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Ethnic Admixture Affects Diabetes Risk in Native Hawaiians: The Multiethnic Cohort

Gertraud Maskarinec¹, Yukiko Morimoto¹, Simone Jacobs², Andrew Grandinetti³, Marjorie K. Mau⁴, and Laurence N. Kolonel¹

¹University of Hawaii Cancer Center, Honolulu, HI

²German Institute of Human Nutrition, Potsdam-Rehbrücke, Germany

³Office of Public Health Studies, University of Hawaii, Honolulu, HI

⁴Department of Native Hawaiian Health, JABSOM, University of Hawaii, Honolulu, HI

Abstract

Background/Objectives—Obesity and diabetes rates are high in Native Hawaiians (NH) who commonly have mixed ancestries. Persons of Asian ancestry experience a high risk of type 2 diabetes despite the relatively low body weight. We evaluated the impact of ethnic admixture on diabetes risk among NH in the Multiethnic Cohort (MEC).

Methods/Subjects—Based on self-reports, 11,521 eligible men and women were categorized into NH/white, NH/other, NH alone, NH/Asian, and the most common three ancestry admixture, NH/Chinese/white. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the NH/white category as the reference group; covariates included known confounders, i.e., body mass index (BMI), dietary and other life-style factors.

Results—The NH alone category had the highest proportion of overweight and obese individuals and the NH/Asian category the lowest proportion. During 12 years of follow-up after cohort entry at 56 years, 2,072 incident cases were ascertained through questionnaires and health plan linkages. All NH categories had higher HRs than the NH/white category before and after adjustment for BMI. In fully-adjusted models, the NH/Asian category showed the highest risk (HR=1.45; 95% CI: 1.27–1.65), followed by NH/other (HR=1.20; 95% CI: 1.03–1.39), NH/Chinese/white (HR=1.19; 95% CI: 1.04–1.37), and NH alone (HR=1.19; 95% CI: 1.03–1.37). The elevated risk by Asian admixture was more pronounced in normal weight than overweight/obese individuals.

Conclusions—These findings indicate that Asian admixture in NHs is associated with higher risk for type 2 diabetes independent of known risk factors and suggest a role for ethnicity-related genetic factors in the development of this disease.

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Address for correspondence: Gertraud Maskarinec, MD, PhD, University of Hawaii Cancer Center, 701 Ilalo Street, Honolulu, HI 96813, Phone: (808) 586-3078, FAX: (808) 586-2982, gertraud@cc.hawaii.edu.

Conflict of Interests. None of the authors have a conflict of interest to declare.

Introduction

With increasing obesity rates, the number of people with type 2 diabetes is rising across the world,^{1;2} but the incidence is considerably higher in Asians and Pacific Islanders than in whites.^{3;4} In the United States, 20–40% higher rates of type 2 diabetes were reported for Asian Americans than whites after adjustment for body mass index (BMI).^{3;5} High rates of obesity among Native Hawaiians (NH) and other Pacific Islanders appear to account for their elevated risk,^{6–8} whereas the high incidence of diabetes in Asian Americans is independent of BMI.^{8–11} After Captain Cook reached the Hawaiian Islands in 1778, the NH population was decimated due to diseases resulting from contact with Westerners, for which NHs had no immunity.^{12;13} As a result of intermarriage with members of other ethnic groups, in particular white and Chinese, the number of Hawaii residents reporting Part-Hawaiian ethnicity increased to 289,970 by 2010.¹⁴ Individuals reporting Hawaiian/Pacific Islander cultural identity have significantly higher BMIs than those reporting Asian American cultural identity that could be only partially explained by variations in educational attainment, socioeconomic status, and lifestyle factors.¹⁵ From research within the Multiethnic Cohort (MEC), it appears that persons with multiple ancestries are more likely to have excess body weight.^{16;17} For example, the prevalence of overweight/obesity in the NH/Asian admixture group was higher than the average of the prevalence estimates for NHs and Asians.¹⁶ Given previous studies showing that Asian Americans experience a 2–3 fold higher risk of type 2 diabetes than whites at the same levels of BMI,^{8;18} we examined whether the incidence of diabetes varies in NHs by admixture. The issue of admixed populations is of global importance since racial and ethnic admixture has become widespread as travel to distant countries from one's place of origin has become exceedingly common. Indeed, increasing mixed racial and ethnic ancestry has been documented across the United States¹⁹, Mexico,²⁰ and Malaysia.²¹ Understanding genetic ancestry and differences in racial admixture within regions has the potential to better inform public health officials to respond to projected health risks of a growing sector of the population, which is interracially mixed.^{19;20}

