The Determinants and Disparities of Gout within the Multiethnic Cohort

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Section 1. Introduction

1.1 The Burden of Acute Gouty Arthritis

Acute Gouty Arthritis, or gout, is one of the most common rheumatologic diseases around the world, and the most prevalent form of inflammatory arthritis in the United States, affecting over eight million Americans.[1] Characterized by moderate to severe pain, limited mobility, and chronic inflammation, gout is a debilitating condition with substantial implications for a patient's quality of life.[2,3] While gout is etiologically different from other rheumatologic diseases, it is clinically comparable to the disease burden associated with rheumatoid arthritis; however, while primary hospitalization rates for rheumatoid arthritis have decreased over the last ten years, annual hospitalizations for gout have doubled in the same timeframe.[4] Moreover, despite the increase in both prevalence and incidence of gout around the world, suboptimal gout management persists.[5,6]

Gout not only presents a substantial societal and personal burden, but a financial burden as well, with the care for this condition estimated at over $3,000 in additional costs annually per patient with gout.[7] In a recent systematic review of the economic burden of gout, gout-related cost may range between $172 to $6,179 annually, with costs considerably greater among elderly and treatment-refractory gouty patients.[8] However, factoring in the various co-morbidities associated with gout, the indirect costs likely exceed these estimates.

The burden and risk of gout differs significantly by demographic characteristics, particularly age and sex.[9] Gout is four times more prevalent in men under 65 years old compared to women within the same age range; however, after 65 years of age, this difference in proportion begins to decrease.[10] A possible explanation for these trends is that estrogen facilitates an increase in uric acid clearance. As a result, menopause, which results in a dramatic decline in the production of estrogen, leads to a significantly higher risk of gout in women when compared to premenopausal women; this effect is further exemplified by post-menopausal women using estrogen and progesterone, who have a significantly lower risk of gout compared to those not using these hormone replacement therapies.[11]

As a condition strongly associated with the aging process, incident cases of gout are expected to increase in the coming decades, having already doubled over the past 20 years.[6,11] The World Health Organization projects a rapid increase in the world's proportion of adults over 60 years old in the next few decades, nearly doubling by 2050 from the most recent estimates.[12]

With cases on the rise, further investigation into the determinants of gout is crucial in assessing the personal, social, and economic burden in a globally aging population. Moreover, recent trends suggest an increasingly ethnically diverse older population, particularly in the US.[13] Understanding differences between populations remains a crucial gap in individualizing care for those affected by gout and other chronic health conditions.

1.2 Etiology and Clinical Features of Gout and Hyperuricemia

Gout is characterized by the accumulation of monosodium urate (MSU) crystals within joints from elevated uric acid levels, or hyperuricemia.[6] Humans are the only known mammal that develops gout, while hyperuricemia is only found in other primates. Uric acid, the final product of purine catabolism, is the well-established causal component to the development of acute gout. Most organisms possess the enzyme uricase, which converts uric acid to the more soluble allantoic acid via oxidative degradation; however, due to mutational silencing events in the gene that encodes uricase, humans and great apes lack this enzyme, and thus, the less soluble uric acid is the final product in the breakdown of endogenous and exogenous purines.[14] As a result, humans generally have higher uric acid levels than other mammals.

Hyperuricemia may be caused by the overproduction of urate from purine catabolism, or its underexcretion by the renal system; most individuals who develop gout have issues with both overproduction and underexcretion, with underexcretion thought to be the more important contributor to the disease state.[15,16] Recent genome-wide associations studies (GWAS) have led to the discovery of risk variants within genes related to the renal urate transport and subsequent excretion.[17] For instance, SLC2A9, a gene that encodes a urate uniporter, was demonstrated as having a large effect on uric acid levels, especially among females.[18] Similarly, ABCG2, a gene that encodes a transporter that mediates urate secretion, was found to explain up to 10% of gout cases among both Whites and Japanese.[19,20] While these findings show that much of hyperuricemia may be attributable to genetic variation, lifestyle factors likely interact with genetics, and modify one's risk of gout.

While there exists little debate on whether gout is a severe and debilitating chronic condition, quantifying the disease burden at a population level depends on differing case definitions.[11] The presence of MSU crystals in joint fluid, or the presence of detectable MSU deposits, is considered the gold standard in diagnosing gout.[11] Unfortunately, the procedure for confirming gout under this criteria is invasive and often infeasible in practice, and thus, rarely

used to establish a diagnosis.[21] Other techniques, including ultrasound, magnetic resonance imaging, and computer tomography, can be used to detect MSU crystals; however, these procedures can be both expensive and inconclusive.[22] Therefore, most cases of gout are diagnosed by professional opinion, and as a result, varying and inconsistent operation characterizations create challenges in investigating the epidemiology of gout.[23,24]

In general, clinical gout progresses through four stages: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, and chronic tophaceous gout or advanced gout. Asymptomatic hyperuricemia is a condition where serum uric acid concentrations are elevated to >6.8 mg/dL, yet no detectable symptoms of gout are present.[25] For this reason, asymptomatic hyperuricemia is sometimes not considered to be part of the disease state, but rather an early warning sign.[16] Gouty flares characterize the acute phase of gout in which the uric acid concentration reaches its saturation threshold and begins to crystallize, depositing in joints, tendons, and related tissues, typically of the lower extremities.[26] The MSU deposits, referred to as tophi, cause a sudden onset of pain, erythema, and limited range of motion, and trigger the inflammatory response.[16] Most individuals living with asymptomatic hyperuricemia do not progress into acute gout; however, prior studies report that patients with urate concentrations exceeding 9.0 mg/dL are six times more likely to experience a gouty flare.[27,28] Following a flare, patients enter an intercritical phase, where symptoms of gout are no longer present for up to several months or years, depending on treatment quality.[29] When gout is left without or with improper treatment, intercritical periods become progressively shorter, and gouty flares become more severe and longer lasting.[11] The final stage, advanced gout, is defined by intercritical periods no longer being pain-free. Because advanced gout is associated with the presence of destructive subcutaneous tophus nodules, it is sometimes referred to as chronic tophaceous gout; however, subcutaneous tophi are not always present or detectable during this phase.

1.3 Modifiable Lifestyle Risk Factors

From a historical perspective, gout is an ancient disease, and its association with modifiable lifestyle factors has long been recognized.[16,30] As previously mentioned, gout is caused by both the overproduction and underexcretion of uric acid. Thus, behaviors that contribute to these two causal pathways may modify one's risk and management of the disease.

Perhaps one of the first, and most widely, established lifestyle factor is alcohol consumption. In a meta-analysis of alcohol use and risk of gout, researchers found an increased

risk among all levels of consumption, with a pooled relative risk (RR) of 2.64 (95% confidence interval [CI]: 2.26, 3.09) among heavy drinkers compared with non/occasional drinkers, across 17 observational studies. Similarly, in a prospective cohort study of men from the Health Professionals Follow-up Study, alcohol intake increased the risk of gout incidence in a dose-dependent gradient; beer consumption, in particular, had the strongest effect estimate (RR=1.49, 95%CI: 1.32, 1.70, for one 12-ounce beer per day).[31] Alcohol most likely contributes to both causal pathways of gout.[11] Many alcohol beverages, namely beer, are purine-rich, and may increase uric acid production through the catabolism of common purines found in beer, such as guanosine.[32] In addition, alcohol use may downregulate excretion of the resulting excess uric acid by producing lactic acid, which competitively inhibits uric acid secretion.[33]

Much of the overproduction of uric acid may be attributed to the overconsumption of purine-rich foods, increasing one's risk of gout. Foods with large amounts of purines include: meats, seafood, other sources of animal proteins, and certain vegetables.[9] A 12-year prospective study of men reported that higher intake of meat and seafood were significantly associated with an increased risk of gout; however, risk of gout was not significantly predicted by purine-rich vegetable intake.[34] One possible explanation for why purine-rich vegetables were not associated with gout might be that plant-based purines are less bioavailable than those found in meats.[11] In the same aforementioned study, dairy products were found to lessen an individual's risk of developing gout, possibly elucidating urate-lowering properties.[34]

Similar to alcohol consumption, sugar sweetened beverages and fructose also may contribute to the risk of gout through a dual-pathway mechanism; fructose and sugar-sweetened beverages increase lactic acid levels, leading to a decreased ability to excrete uric acid.[9] As such, a prospective cohort study found that consumption both of sugar-sweetened beverages and fructose-rich foods were strongly associated with an increased risk of gout incidence among men.[35] Moreover, several studies report interactions between polymorphisms within SLC2A9 and ABCG2 and the handling of fructose and sugar-sweetened beverage intake, possibly further exacerbating the underexcretion pathway.[36]

Finally, adiposity also may have a strong independent role in the development of both hyperuricemia and gout.[11] In a systematic review and meta-analysis of ten prospective studies, greater body mass index (BMI) increased the risk of gout incidence in a dose-dependent manner using five-unit increment measurement, with a pooled RR of 1.55 (95%CI: 1.44, 1.66).[37]

Similarly, a large 7-year intervention trial found that weight-loss was strongly associated with a decrease in serum uric acid among men with a high cardiovascular risk profile, compared to those with no weight change.[38] Researchers postulate that adiposity likely contributes to gout through both underexcretion and overproduction of uric acid.[11]

1.4 Inflammation, Antioxidants, and Uric Acid

Other factors may contribute negatively to gout incidence, possibility elucidating uric acid lowering or antioxidant properties, or through an attenuation of other risk factors. Some examples include coffee consumption[39,40], supplementation[41] and dietary intake[42] of vitamin C, and the aforementioned dairy products. Little is known about how high levels of uric acid might interact with other antioxidants, especially considering gout-related inflammation.

Uric acid plays a complex role in inflammation and subsequent oxidative stress, acting as a pro-inflammatory, and as both an anti-oxidant and a pro-oxidant.[43] Findings from experimental and observational studies report a positive association between inflammatory biomarkers and uric acid, as well as a mechanistic role for uric acid in the reduction of oxidative stress.[44,45] However, some evidence suggests that C-reactive protein (CRP), a commonly used inflammation biomarker, might not be a sound indication of gout risk.[46] Few have investigated the effects of smoking on gout; however, some suggest that smoking may decrease serum uric acid.[47] Given this evidence, smoking cessation might lead to an increased risk of hyperuricemia and gout.[9]

1.5 Ethno-Racial Disparities of Gout

Racial and ethnic disparities in debilitating, and often preventable, chronic diseases are common, and pose important implications for an individual's risk, care, and prognosis. While historically a disease of affluent Europeans, recent findings from a multitude of large epidemiologic studies have reported marked racial/ethnic disparities in gout and hyperuricemia among groups already at an increased risk of morbidity and lack of access to high quality care. For example older African Americans, already at an increased risk of poor health care access and quality of care, have a significantly increased risk of developing gout compared to Whites.[48,49] In a longitudinal study of African American and European American participants from the Atherosclerosis Risk in Communities Study, researchers found the African American participants had an increased risk of incident gout compared to European American participants among both men (Hazard Ratio [HR] =1.92, 95%CI: 1.44, 2.56) and women (HR=1.69, 95%CI:

1.29, 2.22), after adjusting for uric acid levels, BMI, diet, diabetes, hypertension, and diuretic use.[50]

Aside from White and Black Americans, investigation into the prevalence and disparities among other racial/ethnic groups are scarce, with little to no investigation into the growing Hispanic populations in the United States.[51] However, recent evidence suggests many Asian-Pacific Islander groups may be at an increased risk of hyperuricemia and gout, including Filipinos, Micronesians, Maori, and various other Polynesian groups.[15,52] Polynesians, particularly those of Austronesian decent, are reported as having the highest global prevalence of both acute gout and hyperuricemia.[53] Moreover, while the prevalence is higher among males, prior studies report a higher risk of gout among Polynesian women, compared to their White counterparts.[54] Despite the increased risk of gout within the Pacific region, there are few studies examining the determinants or impacts among these communities; however, some have attributed these disparities to the interaction between genetic predisposition and Westernization of indigenous lifestyle.[9,53,55] Nonetheless, while genome-wide associations studies have demonstrated the influence of risk variants within some Asian-Pacific populations, particularly SLC2A9 and ABCG2 among the New Zealand Maori and Japanese, there does not appear to be differences in gout-related risk allele frequencies compared with Europeans.[15,17,48,56,57]

1.6 Specific Aims and Hypotheses

Given the disease burden, economic impact, and paucity of information, especially among underserved minority populations, further investigation into the ethno-racial disparities of gout incidence is warranted. Moreover, racial/ethnic-stratified examination into these associations may further elucidate differences in the effects of modifiable lifestyle factors on gout incidence. Thus, the proposed study aims to examine the determinants and disparities of gout within an understudied population utilizing data from the Hawai‘i -Los Angeles Multiethnic Cohort (MEC).

For the proposed study, we hypothesize that (i) an individual’s behavioral lifestyle factors (smoking, alcohol use, physical activity, and diet), medical histories (hypertension, other cardiovascular conditions, diuretic use, and body mass index), and demographic characteristics (ethnicity, sex, age, place of birth, marital status, and education) contribute to the risk of gout, and (ii) elevated inflammatory biomarkers and indicators of high purine intake, including CRP, γ-tocopherol, and leptin, are positively associated, whereas, carotenoids (α- and β-carotene), α-

tocopherol, cholesterols, and adiponectin are negatively associated, with gout incidence. The objectives of the proposed study are to characterize the disease burden of gout within understudied populations and determine modifiable lifestyle factors that may differ between populations, especially within an ethnically diverse sample as compared with other well-studied populations, and determine the associations between antioxidants, inflammatory biomarkers, and gout.

To address our objective and hypotheses, we plan to accomplish the following specific aims utilizing data from the Hawai‘i-Los Angeles MEC: 1. Ascertain the incidence of gout and examine the total effects, direct effects, and risk clustering of modifiable lifestyle factors on incident gout among all subjects, Native Hawaiian, Black, White, Japanese, and Latino strata, and males and females within the overall and ethnic strata, and 2. Utilizing a sub-sample of participants with blood serum data, examine the associations between inflammatory biomarkers and antioxidants with gout diagnosis.

Section 2. Methods

2.1 The Multiethnic Cohort Study

This study utilized secondary data collected from the longstanding Multiethnic Cohort Study (MEC) to accomplish the objectives and specific aims. The MEC is a large prospective study that has been following a cohort of 215,251 men and women, who were ages 45 to 75 years old at the time of entry (1993-1997), with approximately 51% from the Los Angeles area and 49% from Hawai‘i. When initiated, the study aimed to explore associations between lifestyle factors, primarily dietary components, and cancer within five major racial/ethnic groups with distinct cultural and dietary behaviors: non-Hispanic White, Japanese American, Native Hawaiian, Black, and Latino. At baseline all participants completed a 26-page self-administered questionnaire containing items pertaining to their demographic characteristics, medical histories, physical activity, dietary behaviors, and current and past medication/supplement use. The full questionnaire was repeated between 2003-2007, and brief follow-up questionnaires were repeated for the years 1999-2002 and 2010-2012.

The primary sampling frame from the original MEC utilized drivers' license files from both Hawai‘i and Los Angeles to obtain a representative sample from all demographic strata, including age and sex. In addition, voters' registration files were used to identify some names that were not included in the Hawai‘i drivers' license files, and Health Care Financing Administration files were used to identify some of the Black population from Los Angeles. In order to prevent oversampling of Whites and focus on the racial/ethnic populations of interest, MEC investigators utilized ethnic-specific surnames to estimate the ethno-racial characteristics of the sampling frame from data sources without this information. Because surnames did not distinguish between those of Black or White descent, census tracts of Los Angeles were used to sample from specific areas with a certain proportion of Black residents; in addition, potential Black participants were contacted in southern and northern California counties. The final classification of race/ethnicity was assigned using the responses to the MEC questionnaire, which corrected for any errors during sampling. The 26-page self-administered questionnaire was mailed out in waves of approximately 100,000 subjects between 1993 to 1996. Up to three attempts were made to mail the questionnaire to each potential subject. The final sample ethnic/racial distribution at baseline were as follows: 26.4% Japanese, 22.9% White, 22.0% Latino, 16.3% Black, 6.5% Native Hawaiian, and 5.8% Other.

2.2 Medicare Linkage and Biospecimen Sub-cohort

The MEC participants who responded to the initial questionnaire were linked to Centers for Medicare & Medicaid Services (CMS) claims data (from 1999-2012) using Social Security numbers, sex, and date of birth. Records from 184,299 of the approximately 215,000 participants (85%) were sent to CMS for linkage; the remaining 15% of participants' records were not sent due to ineligibility for Medicare at the time of linkage, death prior to reaching 65 years of age, or lack of a Social Security number. In total, 170,766 participant records (93% of those sent to CMS) were successfully linked to their Medicare data.

