Sex-specific associations of nutrition with hypertension and systolic blood pressure in Alaska N5 re in 2 cm 406 inding 8 rom 4 the

linear trend=0.02). For women not on anti-HTN medications (n=528), after covariate adjustment, average SBP decreased with increasing quartiles of omega 3 fatty acid intake (p for linear trend <0.01).

**Conclusions**—Prospective evaluation of the sex-specific associations of nutritional factors with HTN and SBP on outcomes is needed along with novel interventions to lower the risk of cardiovascular disease.

### Keywords

nutrition; Alaska Native; sex; systolic blood pressure; epidemiology

# INTRODUCTION

Nutrition affects blood pressure and the modification of specific dietary factors has the potential to prevent hypertension (HTN) and/or lower the risk of complications related to blood pressure such as cardiovascular disease (CVD) (1). The risk of CVD increases throughout the range of blood pressure (BP) (2,3) and systolic BP (SBP) is a strong independent risk factor for CVD (2). Therefore, nutritional assessment is important among those with and without established hypertension.

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previously (15). Briefly, a total of 1,214 Alaska Natives, predominantly Inupiat Eskimo, men and women 18 yrs of age from extended families, were recruited from October 2000 through April 2004 in the Norton Sound region on the northwest coast of Alaska. Participants completed an interviewer-administered survey of demographics and medical history and underwent a complete physical examination. The exam included the collection of blood, urine and anthropometric measurements such as height, weight and waist-to-hip ratio.

From the 1,214 GOCADAN participants, we excluded those with diabetes (n=40), without nutritional data (n=41), age <18 years (n=1) or missing data on systolic blood pressure (n=10). We also excluded those with extremes of calorie intake defined as <500 or >8,000 kilocalories in a day (n= 68) (16,17). Thus our study sample included 1,058 participants, or 87% of the baseline cohort. There were no significant differences in covariates of interest among those included in our analysis (n=1058) versus those excluded (n=156) (chi-squared analysis).

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**Demographics and covariates**—Age was calculated in years based on the verified date of birth during the GOCADAN interview and the examination date. Self-reported years of education were dichotomized as <12 years of school versus 12 years of school or general equivalency diploma. BMI was calculated using measured weight and height according to a standard formula and metric conversion [BMI=weight (lb)/height<sup>2</sup> (in)\*704.5kg in<sup>2</sup>/lb m<sup>2</sup>]. We dichotomized BMI as non-obese (BMI<30 kg/m<sup>2</sup>) and obese (BMI 30 kg/m<sup>2</sup>). Physical activity was calculated in metabolic equivalents (METs) from self-reported leisure time activities (20). Blood samples were obtained following a 12-hour overnight fast (15). Lipid measurements were obtained for total cholesterol (total triglyceride [TG], high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]) analysed via an auto analyser (15). Smoking status was obtained by self-report during the structured interview portion of the examination and was dichotomized as never/former or current smoker.

#### Statistical analysis

For the baseline demographics and clinical characteristics, continuous variables with normal distributions were presented as means (standard deviations), variables with highly skewed distributions were presented as medians (first quartiles, third quartiles) and categorical variables were presented as frequencies (proportions). The differences between men and women were compared by t-test, non-parametric rank sum test or chi-square test as appropriate.

Percent energy from carbohydrates, total fat and protein was calculated for each participant. Percent energy from carbohydrates was further characterized as percent energy from simple carbohydrates and from complex carbohydrates. Percent energy from total fat was also further characterized as percent energy from saturated fatty acids, mono-unsaturated fatty acids and trans fatty acids. Given the high consumption of fish among Alaska Natives and in order to capture polyunsaturated fatty acids, we included omega-3 fatty acid and omega-6 fatty acid intakes separately, each presented as grams per day (17). Sodium, potassium, magnesium, calcium, phosphorus and caffeine are presented as milligrams per day. The natural log transformed variables for omega-3 fatty acids and caffeine were used in all analyses because of skewness. We examined each of the nutritional factors by sex. Descriptive statistics were obtained and compared by t-test between 2 groups.

