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Association between iq'mik smokeless tobacco use and cardiometabolic risk among Yup'ik Alaska Native People

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Abstract

Objective—The traditional lifestyle of Yup'ik Alaska Native people, including a diet abundant in marine-based foods and physical activity, may be cardio-protective. However iq'mik, a traditional form of smokeless tobacco (ST) 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 [SBP] and diastolic [DBP] blood pressure, glycated hemoglobin [HbA1c], fasting blood glucose [FBG], waist circumference [WC], and body mass index [BMI]).

Design—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.

Results—Based on either adjustment method, current iq'mik use was significantly and positively associated with at least 5% higher HDL-C, and significantly associated but in an inverse direction with multiple biomarkers of CM status including 7% lower TG, 0.05% lower HbA1c, 2% lower FBG, 4% lower WC, and 4% lower BMI. Observed associations for LDL-C, SBP, and DBP varied by adjustment method.

Conclusions—This inverse association between iq'mik use and cardiometabolic risk status has not been previously reported. Additional research is needed to replicate these findings and explore physiologic mechanisms and/or confounding factors.

Keywords

Iq'mik; smokeless tobacco; Alaska Native; Yup'ik cardiometabolic

1. INTRODUCTION

Between 1990 and 2009, all-cause mortality was 65% higher in Alaska Native (AN) people relative to United States (US) whites, with cardiovascular and metabolic diseases comprising a substantial burden of the mortality (Espey et al. 2014). In AN females, heart disease is the second leading cause of death, stroke is the fourth, and diabetes mellitus is the ninth (Espey et al. 2014). In AN males, heart disease is the third leading cause of death, stroke is the sixth, and diabetes mellitus is the ninth (Espey et al. 2014). Specifically in the Yukon-Kuskokwim Delta, between 2004 and 2007, the heart disease death rate was 192.9 per 100,000 in AN people, slightly lower than the 209.5 per 100,000 in US whites. However, the cerebrovascular death rate was considerably higher, 71.9 per 100,000 in AN people compared to 46.1 per 100,000 in US whites ("Alaska Native Health Status Report" 2014). Several lifestyle factors, including physical activity, stress, depression, alcohol consumption, diet, and tobacco use may contribute to increased or decreased cardiometabolic (CM) disease risk in AN people (Boyer et al. 2007).

Yup'ik AN people primarily reside in 58 remote communities in the Yukon-Kuskokwim Delta region of Southwest Alaska, where they 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 (Zeina Makhoul et al. 2010; Z Makhoul et al. 2011; O'Brien et al. 2014; Bersamin et al. 2013). However, some characteristics of their traditional lifestyle may increase CM risk. Smokeless tobacco (ST) 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 (Smith et al. 2010; Wolsko et al. 2009).

Iq'mik, a type of homemade ST, has been commonly used by Yup'ik people for at least 150 years (Wolsko et al. 2009). 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 (Renner, Enoch, et al. 2005; Piano et al. 2010). The addition of ash to the tobacco raises the pH of the tobacco, increasing the amount of both free (unionized) nicotine available for absorption (Renner, Enoch, et al. 2005; Piano et al. 2010; Patten et al. 2008; Redwood et al. 2010) as well as the available levels of carcinogens (Benowitz et al. 2012; Pappas et al. 2008). A study comparing exposure to nicotine by different forms of tobacco in AN people found nicotine exposure to be highest in iq'mik users (Benowitz et al. 2012). However, because iq'mik preparation is not standardized, estimates of pH and nicotine levels are inconsistent (Renner et al. 2004). Use of iq'mik is considered a social activity strongly associated with a traditional lifestyle, although it is not used for ceremonial or religious reasons (Wolsko et al. 2009; Hurt et al. 2005). Among Yup'ik people, iq'mik use often begins at a young age (e.g., among teething children)(Renner et al. 2013; Piano et al. 2010; Renner et al. 2004) and by

18 years of age approximately 80% of youth in a Yup'ik sample had tried ST (including iq'mik) (Angstman et al. 2007). Iq'mik use is ubiquitous in Yup'ik communities, with more than 50% of adults currently chewing (Renner et al. 2004; Wolsko et al. 2009). Women chew more than men, and iq'mik use during pregnancy is common because it is thought to be healthier than cigarette smoking (Renner et al. 2004; Renner et al. 2013).