Between 2001 and 2006, a biorepository of blood and urine was created using approximately 70,000 of the original MEC participants from both states. Baseline participants were initially recruited for the biospecimen sub-cohort by mailed letter describing the requested biological requirements. Those who agreed to participate were contacted for a phone interview, which included a short screening questionnaire and updates on certain items from the baseline questionnaire. Blood and urine samples were collected either at a clinical laboratory or in the participants' home. Eighty-three percent of blood samples were collected after fasting, and separated into serum, plasma, buffy coat, and red cells under yellow light. Urine samples were collected in the morning from the Los Angeles participants, and collected overnight from Hawai‘i participants. Blood specimens were stored in multiple 0.5 cc aliquots in vapor phase liquid nitrogen, and urine samples were stored in five 2 mL aliquots per subject in freezers set to -80°C.

2.3 Study Population and Design

To address the specific aims in this thesis, two studies were conducted, each employing participants from different sub-samples from the MEC: Aim 1 utilized MEC baseline questionnaire data linked to Medicare claims data, and Aim 2 compared blood serum data from the MEC biorepository to linked data from the baseline questionnaire; from here on, the studies addressing Aim 1 and Aim 2 are referred to as Study 1 and Study 2, respectively. Participants for Study 1 derived from the 170,766 participants whose records were successfully linked to CMS data; analysis was limited to MEC fee-for-service Medicare enrollees, as the outcome was based on Medicare claims. The presence or absence of gout claims observed from baseline to the time of the most recent CMS linkage (2019) were used to ascertain overall incidence, ethnic and sex differences in incidence, and associated modifiable risk factors, of gout among respondents.

Study 2 derived data from the MEC biorepository, existing data on CRP, tocopherols, provitamin A carotenoids, triglycerides, cholesterols, adiponectin, and leptin from prior blood serum analyses was used to examine the relationships with gout cases. Both studies take advantage of the prospective, longitudinal design of the MEC, and exclude cases of gout established prior to the two baselines (baseline questionnaire for Study 1, and blood draw for Study 2). Based on our exclusion criteria, Figure 1 provides the derivation of the final analytic samples the two studies. Use of these data have been approved (as exempt status) by the University of Hawai‘i Office of Research Compliance Human Studies Program (Protocol ID: 2018-00912).

[Figure 1]

2.4 Ascertainment of Gout Cases

For both Study 1 and Study 2, we focused on incident gout based on Medicare claims. ICD-9 code 274.9 and ICD-10 code M10.9 were used to identify gout diagnosis. Individuals reporting gout in the baseline questionnaire were excluded. To exclude prior cases of gout at baseline, we used both the lack of Medicare claims data, along with the baseline questionnaire, which asks participants “has your doctor ever told you that you had any of the following? (Mark all that apply)”. Under this question, one of the responses is “Gout (high uric acid)”. Participants who marked this response were excluded from the analyses of Study 1. Additionally, Study 2 not only excluded cases prior to the 1993-1997 baseline questionnaire, but also cases of gout prior to blood draw, effectively establishing a second start-point (baseline) specific to the Study 2 subsample. In Study 2, we examined incident gout in order to ascertain the predictive capacity of biomolecules outside of the well-established uric acid.

2.5 Demographics, Behavioral Factors, and other Covariates

Data for the demographic characteristics used in both Study 1 and Study 2 were ascertained from self-reported responses to the 1993-1997 MEC baseline questionnaire. These data include items in which participants report their sex (male or female), marital status (married, separated, divorced, widowed, or never married), birth place of participant- mother, and father (USA, Mexico, Central or South America, Europe, Africa, Cuba or Caribbean Islands, China/Hong Kong/Taiwan, Japan/Okinawa, Korea, Philippines, or Other [write in]), racial/ethnic background (Black, Chinese, Filipino, Hawaiian, Japanese, Korean, Mexican/Other Hispanic, White, or Other), current weight (in kilograms or pounds), height (in centimeter or feet/inches), and years of school completed (did not complete 6^{th} grade, 6^{th} – 8^{th} grade, 9^{th}-10^{th} grade, 11^{th}-12^{th}

grade, vocational school, some college, graduated college, or graduate/professional school). Other demographic information was obtained by self-reported responses to the baseline questionnaire, including date of birth, Native Hawaiian ancestry, and sex. Generation in the US was derived from the self-reported birth places of the participant and the participant's mother and father. First generation participants were individuals born in the US, but one or both parents were born in another country; greater than first generation was defined as both parents and the participant were born in the US; and, immigrants were born outside of the US.

Modifiable lifestyle exposures were determined via self-report from the MEC baseline questionnaire including: smoking status (including number of years smoking, average number of cigarettes per day, and time since cessation), vitamin C supplementation, physical activity (including sleep duration, hours per day spend engaging in specific activities, and hours per day engaged in various activity levels), and an exhaustive food frequency questionnaire, including items pertaining to alcohol use, food group intakes (e.g. specific meats, fruits, vegetables, and starches), and beverage intake (e.g. sugar -sweetened beverage, coffee consumption, and tea consumption). A summary of energy expenditure (metabolic equivalent tasks [MET]) was calculated from responses to items pertaining to physical activity with the formula: ([number of hours sleeping × 0.91] + [number of hours sitting × 1.0] + [number of hours in light activity × 2.4] + [number of hours in moderate activity × 4.0] + [number of hours in vigorous activity])/24. Dietary quality was assessed by calculating the Dietary Approaches to Stop Hypertension (DASH) diet adherence scores, utilizing methods pioneered by Fung et al.[58], from the MEC's food frequency questionnaire. Moreover, medication use and histories of other health conditions are also self-reported via the baseline questionnaire, including items on water pill (diuretic) use and history of hypertension, diabetes, other cardiovascular diseases/events, and kidney stones.

2.6 Blood Serum, Inflammatory Biomarkers, and Antioxidants

Blood serum assays were performed by the Analytical Biochemistry Shared Resource at the University of Hawai'i Cancer Center. Laboratory assay procedures have been described elsewhere.[59,60] In brief, serum concentrations of antioxidants, including carotenoids, tocopherols, coenzyme Q_{10} (CoQ_{10}), and retinol, were ascertained through though high-performance liquid chromatography with photo diode array detection and mass spectra. Assays were validated through inclusion of external standards, and by participation in quality assurance programs of the U.S. National Institute of Standards and Technology.[61] Serum C-reactive protein (CRP) levels

were measured using an autoanalyzer, Cobas MiraPlus (Roche Diagnostics, Switzerland) clinical chemistry analyzer.

2.7 Statistical Analyses

Statistical analyses were conducted at the University of Hawai‘i at Mānoa with the assistance of Lynne Wilkens, DrPH, of the UH Cancer Center, and Yan Yan Wu, PhD, of the Office of Public Health Studies. All analyses were conducted using R v3.6.0 with graphic user interface RStudio version 1.1.463.

Aim 1. Ascertain the incidence of gout and examine the total effects, direct effects, and risk clustering of modifiable lifestyle factors on incident gout among all subjects, Native Hawaiian, Black, White, Japanese, and Latino strata within the overall and ethnic strata.

To ascertain the incidence of gout, we calculated the incidence density rate (IDR) of gout based on Medicare claims and plot the cumulative incidence by age of gout claim, for each strata. The cumulative incidence of gout was defined by the number of new gout cases throughout the approximately 20-year duration of the study (from cohort entry at baseline to the CMS linkage) divided by the number of participants at the beginning of the study period. The IDR was defined as the number of new cases in the study sample over the sum of the person-years per 1,000 of the participants (biostat3::survRate [R package::function]). Using both Chi-square and *t*-tests, where appropriate, descriptive statistics summarized the overall baseline characteristics, and contrasted the ethnic-strata and sex-strata within ethnicity on these characteristics.

The demographic and modifiable determinants of gout diagnosis were analyzed using a racial/ethnic-stratified Cox proportional hazard regression with age, in years, of gout diagnosis as the time metric, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The time metric began at the age of cohort entry (age at 1993-1997 baseline questionnaire), and ends either at the age of gout diagnosis or the end of follow-up (CMS linkage in 2019). In addition to crude models, ethnicity-stratified Cox proportional hazard models were constructed utilizing an evidence-based, theoretical directed acyclic graph (DAG) of known covariates and their relationships in relation to gout (Appendix Part I: Figure S1). For the DAG, we reviewed abstracts and full-text articles that characterized the directional and/or temporal effects of demographic and behavioral factors on gout risk, and among one another. Where no literature existed on the topic, we used professional judgement to hypothesize the direction of the

relationship between the covariates. The DAG was then analyzed using Dagitty v2.3 for causal effect identification, producing minimum sufficient adjustment sets for the total and direct effects of each covariate of interest.[62]

From the DAG analyses, we constructed three models for each modifiable behavior to be applied to each sub-analysis. The first model (Model 1) aimed to examine the total effects of each modifiable risk behavior, generally adjusting for demographic characteristic (sex in the ethnicity-stratified analyses), education level, and marital status); however, the total effects model = of DASH diet additionally adjusted for alcohol use Model 2 aimed to determine the theoretical direct effects given the minimum sufficient adjustment sets as defined by the DAG analysis. Aside from sex, BMI, education level, generation in the United States, marital status, each modifiable behavior had different adjustment sets, summarized in Appendix Part I: Table S3. Finally, the third model (Model 3) adjusted for all demographic and all other primary exposure/modifiable lifestyle factors considered in the DAG, including sex, education level, marital status, generation in the United States, BMI, history of cardiovascular disease, and history of kidney stones.

We examined adherence to the proportional hazards assumption by testing for a non-zero slope in a generalized linear regression of a set of scaled Schoenfeld residuals from each covariate with time (survival::cox.zph). Each corresponding Schoenfeld residual that was significantly ($p < 0.05$) associated with time was plotted for further visual examination. If the covariate was determined to be in severe violation of the proportional hazard assumption, transformations were made, including splitting continuous variables into quintiles, and aggregating variable levels with little theoretical difference on the outcome and few individuals within a level. For categorical confounders, a strata term was added to the regression formula. All final models, summarized in Appendix Part I: Table S4, satisfied the proportional hazards assumption to a reasonable degree of certainty, with few exceptions (discussed below).

Risk profiles of gout were elucidated with an exploratory conditional inference survival tree analysis, a non-parametric recursive partitioning method that integrates tree-structured regression modeling into a conditional inference algorithm.[63] Conditional inference (party::ctree) survival trees have been used to identify important predictive factor clusters for other chronic conditions, including cardiovascular disease and chronic kidney disease incidence.[64,65] In short, the recursive partitioning algorithm classifies participants into subgroups based on similar

reports of an event or outcome variable; the survival tree follows three recurring steps: 1. identify a variable with most statistically significant (lowest *p*-value) ability to differentiate incident gout cases from non-cases among a large set of baseline factors from permutation distributions, 2. perform a dichotomous split of the data by the identified variable into subsample or nodes, and 3. repeat the prior two steps for each subsequent node until the stop criteria is met. For continuous explanatory variables, such as BMI, the algorithm will select one cut-point based on the largest differences between subjects on the outcome. The stop splitting criterion will include a 5% level of significance and a minimum sample size to split a node of 1,000. The terminal node displays a Kaplan-Meier curve representing the hazards within the subgroup identified by the survival tree algorithm.

The purpose of the survival tree analysis was to identify important combinations of? lifestyle factors that may not have been captured by the Cox regression, with a primary focus on dietary behaviors. Thus, in addition to the demographic and behavioral factors included in the Cox proportional hazard models, we selected a total of 449 dietary variables, derived directly or calculated from the MEC questionnaires' food frequency questions, relating to intake of specific food items, food groups, calculated micronutrients, and diet quality score components that were included in the ctree algorithm (Appendix Part I: Table S5). A separate survival tree was produced for the overall sample, each ethnic group, and each sex, identifying important predictors of gout among each group.

Aim 2. Utilizing a sub-sample of participants with blood serum data, examine the associations between inflammatory biomarkers and antioxidants and gout diagnosis

Repeating a similar analysis from Aim 1 utilizing the sub-sample from the biorepository, descriptive statistics will be used to summarize the overall and racial/ethnic-strata participant characteristics, and, using both Chi-square and *t*-tests; the characteristics will be further separated by all participants who were diagnosed with gout versus those who exited the observation period without a gout diagnosis (Table 3). To measure the relationships between gout histories and biomolecules, we used Cox proportional hazard models, with age as the time metric, to estimate HRs and 95% CIs for the overall sample.

In addition to the crude, Study 2 includes two adjustment models: Model 1 adjusted for age, sex, and ethnicity, and Model 2 adjusted for additional demographic and lifestyle factors, along with health condition history, from the original baseline questionnaire. Both models

included tocopherols (α- and γ-tocopherol, measured in mg/L), carotenoids (α- and β-carotene, measured in ng/mL), cholesterols (total, low-density lipoproteins [LDL], and high-density lipoproteins [HDL], measured in mg/dL), triglycerides (measured in mg/dL), adipose protein hormones (adiponectin, measured in μg/mL, and leptin, measured in mg/L), and known inflammatory biomarker CRP (measured continuously in mg/L).

Section 3. Results

3.1 Study 1 – Modifiable Lifestyles and Behaviors

[Table 1]

3.1.1 Baseline Characteristics

Table 1 presents the baseline sample characteristics for the 107,105 MEC participants included in Study 1 by ethnic group, and Table 2 reports the baseline sample characteristics for male and female strata within each ethnic group: Black (N = 15,660), Native Hawaiian (N = 7,600), Japanese (N = 32,923), Latino (N = 21,793), and White (N=29,129). Overall, bivariate tests for associations found that each ethnic subsample differed significantly on all baseline characteristics, including demographics and behavioral factors utilizing Chi-Squared tests for association and the Student's T-test.

[Table 2]

3.1.2 Incidence of Gout by Ethnicity and Sex

Figure 2 presents the cumulative incidence of gout over age at Medicare claim by ethnicity, and by sex and ethnicity in Figure 3. The total sample was followed for an average of 18.12 years (Black = 17.45 years, Hawaiian = 17.78 years, Japanese = 18.23 years, Latino = 18.44 years, and White = 18.21 years). 11,369 participants (10.87%) of the total were diagnosed with gout over the period of observation, as defined by Medicare claim ICD-9-CM 274.9 or ICD-10-CM M10.9. The overall incidence rate of gout was 5.997 (95%CI: 5.889, 6.107) per 1,000 person-years for the total, aggregated sample.

Across ethnic groups, Native Hawaiians had the highest incidence of gout compared to all other ethnic groups, with 17.72% becoming cases throughout the study period, resulting in an incidence rate of 9.971 (95%CI: 9.445, 10.518) per 1,000 person-years. Black and Japanese subsamples had similar IDRs (7.39 (95%CI: 7.071, 7.719) and 6.39 (95% CI: 6.192, 6.598) per 1,000 person-years, respectively) with Black participants having slightly more gout cases (12.89%) compared to Japanese (11.65%). The lowest incidence of gout was observed among White and Latino subsamples, with an IDR of 5.07 (95%CI: 4.885, 5.270) per 1,000 among Whites, and an IDR of 4.34 (95%CI: 4.140, 4.550) per 1,000 among Latino participants.

[Figure 1]

Within each ethnicity and across the ethnicity-aggregated sample, males had a higher incidence of gout (Appendix Part I: Table S2 & Figure S2), with an IDR of 7.41 (95%CI: 7.22,

7.60) per 1,000 person-years, overall. The largest IDR (12.90 [95%CI: 11.94, 13.93] per 1,000 person-years) were observed among Native Hawaiian males (Figure 3). Among the male strata, Japanese had the second highest incidence (9.28 [95%CI: 8.91, 9.67] per 1,000 person-years), followed by Blacks (7.57 [95%CI: 7.01, 8.17] per 1,000 person-years), Whites (6.27 [95%CI: 5.95, 6.60] per 1,000 person-years), and Latinos (4.68 [95%CI: 4.38, 5.01] per 1,000 person-years).

While females generally had a lower incidence of gout compared to males (5.01 [95%CI: 4.88, 5.14] per 1,000 person-years), Native Hawaiian women had a greater IDR (8.18 [95%CI: 7.58, 8.82] per 1,000 person-years) than Black, Latino, and White males (Figure 3, Appendix Part I: Table S2). Black women had the second highest incidence among women (7.30 [95%CI: 6.91, 7.70] per 1,000 person-years), followed by Japanese (4.37 [95%CI: 4.16, 4.60] per 1,000 person-years), Whites (4.15 [95%CI: 3.93, 4.39] per 1,000 person-years), and Latinos (4.06 [95%CI: 3.80, 4.33] per 1,000 person-years).