Methods

Study Population

The MEC was established in 1993–1996 to study diet and cancer among different ethnic groups in Hawaii and California,²² but the current analysis was restricted to the Hawaii component of the cohort.⁸ All participants provided informed consent at cohort entry. Although whites, Japanese American, and NHs were targeted for recruitment in Hawaii, a substantial number of participants reported other Asian or multiracial backgrounds. A comparison of white, Japanese, and NH cohort members with census data indicated that the MEC represents all levels of education although cohort members were somewhat better educated than the general population.²² Subjects entered the cohort by completing a 26-page, self-administered mailed survey that asked about demographic background, medical conditions, anthropometric measures, diet, and lifestyle factors. The participants marked all applicable ethnic backgrounds (African American, Chinese, Filipino, NH, Japanese, Korean, Latino, white, and other). Diet was assessed using a validated quantitative food frequency

questionnaire (FFQ) and an extensive nutritional database.^{22;23} After identifying a total of 11,521 persons who reported NH ancestry, we created the following admixture categories: NH alone, NH/white, NH/Asian, i.e., one or more reports of Chinese, Korean, Japanese, or Filipino ancestry, NH/white/Chinese, a common combination for historic reasons,¹³ and NH/other, i.e., combinations of Latino, African American, Other with white and/or Asian.

Identification of Diabetes Cases

Of the original 103,898 members within the Hawaii component of the MEC, 10,028 (9.7%) who reported a diagnosis of diabetes at baseline and 10 subjects with missing information were excluded. Information on diabetes status was available at three time points, i.e., from a follow-up questionnaire in 1999–2003, a medication questionnaire administered during 2003–2006, and a linkage with Hawaii's two major health plans in 2007.⁸ Specific algorithms based on multiple claims for diabetes-related treatment services were used to identify cases with the purpose to be included in diabetes care registries.⁸ One of the two health plans used an algorithm based on multiple claims for diabetes-related treatment services over a 2-year time span. Single diagnostic claims were not classified as cases in order to avoid false positives; physicians had the opportunity to refer or remove cases. One path identified a specified set of diagnosis codes associated with treatment services (inpatient, emergency, or outpatient professional); another path examined outpatient prescription drugs or supplies for diabetes. The other health plan, a health maintenance organization, based their case identification on clinical information (HbA_{1c} testing), pharmacy records (insulin, sulfonylurea drugs, metformin, and blood glucose testing supplies), hospital discharge diagnoses reflecting the presence of diabetes, and outpatient encounters. The Institutional Review Boards of the University of Hawaii and Kaiser Permanente approved the study protocol and all participants signed a consent form at cohort entry. When the health plans did not provide a diagnosis date, the estimated date of diagnosis was the midpoint in time between the last report of not having diabetes and the first indication of diabetes. For incident cases, the follow-up time was calculated as the time between the baseline questionnaire and an estimated diagnosis date. For non-cases, the follow-up time was calculated as the time between the date of the baseline questionnaire and any of the following events if applicable: the date of death, the last date when data on diabetes status was available, i.e., the date of the questionnaire or health plan linkage.

Statistical analysis

The average annual incidence rates were computed by ethnic group as the sum of the number of newly diagnosed diabetes cases divided by the sum of person-years of follow-up. Cox proportional regression using PROC PHREG in the SAS software package, version 9.3 (SAS Institute, Inc., Cary, NC) was applied to estimate diabetes risk by admixture group with NH/white as the reference category because they had the lowest incidence rate. In the first model, we calculated hazard ratios (HR) and 95% confidence intervals (CI) using models stratified by age at cohort entry (continuous) and adjusted for sex and years of education (<12, 12, 13–15, and 16 years). The second model also included BMI (<22.5, 22.5–<25, 25–<30, and 30 kg/m²). In a third model, we further adjusted for all variables that were previously found to be associated with diabetes risk in this dataset, i.e., smoking status and physical activity, as well as intake of total energy, alcohol, red meat, dietary fiber,

sugared sodas, and coffee.^{24;25} Physical activity was expressed as metabolic equivalents (METs) and 711 missing values were replaced with the means for each sex-ethnic group. Daily intakes of dietary fiber and red meat were expressed per 4,184 kJ of energy intake; logarithmic transformations were applied to intakes of dietary fiber, red meat, total energy as well as METs. For alcohol (<1, 1- to <1, 1 drink/day), coffee (almost never, <1, 1, 2, and 3 cups/day), and sugared soda (0, <2, and 2 sodas/week) consumption, categorical variables were created. To evaluate the importance of admixture as compared to the NH/white group independent of BMI, stratified models by BMI category were performed.

