iq'mik use compared to past/never use			
Biomarker of CM	Among non-smokers		Among cigarette smokers	
status	β	P	β	P
LDL-C (mg/dL)	**-8.37**	**0.02**	2.88	0.44
Log HDL-C (mg/dL)	**0.08**	**0.004**	0.01	0.65
Log TG (mg/dL)	**-0.10**	**0.03**	-0.04	0.44
SBP (mm Hg)	**-4.20**	**0.002**	0.72	0.60
DBP (mm Hg)	**-2.85**	**0.01**	0.61	0.60
HbA1c (%)	**-0.07**	**0.03**	-0.03	0.47
Log FBG (mg/dL)	**-0.03**	**0.001**	0.00	0.82
Log WC (cm)	**-0.05**	**<0.001**	-0.01	0.41
BMI (kg/m^2)	**-0.07**	**0.001**	0.00	0.87

Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, WC = waist circumference, and BMI = body mass index.

Bold indicates a p-value <0.05

† Estimates obtained from a model with an interaction term for current smoking and current iq’mik use, accounting for community with a random intercept, and adjusted for male sex, >5 members of the household, past smoker, Yup'ik as the primary language spoken at home, identifies a lot with Yup’ik lifestyle, identifies a lot with white lifestyle, and the centered linear terms: age, red blood cell δ^{15}N, and log counts per day of physical activity.

CHAPTER 5. CONCLUSION

We identified several features of the current Yup'ik lifestyle that may provide a combination of protective and risk factors for cardiometabolic (CM) diseases. In this dissertation, we identified dietary patterns in Yup'ik people that were reproducible and reliable, and were found to be associated with biomarkers of CM status. We also found iq'mik use to be associated with biomarkers of CM status. Specifically we found evidence that the consumption of processed foods was associated with measures of CM risk and that consumption of subsistence foods as well as current iq'mik use were associated with measures of CM protection in this sample of Yup'ik people.

The associations we observed between processed foods and subsistence foods and CM risk align with results from other studies.(56,62,69,72,73) Specifically, a different study in the same Yup'ik study population also identified a positive association between eating processed foods using a dietary biomarker ($\delta^{13}C$) and TG.(69) Other studies have also reported on the protective effect of eating a subsistence diet based on observed negative associations between a traditional subsistence diet and TG and blood pressure.(56,62,72,73) In contrast, there is a paucity of research on fruit and vegetable consumption in relation to CM risk among Alaska Native people, possibly because of limited historical consumption of fruits and vegetables.(105) Our findings suggest a somewhat conflicting interpretation of fruit and vegetable consumption and CM risk. We found evidence of reduced CM risk based on the HbA1c biomarker and increased CM risk based on the DBP biomarker. Additional research is needed to better understand these associations.

The iq'mik associations we observed require further study as this is the first study characterizing iq'mik use and CM risk, and the only smokeless tobacco analysis(67,86,90) that reports an inverse relationship between smokeless tobacco use and CM risk. This finding was unexpected and we are not aware of any causal mechanism supporting the observed association. Use of iq'mik is considered a social activity strongly associated with a traditional lifestyle.(6,7) Knowing this, we attempted to adjust for confounding factors such as lifestyle using two different statistical approaches. Even so, there is the potential that the observed protective effect could be due to unmeasured confounding or a combination of unmeasured confounding and health benefits associated with living a traditional Yup'ik lifestyle of which iq'mik use is a component.

Our findings suggest that aspects of the traditional Yup'ik lifestyle including the diet and iq'mik use may be protective from a CM disease risk perspective, supporting beliefs among Yup'ik people in the value of their traditional subsistence lifestyle for health.(106) Both eating a subsistence diet and using iq'mik are important aspects of Yup'ik lifestyle and cultural identity. Aspects of the traditional Yup'ik lifestyle have been reported to be mutually reinforcing, such that for example the use of iq'mik increases when other traditional behaviors (e.g., subsistence gathering of food and medicine) are increased and vice versa.(7) This strong correlation between traditional practices makes it complicated to disentangle individual traditional practices (e.g., iq'mik use, diet) from the collective, possibly synergic, lifestyle. As such, the observed protective effects of eating subsistence diet and iq'mik use may be in part due to enculturation.(2,106) Being enculturated may possibly encompass other benefits associated with CM health including regular physical activity, stress and coping approaches, and enhanced social support networks. As Wolsko and colleagues stated, "enculturation has been characterized as part of a healthy lifestyle that buffers the harmful effects of stress and enables one to engage in healthier behaviors".(7)

