HHS Public Access

Author manuscript

*Int J Cancer*. Author manuscript; available in PMC 2022 March 14.

Published in final edited form as:

*Int J Cancer*. 2020 August 15; 147(4): 948–957. doi:10.1002/ijc.32853.

# Lifestyle factors and risk of myeloproliferative neoplasms in the NIH-AARP diet and health study

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## Abstract

The etiology of Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) is largely unknown. We assessed potential associations between lifestyle factors and MPN risk in the NIH-AARP Diet and Health Study. In this prospective cohort with 463,049 participants aged 50–71 years at baseline (1995–1996) and a median follow-up of 15.5 years, we identified 490 MPN cases, including 190 with polycythemia vera (PV) and 146 with essential thrombocythemia (ET). Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Smoking was not associated with MPN risk in the overall cohort, but analyses stratified by sex suggested that smoking increased the risk of MPN in women (former smoker *vs.* nonsmokers, HR = 1.43, 95% CI: 1.03–2.00, $p = 0.03$; current smokers *vs.* nonsmokers, HR = 1.71, 95% CI: 1.08–2.71, $p = 0.02$). Coffee consumption was inversely associated with the risk of PV (high *vs.* low intake, HR = 0.53, 95% CI: 0.33–0.84, $p$-trend < 0.01), but not the risk of ET or MPN overall. Further analysis revealed an inverse association between the amount of caffeine intake and PV risk (high *vs.* low intake, HR = 0.55, 95% CI: 0.39–0.79, $p$-trend < 0.01). While the consumption of caffeinated coffee appeared to confer a protective effect against PV, the consumption of decaffeinated coffee did not. This large prospective study identified smoking as a risk factor for MPN in women and suggests that caffeine intake is associated with a lower risk of PV.

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Conflict of interest

N.A.P. received research funding (institutional) from Boehringer Ingelheim, Astellas Pharma, Daiichi Sankyo, Sunesis Pharmaceuticals, Jazz Pharmaceuticals, Pfizer, Astex Pharmaceuticals, CTI Biopharma, Celgene, Genentech, AI Therapeutics, Samus Therapeutics, Arog Pharmaceuticals, Kartos Therapeutics. N.A.P. received grant funding from Celgene. N.A.P. had a consultancy with and received honoraria from Alexion, Pfizer, Agios Pharmaceuticals, Blueprint Medicines, Incyte, Novartis, Celgene, Bristol-Myers Squib, CTI biopharma. A.M.Z. received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, ADC Therapeutics. A.M.Z had a consultancy with and received honoraria from AbbVie, Otsuka, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Trovagene, Takeda, Ionis and Epizyme. A.M.Z received travel support for meetings from Pfizer, Novartis and Trovagene. R. M. had a consultancy with Novartis, Sierra Oncology, La Jolla, Pharma. R. M. received research funding from Celgene, Incyte, Abbvie, Samus, Genotech, Promedior, CTI.

**Keywords**

myeloproliferative neoplasms; lifestyle factors; epidemiology

## Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) are a group of hematological malignancies characterized by the overproliferation of cells of the myeloid lineage. Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are three major types of MPN.[1] A gain-of-function mutation within the Janus kinase 2 gene (JAK2 V617F) occurs among 81–97% of patients with PV, 41–57% of patients with ET and 43–50% of patients with PMF.[2,3] Most MPN patients are diagnosed after the age of 60 years, with a median age of 65 years for PV, 68 years for ET and 70 years for PMF.[4]

To date, multiple environmental, medical and familial factors have been linked to the risk of MPN.[5] The Iowa Women's Health Study (IWHS)[6] reported that smokers had a higher risk to develop MPN, and the Million Women Study[7] observed a similar association between smoking and the risk of myeloproliferative/myelodysplastic disease (without distinguishing the two different entities). The IWHS also found that physical activity, obesity, early-onset diabetes and the use of aspirin may play a role in the development of various subtypes of MPN. In addition, previous studies suggested that Ashkenazi Jewish descent[8] and family history of MPN[9-12] increased the risk of MPN. A common challenge of the existing studies, however, is the relatively small number of MPN patients included due to the rarity of MPN. While lifestyle factors have been implicated in the etiology of MPN, they remain severely understudied, hampering our understanding of the pathogenesis of MPN and potential preventive strategies.

To address these knowledge gaps, we evaluated the possible association between lifestyle factors and MPN risk in a large prospective cohort study with extensive follow-up—the National Institutes of Health (NIH)-AARP Diet and Health Study. AARP is a nonprofit organization in the United States whose mission is to "empower people to choose how they live as they age".