Results

After excluding subjects with prevalent diabetes or missing data at baseline, 11,521 cohort members (4,961 men and 6,560 women) who reported any Native Hawaiian ancestry were part of this analysis (Table 1). The mean age of the participants was 56 years at cohort entry and the mean follow-up time was 11.9±3.4 years. When divided into admixture groups (Table 2), 23% were NH/white, 16% NH/other, 21% NH/white/Chinese, 16% NH alone, and 24% NH/Asian. The distribution of BMI, smoking (except in men), education, physical activity, and dietary intakes differed significantly across admixture groups. The overall incidence of new cases was 16.0 per 1,000 pyrs with the highest rates in NH/Asian (18.3 per 1,000 pyrs) and NH alone (17.8 per 1,000 pyrs) and the lowest rate in the NH/white group (13.4 per 1,000 pyrs). After stratification by BMI category, the incidence was approximately 2-fold higher in the overweight and 5-fold higher in the obese participants when compared to the normal weight category. Within each BMI category, the pattern by admixture group was similar as in the total study population: the incidence rates were lowest for the NH/white group (3.8, 12.3, and 26.4 per 1,000 pyrs across BMI categories) and highest for those with Asian ancestry (8.8, 18.8, and 34.7 per 1,000 pyrs). For those who reported NH alone, the respective rates were similar to the NH/Asian group (6.7, 13.3, and 31.3 per 1,000 pyrs).

The basic Cox regression models stratified by age at cohort entry and adjusted for sex and years of education showed a similar pattern of ethnic differences as the incidence rates (Table 2). When compared to the NH/white group, the risk estimates for NH/Asian and NH alone were 1.36 and 1.27, respectively, in the simple model, whereas the risk was elevated by 12 and 16% for the NH/other and NH/Chinese/white admixture groups. Including BMI into the models primarily increased the relative risk for the NH/Asian group (HR=1.52; 95%CI: 1.34–1.73), while further adjustment for diet and lifestyle factors only modified the risk estimates minimally. Stratification by BMI category again indicated that the NH/Asian admixture group experienced the highest risk of diabetes as compared to other admixture groups; the respective HRs for normal weight, overweight, and obese participants were 2.33 (95%CI: 1.60–3.39), 1.54 (95%CI: 1.25–1.90), and 1.30 (95%CI: 1.08–1.56), whereas the HRs for the other admixture groups were 1.66–1.83 in the normal weight individuals, 1.07–1.26 among overweight persons, and 1.10–1.20 in the obese category.

Discussion

Within this population of more than 10,000 middle-aged and elderly individuals with NH ancestry who were followed for nearly 12 years, the incidence and risk of developing type 2

diabetes varied distinctly according to self-reported admixture. NH participants who reported only white admixture were least likely to develop diabetes even after adjustment for potential confounders, whereas any Asian ancestry predicted a more than 2-fold higher risk to be diagnosed with diabetes. As shown in previous reports,^{8,18} the incidence rates for participants with white and Asian ancestry in the MEC were 9.9 and 17.9–21.3 per 100,000 pyrs, respectively; this indicates that the incidence in the NH/white group (13.4 per 100,000 pyrs) was one third higher than in whites, while incidence rate for the NH/Asian category (18.3 per 100,000 pyrs) was similar to the different Asian groups.¹⁸ The type of admixture influenced diabetes risk more among normal weight than overweight/obese participants. One possible explanation, which needs to be explored in future research, is that genetic factors in Asians predispose to type 2 diabetes and other weight-related diseases,²⁶ but heavier Asian individuals develop diabetes primarily as a consequence of excess body weight.