Yet, even though there is recognition by Yup'ik people of the benefits in maintaining a traditional diet and lifestyle, it may not always be feasible. For example the availability of subsistence foods may be restricted by government hunting and fishing regulations, forcing Yup'ik people to negotiate a balance between their traditional Yup'ik lifestyle and a more western lifestyle in their remote communities in Southwest Alaska.(106) As such, any recommendations related to maintaining healthy aspects of a traditional lifestyle should be designed to acknowledge these realities. As an example, developing a recommendation to eat more subsistence foods may be limited by hunting and fishing regulations. Thus factors outside the control of Yup'ik people could inhibit consumption of subsistence foods, pushing people toward market-based foods.(2,106) Further, reduced access to such aspects of their traditional lifestyle and a subsequent move to a more modern or western lifestyle has been reported as a source of stress among Yup'ik people.(2,106) Health promotion recommendations that do not consider this wider context could thus increase stress, another risk factor for CM diseases. In a recent study of Yup'ik people, perceived stress was found to be associated with greater body mass index, waist circumference, percent body fat, and DBP,(10) all risk factors for CM disease.

Additional research into understanding the association between fruit and vegetable consumption and CM risk make an interesting case for using research evidence to develop recommendations reflecting the dietary choices for Yup'ik people. That is, while attempting to maintain a diet high in traditional foods, market-based foods are available. Dietary recommendations that incorporate both subsistence foods and market-based foods will likely be the most feasible for Yup'ik people to implement. The dietary recommendations for market-based foods may be unique in this population living primarily in remote communities, particularly for fruits and vegetables.(105) Although the consumption of fruits and vegetables are typically considered cardio-protective,(107) in remote communities in the Yukon-Kuskokwim Delta there is a limited availability of fresh fruits and vegetables,(105) stores primarily stock canned or frozen fruits and vegetables. Canned or frozen fruits and vegetables may provide different cardiovascular and metabolic benefit. Thus, additional research into fruits and vegetable consumption and CM risk would be valuable in developing realistic and actionable dietary recommendations in this population.

These dissertation findings are based on a rich set of data including detailed exposure, covariate, and outcome measures rigorously collected from more than 600 Yup'ik adults living in the Yukon-Kuskokwim Delta of Southwest Alaska. However the convenience sampling approach, cross-sectional nature of the data, and use of biomarkers rather than CM disease outcomes limit the strength of our conclusions. As such, in order to strengthen further studies CANHR should continue to collect longitudinal data on study participants and obtain disease outcome (diabetes and cardiovascular disease) data. In addition, randomized community interventional trials could be valuable both in further strengthening research findings as well as by returning benefit to communities.

In the spirit of community based participatory research, we hope the findings from this dissertation will be of value to Yup'ik people and the CANHR and others working with Alaska Native communities in developing recommendations and interventions to reduce the burden of CM diseases among Yup'ik people.

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APPENDICES

APPENDIX 1.

A summary of the foods that loaded on each dietary pattern in the exploratory factor analysis and those foods included in the Confirmatory Factor Analysis. *Adapted from Ryman, 2013.*(32)

Dietary Patterns			Exploratory Factor Analysis Loading	Included in Confirmatory Factor Analysis
Processed foods	Fruits and vegetables	Subsistence foods		
▪ Salty snacks ▪ Sweetened cereals ▪ Pizza ▪ Sweetened drinks ▪ Hot dogs/lunch meat ▪ Fried chicken	▪ Fresh citrus ▪ Potato salad ▪ Citrus juice ▪ Corn ▪ Green beans ▪ Green salad	▪ Seal or walrus soup ▪ Non-oily fish ▪ Wild greens	> 0.35	Yes
▪ Canned tuna	▪ Market berries in akutaq	▪ Bird soup	≤ 0.35	
	▪ Pudding and Jello ▪ Dried Salmon ▪ Wild game soup ▪ Pancakes		≤ 0.35	No