ST 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 (Piano et al. 2010). The association between these forms of ST and biomarkers of CM status (e.g., lipids, blood pressure, glucose, adiposity) and CM disease has been studied in non-AN populations (Lee 2007; Boffetta and Straif 2009; Teo et al. 2006). These studies, primarily in Sweden and the US, have reported inconsistent associations between ST use and CM risk (Colilla 2010; Critchley and Unal 2004; Winn 1997). One of two recent meta-analyses reported no association between snus and heart disease or stroke (Lee 2011). In comparison, a different meta-analysis found ever-use of ST to be significantly associated with an increased risk of fatal myocardial infarction (relative risk = 1.1) and fatal stroke (relative risk = 1.4) (Boffetta and Straif 2009). 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) (Teo et al. 2006). One study found greater than 4 cans a week of snus use associated with the metabolic syndrome (odds ratio = 1.6 relative to no use) (Norberg et al. 2006). In two studies of snus use and type 2 diabetes, one found a significant association (odds ratio = 2.7) (Persson et al. 2000) and the other did not (Eliasson et al. 2004). To our knowledge there are no studies of the association between iq'mik ST use and CM risk.

With a rate of nearly three times as many users of ST among AN people as the general US population (Renner et al. 2013; Renner, Patten, et al. 2005), and the especially high prevalence of iq'mik use specifically among Yup'ik people, additional research about its potential health effects is needed. Specifically, we set out to characterize the association between iq'mik use and measures of CM risk to guide future development of health messaging and interventions.

2. METHODS

2.1 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 (Boyer et al. 2005; Mohatt et al. 2007). In brief, CANHR conducts recurring cross-sectional research in 11 Yup'ik communities in the Yukon-Kuskokwim Delta (Ryman et al. 2013). Study participants within these communities were recruited using convenience sampling methods (Boyer et al. 2005; Mohatt et al. 2007). All individuals who self-identified as AN or who were married to an AN descendent, were equal to or greater than 14 years of age, and were non-pregnant, were invited to participate in the research (Boyer et al. 2005; Mohatt et al. 2007). 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 and the Yukon-Kuskokwim Health Corporation Human Studies Committee.

2.2 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/movement monitor, as described below.

2.2.1 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). They also self-reported tobacco use, providing dose and duration information for current or past use of iq'mik, commercial chew, and cigarettes. Current use was defined as any use within the previous month. Finally, they reported use of medications to treat CM risk factors (for lowering lipids, glucose, and blood pressure).

2.2.2 Blood Samples—Participants were asked to fast for 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 (O'Brien et al. 2009). The nitrogen isotope ratio ($\delta^{15}\text{N}$) is elevated in traditional marine foods, such that red blood cell $\delta^{15}\text{N}$ is strongly correlated with traditional marine food intake (Nash et al. 2012) and intake of the omega-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid (O'Brien et al. 2009). By convention and for ease of interpretation, isotope ratios are presented as delta values in “permil” relative to international standards : $\delta^{15}\text{N} = [(R_{\text{sample}} - R_{\text{standard}}) / (R_{\text{standard}})] \cdot 1000\text{‰}$, R is the ratio of heavy to light isotope, and the standards are atmospheric nitrogen.

2.2.3 Physical exam—Systolic (SBP) and diastolic (DBP) blood pressure were obtained using an OMRON HEM907 automated blood pressure cuff. After a 5 minute resting period, 3 measures were taken with a 1-minute interval between each. The mean of the last 2 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.

Waist circumference (WC) was measured twice using a Gulick II 150 cm anthropometric tape attached with a tension-meter (Country Technologies, Inc., Gays Mills, WI) directly on the skin immediately below the lowest lateral portion of the rib case. If the 2 WC measures differed by more than 2 cm then a third measure was taken, and the final measure was the average of the 2 closest measures. Height was measured in inches and weight in pounds, 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 (CamNtech Ltd, Papworth UK) which they wore for 4 consecutive days.

2.3 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 normality of the distribution of the biomarkers of CM status, we natural log transformed HDL-C, TG, FBG, WC, and BMI. We *a priori* elected to include BMI as an outcome rather than a covariate in our models because BMI may be on the causal pathway between iq'mik use and CM biomarkers. Unpublished results have shown an association between iq'mik and BMI independent of physical activity (personal communication J Philip December 2015). All analyses were performed using SAS and Stata. P-values < 0.05 were considered statistically significant.

We excluded 18 participants who reported currently using commercial chew, 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 >4 standard deviations from the mean were excluded from analyses as they were considered implausible values; 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 (Vittinghoff et al., n.d.). We modeled the association using 3 different sets of covariates. First, we modeled the association adjusting only for age and sex. 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 (Wolsko et al. 2009), we used 2 different modeling approaches to adjust for confounding, as described in detail below. In the first 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. Second, 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 (Vittinghoff et al., n.d.). Specifically, we adjusted for gender, more than 5 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, $\delta^{15}\text{N}$, 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 previous smokers (Ockene and Miller 1997; Teo et al. 2006).