A limited number of studies have described the effects of ethnic admixture. In addition to the obesity studies within the MEC,^{16,17} the prevalence of type 2 diabetes in two rural communities in Hawaii was not significantly associated with the percentage of Hawaiian ancestry after adjusting for age,²⁷ but in a later report from the same population, a higher Hawaiian blood quantum was significantly associated with higher fasting glucose, BMI, and waist-to-hip ratio.²⁸ When descent from other ethnic groups was examined, full-Hawaiians had significantly higher fasting glucose concentrations than part-Hawaiians. In contrast, part-Hawaiians of predominantly Asian ancestry had the highest 2-hour postprandial glucose concentrations.

A number of different conditions have been investigated in relation to admixture among other ethnic groups. The percentage of African ancestry improved the prediction of lung function and allowed more accurate disease severity classification.²⁹ Similarly, significant associations of indigenous ancestry in admixed mestizos across Mexico with lung function have been reported.²⁰ In Latina women, the proportion of European vs. Indigenous American ancestry was associated with higher breast cancer risk after adjustment for known risk factors.³⁰ Among Latinos in the south western United States³¹ and among Tohono O’odham (Pima) Indians in Arizona,³² a higher proportion of Native American blood quantum was associated with a higher risk of type 2 diabetes.

The presence of insulin resistance syndrome among NHs was shown to be similar as in other high risk indigenous populations, e.g., individuals from the Tohono O’odham tribe in Arizona.³² However, Asians are more likely to manifest a β -cell secretion defect measured as elevated post-glucose challenge hyperglycemia.³³ Thus, NHs who are an admixture of NH and Asian ancestry may be at higher risk because of a “double whammy” metabolic load of both insulin resistance and β -cell secretion defects within the same individual, who is unable to compensate for hyperinsulinemia and, thus, presents with elevated fasting and postprandial hyperglycemia defined as diabetes mellitus.

Given the history of NHs who probably started to settle on the Hawaiian Islands in 1025–1120 as seafarers migrating from East Asia across the Pacific,^{34,35} the population genetic structure of NHs is highly complex. In a group of NH MEC participants, 27% East Asian, 27% European, and 46% NH ancestry was detected.³⁶ In a later analysis using high-

resolution genome-wide SNP data and mitochondrial genomes of 148 and 160 NHs,³⁵ the genome of NHs who self-reported full NH heritage contained 78% NH, 12% European, and 8% Asian ancestry. The estimated proportions of NH ancestry for those who reported mixed ancestry were found to be consistent with their self-reported heritage.³⁵ However, the impact of genetic markers to predict onset of type 2 diabetes has been thus far poorly delineated; therefore, self-report ethnic and racial ancestry has been most useful in terms of clinical care and prevention strategies.

This analysis had several strengths including the large sample size, the long follow-up, the detailed ethnicity information, the availability of self-reported data on dietary and lifestyle factors, and the multiple data sources to establish a diabetes diagnosis. A number of limitations need to be noted. Given the design of the questionnaire, we were not able to compute the percentage of NH or various Asian ancestries. Ideally, the self-reported ethnic background would be compared to genetic markers but these are not available for this large number of NH participants. Although no validations of self-reports and diabetes care registries are available for Hawaii, self-reported diabetes diagnoses^{37;38} and care registries were found to be valid in other studies.³⁹ Given the age distribution of the MEC, which did not include persons less than 45 years of age at cohort entry, the current report pertains primarily to older individuals and excludes cases with early onset diabetes. The increasing number of cases diagnosed in younger Asians,⁴⁰ may have different etiologic features and/or genetic predispositions that need to be explored in appropriate study populations.

The current findings are of interest to other populations because fine-scale ancestry patterns are critical for medical studies in many countries with highly admixed populations.²⁰ Efforts to develop more accurate disease prediction models based on genetic and lifestyle risk factors may have to consider the inclusion of differentiated ancestries instead of using simple self-reported categories.²⁰ The potential influence on public health and clinical care lies in targeted prevention approaches in high-risk populations.

The current findings among a study population aged 50 years and older indicate that NHs with Asian admixture are at higher risk for type 2 diabetes than those with white admixture or NH alone independent of BMI status, diet, and other known lifestyle related factors. Several complex biologic mechanisms for the high susceptibility of Asians to type 2 diabetes have been proposed,^{41;42} including a role of visceral adipose tissue in glucose metabolism⁴³ and higher insulin sensitivity combined with lower insulin response in East Asians compared with whites.⁴² These findings confirm that even among high risk populations, a broad range of risk assessment approaches may inform strategies to delay the onset of diabetes, can be tailored to individuals at highest risk, and should be implemented at earlier stages of the disease process, such as lower BMI and earlier age.