[Figure 3]

3.1.3 Ethnicity-Stratified Cox Proportional Hazards Models

Table 3 summarizes the crude, total and direct through minimum sufficient adjustment, and over-adjusted Model 3, effects of modifiable behaviors on gout incidence by each ethnic subsample, estimated by multiple Cox proportional hazard regressions. Effects of modifiable behaviors for the ethnicity disaggregated sample are also reported. Given the near ubiquitous lack of appreciable attenuation of the observed effects between Model 2 and Model 3, we discuss the following findings of Model 2 as the direct effects of each behavioral risk factor, along with the total effects observed in Model 1.

[Table 3]

Diet Quality

Higher tertiles of the total DASH scores were significantly associated with a decreased risk of gout incidence across most ethnic subsamples in all models compared to the lowest tertile, apart from Latinos (tertile 2 HR: 0.91, 95%CI: 0.80, 1.04; tertile 3 HR: 0.90, 95%CI: 0.78, 1.03). The direct effect of DASH score was largest among White and Japanese participants in both tertile 2 (HR: 0.81, 95%CI: 0.75, 0.88 among Japanese, and HR: 0.79, 95%CI: 0.71, 0.87 among Whites) and tertile 3 (HR: 0.77, 95%CI: 0.70, 0.84 among Japanese, and HR: 0.70, 95%CI: 0.63, 0.78 among Whites). Black and Native Hawaiian participants risk of gout was similarly

decreased by tertiles of DASH scores; DASH tertile 2 was associated with a 15% (95%CI: 2-30%) and 16% (95%CI: 2-33%) decreased risk, and DASH tertile 3 was associated with a 22% (95%CI: 8-39%) and 23% (95%CI: 6-45%) decreased risk, among Black and Native Hawaiian groups, respectively.

Alcohol Consumption

Across most ethnic groups, increasing alcohol consumption was associated with an increased risk of incident gout, with the largest effects observed among Japanese and Black participants, with little attenuation between models 1-3. Among Japanese drinkers, the direct effects of one to two alcoholic drinks per day was associated with a 21% (HR: 1.21, 95%CI: 1.09, 1.34) increased risk of gout, and three or more alcoholic drinks per day was associated with a 47% (HR: 1.47, 95% CI: 1.28, 1.69) increased risk, compared to those reporting no alcohol use per day. Similar effects in both higher (HR: 1.55, 95%CI: 1.23,1.94) and lower levels (HR: 1.20, 95%CI: 1.03, 1.40) of alcohol use were observed among Black participants. The direct effect of alcohol use was similar among Native Hawaiian and White subjects, with no significant effect detected in the lower (one to two alcoholic drinks per day) level, but a 34% (95%CI: 9-64%) and 33% (95%CI: 18-51%) increased risk of gout, within the three or more alcoholic drinks groups compared to no alcohol use, for Native Hawaiians and Whites, respectively. Alcohol use was not significantly associated with risk of gout among Latinos for both one to two (HR: 1.09, 95%CI: 0.93, 1.27) and three or more (HR: 1.16, 95%CI: 0.93, 1.45) alcoholic drink levels compared to no alcohol use.

Smoking, Vitamin C Supplementation, and Physical Activity

The observed total and direct effects of smoking, vitamin C supplementation, and physical activity on incident gout risk differed by ethnic subsample compared to DASH and alcohol use. After adjusting for sex, education level, generation in the US, and marital status (total effect, Model 1), current smoking was only significantly associated with an increased risk of gout among Black (HR: 1.33, 95%CI: 1.18, 1.52) and Japanese (HR: 1.27, 95%CI: 1.14, 1.42) subsample, compared to never smokers; these effect attenuated but persisted in statistical significance in the direct effects model 2, with current smoking associated with a 31% (95%CI: 13-52%) and 18% (95%CI: 4-33%) increased risk among Blacks and Japanese, respectively. While the total effects of past smoking was significantly associated with an increased risk of gout among Black (HR: 1.13 [1.01, 1.25]), Japanese (HR: 1.14 [1.06, 1.23]), Latino (HR: 1.12

[1.01, 1.26]), and White (HR: 1.14 [1.04, 1.24]) groups, past smoking was not significant in the direct effects model among any of the ethnic groups.

The total effects of vitamin C supplementation was associated with a significant decreased risk of gout incidence among Native Hawaiians (HR: 0.81, 95%CI: 0.71, 0.92), Japanese (HR: 0.86, 95%CI: 0.80, 0.92), and Latinos (HR: 0.88, 95%CI: 0.79, 0.98). In the direct effects model, vitamin C supplementation was associated with a 15% (95%CI: 0.3-32%) decreased risk of incident gout among Native Hawaiians, and a 10% (95%CI: 2-18%) among Japanese. Among Latinos, vitamin C supplementation was not significantly associated with incident gout in the direct effects model (HR: 0.99, 95%CI: 0.88, 1.11).

Finally, the total effects of physical activity, measured by metabolic equivalent score, was associated with a 42% (95%CI: 19-69%) decreased risk of gout among Latino, and a slight decreased risk among Black participants (HR: 0.82, 95%CI: 0.68, 0.99). Physical activity was only significantly associated with a decreased gout incidence in the direct effects model among Latinos (HR: 0.77, 95%CI: 0.64, 0.93).

Model Diagnostics

The proportional hazards assumption was tested for each model within the ethnic strata; final covariate transformations and assumption results from these tests are available in the Appendix Part II: Page 84-101. In brief, diagnostic tests for models used to assess the direct effects of alcohol use showed that that the results presented for Native Hawaiian, Japanese, Latino, and White subsamples met the cox proportional hazards assumption; the Black subsamples slightly failed on one of the two levels of alcoholic drinks per day, showing a very slight negative slope with time for the one to two drinks per day level among Blacks in the direct effects model (rho = -0.05203, p = 0.0448). Similarly, smoking status met the assumption in all ethnic sub-analyses, apart from the Black regression, in which current smoking residuals were slightly associated with the time metric (rho = -0.05293, p = 0.0411). Nearly all DASH score models failed to meet the proportional hazards assumption, except for Latino subsamples; however, these violations were limited to the third tertile residual comparison, while the second tertile met the assumption in all models.

Overall, visual inspection of corresponding weighted Schoenfeld residual plots (Appendix Part II) further revealed little non-proportionality across levels of the primary covariates. Among models that found a statistically significant violation of the proportional

hazard assumption, residual plots against time qualitatively suggested a negligible association, specifically regarding smoking status and alcohol use. However, Schoenfeld residual plots of the third tertile DASH score suggested a notable deviation from the proportional hazard assumption.

3.1.4 Risk Clusters Identified Through Recursive Partitioning

[Figure 4]

The conditional inference survival tree analysis for the total, ethnic-disaggregated sample is presented in Figure 4, and survival trees for each ethnicity are presented in Figure 5a-e. For each survival tree, the terminal node produced a survival curve (proportion of individuals without a gout claim by time (age in years)) for those within the preceding risk profile above.

In the total sample, the ctree algorithm first split the root node by BMI with the cut-point 25.843 kg/m^2 ($p < 0.001$). On the left-most side (Appendix Part I: Figure S3a) of the total survival tree, less than or equal to BMI 25.843 kg/m^2, subgroups were split by density of potassium intake (cut-point: 1,305.794 mg/kcal/day; $p < 0.001$). For those that consumed less potassium (≤1,305.794 mg/kcal/day), nodes were then split by BMI cut-point 22.545 kg/m^2, with lower BMI further split by calculated density of nitrosamine intake (cut-point: 0.097 mcg/kcal/day; $p < 0.001$), and higher BMI split by alternative Healthy Eating Index-2010 component: Omega-3 Fatty Acid intake (cut-point: 7.422; $p < 0.001$). Among those of who consumed more potassium (> 1,305.794 mg/kcal/day), subgroups were split by >1st generation in the US and immigrants to the US versus 1st generation; >1st generation and immigrants were split by Ethnicity (Black, Latino, and White vs. Native Hawaiian and Japanese; $p < 0.001$), and 1st generation citizens were split by BMI (cut-point: 22.921 kg/m^2; $p < 0.001$).

On the right side of the first split (Appendix Part I: Figure S3b), greater than BMI 25.843 kg/m^2, the subgroup was split by Ethnicity (Black, Japanese, Latino, and White versus Native Hawaiian; $p < 0.001$). Within the Black, Japanese, Latino, and White node 18, Ethnicity was split again ($p < 0.001$) into a node of Black, Japanese, and White, which were subsequently split by sex ($p < 0.001$), and a Latino node, which was split by White Rice intake (cut-point: 285.526 g/day; $p < 0.001$). The Native Hawaiian subgroup (node 17 split) was subsequently split by History of Hypertension ($p < 0.001$); those (Native Hawaiian with BMI > 25.843 kg/m^2) without a History of Hypertension were then split by sex ($p < 0.001$), while those with a History of Hypertension were split by White Rice intake (cut-point: 285.526 g/day; $p < 0.001$). Overall, covariates on the right-most side of the tree corresponded with the most important factors and

levels in risk of incident gout; that is, the survival tree identified Native Hawaiians with a BMI of > 25.843, a history of hypertension, and high consumption of white rice (> 285.526 g/day) had the highest risk of gout, as shown in the terminal node 31.

[Figure 5a-e]

Within the ethnic-specific conditional inference analyses (Figures 5a-e), BMI was identified across all ethnicities, being the first splitting variable among all, except the Japanese, subsamples, indicating its relative importance over other covariates. First-level BMI cut-points differed slightly between most ethnic groups, with the lowest among Whites (BMI = 26.737 kg/m^2; $p < 0.001$); however, after splitting by sex ($p < 0.001$), BMI among Japanese males split at 25.97 kg/m^2 ($p < 0.001$), and females at 23.964 kg/m^2 ($p < 0.001$). Similarly, History of Hypertension was also consistently identified as a subsequent (second tier) splitting variable among nearly all ethnic groups, again apart from Japanese, in which History of Hypertension was not selected in any node. The algorithm also selected white rice consumption among Native Hawaiians, Latinos, and Whites, showing a steeper survival curve within higher levels of consumption.

Despite its suggested importance in the overall sample, Potassium intake (cut-point: 1,608.923 mg/kcal/day; $p < 0.001$) was only identified within the Black subsample. Other unique factors identified within specific ethnic groups included: percent of calories from dairy fats (cut-point: 1.877%; $p = 0.003$) and Poultry/Fish intake (cut-point: 9.128 cups/day; $p = 0.005$) among Blacks (Figure 5a); Spam/Bologna/Pastrami intake (cut-point: 5.14 g/day; $p = 0.006$) and Dietary Fiber intake density (cut-point: 7.49 g/kcal/day; $p < 0.001$) among Native Hawaiians (Figure 5b); Generation in the US (>1^{st} generation and immigrant versus 1^{st} generation Americans; $p < 0.001$), Fruit component of the energy-adjusted Mediterranean Diet score (cut-point: 0, $p = 0.034$), diuretic use (Never versus Past and Current; $p < 0.001$), total DASH score (cut-point: 21; $p < 0.001$), and copper intake density (cut-point: 0.63 mg/kcal/day; $p = 0.004$) among Japanese (Figure 5c). The White subsample ctree (Figure 5e) identified the most unique variables relative to the other ethnicities, including: Omega-3 Fatty Acid component of the adjusted Healthy Eating Index 2010 (cut-point: 5.782; $p < 0.001$), dairy product intake density (cut-point: 161.477 g/kcal/day; $p < 0.001$), salted and dried fish intake (cut-point: 0 g/day; $p < 0.001$), number of alcoholic drinks per day (0 and 1-2 drinks versus three or more drinks; $p = 0.02$), riboflavin

intake density (cut-points: 0.803 and 0.820 mg/kcal/day; $p = 0.012$ and $p = 0.044$, respectively), and meat intake (cut-point: 1.148 oz/day; $p < 0.001$).

3.2 Study 2 – Biomarkers and Antioxidants

[Table 4]

3.2.1 Baseline Characteristics and Biomolecule Summary

A summary of the univariate baseline characteristics of Study 2 participants is available in the Appendix Part I: Table S7. At baseline, the Study 2 subsample was disproportionately Latino (32.68%), Female (54.59%), born in the US (80.27%), married (70.68%), overweight (41.17%), never smokers (47.94%), non-daily drinkers (76.35%), non-vitamin C users (61.33%), and with no history of diuretic use (80.98%); additionally, at baseline, Study 2 participants had a mean METs score of 1.63±0.31 and a mean DASH score of 24.05±4.34. Blood draws took place between 1994 and 2006 (the majority between 2002-2004), with a mean age at blood draw of 67.63±7.72 years.

Baseline sample characteristics by incident gout for the 6,567 MEC participants with blood draw data are shown in Table 4. Table 5 presents the bivariate summary of the serum concentrations (analyzed continuously and categorized into tertiles) of C-reactive protein, cholesterols, triglycerides, tocopherols, carotenes, adiponectin, and leptin at blood draw by gout incidence.

[Table 5]

3.2.2 Cox Proportional Hazards Models

Table 6 presents the crude, sex- & ethnicity-adjusted (Model 1), and baseline characteristic-adjusted (Model 2) hazard ratios for tertiles of biomolecule serum concentrations, as estimated by multiple Cox proportional hazards regressions. Each model met the proportional hazards assumption (Appendix Part II: Page 103-107) after making the appropriate transformations, with the exception of Model 1 α- and γ-tocopherol; all corresponding final formulae are presented in Appendix Part II: Page 103-107.

[Table 6]

Compared to the lowest tertile, the highest tertile of serum CRP (HR: 1.84, 95%CI: 1.51, 2.25), triglycerides (HR: 1.83, 95%CI: 1.50, 2.23), γ-tocopherol (HR: 1.69, 95%CI: 1.35, 2.11), and leptin (HR: 2.73, 95%CI: 2.14, 3.47) was significantly increased among incident gout cases, after adjusting for age of diagnosis, sex, and ethnicity. The middle tertile for triglycerides (HR:

1.34, 95%CI: 1.10, 1.65) and leptin (HR: 1.55, 95%CI: 1.26, 1.91) were also associated with a significantly higher risk of incident gout, compared to the lowest tertile; while tertile 2 CRP (HR: 1.21, 95%CI: 0.98, 1.49) and γ-tocopherol (HR: 1.17, 95%CI: 0.93, 1.47) concentrations followed the same (risk-elevating) directionality as tertile 3 comparisons, these associations were not statistically significant in the adjusted models. None of the risk-increasing associations attenuated to statistical insignificance after additionally adjusting for education level, place of birth, BMI, marital status, smoking status, vitamin C supplementation, physical activity, alcohol consumption, diuretic use, and dietary quality.

Compared to tertile 1, Model 1 adiponectin concentrations were associated with a decreased risk of gout in both tertile 2 (HR: 0.76, 95%CI: 0.63, 0.92) and tertile 3 (HR: 0.67, 95%CI: 0.54, 0.82). Similarly, the highest tertile concentration of both α- and β-carotene were both associated with a decreased risk of gout by 79% (95%CI: 43-127%), and 92% (95%CI: 52-144%), respectively, versus the lowest tertile. Moreover, the middle tertile of both α-carotene (HR: 0.68, 95%CI: 0.55, 0.84) and β-carotene (HR: 0.62, 95%CI: 0.50, 0.76) significantly reduced gout risk in Model 1. HDL-cholesterol was associated with a 61% (95%CI: 30-96%) decreased risk of incident gout for the highest versus the lowest tertile serum concentrations, after adjusting for age, sex, and ethnicity; however, the middle tertile was not. After adjusting for other baseline characteristics (Model 2), the inverse associations attenuated, but remained statistically significant. Finally, despite their crude associations, serum concentrations of total cholesterol (tertile 1 vs. 2 HR: 0.85, 95%CI: 0.70, 1.02; tertile 1 vs. 3 HR: 0.84, 95%CI: 0.69, 1.03) and α-tocopherol (tertile 1 vs. 2 HR: 0.93, 95%CI: 0.75, 1.15; tertile 1 vs 3 HR: 0.84, 95%CI: 0.67, 1.05) were not significantly associated with risk of subsequent gout after the first adjustment set.