The propensity score adjustment model included current iq'mik use and a continuous propensity score measure in the linear regression model (Vittinghoff et al., n.d.). 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 (D'Agostino 1998). 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 (Weitzen et al. 2004; D'Agostino 1998). 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 significant association with the biomarkers of CM status in our study using univariate analyses (Brookhart et al. 2006). 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). We included the following covariates in the logistic regression model: age (spline), sex, smoking status (current including within the previous year or past relative to never), more than 5 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, $\delta^{15}\text{N}$, and physical activity counts per day. We excluded 6 participants with propensity scores below 0.20 so that there was balance in propensity score distributions between current iq'mik users and past/never users (Supplemental Figure 1). These participants were also excluded from the other models for consistency of interpretation.

Finally, given the well-established association between cigarette smoking and cardiovascular disease (Ambrose and Barua 2004; Piano et al. 2010) we ran an additional model that included an interaction between the binary variables current iq'mik use and current cigarette smoking. With this model, we estimated the association between iq'mik use and biomarkers of CM status among non-smokers and current smokers. We adjusted for all of the same variables as in the lifestyle covariate model. We elected to characterize this association using only one adjustment approach and selected the lifestyle covariate model because it is a more familiar adjustment approach.

3. RESULTS

Participants ranged in age from 18 to 95, with a mean age of 39 (Table 1). Females comprised 54% of the sample (Table 1). Iq'mik was currently used by two-thirds of study participants, was previously used by 11% of participants, and never used by 23% (Table 1). Initiation of iq'mik use ranged from as young as 1 to as old as 69 (older participants were primarily participants who quit smoking), with 14 years of age being the mean age when participants started chewing (Table 1). Thirty-eight percent of participants currently smoked (Table 1), 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 1).

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 2). Participant characteristics differed within strata of iq'mik use and cigarette smoking as reported in Table 2. Among both smokers and non-smokers iq'mik users were generally younger (29 v. 34 years and 43 v. 48 years, 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 ($\beta=0.05$, $P=0.02$) and inversely associated with log TG ($\beta= -0.10$, $P<0.01$), log FBG ($\beta= -0.02$, $P=0.01$), and log WC ($\beta= -0.03$, $P<0.01$) (Table 3, Model A). After adjusting for confounding using lifestyle covariate adjustments, current iq'mik use was significantly inversely associated with HbA1c ($\beta= -0.05$, $P=0.04$) and log BMI ($\beta= -0.04$, $P=0.01$), and remained associated with log HDL-C ($\beta=0.05$, $P=0.02$), log TG ($\beta= -0.07$, $P=0.04$), log FBG ($\beta= -0.02$, $P=0.01$), and log WC ($\beta= -0.04$, $P<0.01$) (Table 3, Model B). In the model adjusting for confounding using the propensity score approach, current iq'mik use was also positively associated with HDL-C ($\beta=0.05$, $P=0.02$) and inversely associated with log FBG ($\beta= -0.02$, $P<0.01$), log WC ($\beta= -0.04$, $P<0.01$), and log BMI ($\beta= -0.04$, $P=0.03$) (Table 3, 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. LDL-C, SBP, and DBP were not significantly associated with current iq'mik use irrespective of the model.

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 4). That is, among current non-smokers, current iq'mik use was associated with 8.37 mg/dL lower LDL-C ($P=0.02$), 8% higher HDL-C ($P<0.01$), 10% lower TG ($P=0.03$), 4.20 mm Hg lower SBP ($P<0.01$), 2.85 mm Hg lower DBP ($P=0.01$), 0.07% lower HbA1c ($P=0.03$), 3% lower FBG ($P<0.01$), 5% lower WC ($P<0.01$), and 7% lower BMI ($P<0.01$).

4. DISCUSSION

Among this sample of Yup'ik study participants, 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 even after adjustment for confounding, current use of iq'mik 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.

Given the well-established association between cigarette smoking and cardiovascular disease (Ambrose and Barua 2004; Piano et al. 2010), we analyzed the association between iq'mik use and biomarkers of CM status among smokers and non-smokers. We found that all 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 CM risk associated with smoking (Ambrose and Barua 2004; Piano et al. 2010; Foody et al. 2001) is so much stronger than that of iq'mik use that it dwarfs the contribution of iq'mik use.