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Table 1
 Characteristics of participants with Native Hawaiian (NH) ancestry, Multiethnic Cohort*

	Male (N=4,961)							Female (N=6,560)						
	NH/white	NH/other	NH/Chinese/white	NH alone	NH/Asian	P value [^]	NH/white	NH/other	NH/Chinese/white	NH alone	NH/Asian	P Value [^]		
N	1,078	714	983	905	1,281		1,554	1,084	1,489	926	1,507			
Age at cohort entry (years)	57.6±9.0	53.7±7.6	55.6±8.4	57.2±8.6	56.6±8.6	<0.001	57.4±8.8	52.8±7	55.0±8.5	57.3±8.7	56.7±8.7	<0.001		
Follow up time (years)	11.1±3.9	11.5±3.7	11.3±3.7	10.3±4.2	10.8±4.0	<0.001	11.5±3.7	11.8±3	11.6±3.6	11.1±3.9	11.4±3.6	<0.001		
Body mass index (kg/m ²)														
<22	72 (6.7)	40 (5.6)	70 (7.1)	58 (6.4)	105 (8.2)		237 (15.3)	188 (17.3)	223 (15.0)	119 (12.9)	282 (18.7)			
22–25	222 (20.6)	133 (18.6)	179 (18.2)	139 (16.4)	296 (23.1)		306 (19.7)	252 (23.3)	334 (22.4)	181 (20.0)	385 (25.6)			
25–30	471 (43.7)	326 (45.7)	484 (49.2)	363 (40.1)	539 (42.1)		528 (34.0)	364 (33.6)	502 (33.7)	288 (31.1)	495 (32.8)			
30+	313 (29.0)	215 (30.1)	250 (25.4)	345 (38.1)	341 (26.6)		483 (31.1)	280 (25.8)	430 (28.9)	338 (36.5)	345 (22.9)			
Smoking						0.09						<0.001		
Never	333 (30.9)	207 (29.0)	334 (34.0)	304 (33.6)	455 (35.5)		658	469 (43.3)	667 (44.8)	368 (39.7)	802 (53.2)			
Passive	498 (46.2)	345 (48.3)	440 (44.8)	392 (43.3)	538 (42.0)		517	350 (32.3)	475 (31.9)	299 (32.3)	404 (26.8)			
Current	247 (22.9)	162 (22.7)	209 (21.3)	209 (23.1)	288 (22.5)		379	265 (24.5)	347 (23.3)	259 (28.0)	301 (20.0)			
Education (years)						<0.001						<0.001		
<12	135 (12.5)	63 (8.8)	75 (7.6)	179 (19.8)	154 (12.0)		151 (9.7)	57 (5.3)	104 (7.0)	177 (19.1)	158 (10.5)			
12	371 (34.4)	236 (33.1)	327 (33.3)	370 (40.9)	516 (40.3)		715	425 (39.2)	641 (43.1)	426 (46.0)	694 (46.1)			
13–15	354 (32.8)	244 (34.2)	349 (35.5)	233 (26.8)	364 (28.4)		467	384 (35.4)	476 (31.8)	195 (10.2)	391 (26.0)			
16+	218 (22.0)	171 (24.0)	232 (23.6)	123 (12.4)	247 (19.3)		221	218 (20.1)	271 (18.2)	128 (13.8)	264 (17.5)			
Physical activity (METs)														
N with missing values	1.7±0.4 (57)	1.7±0.4 (20)	1.7±0.4 (44)	1.8±0.4 (75)	1.7±0.4 (69)	0.04	1.6±0.3 (105)	1.6±0.3 (50)	1.6±0.3 (90)	1.6±0.3 (102)	1.6±0.3 (99)	0.01		
Total energy intake (kcal)	2763 ±1227	2803 ±1317	2772 ±1295	3007 ±1510	2791 ±1359	0.01	2309 ±1175	2284 ±1161	2390 ±1210	2791 ±1359	2373 ±1265	<0.001		
Dietary fiber (g/4,184 kJ/day)	9.2±3.8	8.6±3.4	8.9±3.5	9.3±4.0	8.6±3.5	<0.001	11.2±4.2	10.6±4.0	10.8±4.1	11.0±4.4	10.8±4.0	0.01		
Red meat (g/4,184 kJ/day)	31.0±16.5	32.2±15.8	32.3±15.8	31.1±16.3	31.6±15.3	0.08	27.1±15.7	28.6±15.5	29.2±15.7	27.6±16.2	28.4±15.1	<0.001		
Coffee (cups/day)	1.3±1.2	1.3±1.3	1.2±1.3	1.2±1.3	1.2±1.3	0.01	1.2±1.3	1.1±1.2	1.2±1.2	1.1±1.3	1.1±1.2	<0.001		
Alcohol intake (g/day)	18.4±32.8	16.4±38.0	17.3±34.9	16.4±41.8	14.3±35.7	<0.001	6.3±22.1	4.1±14.7	5.7±22.3	4.2±14.2	3.3±15.4	<0.001		