To assess whether differences among those with and without prevalent HTN (by sex) differ in dietary intake, we examined each of the nutritional factors by HTN status in men and in women. Because the participants were members of large and inter-related families, we also performed the analyses using a method developed by Wang et al. to assess the potential impact of relatedness (21).

Lastly, we used analysis of variance (ANOVA) to assess the potential relationships between nutritional factors and SBP (by sex) in those not treated with anti-hypertensive medications. We first estimated, by sex, the mean SBP and standard deviation for each quartile of dietary intake in a univariate model. We then estimated, in single multivariate models stratified by sex, the adjusted mean SBP and standard deviation for each quartile of dietary intake, adjusting for the following covariates: age, BMI, total energy intake, smoking status and

physical activity. The test of the linear trend across increasing quartiles of nutritional factors was conducted using the statement CONTRAST in the general linear models procedure (PROC GLM) in SAS.

SAS version 9.1 (SAS Institute, Cary, NC) was used for all data manipulation and statistical analysis. All probability values were 2-tailed, and values <0.05 were considered significant.

# RESULTS

The mean age was 42 years for men and women and 57% (n=602) were women (Table I). Men had a lower BMI compared to women and obesity prevalence differed. LDL-C and TG did not differ between men and women, but HDL-C was higher in women. Smoking rates were high but did not differ significantly between sexes. HTN was more common among men than women (23% vs. 16%, p=0.006).

Total calorie intake was significantly higher among men, who consumed on average 3,474 kilocalories a day, compared to 2,859 kilocalories a day among women. Men also consumed a higher amount of omega-6 fatty acids but no sex difference was observed for omega-3 fatty acid intake (Table II). Men consumed higher amounts of sodium, potassium, magnesium, calcium, phosphorus and caffeine compared to women.

In comparing those with and without HTN, men with HTN (n=106) consumed a higher percentage of calories from fat (39% vs. 37%, p=0.0148), with a significantly higher proportion of those calories coming from saturated fatty acids, monounsaturated fatty acids and trans fatty acids compared to men without HTN (Table III). Men with HTN also had a higher average caffeine intake compared to men without HTN. Women with HTN (n=99) also consumed more total fat (39% vs. 37%, p-value=0.023), with a significantly higher proportion being from monounsaturated fatty acids compared to women without HTN. Women with HTN. Women with HTN consumed more protein, and less total and simple carbohydrates. There were no differences in sodium or other micronutrient intake among men or women with and without HTN. These associations did not change with adjustment for relatedness.

A total of 49 men had been prescribed an antihypertensive medication. In covariate-adjusted regression analyses among men not on anti-hypertensive medications (n=407), average SBP was higher with increasing quartiles of trans fatty acids and of sodium (Table IVa). A similar, but non-significant trend was observed for monounsaturated fatty acids.

A total of 74 women had been prescribed an anti hypertensive medication. In covariateadjusted regression analyses among women not on anti hypertensive medications (n=528), average SBP was lower with increasing quartiles of omega-3 fatty acids (Table IVb). However, in women, there was no association of average SBP with either sodium or monounsaturated fatty acid intake.

# DISCUSSION

Overall, we observed a high energy intake among both men and women. In our study among Alaska Natives, intake of sodium was higher among both men (4,830 mg/day) and women

Though the diet and other factors are unique to our study population, the relations of nutritional factors and BP we observed are consistent with those reported in other populations. There was an association of higher BP with higher sodium intake as previously reported (30), though only among men. The evidence for the association of salt intake, offen the major source of sodium in the diet, and risk of CVD is strong (1,30–33). The renin-angiotensin system has a central role in long-term BP control by modulating renal sodium homeostasis (34,35). A relationship between high trans fatty acid intake and risk of hypertension has been reported (36,37). This is in accord with our observed association between lower BP and higher omega-3 fatty acid intake, albeit only in women. Our findings are similarly consistent with the International Study of Macro- and Micro-Nutrients and Blood Pressure which found an inverse relationship between higher intakes of omega-3 fatty acids derived from food sources and BP, including in non-hypertensive persons; however, sex differences were not described (38).