Section 4. Discussion

4.1 Key Findings

Our study aimed to establish the crude incidence of gout, the risk effect of modifiable behaviors, and associations between objectively measured biomolecules and subsequent gout within a large, multiethnic longitudinal cohort of older adults. We observed substantial evidence of ethnic disparities with regards to gout incidence, as measured by both overall accumulation and rate of Medicare claims over an approximately 20-year observation period. Overall, Native Hawaiians had the highest rates of gout, with over two times the rate of the lowest incidence ethnic group (Latinos). Focusing on sex differences, Native Hawaiian men had the highest incidence of gout across the total sample; additionally, Native Hawaiian women had a greater incidence than men of nearly all other ethnic groups. The second greatest incidence was observed among the Black subsamples, followed successively by Japanese, White, and Latino. Men consistently maintained a higher gout incidence than women over the study period; Japanese men, whom had the second highest rate overall, had the greatest sex difference within an ethnic group, with new cases of gout more than doubling those of Japanese women. Finally, we observed that Latinos had the lowest incidence of gout relative to the other ethnic groups in our sample.

Examination of modifiable lifestyle behaviors on incident gout using ethnic-specific Cox proportional hazard models provided evidence of both general and differential effects between subsamples, indicating that the effects of some behaviors may be modified by ethnicity, while others may be more universally related to gout risk. These analyses revealed that only high levels of alcohol use significantly elevated risk of incident gout among Native Hawaiians and Whites, possibly indicating that moderate use does not contribute to one's risk of gout within these groups; however, consuming one to two alcoholic drinks per day led to an elevation of gout risk among the Black and Japanese participants. Similarly, current smoking independently contributed to gout risk among Black and Japanese groups in the direct effects models, while no such association was observed among Native Hawaiians and Whites. We also observed a slight protective association between Vitamin C supplementation and incident gout among Native Hawaiians and Japanese, but not within other ethnic groups. Lack of adherence to the DASH diet and consumption of three or more alcoholic drinks per day were the most ubiquitous predictors of gout across most ethnic groups, whereas smoking, physical activity, and vitamin C appeared

to predict incident gout differently according to race/ethnicity. Almost none of the behavioral factors in our model had a direct effect on disease incidence among Latinos, with the notable exception of a strong inverse relationship between MET score and gout. Interestingly, MET score was not associated with gout within any other ethnic group, indicating that its protective effects may be specific to those of Latino decent.

In our exploratory survival tree analysis, we both further confirmed the importance of several behavioral and demographic factors identified through the Cox regressions, as well as specific dietary factors across and within ethnic strata that may not have been encapsulated by the DASH score tertiles. More specifically, we observed gout risk clustering of 1.) demographic characteristics, including: sex, ethnicity, and generation in the United States, 2.) medical conditions, including: body mass index, history of hypertension, and diuretic usage, and 3.) specific dietary components, including: white rice consumption, potassium intake, omega-3 fatty acids, alcohol use, riboflavin intake, and consumption of various meat products.

Lastly, utilizing a subsample of participants with blood serum measurements, we determined the tertile effects of objectively measured biomolecules, including antioxidants, hormones, and C-reactive protein, on incident gout claims. We found that elevated serum concentrations of C-reactive protein, triglycerides, γ-tocopherol, and leptin were significantly associated with an increased risk of subsequent gout, all appearing to follow a 'dose-dependent' pattern. Conversely, HDL-cholesterol, α- and β-carotene, and adiponectin were inversely related to gout risk, even after adjustment for baseline confounders.

4.2 Convergence with Existing Literature

While our study is the first to examine gout incidence among Native Hawaiians, our findings are consistent with the long-standing literature of epidemiological studies on the incidence and prevalence of gout within other indigenous Pacific Islander groups, primarily conducted on New Zealand Māori.[15] A recent systematic review of the distribution of arthritic condition within indigenous populations found consistently an approximately three times higher proportion of gout cases among the Māori, relative to their White counterparts.[66] Nonetheless, information on gout within these communities is scarce; in 1978, Brauer & Prior[67] published the only investigation into the incidence of gout among Pacific Island populations, observing an 11-year cumulative incidence of 10.3% among Māori men and 4.3% among women. Our 20-year cumulative incidence estimates among Native Hawaiians are over twice as high as those

observed in Māori men and women; while this may indicate a greater risk, our estimated cumulative incidence does not account for differences in age distribution. Nonetheless, prevalence estimates show that Native Hawaiians may be disproportionately affected by arthritic conditions compared to Asians and White; our findings suggest that much of this disparity may be attributed to gout.[68]

Prior literature on the disparity between Black and White populations in gout incidence are consistent with our findings. As mentioned, investigation of racial differences within the ARIC Study in 2014[50] found that Black participants had a disproportionately higher gender-specific incidence of gout compared to Whites. Additionally, these researchers found that the cumulative incidence of Black women was higher than White men after individuals reached approximately 75 years of age.[50] While we observed a similar trend comparing gender-specific incidence between Black and White subjects, the cumulative incidence of gout among Black women did not exceed that of White men until much older ages than reported in previous studies (Appendix Part I: Figure S4a).

Another consistent finding with prior literature is the notably low incidence of gout among Latino participants relative to other ethnicities in our sample. While no previous investigators have examined incident gout within Latino-American populations, the known prevalence estimates from Mexico[69], Cuba[70], and Guatemala[71] are very low compared to other regions of the world, suggesting that these groups may not be as affected by the disease.

While recent trends have suggested that gout may be on the rise within Japanese national populations, our findings of relatively high incidence among Japanese participants are generally inconsistent with the markedly low prevalence reported from within Japan.[72] This is especially true when examining sex differences, in which Japanese males from the MEC were among the highest in incident gout claims across all other sex and ethnic strata. This inconsistency with existing literature may largely be attributed to the acculturation of Western lifestyles in Hawai‘i[55], possibly indicating a predisposition to gout when deviating from traditional Japanese lifestyles. In addition, some of this inconsistency may be due to the fundamentally different ethnic background of Japanese in Hawai‘i, where we derived the majority of our Japanese subjects, compared to Japanese from Japan; that is, a large proportion of the Hawai‘i-born ‘Japanese American’ population are Okinawan.[73] While the exact proportion of Okinawan to mainland Japanese is unknown within both Hawai‘i and our sample, Okinawans are not only

culturally, but genetically distinct, showing notable signs of long-term island-based isolation, compared to mainland Japanese individuals.[74,75] Our findings may suggest that Okinawans in Hawai‘i have a much higher rate of gout than mainland Japanese, possibility mirroring the high rates observed in geographically and genetically similar Taiwan aboriginals (i.e. Ryukyuan descendants).[75,76]

Across ethnic groups, behavioral risk factor analyses though Cox regression models revealed similar relationships from prior literature utilizing other, less diverse, populations. While slight modification of the effects by ethnic group was observed, the overall direction of the point estimates did not differ from our evidence-based expectations, outlined in our hypotheses; specifically, our results further confirmed the previous findings of gout risk, or uric acid, elevation from alcohol use and smoking[77], and protective effects from vitamin C supplementation[41,78], physical activity[79], and DASH diet.[80,81] However, there is a notable lack of consensus with regards to smoking status and gout. In a recent meta-analysis utilizing five studies examining the effects of smoking status on gout risk, researchers found conflicting effects from several large studies, suggested that smoking may not be directly involved in the risk of gout, but rather attributable to confounding.[82] One possible explanation for our results may be that the risk-elevating associations are specific to Black and Japanese/Okinawan groups, neither of which were included in the aforementioned meta-analysis; however, further research is needed to confirm or reject this proposition. In addition, findings from our survival tree analysis identified similar demographic and lifestyle factors described in prior literature and within our Cox regression models, including BMI, hypertension, sex, and ethnicity, while many of the specific dietary factors were novel, including white rice, potassium, nitrosamines, and copper intake. These findings warrant further investigation to ascertain their direct effects on gout and elucidate any plausible mechanisms that might explain or disprove their importance.

Finally, the results from Study 2 were largely consistent with prior biomolecular associations with gout and hyperuricemia. For example, a recent study found higher levels of leptin, the biomolecule with the strongest effect in our study, among patients with acute gout, which in turn promoted MSU-induced inflammation.[83] Similarly, CRP, a commonly used inflammatory biomarker, has been previously shown to have a direct association with hyperuricemia;[84] to our knowledge, our study is the first to show this relationship in the disease state. Elevations in γ-tocopherol are also thought to be related to a possible response to chronic

inflammation, as demonstrated in both in vivo and in vitro studies of cancer[85-87], cardiovascular disease[88], and other age-related morbidities[89-92]. While not previously investigated with regards to acute gout, inverse association between serum uric acid levels and β-carotene[93], adiponectin[94], and HDL-cholesterol[95] have been observed in prior literature.

4.3 Implications in Public Health

Our studies provide substantial implications for the field of public health by providing crucial information on ethnic disparities, behavioral risk factors, and possible biomarker efficacy in gout. First, benefitting from Hawai'i's large population of Native Hawaiians and Japanese Americans, along with the diverse populations of Latinos and Blacks from the Los Angeles area, our findings provide crucial evidence that may inform precision in both the screening and intervention of gout. Considering the substantial differences in incidence by ethnicity, healthcare professionals and public health programs may utilize our findings to help identifying those at high risk of gout. While sex differences were observed, as expected, the decreasing magnitude of this difference in the crude incidence among many ethnic strata may help to dispel the myth that gout is a male-specific condition, especially when approaching older adulthood. The finding that Native Hawaiian women have higher incidence rates compared to males of other ethnic groups is crucial in this regard, showing that ethnic disparities in gout may outweigh the well-known sex differences.

This study contributes ethnic-specific total and direct effect estimates to highlight areas where individuals within these groups can best benefit from lifestyle modification to mitigate the risk of gout. For example, our findings further support that adherence to the DASH diet, regardless of ethnic background, may not only decrease risk of hypertension, but also may independently reduce gout incidence. Conversely, protective direct effects from physical activity was only observed among Latinos, suggesting that physical activity may not be as important in reducing gout among other groups. Thus, observing these differences can help target direct or underlying behaviors where more general inventions fail. Moreover, addressing the disparities of gout among underserved populations can help decrease other subsequent co-morbidities associated with gout within populations that already have an increased risk. As a disease strongly linked to other co-occurring chronic conditions, preventing gout among older populations that are financially disadvantaged may help alleviate future health expenditures in older age.

Lastly, establishing biomolecule associations can provide evidence for objectively measuring early indication of gout risk, without reliance on self-reported risk factors. While uric acid measurements are standard in confirmatory screening and diagnosis, understanding the relationships between biomolecules tested in other health-related situations, such as leptin, CRP, and γ-tocopherol may provide health providers with early warning signs of gout. Detecting and treating disordered levels of these biomolecules in patients with elevated risk profiles may help prevent the onset of acute gout.

4.4 Strengths and Limitations

There are many strengths to our two studies. First, to our knowledge, this is the first study to investigate gout with regards to the incidence, risk factors, and predictive potential of biomolecules utilizing large samples of Native Hawaiians, Japanese Americans, Latinos, Blacks, and Whites. Through ethnically stratified analyses of the over 100,000 MEC participant, we provide important insights into understudied, and often underserved, ethnic minority groups and their risk of gout. Secondly, compared to the few prior longitudinal studies on gout, this study benefits from a relatively long follow-up period and a small number of lost individuals to follow-up as a result of linkage with the Medicare claims database; that is, Medicare linkage eliminated the need to physically recontact participants after baseline in order to ascertain the outcome. Thirdly, we are the first to provide evidence on gout risk factors derived from both traditional time-to-event model-based methods, as well as an innovative, data-driven machine learning algorithm. A major advantage of survival tree analysis is the ease of interpretation by practitioners that may not be accustomed to complex statistical modeling. Furthermore, it has been reported that the conditional inference framework provides a more parsimonious clustering of participants into subgroups based on time-to-event risk than Cox models. Finally, biomarkers are objective measures of health, and drawing connections between specific health conditions may glean important implications for, not only mechanistic functions, but screening capabilities of these molecules. As mentioned, the objectivity of these measures provides an advantage over self-reported measures by avoiding information bias and providing possible insights into metabolic/immunologic pathways of gout.

Despite the many advantages in our approach, these studies are not without limitations. First, all baseline items are derived from self-reported responses to questionnaires, which may have led to misclassification, particularly with regards to adverse behaviors, such as smoking and

alcohol use due to social desirability bias. This would likely have resulted in a nondifferential underreporting across the samples, biasing towards the null; that is, there is no substantial reason to suspect that individuals that developed gout would differentially misreport behaviors at a higher or lower rate than those who did not. Second, while using Medicare claims data likely lessened the expected loss to follow-up, it was not possible to ascertain the number of participants lost due to the lack of re-contacting. As a result, participants belonging to groups that frequently migrate out of the US healthcare system may have been disproportionality lost over the observation period, namely Latinos. Moreover, access to care may be different depending on socio-economic status and other environmental factors, which may have contributed to delays in time-to-event analyses. However, given the age of our sample, Medicare coverage is likely available to all participants. Another issue with regards to the use of Medicare claims data is that a Medicare claim of gout is not the same as a definitive diagnosis of gout; while this may have affected our ability to accurately define the temporal relationship between exposure and outcome, the long follow-up period likely mitigated the effects of this limitation. Thirdly, some of our Cox models failed the proportional hazards assumption, potentially biasing our results towards the alternative hypothesis; namely, DASH adherence scores failed in nearly all models. In order to account for this limitation, we conducted the survival tree analysis to examine specific dietary components associated with incident gout. Another factor that may have led to misclassification of the outcome is misdiagnosis among females; clinical gout has been shown to mimic the symptoms of rheumatoid arthritis, which is more common in women than men, which may have resulted in a misclassification of the outcome.[96,97] Lastly, examining gout in adults aged 50-100 years of age limits the generalizability of our findings to older adults, missing cases that occur earlier in life.

4.5 Conclusion and Future Directions

Overall, we found significant ethnic differences in both the incidence and effects of modifiable risk factors in gout. In addition, we found several biomolecular associations consistent with prior literature, which may serve as biomarkers of gout. To address some of the limitations in methodology and scope, there are several ways future investigations can expand on this work. First, researchers could examine the modifying effects of sex within ethnic strata to possibly uncover differential effects of behavioral risk factors. Second, gout is a self-limited disease, and identifying predictors of recurring gouty attacks may further elucidate the long-term

effects of poorly treated gout. Thus, while our study focuses only on gout claims, future studies should investigate the time-varying nature of gout and determine which groups are at risk for readmission. Finally, updating the direct and indirect costs of gout within underserved groups, such as Native Hawaiians, may provide crucial funding information to areas with limited financial resources.