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	Male (N=4,961)					Female (N=6,560)					P Value ^	
	NH/white	NH/other	NH/Chinese/white	NH alone	NH/Asian	P value ^	NH/white	NH/other	NH/Chinese/white	NH alone		NH/Asian
Sugared soda (g/day)	218±491	238±540	215±448	292±663	298±613	<0.001	186±522	160±438	188±500	235±605	178±456	<0.001

* Data are presented as mean±SD or N (%); percentages may not add to 100 due to rounding.

^ Comparisons of ethnic groups within each sex were performed using generalized linear model on log-transformed, continuous variables (except for age at cohort entry) or chi-square test on categorical variables.

Table 2
Diabetes incidence rates and risk by Native Hawaiian (NH) admixture across body mass index (BMI) categories*

Variable/Admixture group	NH/white	NH/other	NH/Chinese/white	NH alone	NH/Asian	All
Number of participants	2,632	1,798	2,472	1,831	2,788	11,521
Incident diabetes cases	400	317	438	348	569	2,072
Diabetes incidence (1,000 pyrs)						
All	13.4	15.1	15.4	17.8	18.3	16.0
Normal weight	3.8	5.7	5.5	6.7	8.8	6.2
Overweight	12.3	14.9	13.9	13.3	18.8	14.7
Obese	26.4	29.3	32.0	31.3	34.7	30.6
Diabetes risk						
Model 1 [*]	1.00	1.12 (0.97–1.30)	1.16 (1.01–1.32)	1.27 (1.10–1.46)	1.36 (1.20–1.54)	
Model 1 plus BMI [^]	1.00	1.23 (1.06–1.42)	1.23 (1.07–1.40)	1.19 (1.03–1.37)	1.52 (1.34–1.73)	
Model 1 plus BMI, diet, and lifestyle [¶]	1.00	1.20 (1.03–1.39)	1.19 (1.04–1.37)	1.19 (1.03–1.37)	1.45 (1.27–1.65)	
By BMI category						
Normal weight (<25 kg/m ²)	1.00	1.81 (1.16–2.83)	1.66 (1.09–2.53)	1.83 (1.16–2.91)	2.33 (1.60–3.39)	
Overweight (25–30 kg/m ²)	1.00	1.26 (0.99–1.62)	1.15 (0.92–1.44)	1.07 (0.83–1.39)	1.54 (1.25–1.90)	
Obese (≥30 kg/m ²)	1.00	1.10 (0.89–1.36)	1.20 (0.99–1.45)	1.19 (0.99–1.44)	1.30 (1.08–1.56)	

* Hazard ratios and 95% confidence intervals were obtained by Cox proportional hazard models, stratified by age at cohort entry and adjusted for, sex, and years of education (<12, 12, 13–15, and 16 years)

[^] Additionally adjusted for BMI (<22, 22–<25, 25–<30, and ≥30 kg/m²)

[¶] Further adjustment for physical activity (log-transformed metabolic equivalents, 711 missing values were replaced with means for each sex-ethnic group), smoking (never, past, and current), years of education (<12, 12, 13–15, and 16 years), total energy intake (log-transformed), coffee (almost never, <1, 1, 2, and ≥3 cups/day) sugared soda (0, <2, and ≥2/week), alcohol (<1 drink/month, 1 drink/month to <1 drink/day, 1 drink/day), and intake of dietary fiber and red meat (both variables were log-transformed continuous, density per 4,184 kJ/day)