The sex differences which we observed are likely multifactorial, with differences in preference of intake, physiological response to nutrients and genetics playing a role. Sex differences in BP response to a salt load have been described in rat models and are thought to be related to differences in endothelial response and renal hemo-dynamics (39–41). HTN is also more common in men and postmenopausal women than in premenopausal women, and putative vascular protective effects of endogenous estrogen have been suggested (42).

While there are significant strengths of our study with the use of a validated, culturally appropriate dietary questionnaire and rigorous epidemiologic methods of data acquisition, there are important limitations as well. This was a cross-sectional study and therefore we cannot assess causality or account for change in outcomes or covariates over time. Though the questionnaire has been validated and used in other Alaska Native populations, recall bias is possible and therefore misclassifications may occur (17,24). True sodium intake is difficult to ascertain; furthermore, added table salt is not accounted for in our dietary data, and thus sodium intake for some participants is likely under-reported. Our data and methods do not allow us to exclude psychosocial or behavioural differences, such as stating an answer to please an interviewer, which might impact accuracy of the FFQ in a sex-specific manner. Measures of basal metabolic rate were not performed in GOCADAN. Estimates of vitamin and mineral supplements were not included and therefore actual dietary intake of certain nutritional factors examined may be greater, although the data from GOCADAN indicate that vitamin and mineral supplementation is not common. Lack of association among those with HTN and such factors as saturated fatty acids may reflect adherence to lifestyle modifications recommended by their health care providers. We cannot account for those newly identified with disease or for any effect dietary counselling (that might have taken place) had on their intake and thus these results.

The American Heart Association (1) and the Institute of Medicine (41) recently released a statement on dietary approaches to prevent and treat HTN. Based on the current state of the evidence, five recommendations were made – weight loss; reduced salt intake; a dietary pattern rich in fruits, vegetables and low-fat dairy products, but reduced in saturated fatty acid and cholesterol; increased potassium intake; and moderation of alcohol intake among those who drink (<2 drinks per day for men; <1 drink per day for women) (1). The

recommendation for sodium in the Dietary Guidelines for Americans from the U.S. Department of Health and Human Services as well as that from the American Heart Association is 2,400 milligrams daily for adults. Our data indicate that Alaska Natives with hypertension are not following these guidelines. Adoption of these recommendations should be stressed in this population for prevention and treatment of HTN, though with the caveat that the evidence used to make the recommendations did not include Alaska Natives. Evaluation of such interventions and how they affect this unique population is needed. Public health and public policy measures aimed at reducing sodium intake are needed. Future dietary intervention studies among Alaska Native peoples are needed to examine the potential benefit of these interventions in controlling SBP in this population that is experiencing a rise in cardiovascular disease.

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### Table I

Demographic and clinical characteristics of GOCADAN participants (n=1058).

Demographic and clinical characteristics	Men (n=456)	Women (n=602)	p-value
Age (years)	$42\pm15$	$42\pm16$	0.77
High school education or higher, n (%)	363(80)	469(78)	0.46
Height (inches)	$67\pm3$	$62\pm2$	< 0.0001
Weight (pounds)	$170\pm36$	$155\pm35$	< 0.0001
Body mass index (kg/m <sup>2</sup> )	$27\pm5$	$28\pm 6$	< 0.0001
Waist-to-hip ratio	$0.9\pm0.1$	$0.8\pm0.1$	< 0.0001
Physical activity (MET/week)*	52 (24–101)	47 (21–94)	0.10
Systolic blood pressure	$122\pm13$	$117\pm15$	< 0.0001
Diastolic blood pressure	$78\pm9$	$74\pm9$	< 0.0001
Total cholesterol (mg/dL)	$196\pm40$	$203\pm41$	0.01
High density lipoprotein (mg/dL)	$55\pm18$	$64\pm18$	< 0.0001
Low density lipoprotein (mg/dL)	$117\pm36$	$114\pm36$	0.31
Triglycerides (mg/dL)*	106 (79–146)	107 (77–153)	0.87
Obesity (BMI 30 kg/m <sup>2</sup> ), n (%)	92 (20)	223 (37)	< 0.0001
Hypertension, n (%)	106 (23)	99 (16)	0.01
Current smoker, n (%)	281 (62)	353 (59)	0.33