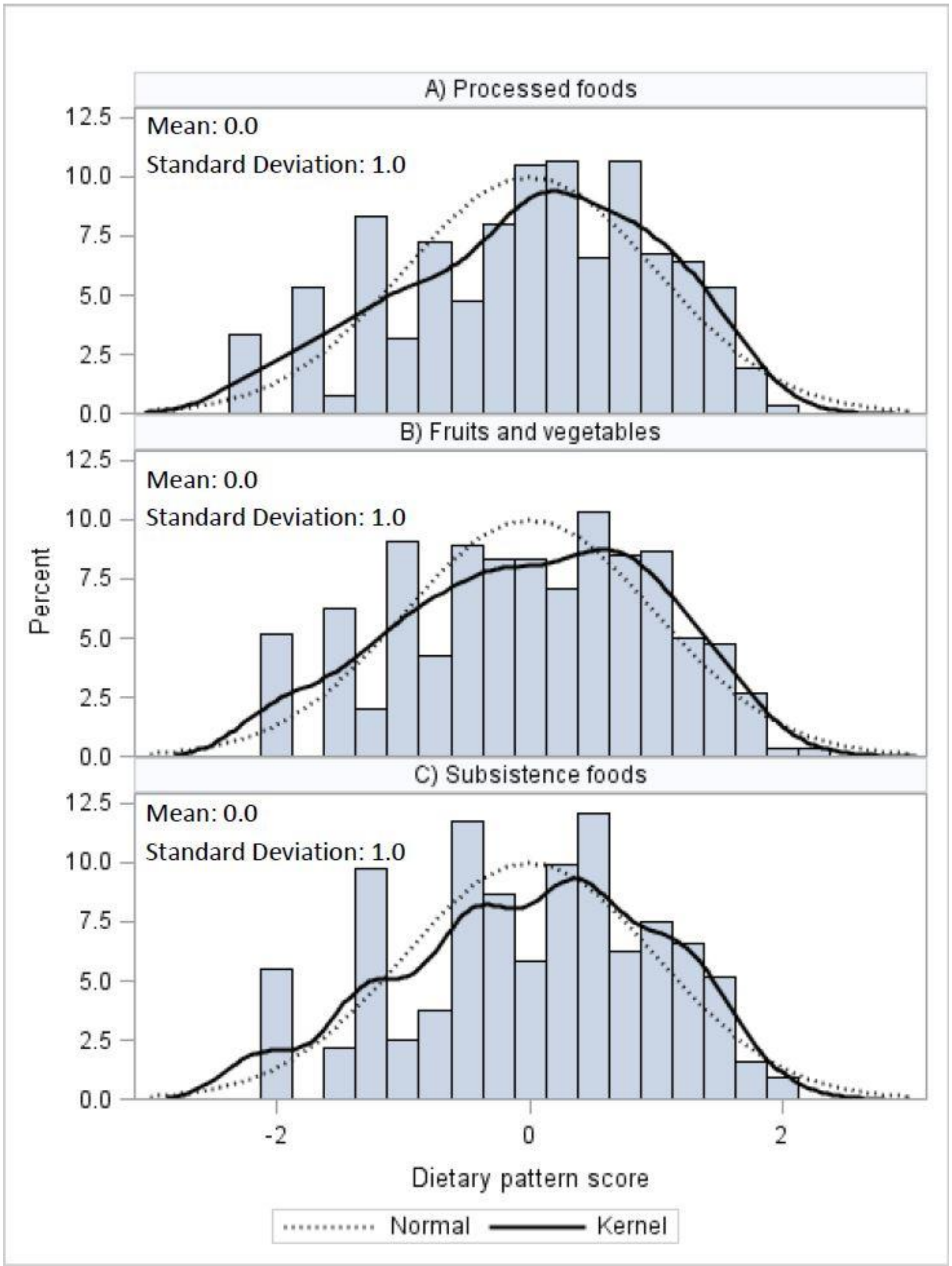
APPENDIX 2.

Formulas used for calculating dietary pattern scores. Specifically, scores were calculated as the sum of the natural log transformed frequency of consumption for each food measuring the dietary pattern divided by the number of foods measuring each dietary pattern.