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Figures

Figure 1. Flowchart of the Final Analytic Samples Derivation

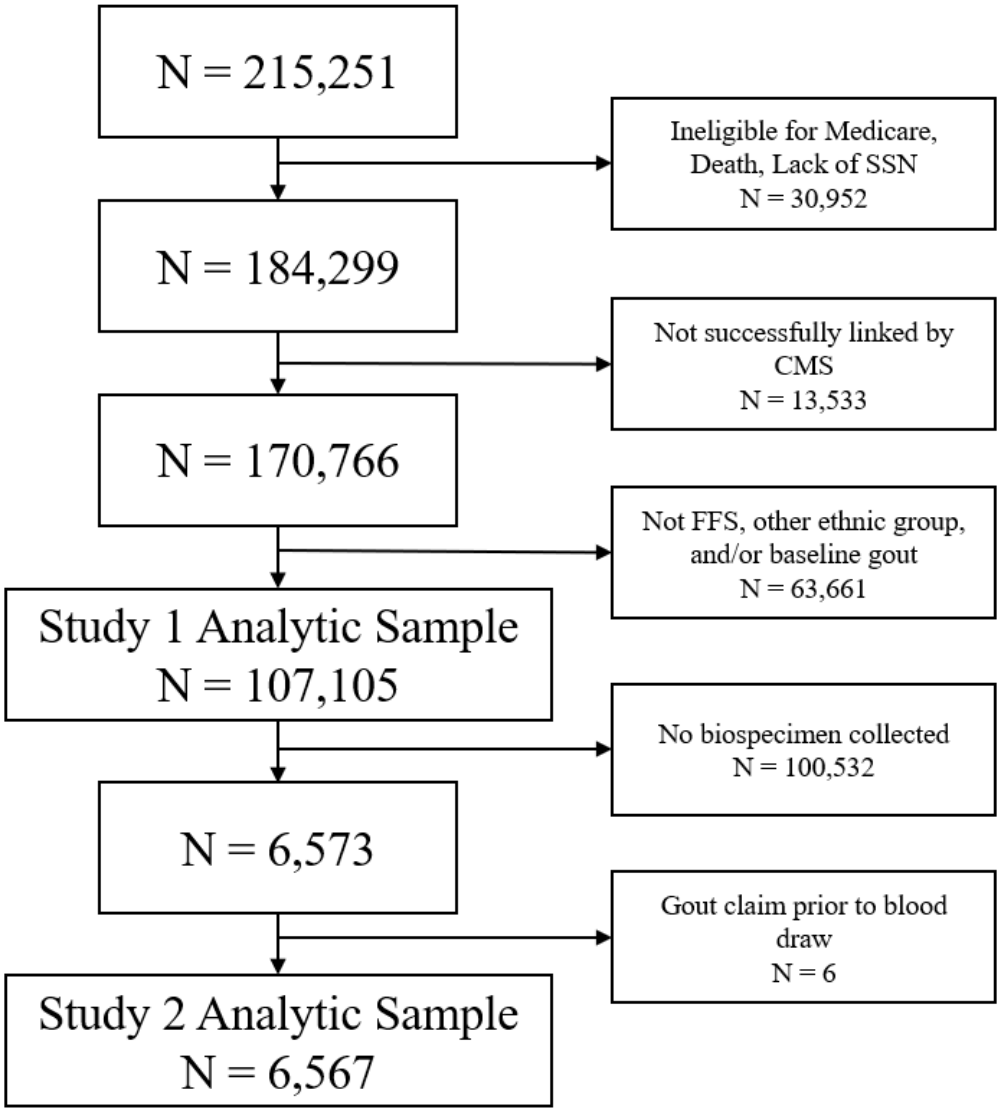


Figure 2. Cumulative Incidence of Gout by Ethnicity

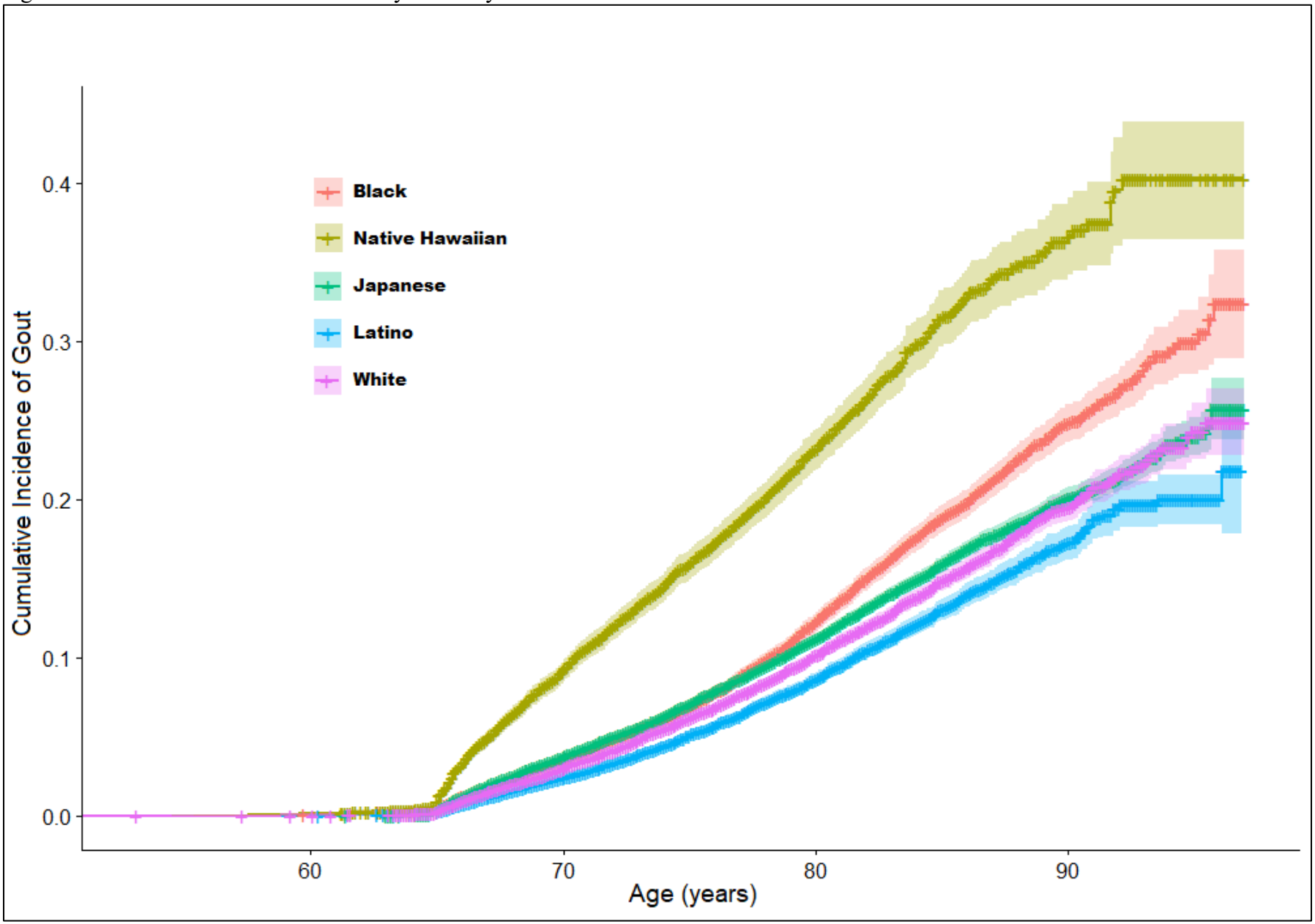


Figure 3. Cumulative Incidence of Gout by Sex and Ethnicity

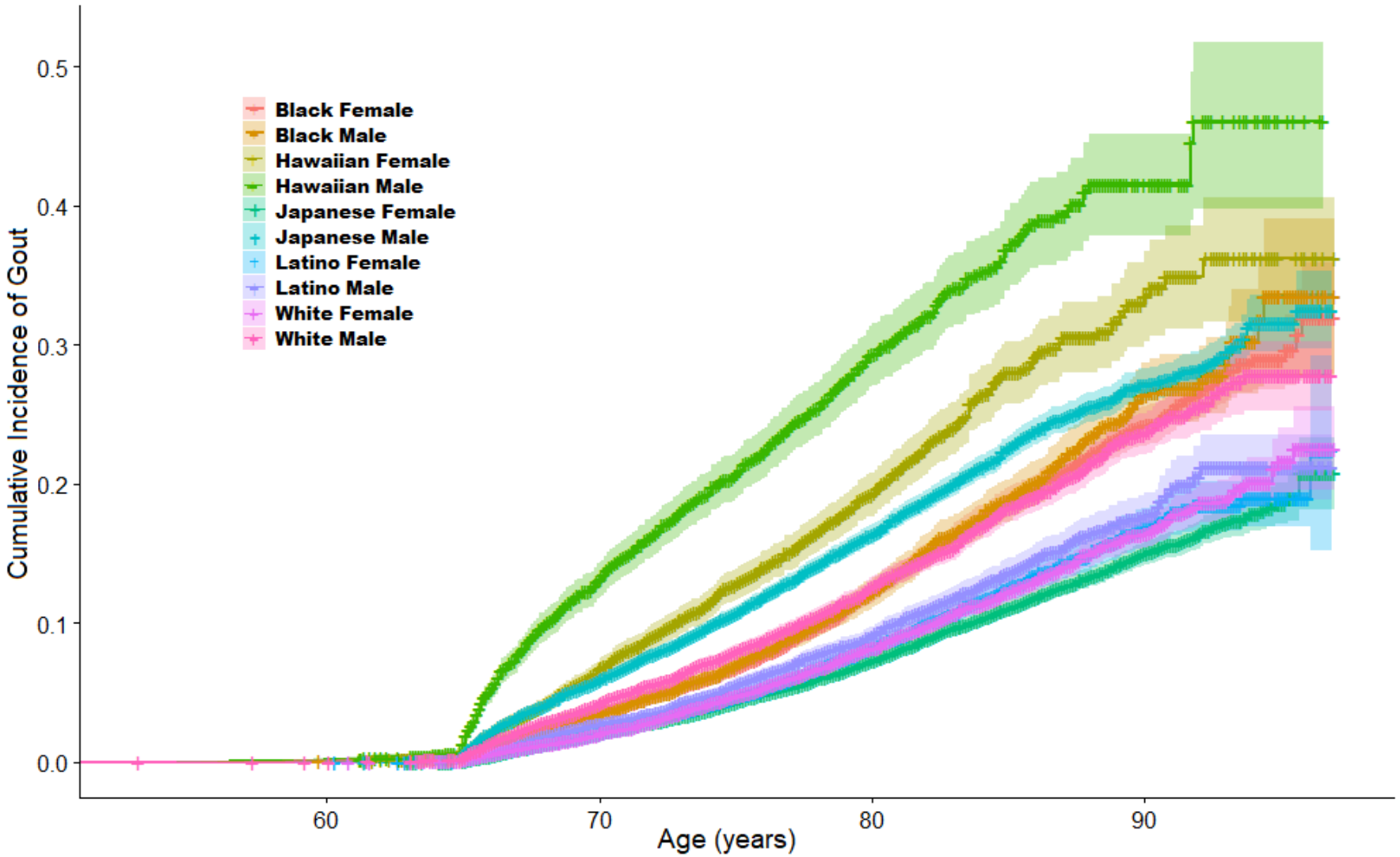


Figure 4. Risk Clusters of Gout Incidence for the Total Sample Controlling for Age at Diagnosis