Data are mean±standard deviation or number (%).

\* Median (1st quartile, 3rd quartile).

## Table II

Nutritional intake characteristics among GOCADAN participants by sex (n=1058).

Nutritional factor

Men (n=456)

Women (n=602) p-value

# Table III

Relationships of nutritional intake among Alaska Native men and women with and without hypertension.

	p-value adjusted for relatedness
	p-value
	Hypertension (n=99)
Women (n=612)	No hypertension (n=503)
	p-value adjusted for relatedness
	p-value
	Hypertension (n=106)
Men (n=456)	No hypertension (n=350)
	Nutritional factor

<sup>b</sup>Median (1st quartile, 3rd quartile); tested after log-transformation.

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# Table IVa

Association of mean systolic blood pressure by quartiles of dietary intake among Alaska Native men not on anti-hypertensive medications (n=407).

		Quartiles of d	ietary intake			ly et al.
	1st quartile	2nd quartile	3rd quartile	4th quartile	P for trend	
Total energy intake (kca	1)					
Univariate model	$119 \pm 1.1$	$121 \pm 1.3$	$122 \pm 1.3$	$121 \pm 1.2$	0.21	
Multivariate model <sup>a</sup>	$120 \pm 2.3$	$120 \pm 1.5$	$122 \pm 1.3$	$121 \pm 2.6$	0.77	
% energy from carbohyd	lrate					
Univariate model	$122 \pm 1.3$	$121 \pm 1.3$	$121 \pm 1.1$	$119 \pm 1.2$	0.16	
Multivariate m		$120 \pm 1.2$	$121 \pm 1.2$	$120 \pm 1.2$	0.40	
% energy from si	rbohydrate					
Univariate mode	$21 \pm 1.2$	$121 \pm 1.2$	$-20 \pm 1.3$	$121 \pm 1.2$	06:0	
Multivariate model	+ 1.2	$121 \pm 1.2$	2	$121 \pm 1.3$	0.96	
% energy from complex	c					
Univariate model	126	$123\pm1.3$	$121 \pm 1.1$	+ 1.1	0.53	
Multivariate model <sup>a</sup>	$120 \pm 1$	$22 \pm 1.2$	$121 \pm 1.3$		66:0	
% energy from protein						
Univariate model	$121 \pm 1.3$		$121 \pm 1.1$	$121 \pm 1.3$		
Multivariate model <sup>a</sup>	$121 \pm 1.3$	$120 \pm 3$	$120 \pm 1.2$	$121 \pm 1.3$		
% energy from total fat						
Univariate model	$119 \pm 1.2$	$121 \pm 1.1$	Iz	$123 \pm 1.4$	0.04*	
Multivariate model <sup>a</sup>	$120 \pm 1.2$	$120 \pm 1.3$	$120 \pm 1.2$	$22 \pm 1.2$	0.38	
% energy from saturated	l fat					
Univariate model	$120 \pm 1.2$ $120 \pm 1.2$	119 ± 1.1	122 ± 1.2	$122 \pm 1.5$		



 $b_{
m MUFA=monounsaturated fatty acids.}$ 

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# Table IVb

Association of mean systolic blood pressure by quartiles of dietary intake among Alaska Native women not on anti-hypertensive medications (n=528).