Dietary Pattern	Formula
Processed foods	(natural log annual frequency for **salty snacks** + natural log annual frequency for **sweetened cereals** + natural log annual frequency for **pizza** + natural log annual frequency for **sweetened drinks** + natural log annual frequency for **hot dogs and lunch meat** + natural log annual frequency for **fried chicken** + natural log annual frequency for **canned tuna**) / 7
Fruits and vegetables	(natural log annual frequency for **fresh citrus** + natural log annual frequency for **potato salad** + natural log annual frequency for **citrus juice** + natural log annual frequency for **corn** + natural log annual frequency for **green beans** + natural log annual frequency for **green salad** + natural log annual frequency for **market berries in akutaq**) / 7
Subsistence foods	(natural log annual frequency for **seal or walrus soup** + natural log annual frequency for **non-oily fish** + natural log annual frequency for **wild greens** + natural log annual frequency for **bird soup**) / 4

APPENDIX 3.

Percent frequency distributions of estimated dietary pattern factor scores for each of the three dietary patterns: A) Processed foods; B) Fruits and vegetables; and C) Subsistence foods, with the normal and Gaussian kernel density curves superimposed. Yupik study participants (n=637), September 2009 – May 2013.



APPENDIX 4.

Mean annual frequency of consumption for foods included in each dietary pattern and the magnitude of difference*, by dietary pattern quartile (only 1st and 4th quartile reported), Yupik study participants (n=637), September 2009 – May 2013.

Dietary Pattern		Processed Foods			Fruits and vegetables			Subsistence foods		
Food	Overall	1st Quartile	4th Quartile	Magnitude of difference*	1st Quartile	4th Quartile	Magnitude of difference*	1st Quartile	4th Quartile	Magnitude of difference*
Processed foods										
Salty snacks	55.98	10.30	105.59	0.10	34.48	79.94	0.43	61.55	50.22	1.23
Sweetened cereals	45.86	6.84	94.28	0.07	24.01	69.04	0.35	48.17	49.98	0.96
Pizza	29.48	3.78	60.65	0.06	17.65	43.38	0.41	27.20	36.82	0.74
Sweetened drinks	233.96	54.07	402.22	0.13	191.18	301.72	0.63	249.92	209.01	1.20
Hot dogs and lunch meat	33.93	8.15	73.57	0.11	16.87	49.15	0.34	36.39	32.27	1.13
Fried chicken	22.00	9.04	39.69	0.23	13.53	31.04	0.44	22.13	21.09	1.05
Canned tuna	9.69	1.62	24.85	0.07	5.53	20.50	0.27	9.74	12.49	0.78
Fruits and vegetables										
Fresh citrus	32.51	18.94	46.58	0.41	9.62	60.88	0.16	35.32	33.44	1.06
Potato salad	11.10	5.31	21.06	0.25	0.83	27.43	0.03	11.22	14.10	0.80
Citrus juice	62.38	28.43	100.28	0.28	11.16	148.99	0.07	49.26	59.46	0.83
Corn	61.52	25.33	92.95	0.27	18.17	105.15	0.17	66.00	66.83	0.99
Green beans	42.92	19.47	64.02	0.30	11.88	81.92	0.15	35.87	52.35	0.69
Green salad	11.23	3.98	21.92	0.18	0.38	29.33	0.01	12.08	12.08	1.00
Market berries in akutaq†	18.14	10.59	25.30	0.42	5.09	37.66	0.14	17.63	22.35	0.79
Subsistence foods										
Seal or walrus soup‡	24.66	17.96	31.48	0.57	19.61	32.21	0.61	3.99	53.58	0.07
Non-oily fish (not dried)‡	18.72	16.35	27.57	0.59	14.29	31.20	0.46	0.97	49.36	0.02
Wild greens‡	8.37	8.23	8.76	0.94	6.29	14.74	0.43	0.56	24.43	0.02
Bird soup‡	39.72	30.55	47.26	0.65	36.38	46.62	0.78	22.86	60.40	0.38

* magnitude of difference calculated as 1st quartile divided by 4th quartile, would expect a greater difference (smaller number) for the foods associated with a specific dietary pattern.