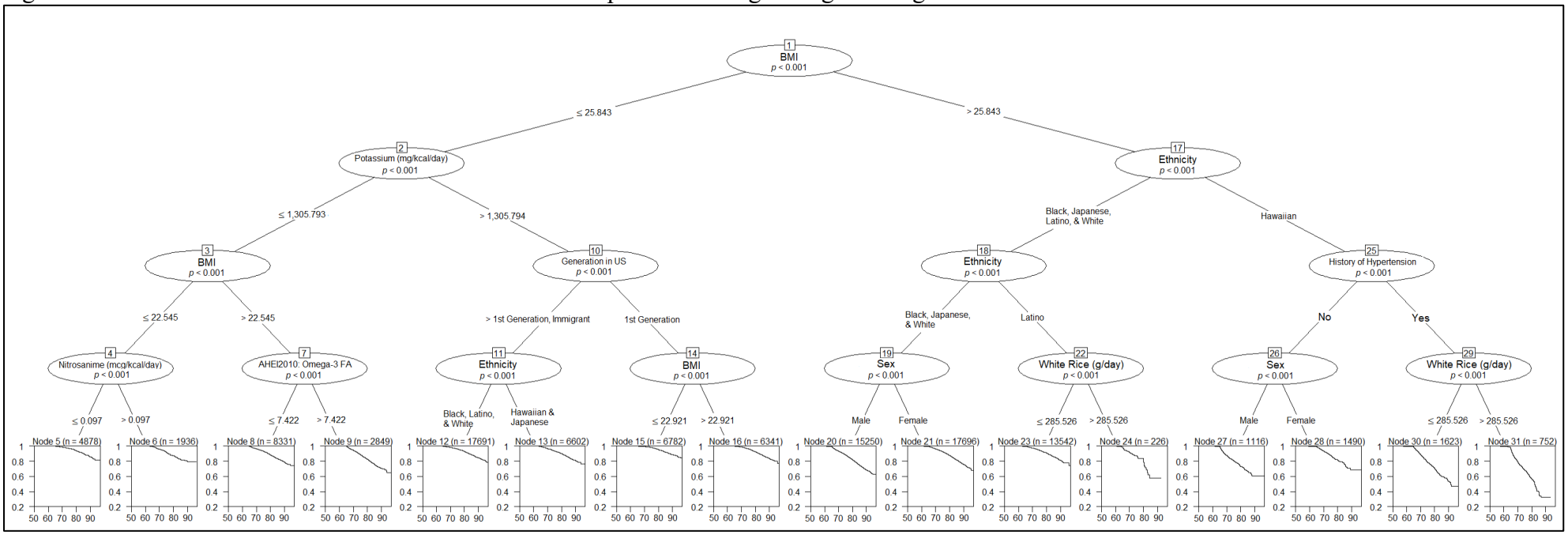


Figure 5a. Risk Clusters among Black participants for Incident Gout

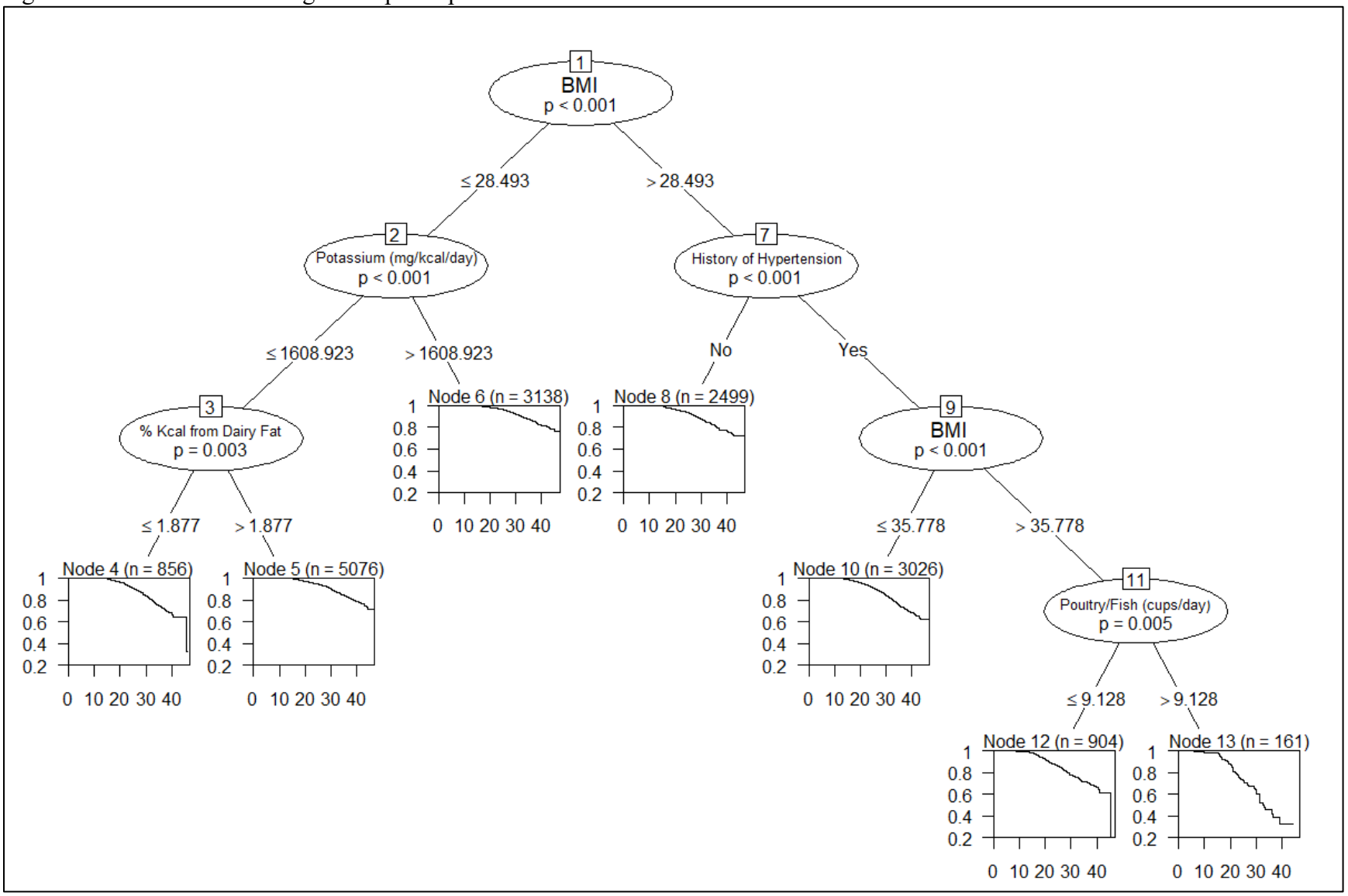


Figure 5b. Risk Clusters for the Native Hawaiian Subsample

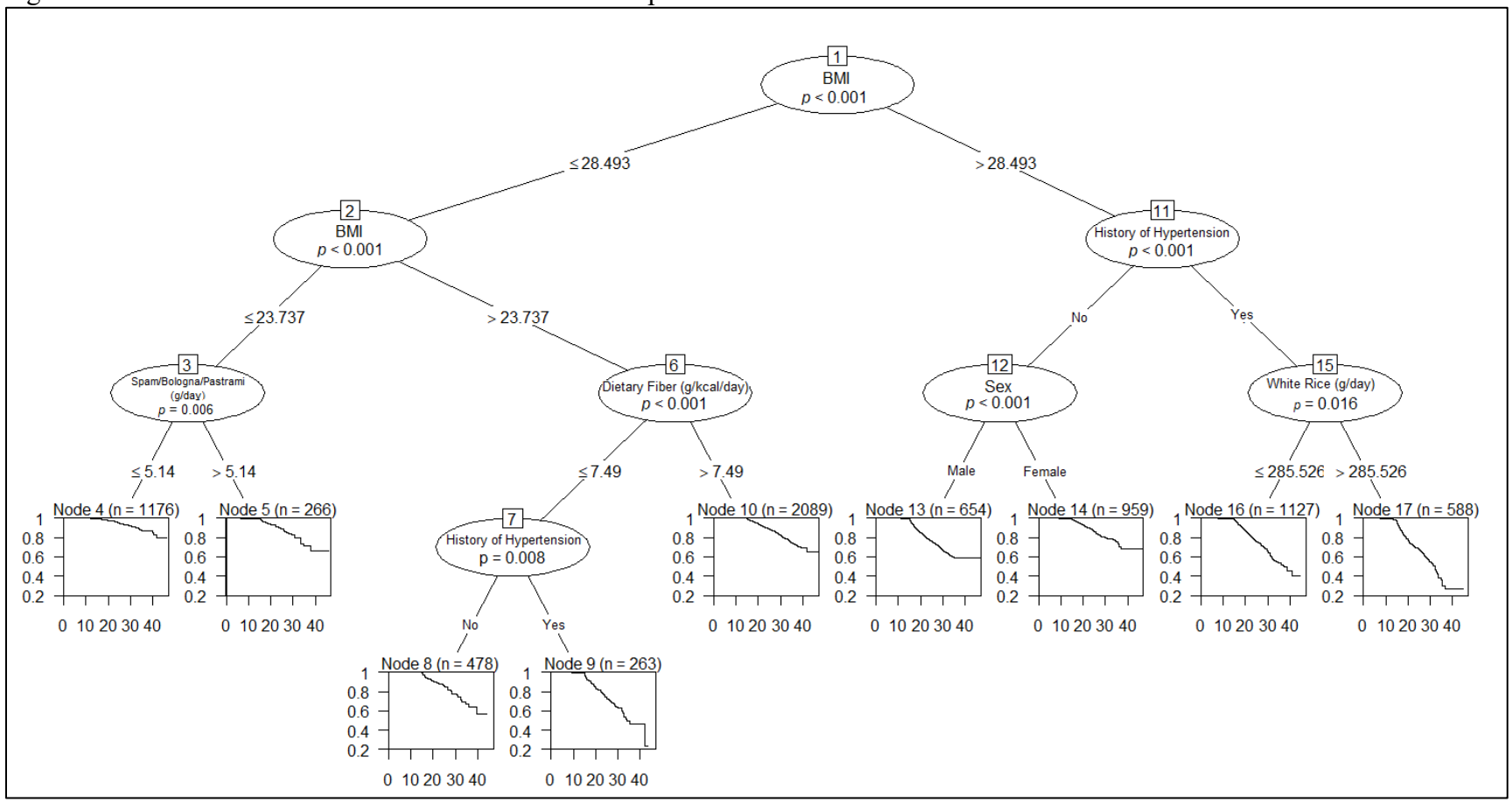


Figure 5c. Risk Clusters for the Japanese Subsample

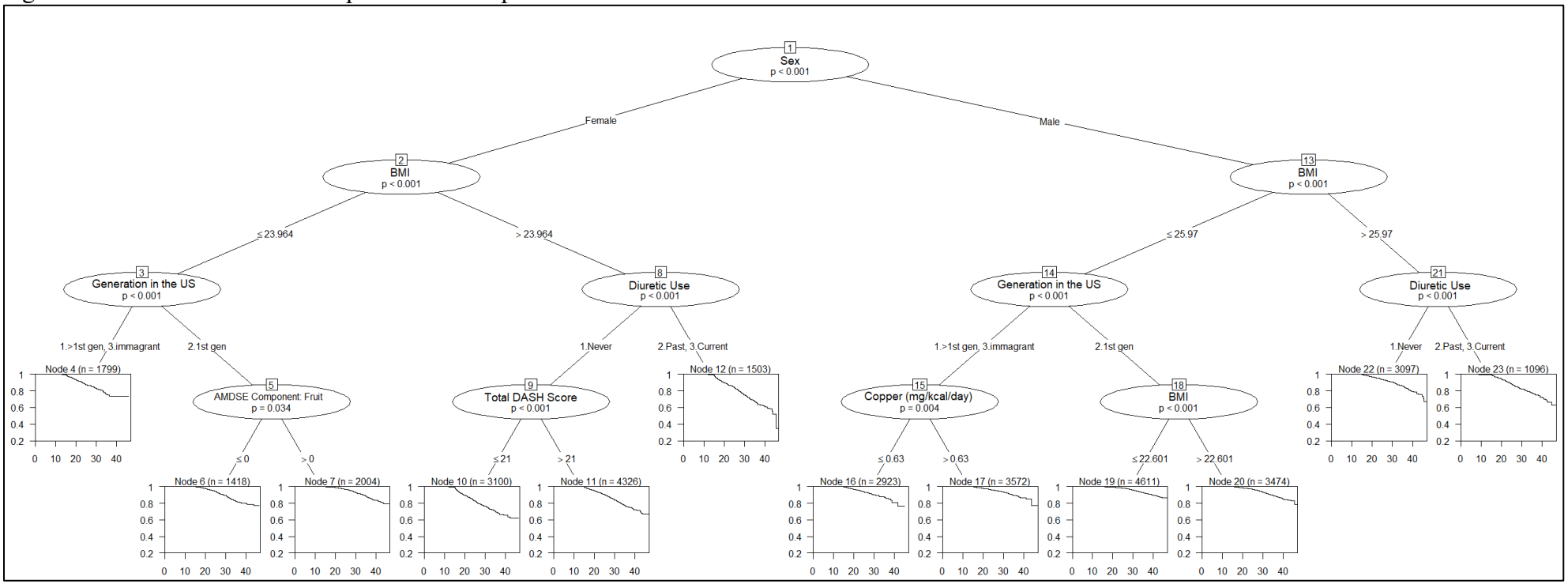


Figure 5d. Risk Clusters for the Latino Subsample

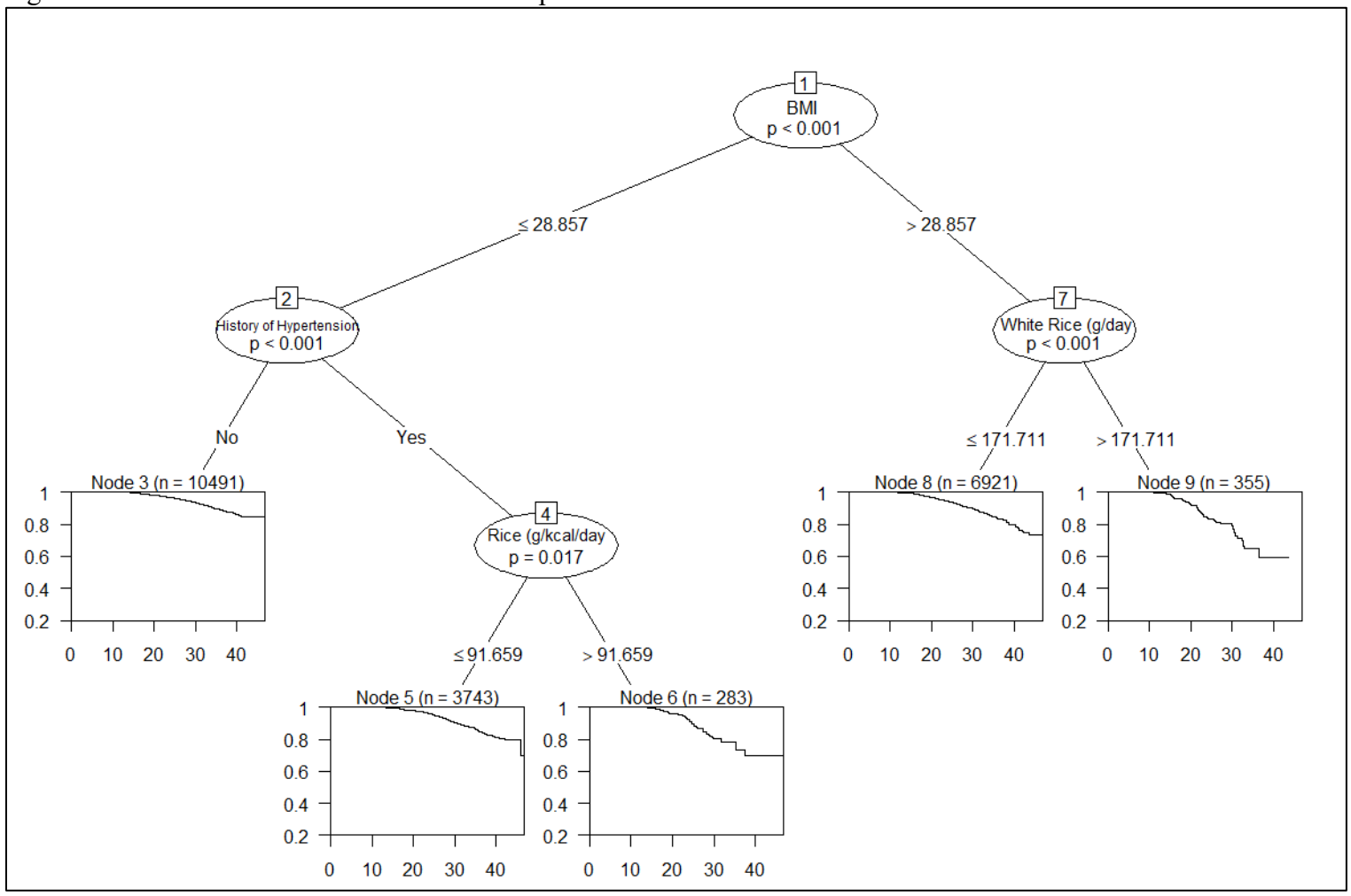
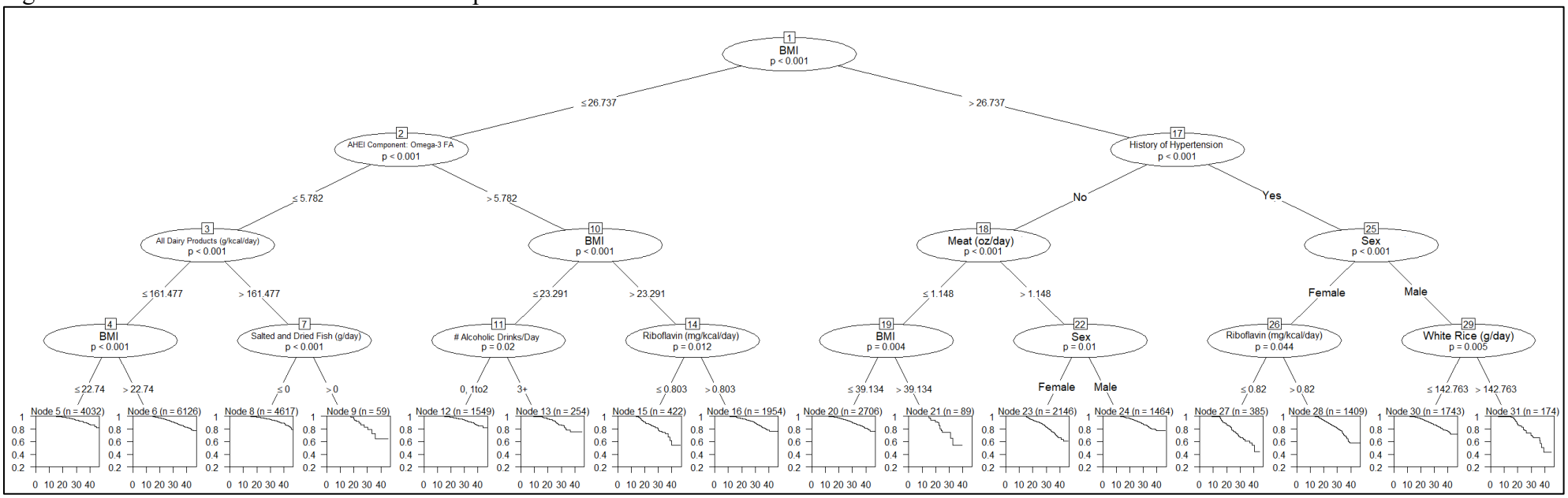


Figure 5e. Risk Clusters for the White Subsample



Tables

Table 1. Baseline Characteristics of the Multiethnic Cohort by Ethnicity, 1993-1997 (N=107,105)

	Levels/Statistic	Black	Hawaiian	Japanese	Latino	White	*p*-value
Sex	Male	5,290 (33.78%)	2,969(39.07%)	14,150(42.98%)	10,082(46.26%)	12,929(44.39%)	<.0001
	Female	10,370 (66.22%)	4,631(60.93%)	18,773(57.02%)	11,711(53.74%)	16,200(55.61%)	
Baseline Age	mean(SD)	60.50 (8.93)	56.35(8.04)	60.15(8.75)	58.77(7.31)	58.54(8.74)	<.0001
Education	High School or Less	6,340 (41.15%)	3,931(52.22%)	11,752(35.97%)	14,663(68.65%)	7,097(24.55%)	<.0001
	Vocational/Some college	5,479 (35.56%)	2,243(29.80%)	9,781(29.94%)	4,372(20.47%)	9,113(31.53%)	
	Grad College/Grad School	3,588 (23.29%)	1,354(17.99%)	11,135(34.09%)	2,324(10.88%)	12,693(43.92%)	
Generation US	>1st gen	14,509 (94.82%)	6,597(87.66%)	11,414(34.80%)	3,112(14.35%)	20,912(72.50%)	<.0001
	1st gen	262 (1.71%)	902(11.99%)	18,468(56.31%)	6,642(30.62%)	4,760(16.50%)	
	immigrant	530 (3.46%)	27(0.36%)	2,917(8.89%)	11,939(55.04%)	3,173(11.00%)	
Marital Status	Married	6,598 (42.86%)	5,224(69.10%)	25,543(77.89%)	14,028(65.11%)	19,537(67.53%)	<.0001
	Separated/Divorced	4,942 (32.10%)	1,164(15.40%)	2,568(7.83%)	4,021(18.66%)	5,234(18.09%)	
	Widowed	2,788 (18.11%)	767(10.15%)	2,511(7.66%)	1,979(9.18%)	2,257(7.80%)	
	Never	1,067 (6.93%)	405(5.36%)	2,173(6.63%)	1,518(7.05%)	1,901(6.57%)	
Body Mass Index	<25 kg/m^2	3,958 (26.34%)	2,093(27.93%)	20,119(61.47%)	6,150(28.48%)	13,751(47.43%)	<.0001
	25-30 kg/m^2	6,219 (41.39%)	2,872(38.33%)	10,426(31.86%)	10,088(46.71%)	10,520(36.28%)	
	>30 kg/m^2	4,849 (32.27%)	2,528(33.74%)	2,183(6.67%)	5,358(24.81%)	4,723(16.29%)	
Smoking Status	Never	6,018 (39.06%)	2,993(39.81%)	17,208(52.73%)	10,403(49.54%)	11,535(39.93%)	<.0001
	Past	5,988 (38.87%)	2,823(37.54%)	11,760(36.04%)	7,639(36.38%)	12,792(44.28%)	
	Current	3,400 (22.07%)	1,703(22.65%)	3,664(11.23%)	2,958(14.09%)	4,562(15.79%)	
Vitamin C Supplementation	No	8,543 (58.83%)	5,040(69.19%)	18,778(58.61%)	12,934(64.42%)	15,761(55.83%)	<.0001
	Yes	5,978 (41.17%)	2,244(30.81%)	13,260(41.39%)	7,143(35.58%)	12,469(44.17%)	
METs	mean(SD)	1.59 (0.29)	1.65(0.35)	1.61(0.27)	1.68(0.32)	1.63(0.30)	<.0001
# of Alcoholic Drinks/Day	None	12,208 (81.82%)	5,573(76.46%)	26,308(82.82%)	16,515(78.94%)	17,195(61.35%)	<.0001
	1 to 2	1,986 (13.31%)	1,151(15.79%)	3,909(12.31%)	3,184(15.22%)	7,626(27.21%)	
	3 or more	726 (4.87%)	565(7.75%)	1,550(4.88%)	1,223(5.85%)	3,206(11.44%)	
Diuretic Use	Never	8,534 (58.47%)	5,750(79.05%)	26,831(84.30%)	15,996(80.41%)	23,737(84.22%)	<.0001
	Past	2,271 (15.56%)	596(8.19%)	1,880(5.91%)	1,666(8.37%)	1,919(6.81%)	
	Current	3,791 (25.97%)	928(12.76%)	3,118(9.80%)	2,231(11.22%)	2,530(8.98%)	
DASH Score	mean(SD)	23.66 (4.33)	22.97(4.61)	23.29(4.48)	24.34(4.12)	25.40(4.25)	<.0001
DASH quintiles	Q1 [8,20]	3,723 (24.95%)	2,250(30.87%)	8,897(28.01%)	3,920(18.74%)	3,728(13.30%)	<.0001
	Q2 (20,23]	3,615 (24.23%)	1,623(22.27%)	7,661(24.12%)	4,869(23.27%)	5,312(18.95%)	
	Q3 (23,25]	2,438 (16.34%)	1,124(15.42%)	5,064(15.94%)	3,760(17.97%)	4,830(17.23%)	
	Q4 (25,28]	3,103 (20.80%)	1,457(19.99%)	5,994(18.87%)	5,033(24.06%)	7,371(26.30%)	
	Q5 (28,40]	2,041 (13.68%)	835(11.46%)	4,151(13.07%)	3,340(15.96%)	6,786(24.21%)	
History of Hypertension	No	7,380 (47.13%)	4,470(58.82%)	20,737(62.99%)	14,677(67.35%)	21,472(73.71%)	<.0001
	Yes	8,280 (52.87%)	3,130(41.18%)	12,185(37.01%)	7,115(32.65%)	7,657(26.29%)	
History of Heart Attack	No	13,878 (88.62%)	7,075(93.09%)	31,196(94.76%)	19,982(91.69%)	27,270(93.62%)	<.0001
	Yes	1,782 (11.38%)	525(6.91%)	1,726(5.24%)	1,810(8.31%)	1,859(6.38%)	
History of Stroke	No	15,072 (96.25%)	7,435(97.83%)	32,282(98.06%)	21,399(98.20%)	28,648(98.35%)	<.0001
	Yes	588 (3.75%)	165(2.17%)	640(1.94%)	393(1.80%)	481(1.65%)	
History of Diabetes	No	13,437 (85.80%)	6,643(87.41%)	29,839(90.64%)	18,667(85.66%)	27,802(95.44%)	<.0001
	Yes	2,223 (14.20%)	957(12.59%)	3,083(9.36%)	3,125(14.34%)	1,327(4.56%)	
History of Kidney Stones	No	15,259 (97.44%)	7,148(94.05%)	31,085(94.42%)	20,770(95.31%)	27,070(92.93%)	<.0001
	Yes	401 (2.56%)	452(5.95%)	1,837(5.58%)	1,022(4.69%)	2,059(7.07%)	