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		Quartiles of d	lietary intake		
	1st quartile	2nd quartile	3rd quartile	4th quartile	P for trend
Total energy intake (kcal	(1			-	
Univariate model	$116 \pm 1.1$	$116 \pm 1.2$	$114 \pm 1.0$	$113\pm1.2$	0.07
Multivariate model <sup>a</sup>	$113\pm1.8$	$115 \pm 1.3$	$115 \pm 1.1$	$116 \pm 2.1$	0.53
% energy from carbohyd	lrate				
Univariate model	$116\pm1.2$	$115\pm1.6$	$114 \pm 1.1$	$114 \pm 1.1$	0.15
Multivariate model <sup>a</sup>	$115 \pm 1.1$	$114 \pm 1.1$	$114 \pm 1.1$	$115 \pm 1.1$	0.66
% energy from simple c	arbohydrate				
Univariate model	$116\pm1.2$	$115 \pm 1.1$	$114\pm1.2$	$113 \pm 1.0$	0.06
Multivariate model <sup>a</sup>	$114 \pm 1.1$	$114 \pm 1.1$	$115 \pm 1.1$	$115 \pm 1.1$	0.50
% energy from complex	carbohydrate				
Univariate model	$113 \pm 1.1$	$115\pm1.2$	$114\pm1.2$	$116 \pm 1.1$	0.09
Multivariate model <sup>a</sup>	$113 \pm 1.1$	$116 \pm 1.1$	$115 \pm 1.1$	$115 \pm 1.1$	0.48
% energy from protein					
Univariate model	$114 \pm 1.1$	$115\pm1.2$	$115\pm1.2$	$115\pm1.2$	0.29
Multivariate model <sup>a</sup>	$115 \pm 1.1$	$115 \pm 1.1$	$115 \pm 1.1$	$114 \pm 1.1$	0.61
% energy from total fat					
Univariate model	$114 \pm 1.0$	$114\pm1.2$	$114 \pm 1.3$	$117 \pm 1.2$	0.21
Multivariate model <sup>a</sup>	$115 \pm 1.1$	$115 \pm 1.1$	$114 \pm 1.1$	$115 \pm 1.1$	0.55
% energy from saturated	fat				
Univariate model	$115 \pm 1.0$	$114\pm1.2$	$115 \pm 1.1$	$115\pm1.3$	0.78
Multivariate model <sup>a</sup>	$116 \pm 1.1$	$113 \pm 1.1$	$115 \pm 1.1$	$114 \pm 1.1$	0.32
% energy from MUFA $^{b}$					
Univariate model	$114 \pm 1.0$	$115 \pm 1.2$	$114 \pm 1.2$	$116\pm1.2$	0.25
Multivariate model <sup>a</sup>	$115 \pm 1.1$	$114 \pm 1.1$	$114 \pm 1.1$	$114 \pm 1.1$	0.57
% energy from trans fatt.	y acids				
Univariate model	$114 \pm 1.1$	$114 \pm 1.2$	$115\pm1.3$	$115 \pm 1.1$	0.30

		Quartiles of d	lietary intake		
	1st quartile	2nd quartile	3rd quartile	4th quartile	P for trend
Multivariate model <sup>a</sup>	$114 \pm 1.1$	$115 \pm 1.1$	$115 \pm 1.1$	$114 \pm 1.1$	0.98
Omega-3 fatty acids, gra	ıms/day				
Univariate model	$117 \pm 1.1$	$114 \pm 1.1$	$114 \pm 1.3$	$114 \pm 1.1$	0.19
Multivariate model <sup>a</sup>	$118 \pm 1.1$	$114 \pm 1.1$	$113 \pm 1.1$	$113\pm1.2$	<0.01
Omega-6 fatty acids, gra	ums/day				
Univariate model	$116 \pm 1.1$	$115\pm1.2$	$114 \pm 1.0$	$114 \pm 1.2$	0.17