† Traditional dessert commonly made with berries, Crisco, sugar and sometimes fish

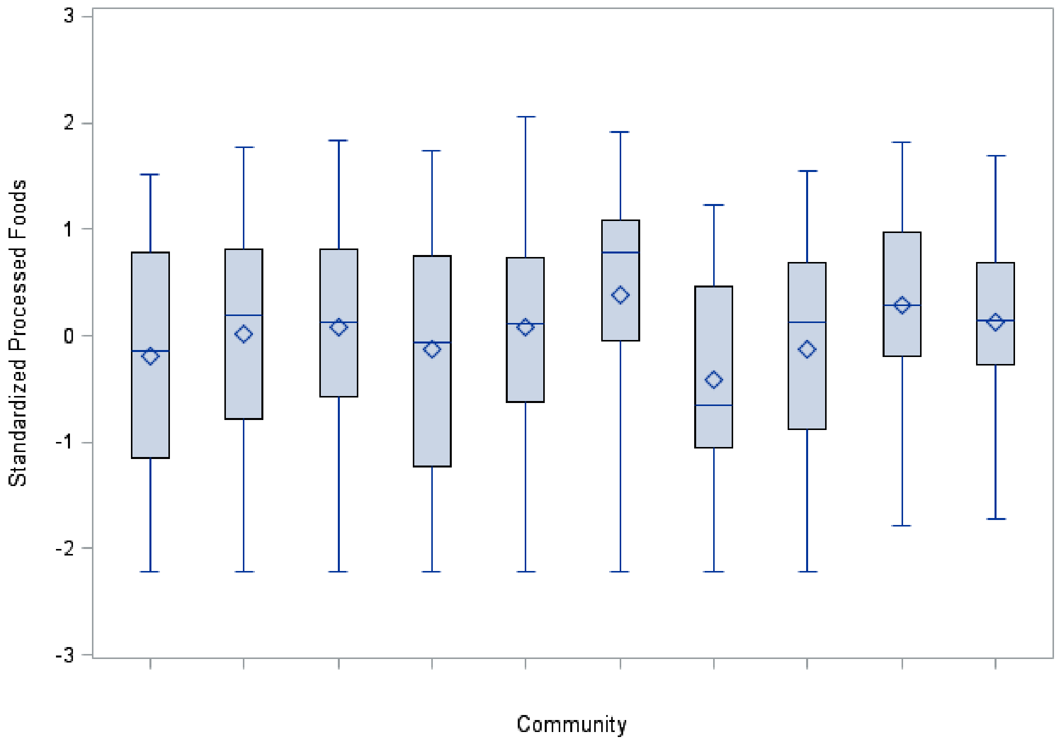
‡ Seasonal food items

APPENDIX 5.

Dietary pattern factor score distributions for each of the 10 communities, to compare within versus between community variation, Yupik study participants (n=637), September 2009 – May 2013.

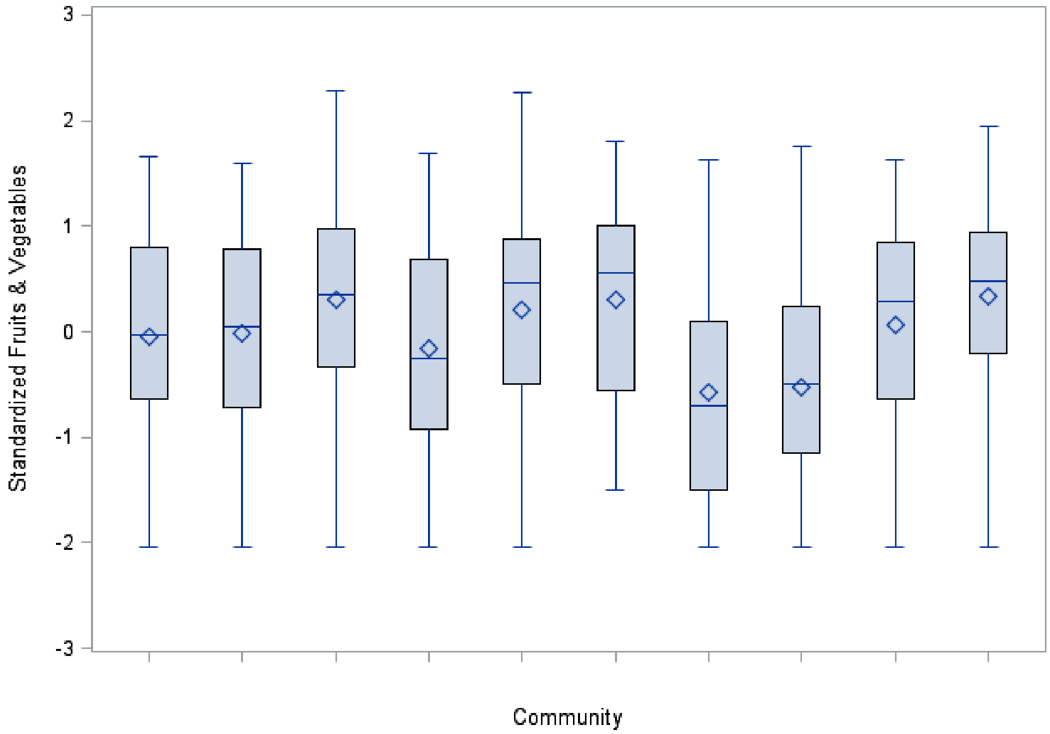
Box plot description: The upper line indicates the maximum value and the lower line indicates the minimum value (no values were more than 1.5 times the interquartile range above the 75th percentile or below the 25th percentile). The upper line of the box indicates the 75th percentile, the middle line the 50th percentile, and the bottom line the 25th percentile. The diamond indicates the mean value.