Table 2. Baseline Characteristics by Sex and Ethnicity

		Black		Hawaiian		Japanese		Latino		White	
		Female	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*
Baseline Age	*mean(SD)*	60.37(8.97)	60.76(8.85)	56.35(8.07)	56.36(8.01)	60.16(8.65)	60.14(8.89)	58.53(7.32)	59.04(7.30)	58.60(8.76)	58.46(8.72)
Education	*High School or Less*	41.90%	39.69%	54.91%	48.03%	38.17%	33.07%	72.46%	64.22%	27.92%	20.34%
	Vocational/Some college	35.44%	35.80%	28.53%	31.76%	29.67%	30.30%	18.76%	22.46%	33.51%	29.06%
	Grad College/Grad School	22.66%	24.52%	16.56%	20.21%	32.16%	36.64%	8.78%	13.32%	38.57%	50.60%
Generation US	*>1st gen*	95.00%	94.48%	87.52%	87.86%	34.05%	35.79%	14.76%	13.86%	71.72%	73.47%
	1st gen	1.64%	1.85%	12.08%	11.83%	54.21%	59.08%	30.46%	30.80%	16.56%	16.43%
	immigrant	3.36%	3.67%	0.39%	0.31%	11.73%	5.12%	54.78%	55.34%	11.71%	10.11%
Marital Status	*Married*	33.61%	60.92%	64.33%	76.54%	73.61%	83.55%	52.98%	79.17%	62.02%	74.44%
	Separated/Divorced	35.53%	25.40%	16.48%	13.71%	8.77%	6.58%	23.33%	13.25%	20.81%	14.69%
	Widowed	24.18%	6.25%	14.46%	3.42%	11.39%	2.72%	14.47%	3.06%	11.75%	2.86%
	Never	6.68%	7.43%	4.73%	6.33%	6.23%	7.15%	9.22%	4.52%	5.42%	8.01%
Body Mass Index	*<25 kg/m²*	24.32%	30.24%	31.82%	21.95%	69.83%	50.48%	31.58%	24.90%	54.79%	38.25%
	25-30 kg/m²	38.10%	47.75%	33.85%	45.22%	23.89%	42.34%	40.03%	54.44%	28.18%	46.38%
	>30 kg/m²	37.58%	22.00%	34.33%	32.83%	6.29%	7.17%	28.40%	20.67%	17.03%	15.37%
Smoking Status	*Never*	45.80%	25.91%	44.58%	32.39%	68.92%	31.39%	64.36%	32.71%	45.70%	32.72%
	Past	34.61%	47.19%	32.44%	45.47%	22.27%	54.20%	25.09%	49.18%	38.66%	51.31%
	Current	19.60%	26.90%	22.98%	22.14%	8.81%	14.41%	10.54%	18.11%	15.65%	15.97%
Vitamin C Supplementation	*No*	57.02%	62.33%	67.16%	72.32%	56.34%	61.60%	61.53%	67.70%	53.68%	58.50%
	Yes	42.98%	37.67%	32.84%	27.68%	43.66%	38.40%	38.47%	32.30%	46.32%	41.50%
METs	*mean(SD)*	1.57(0.27)	1.63(0.32)	1.61(0.32)	1.72(0.38)	1.58(0.24)	1.64(0.29)	1.63(0.28)	1.73(0.36)	1.60(0.27)	1.66(0.33)
# of Alcoholic Drinks/Day	*None*	88.13%	69.53%	86.09%	61.48%	94.42%	67.43%	91.25%	64.68%	69.91%	50.62%
	1 to 2	9.43%	20.87%	11.02%	23.20%	4.92%	22.09%	7.33%	24.36%	23.80%	31.48%
	3 or more	2.43%	9.60%	2.89%	15.32%	0.66%	10.48%	1.43%	10.97%	6.29%	17.90%
Diuretic Use	*Never*	53.72%	67.72%	76.46%	83.06%	83.62%	85.18%	76.45%	84.89%	80.71%	88.60%
	Past	17.45%	11.88%	9.41%	6.31%	6.05%	5.72%	9.98%	6.56%	8.48%	4.72%
	Current	28.83%	20.40%	14.13%	10.63%	10.33%	9.10%	13.56%	8.56%	10.82%	6.68%
DASH Score	*mean(SD)*	23.59(4.34)	23.79(4.30)	23.03(4.60)	22.89(4.63)	23.46(4.40)	23.07(4.57)	24.30(4.17)	24.39(4.05)	25.36(4.23)	25.45(4.28)
DASH quintiles	*Q1 [8,20]*	25.88%	23.14%	30.21%	31.90%	25.84%	30.88%	19.51%	17.84%	13.07%	13.60%
	Q2 (20,23]	23.38%	25.89%	22.11%	22.50%	24.69%	23.36%	22.46%	24.21%	19.65%	18.08%
	Q3 (23,25]	16.28%	16.46%	15.49%	15.32%	16.78%	14.83%	18.02%	17.92%	17.31%	17.13%
	Q4 (25,28]	21.29%	19.84%	20.54%	19.14%	19.37%	18.21%	23.85%	24.29%	26.33%	26.27%
	Q5 (28,40]	13.17%	14.66%	11.65%	11.15%	13.32%	12.73%	16.16%	15.74%	23.64%	24.92%
History of Hypertension	*No*	46.08%	49.19%	58.97%	58.57%	65.10%	60.18%	65.67%	69.30%	74.36%	72.90%
	Yes	53.92%	50.81%	41.03%	41.43%	34.90%	39.82%	34.33%	30.70%	25.64%	27.10%
History of Heart Attack	*No*	88.40%	89.05%	94.08%	91.55%	97.02%	91.76%	92.10%	91.22%	95.40%	91.38%
	Yes	11.60%	10.95%	5.92%	8.45%	2.98%	8.24%	7.90%	8.78%	4.60%	8.62%
History of Stroke	*No*	96.14%	96.45%	97.69%	98.05%	98.58%	97.36%	98.38%	97.99%	98.47%	98.20%
	Yes	3.86%	3.55%	2.31%	1.95%	1.42%	2.64%	1.62%	2.01%	1.53%	1.80%
History of Diabetes	*No*	85.95%	85.52%	87.86%	86.70%	91.59%	89.36%	85.87%	85.42%	95.71%	95.11%
	Yes	14.05%	14.48%	12.14%	13.30%	8.41%	10.64%	14.13%	14.58%	4.29%	4.89%
History of Kidney Stones	*No*	97.97%	96.41%	95.14%	92.35%	97.07%	90.90%	96.61%	93.80%	95.97%	89.13%
	Yes	2.03%	3.59%	4.86%	7.65%	2.93%	9.10%	3.39%	6.20%	4.03%	10.87%

Table 3. Ethnic-Stratified Hazard Ratios and 95% Confidence Intervals for Modifiable Lifestyle Factors

		Black (N=15,660)	Hawaiian (N=7,600)	Japanese (N=32,923)	Latino (N=21,793)	White (N=29,129)	Total (N=107,105)
Past Smoking (ref. Never)	***Crude***	1.13 (1.02, 1.24) *	1.07 (0.95, 1.21)	1.57 (1.47, 1.68) ***	1.14 (1.03, 1.27) **	1.21 (1.12, 1.32) ***	1.29 (1.24, 1.34) ***
	Model 1	1.13 (1.02, 1.25) *	1.00 (0.88, 1.13)	1.15 (1.07, 1.24) ***	1.12 (1.01, 1.26) *	1.14 (1.05, 1.24) **	1.14 (1.09, 1.19) ***
	Model 2[‡]	1.06 (0.94, 1.19)	0.93 (0.82, 1.06)	1.03 (0.94, 1.11)	1.04 (0.92, 1.18)	1.07 (0.98, 1.18)	1.05 (1.01, 1.10) *
	Model 3	1.04 (0.92, 1.17)	0.91 (0.79, 1.04)	1.00 (0.92, 1.09)	1.02 (0.90, 1.16)	1.08 (0.98, 1.19)	1.04 (1.00, 1.09)
Current Smoking (ref. Never)	***Crude***	1.33 (1.17, 1.51) ***	1.13 (0.97, 1.31)	1.67 (1.50, 1.86) ***	1.12 (0.96, 1.31)	1.13 (1.00, 1.28)	1.38 (1.30, 1.46) ***
	Model 1	1.33 (1.18, 1.52) ***	1.10 (0.94, 1.28)	1.26 (1.13, 1.41) ***	1.09 (0.93, 1.28)	1.11 (0.97, 1.26)	1.22 (1.15, 1.29) ***
	Model 2[‡]	1.28 (1.10, 1.49) **	1.15 (0.97, 1.36)	1.17 (1.03, 1.32) *	1.03 (0.86, 1.24)	1.09 (0.95, 1.26)	1.18 (1.11, 1.26) ***
	Model 3	1.30 (1.11, 1.51) **	1.14 (0.96, 1.35)	1.16 (1.02, 1.31) *	0.98 (0.81, 1.19)	1.09 (0.95, 1.26)	1.17 (1.10, 1.25) ***
Vitamin C Use (ref. No Use)	***Crude***	1.00 (0.91, 1.10)	0.78 (0.69, 0.89) ***	0.82 (0.77, 0.88) ***	0.89 (0.81, 0.99) *	0.92 (0.85, 0.99) *	0.86 (0.83, 0.90) ***
	Model 1	1.00 (0.91, 1.10)	0.81 (0.71, 0.92) **	0.86 (0.81, 0.92) ***	0.88 (0.79, 0.98) *	0.93 (0.86, 1.01)	0.89 (0.86, 0.93) ***
	Model 2[‡]	1.02 (0.92, 1.14)	0.85 (0.75, 0.98) *	0.91 (0.85, 0.98) *	0.99 (0.88, 1.11)	1.09 (0.94, 1.26)	0.97 (0.93, 1.01)
	Model 3	1.03 (0.92, 1.16)	0.85 (0.74, 0.98) *	0.91 (0.85, 0.98) *	0.95 (0.84, 1.08)	1.08 (0.93, 1.26)	0.96 (0.92, 1.00)
MET Score	***Crude***	0.81 (0.68, 0.97) *	0.98 (0.82, 1.16)	0.96 (0.84, 1.09)	0.69 (0.58, 0.82) ***	0.92 (0.80, 1.06)	0.87 (0.81, 0.94) ***
	Model 1	0.82 (0.68, 0.99) *	0.87 (0.73, 1.03)	0.91 (0.80, 1.03)	0.70 (0.58, 0.84) ***	0.83 (0.74, 0.99) *	0.83 (0.78, 0.89) ***
	Model 2[‡]	1.05 (0.86, 1.28)	1.04 (0.87, 1.24)	0.97 (0.84, 1.11)	0.77 (0.64, 0.93) **	1.10 (0.95, 1.27)	1.00 (0.93, 1.08)
	Model 3	1.04 (0.84, 1.28)	1.05 (0.87, 1.26)	0.97 (0.85, 1.12)	0.78 (0.64, 0.94) *	1.09 (0.94, 1.26)	1.00 (0.93, 1.08)
1 to 2 Alcoholic Drinks per Day (ref. None)	***Crude***	1.15 (1.01, 1.32) *	1.10 (0.95, 1.28)	1.61 (1.48, 1.76) ***	1.07 (0.94, 1.23)	1.03 (0.94, 1.13)	1.16 (1.11, 1.22) ***
	Model 1	1.15 (1.00, 1.32) *	0.96 (0.82, 1.12)	1.18 (1.08, 1.30) ***	1.04 (0.90, 1.20)	0.97 (0.89, 1.07)	1.07 (1.01, 1.12) *
	Model 2[‡]	1.20 (1.03, 1.40) *	1.07 (0.90, 1.26)	1.21 (1.09, 1.34) ***	1.09 (0.93, 1.27)	1.04 (0.94, 1.15)	1.12 (1.06, 1.19) ***
	Model 3	1.20 (1.03, 1.41) *	1.07 (0.90, 1.27)	1.22 (1.10, 1.35) ***	1.06 (0.90, 1.24)	1.03 (0.94, 1.15)	1.12 (1.06, 1.19) ***
3+ Alcoholic Drinks per Day (ref. None)	***Crude***	1.45 (1.19, 1.77) ***	1.58 (1.32, 1.89) ***	2.27 (2.01, 2.56) ***	1.21 (0.99, 1.48)	1.52 (1.37, 1.70) ***	1.61 (1.51, 1.72) ***
	Model 1	1.44 (1.18, 1.77) ***	1.22 (1.01, 1.48) *	1.52 (1.34, 1.73) ***	1.18 (0.95, 1.45)	1.34 (1.20, 1.50) ***	1.38 (1.29, 1.48) ***
	Model 2[‡]	1.55 (1.23, 1.94) ***	1.34 (1.09, 1.64) **	1.47 (1.28, 1.69) ***	1.16 (0.93, 1.45)	1.33 (1.18, 1.51) ***	1.39 (1.29, 1.49) ***
	Model 3	1.46 (1.14, 1.85) **	1.42 (1.15, 1.75) ***	1.54 (1.34, 1.77) ***	1.20 (0.95, 1.52)	1.35 (1.19, 1.53) ***	1.42 (1.32, 1.52) ***
DASH Tertile 2 [22-26] (ref. Tertile 1)	***Crude***	0.82 (0.73, 0.91) ***	0.81 (0.72, 0.92) **	0.73 (0.68, 0.79) ***	0.89 (0.79, 1.00)	0.77 (0.69, 0.85) ***	0.77 (0.73, 0.80) ***
	Model 1[†]	0.83 (0.74, 0.92) ***	0.84 (0.74, 0.96) **	0.81 (0.75, 0.87) ***	0.90 (0.79, 1.01)	0.76 (0.69, 0.84) ***	0.80 (0.76, 0.84) ***
	Model 2[‡]	0.85 (0.75, 0.97) *	0.86 (0.75, 0.98) *	0.83 (0.76, 0.90) ***	0.91 (0.80, 1.04)	0.77 (0.69, 0.85) ***	0.82 (0.78, 0.86) ***
	Model 3	0.84 (0.74, 0.95) **	0.87 (0.75, 1.00) *	0.84 (0.77, 0.91) ***	0.90 (0.78, 1.03)	0.77 (0.69, 0.85) ***	0.83 (0.79, 0.87) ***
DASH Tertile 3 [26-40] (ref. Tertile 1)	***Crude***	0.75 (0.67, 0.83) ***	0.70 (0.61, 0.80) ***	0.65 (0.60, 0.70) ***	0.89 (0.79, 1.00) *	0.64 (0.58, 0.71) ***	0.68 (0.65, 0.71) ***
	Model 1[†]	0.74 (0.66, 0.83) ***	0.72 (0.62, 0.83) ***	0.73 (0.67, 0.79) ***	0.89 (0.79, 1.01)	0.65 (0.58, 0.71) ***	0.71 (0.67, 0.74) ***
	Model 2[‡]	0.81 (0.70, 0.93) **	0.80 (0.69, 0.93) **	0.77 (0.70, 0.85) ***	0.90 (0.78, 1.03)	0.70 (0.63, 0.78) ***	0.76 (0.72, 0.80) ***
	Model 3	0.80 (0.69, 0.91) **	0.80 (0.68, 0.93) **	0.78 (0.71, 0.86) ***	0.90 (0.78, 1.03)	0.69 (0.62, 0.77) ***	0.76 (0.72, 0.81) ***