Findings from other studies of ST have either found no significant association between ST use and CM risk/disease or that ST increases CM risk/disease (Boffetta and Straif 2009; Piano et al. 2010; Lee 2011). Inconsistent findings across studies could be due in part to the variety of ST products used globally, with differing manufacturing processes and additives (Piano et al. 2010). A study in Bangladesh found no association between ST and coronary heart disease, with the exception of a specific type of ST that was higher in nicotine content, raising the question that nicotine content could be an important aspect in observed associations (Rahman et al. 2012). This further highlights the challenge of comparing findings across studies because the ingredient composition (e.g., nicotine bioavailability and speed of absorption) as well as degree of processing differ substantially both within and between countries. Iq'mik is different from any of the other ST products studied (e.g. less processing, different additives), however we are not aware of any studies that have found ST to be inversely associated with CM risk.

One possibility is that the observed associations could be due to residual confounding resulting from our inability to adequately adjust for Yup'ik lifestyle (Wolsko et al. 2009). 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 (O'Brien et al. 2014; Bersamin et al. 2013). In both the covariate lifestyle and propensity score models we adjusted for $\delta^{15}\text{N}$, 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 $\delta^{15}\text{N}$. 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 (Ryman et al. 2013; Ryman et al. 2015). In the

subset analysis, the associations 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). Although the sample is smaller, this sensitivity analyses suggest the potential for residual confounding due to diet. Though our dataset included a rich set of covariates, we were not able to adjust for alcohol use or stress, both of which could be confounders (Bersamin et al. 2013). In addition, there could be unmeasured confounders such as those related to social determinants of health (e.g., social support networks).

Another possibility is that although the potential 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 (Renner et al. 2004). However, chemical analyses of iq'mik have found it to contain high levels of nicotine along with known carcinogens, refuting the perception among Yup'ik people that iq'mik is less hazardous due to the "natural" ingredients (Piano et al. 2010; Hearn et al. 2013; Pappas et al. 2008). Moreover the Rahman et al. paper posited that based on their findings ST products with higher levels of nicotine might be associated with increased coronary heart disease risk (Rahman et al. 2012).

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" (Wolsko et al. 2009). Moreover, Yup'ik people report that enculturation and practicing the traditional Yup'ik lifestyle is at the core of wellness and health (Wolsko et al. 2007). As such, the use of iq'mik could be protective because its use is one aspect related to being more enculturated in the Yup'ik lifestyle and leading to improved health. In partial agreement, Boden-Albala et al., reported a marginal increased risk of hypertension for those with strong Yup'ik identification vs. white only, however they also reported that bicultural identification among Yup'ik people reduces the effects of other deleterious risk factors for high blood pressure (Boden-Albala et al. 2013); the authors point out that this result is compatible with Yup'ik health views, where competence in both cultures is necessary for good health. This speaks to the complexity of the relationship between culture identification and both risk and protective factors of health outcomes.

Strengths of this study include detailed exposure and covariate measures collected consistently for all study participants. The availability of a rich set of covariates 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, stress, social determinants of health such as social support networks, second hand smoke exposure) 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), our use of a binary exposure variable, 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 ST products, we are not aware of any studies that have found ST to be inversely associated with CM risk. Additional research is needed to replicate these findings, identify potential unmeasured confounders, and explore possible physiologic mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

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, number (%)	874	468 (53.5)
>5 household members, number (%)	874	444 (50.8)
Identify a lot with Yup'ik lifestyle, number (%)	870	461 (53.0)
Identify a lot with Kass'aq (white) lifestyle, number (%)	870	153 (17.6)
Yup'ik as the primary language spoken at home, number (%)	874	616 (70.5)
Red blood cell $\delta^{15}\text{N}$, 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, number (%)	874	577 (66.0)
Past iq'mik use, number (%)	874	93 (10.6)
Never used iq'mik, number (%)	874	204 (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, number (%)	874	328 (37.5)
Past smoker, number (%)	874	248 (28.4)
Never smoked, number (%)	874	298 (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

[†] Calculated as (counts per day/4)*(years of use)

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Table 2

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

Participant characteristics	Current cigarette smoking			
	Non-smoker		Smoker	
	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 $\delta^{15}\text{N}$, 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 3

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 $\delta^{15}\text{N}$, 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 $\delta^{15}\text{N}$, and log counts per day of physical activity.

Table 4

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

Biomarker of CM status	Current iq'mik use compared to past/never use			
	Among non-smokers		Among cigarette smokers	
	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 $\delta^{15}\text{N}$, and log counts per day of physical activity.