Processed foods

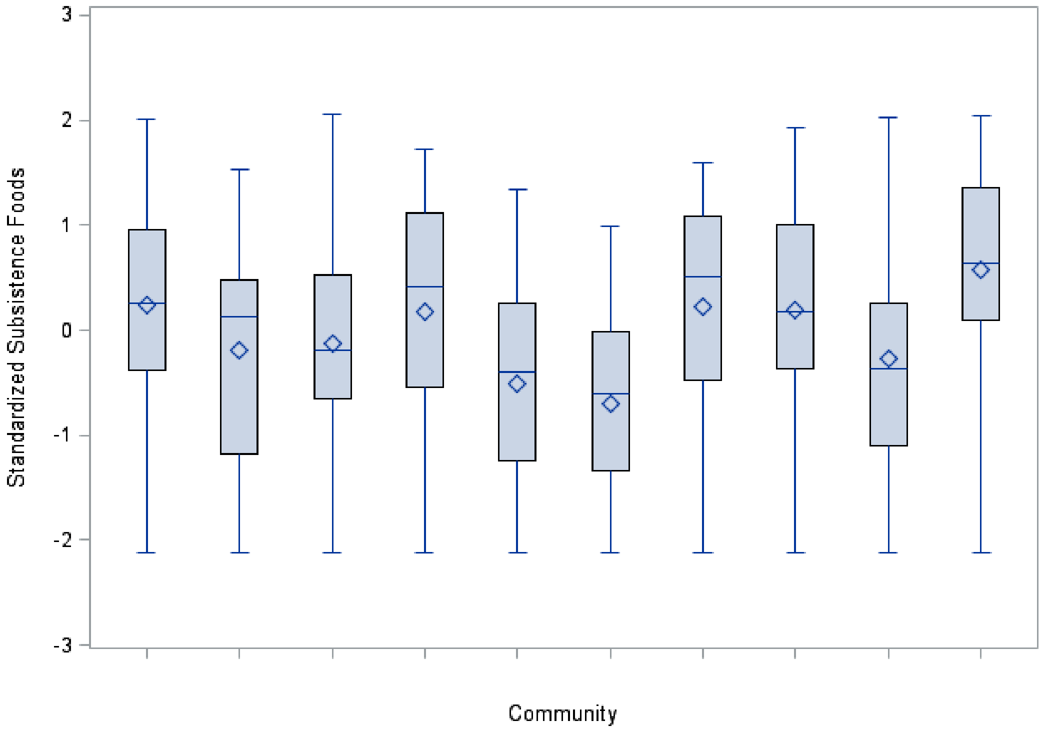


APPENDIX 5 (cont.)

Fruits and vegetables



Subsistence foods



APPENDIX 6.

Propensity score distributions before (n=874) and after (n=868) excluding participants with propensity scores <0.20, in order to better balance propensity score distributions between current-iq'mik users and past/never users. Yupik study participants (n=874), October 2007 - May 2013.