Model 1 (Total Effects Model) is adjusted for sex, education level, generation in the United States, and marital status. [†]In addition, Model 1 is adjusted for number of alcoholic drinks per day for the total effects of DASH tertiles.
[‡]Model 2 is adjusted for the minimum sufficient adjustment set for the direct effect of each covariate as determined by directed acyclic graphs; in Model 2 the effects of:
Smoking Status is adjusted for sex (male/female), BMI (continuous), education level, generation in the United States, marital status, history of cardiovascular disease (hypertension, heart attack, angina, and stroke (yes/no)), history of kidney stones (yes/no), total DASH score (continuous), number of alcoholic drinks per day, and physical activity (METs Score, continuous).
Vitamin C Use is adjusted for sex (male/female), BMI (continuous), education level, generation in the United States, total DASH score (continuous), number of alcoholic drinks per day, and smoking status.
MET Score is adjusted for sex (male/female), BMI (continuous), education level, generation in the United States, marital status, history of cardiovascular disease, history of kidney stones, total DASH score, number of alcoholic drinks per day, and smoking status.
Alcoholic Drinks is adjusted for sex (male/female), BMI (continuous), education level, generation in the United States, marital status, history of cardiovascular disease, history of kidney stones, total DASH score, physical activity, and smoking status.
DASH Score is adjusted for sex (male/female), BMI (continuous), education level, generation in the United States, marital status, history of cardiovascular disease, history of kidney stones, number of alcoholic drinks per day, physical activity, and smoking status.
Model 3 is adjusted for all covariates.
Acronyms: BMI = Body Mass Index, MET = Metabolic Equivalent, DASH = Dietary Approaches to Stop Hypertension
MET = [(# Hours Sleeping × 0.91) + (# Hours Sitting × 1.0) + (# Hours in Light Activities × 2.4) + (# Hours in Moderate Activity × 4.0) + (# Hours in Vigorous Activity × 7.2)] / 24
***p<0.05, **p<0.01, ***p<0.001**

Table 4. Study 2 Subsample Baseline Characteristics by Gout Cumulative Incidence (N=6,567)

		Gout	No Gout	*p*-value
Ethnicity	*Black*	125 (11.43%)	969 (88.57%)	<.0001
	Hawaiian	171 (13.98%)	1,052 (86.02%)	
	Japanese	151 (9.10%)	1,508 (90.90%)	
	Latino	135 (6.29%)	2,011 (93.71%)	
	White	37 (8.31%)	408 (91.69%)	
Sex	*Female*	344 (11.54%)	2,638 (88.46%)	<.0001
	Male	275 (7.67%)	3,310 (92.33%)	
Age at Blood Draw	*Mean ± SD*	68.71 ± 7.37	67.52 ± 7.74	0.0003
	Median (Q1, Q3)	68.18 (62.80, 74.21)	66.76 (61.64, 73.31)	
Education Level at Baseline	*High School or Less*	227 (9.07%)	2,275 (90.93%)	0.2953
	Some College/Vocational	188 (9.10%)	1,877 (90.90%)	
	Grad College/Professional	201 (10.32%)	1,746 (89.68%)	
Place of Birth	*US born*	538 (10.23%)	4,720 (89.77%)	<.0001
	Foreign Born	79 (6.11%)	1,213 (93.89%)	
Marital Status	*Married*	441 (9.58%)	4,164 (90.42%)	0.5013
	Not Married	172 (9.01%)	1,738 (90.99%)	
Body Mass Index	*< 25 kg/m^2*	169 (6.48%)	2,440 (93.52%)	<.0001
	25 – 30 kg/m^2	281 (10.43%)	2,412 (89.57%)	
	> 30 kg/m^2	167 (13.48%)	1,072 (86.52%)	
Smoking Status	*Never*	262 (8.45%)	2,839 (91.55%)	0.0158
	Past	264 (10.28%)	2,304 (89.72%)	
	Current	89 (11.14%)	710 (88.86%)	
Vitamin C Supplementation	*No*	383 (9.93%)	3,475 (90.07%)	0.2879
	Yes	221 (9.08%)	2,212 (90.92%)	
Physical Activity (MET)	*Mean ± SD*	1.62 ± 0.29	1.63 ± 0.31	0.2745
	Median (Q1, Q3)	1.61 (1.43,1.79)	1.62 (1.42,1.79)	
Number of Drinks per Day	*None*	418 (8.55%)	4,472 (91.45%)	0.0001
	1 to 2	131 (11.93%)	967 (88.07%)	
	3 or More	53 (12.71%)	364 (87.29%)	
Diuretic Use	*Never*	424 (8.34%)	4,659 (91.66%)	<.0001
	Past	63 (12.45%)	443 (87.55%)	
	Current	107 (15.55%)	581 (84.45%)	
DASH Score	*Mean (SD)*	23.80 (4.34)	24.07 (4.34)	0.1437
	Median (Q1, Q3)	24 (21, 27)	24 (21, 27)	

Table 5. Biomarker Summary by Gout Cumulative Incidence

		Gout	No Gout	*p*-value[†]
C-Reactive Protein mg/L	*Mean ± SD*	3.53 ± 4.38	3.01 ± 3.89	0.002
	Tertile 1	199 (8.26%)	2,209 (91.74%)	
	Tertile 2	175 (8.86%)	1,800 (91.14%)	
	Tertile 3	245 (11.25%)	1,932 (88.75%)	
Total Cholesterol mg/dL	*Mean ± SD*	189.27 ± 40.20	195.12 ± 39.73	0.005
	Tertile 1	248 (11.35%)	1,937 (88.65%)	
	Tertile 2	192 (8.79%)	1,993 (91.21%)	
	Tertile 3	177 (8.10%)	2,007 (91.90%)	
HDL-Cholesterol mg/dL	*Mean ± SD*	43.41 ± 14.80	46.31 ± 16.07	<.0001
	Tertile 1	261 (11.19%)	2,071 (88.81%)	
	Tertile 2	198 (9.60%)	1,864 (90.40%)	
	Tertile 3	158 (7.34%)	1,994 (92.66%)	
LDL-Cholesterol mg/dL	*Mean ± SD*	120.23 ± 37.65	124.59 ± 37.00	0.0057
	Tertile 1	231 (10.64%)	1,940 (89.36%)	
	Tertile 2	207 (9.57%)	1,957 (90.43%)	
	Tertile 3	173 (7.98%)	1,994 (92.02%)	
Triglycerides mg/dL	*Mean ± SD*	131.27 ± 81.33	123.45 ± 81.56	0.0232
	Tertile 1	185 (8.33%)	2,036 (91.67%)	
	Tertile 2	198 (9.12%)	1,973 (90.88%)	
	Tertile 3	235 (10.85%)	1,931 (89.15%)	
α-Tocopherol mg/L	*Mean ± SD*	9.54 ± 4.73	9.97 ± 5.09	0.074
	Tertile 1	182 (11.60%)	1,387 (88.40%)	
	Tertile 2	169 (10.78%)	1,399 (89.22%)	
	Tertile 3	149 (9.50%)	1,420 (90.50%)	
γ-Tocopherol mg/L	*Mean ± SD*	2.02 ± 1.11	1.88 ± 1.53	0.0649
	Tertile 1	140 (8.93%)	1,428 (91.07%)	
	Tertile 2	161 (10.27%)	1,407 (89.73%)	
	Tertile 3	199 (12.69%)	1,369 (87.31%)	
α-Carotene ng/mL	*Mean ± SD*	72.47 ± 71.30	85.66 ± 93.67	0.0023
	Tertile 1	213 (13.58%)	1,356 (86.42%)	
	Tertile 2	159 (10.14%)	1,409 (89.86%)	
	Tertile 3	128 (8.16%)	1,441 (91.84%)	
β-Carotene ng/mL	*Mean ± SD*	277.32 ± 254.66	355.52 ± 402.96	<.0001
	Tertile 1	216 (13.77%)	1,353 (86.23%)	
	Tertile 2	153 (9.76%)	1,415 (90.24%)	
	Tertile 3	131 (8.35%)	1,438 (91.65%)	
Adiponectin µg/mL	*Mean ± SD*	7.66 ± 5.39	8.46 ± 5.77	0.001
	Tertile 1	247 (11.34%)	1,932 (88.66%)	
	Tertile 2	194 (8.91%)	1,984 (91.09%)	
	Tertile 3	177 (8.13%)	2,001 (91.87%)	
Leptin mg/L	*Mean ± SD*	23.18 ± 24.15	19.08 ± 19.52	<.0001
	Tertile 1	183 (8.36%)	2,005 (91.64%)	
	Tertile 2	204 (9.33%)	1,983 (90.67%)	
	Tertile 3	232 (10.61%)	1,955 (89.39%)	

[†]*p*-values based on bivariate Student T-Test for mean differences

Acronyms: SD = standard deviation, LDL = low-density lipoprotein, HDL = high-density lipoprotein

Table 6.

		Tertiles of Serum Biomolecule Concentrations		
Biomolecule		**1**	**2**	**3**
C-reactive Protein mg/L	*Range*	[0, 1.0]	(1.0, 2.8]	(2.8, 21.0]
	Crude, HR (95% CI)	ref	1.02 (0.83, 1.24)	1.42 (1.18, 1.71) ***
	Model 1, HR (95% CI)	ref	1.21 (0.98, 1.49)	1.84 (1.51, 2.25) ***
	Model 2, HR (95% CI)	ref	1.14 (0.91, 1.42)	1.48 (1.18, 1.87) ***
Total Cholesterol mg/dL	*Range*	[42.3, 176]	(176, 210]	(210, 405]
	Crude, HR (95% CI)	ref	0.82 (0.68, 0.99) *	0.78 (0.65, 0.95) *
	Model 1, HR (95% CI)	ref	0.85 (0.70, 1.02)	0.84 (0.69, 1.03)
	Model 2, HR (95% CI)	ref	0.88 (0.71, 1.08)	1.00 (0.80, 1.24)
LDL-Cholesterol mg/dL	*Range*	[10.2, 108]	(108, 138]	(138, 364]
	Crude, HR (95% CI)	ref	0.97 (0.80, 1.17)	0.84 (0.69, 1.03)
	Model 1, HR (95% CI)	ref	0.93 (0.77, 1.13)	0.80 (0.65, 0.98) *
	Model 2, HR (95% CI)	ref	1.00 (0.81, 1.23)	0.91 (0.72, 1.13)
HDL-Cholesterol mg/dL	*Range*	[4.0, 38]	(38, 50]	(50, 205]
	Crude, HR (95% CI)	ref	0.83 (0.69, 1.00) *	0.57 (0.47, 0.70) ***
	Model 1, HR (95% CI)	ref	0.86 (0.71, 1.04)	0.62 (0.51, 0.77) ***
	Model 2, HR (95% CI)	ref	0.97 (0.79, 1.19)	0.74 (0.59, 0.94) *
Triglycerides mg/dL	*Range*	[12.0, 83]	(83, 131]	(131, 1000]
	Crude, HR (95% CI)	ref	1.18 (0.96, 1.44)	1.48 (1.22, 1.79) ***
	Model 1, HR (95% CI)	ref	1.34 (1.10, 1.65) **	1.83 (1.50, 2.23) ***
	Model 2, HR (95% CI)	ref	1.27 (1.02, 1.59) *	1.54 (1.23, 1.92) ***
α-Tocopherol mg/L	*Range*	[0, 7.32]	(7.32, 10.60]	(10.60, 124.00]
	Crude, HR (95% CI)	ref	0.81 (0.66, 1.00)	0.65 (0.52, 0.81) ***
	Model 1, HR (95% CI)	ref	0.93 (0.75, 1.15)	0.84 (0.67, 1.05)
	Model 2, HR (95% CI)	ref	0.95 (0.75, 1.20)	0.92 (0.72, 1.19)
γ-Tocopherol mg/L	*Range*	[0.268, 1.32]	(1.32, 2.04]	(2.04, 46.70]
	Crude, HR (95% CI)	ref	1.24 (0.99, 1.55)	1.74 (1.40, 2.16) ***
	Model 1, HR (95% CI)	ref	1.17 (0.93, 1.47)	1.69 (1.35, 2.11) ***
	Model 2, HR (95% CI)	ref	1.07 (0.83, 1.37)	1.47 (1.15, 1.89) **
α-Carotene ng/mL	*Range*	[0, 45.5]	(45.5, 87.2]	(87.2, 3170]
	Crude, HR (95% CI)	ref	0.67 (0.54, 0.82) ***	0.51 (0.41, 0.64) ***
	Model 1, HR (95% CI)	ref	0.68 (0.55, 0.84) ***	0.56 (0.44, 0.70) ***
	Model 2, HR (95% CI)	ref	0.75 (0.59, 0.95) *	0.76 (0.58, 0.98) *
β-Carotene ng/mL	*Range*	[0, 169]	(169, 352]	(352, 11300]
	Crude, HR (95% CI)	ref	0.60 (0.48, 0.73) ***	0.46 (0.37, 0.57) ***
	Model 1, HR (95% CI)	ref	0.62 (0.50, 0.76) ***	0.52 (0.41, 0.66) ***
	Model 2, HR (95% CI)	ref	0.70 (0.56, 0.89) **	0.72 (0.55, 0.94) **
Adiponectin µg/mL	*Range*	[0, 5.06]	(5.06, 9.05]	(9.05, 26.5]
	Crude, HR (95% CI)	ref	0.69 (0.57, 0.83) ***	0.54 (0.45, 0.66) ***
	Model 1, HR (95% CI)	ref	0.76 (0.63, 0.92) **	0.67 (0.54, 0.82) ***
	Model 2, HR (95% CI)	ref	0.81 (0.66, 1.00) *	0.73 (0.58, 0.92) **
Leptin mg/L	*Range*	[0, 7.68]	(7.68, 20.60]	(20.60, 106.00]
	Crude, HR (95% CI)	ref	1.19 (0.97, 1.45)	1.50 (1.24, 1.83) ***
	Model 1, HR (95% CI)	ref	1.55 (1.26, 1.91) ***	2.73 (2.14, 3.47) ***
	Model 2, HR (95% CI)	ref	1.36 (1.07, 1.71) *	2.09 (1.56, 2.81) ***

Model 1 adjusted for sex and ethnicity

Model 2 adjusted for strata(sex), ethnicity, education level, place of birth, and other baseline characteristics (body mass index, marital status, smoking status, vitamin C supplementation, physical activity level, number of alcoholic drinks per day, history of diuretic use, and strata(tertiles of DASH diet adherence score)

Acronyms: HR = hazard ratio from cox proportional hazard model, CI = confidence interval, ref = reference group, LDL = low-density lipoprotein, HDL = high-density lipoprotein

All models pass the proportional hazards assumption

*p<0.05, **p<0.01, ***p<0.001