## Materials and Methods

### Study population

The NIH-AARP Diet and Health Study was established in 1995–1996. Details of the study have been previously described.[13] Briefly, self-administered questionnaires on dietary habits and health were mailed to AARP members aged 50–71 years in six states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). Of 3.5 million AARP members, 566,398 satisfactorily completed and returned the questionnaire. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute, and all

participants gave written informed consent by virtue of completing and returning the questionnaire.

For this analysis, we excluded participants whose questionnaires were filled by a proxy responder ($n$ = 15,760), who had prevalent cancer ($n$ = 51,260), poor health ($n$ = 8,365), end-stage renal disease ($n$ = 769), cancer diagnoses reported only from death certificate ($n$ = 4,117), zero person-years of follow-up ($n$ = 48), missing body mass index (BMI; $n$ = 11,390), total energy intake ($n$ = 4,270) or BMI ($n$ = 3,885) outside of three times the interquartile range (IQR) above the 75th or below the 25th percentile of the corresponding log-transformed value of the study population. In addition, we excluded 3,485 participants whose BMI was lower than 18.5.

## Case ascertainment

Incident cancer cases were identified through probabilistic linkage with cancer registries in the eight original states and three additional states where participants most frequently moved during follow-up (Arizona, Nevada and Texas). Cancer registry linkage with eight states was shown to ascertain approximately 90% of all cancer incidences in this cohort.[14] Incident cancer occurring during follow-up was ascertained through December 31, 2011, and vital status ascertained through December 31, 2011, using the National Death Index. Incident MPN cases were identified using histologic codes from the International Classification of Diseases for Oncology, third edition: 9950 for PV, 9961 for PMF, 9962 for ET, 9960 for not otherwise specified MPN and 9975 for unclassifiable MPN.

## Exposure assessment

The NIH-AARP baseline questionnaire elicited information on a variety of demographic, medical and lifestyle factors, including family history of cancer, personal history of multiple health conditions (e.g., heart disease, emphysema, diabetes and stroke), physical activity (defined as activities that lasted at least 20 min and caused increases in breathing or heart rate or to sweat at work and outside of work) and smoking history. Physical activity was categorized as <1, 1–2, 3–4 and ≥5 times per week, and smoking status was categorized into nonsmoker, former smoker or current smoker. Self-reported body weight and height were used to calculate BMI, which was categorized as normal (18.5–24.9), overweight (25–29.9) or obese (≥30).

At the baseline, participants also completed a 124-item Food Frequency Questionnaire, including intake of alcohol, coffee, tea and other caffeinated drinks. Participants were asked to report their usual intake over the past 12 months in both frequency of intake and portion size. MyPyramid Equivalents Database values were used in the study. Alcohol intake was categorized as nondrinker, <1.91 g/day, or ≥1.91 g/day. Total caffeine intake was calculated by summing the product of the estimated caffeine content of each beverage by the daily amount consumed. For this analysis, coffee and caffeine intake were evaluated as binary variables (never *vs.* ever) or tertiles based on their distribution in the overall study population.

### Statistical analysis

We used multivariable Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Person-years were calculated from the date the questionnaire was returned through the date of cancer diagnosis or the date of censoring, which included relocation out of the registry area, loss to follow-up, death or the end of follow-up (December 31, 2011), whichever came first. For all variables, missing values were categorized as a separate group. In our multivariable models, we adjusted for age (<55, 55–59, 60–64, 65–69 and ≥70 years), sex, ethnic (white, nonwhite and unknown), education (<12 years, 12–15 years, ≥16 years and unknown), marital status (married, not married and unknown), and self-reported chronic diseases (heart disease, emphysema, diabetes and stroke as four binary variables). Tests for linear trend were performed by ordering the ordinal exposure categories from the lowest to the highest levels and including the variable as a 1 degree-of-freedom linear term in the Cox regression models. All analyses were conducted for MPN overall and two specific types of MPN: PV ($n = 190$) and ET ($n = 146$). We chose not to carry out separate analyses for PMF due to the small number of patients identified ($n = 67$), or MPN that is unclassifiable or not otherwise specified ($n = 87$) due to the heterogeneity of this group. To compare with findings from the IWHS and the Million Women Study, we conducted stratified analyses by sex. As the IWHS reported that regular use of aspirin lowered the risk of ET,[6] we also conducted additional analyses with aspirin as a potential confounder. All statistical analyses were two-sided with a type I error of 0.05 for statistical significance and were performed using SAS Version 9.4 (SAS Inc., Cary, NC).

To help provide a context for the interpretation of our findings, we estimated statistical power using a range of hazard ratios from 1.1 through 2.0 and a range of exposure prevalence from 0.1 through 0.5, and all power estimates were above 0.80.

## Data availability

The data that support the findings of our study are available from the NIH-AARP Diet and Health Study. Restrictions apply to the availability of these data, which we obtained with a specific data use agreement for our study.

## Results

The final cohort included 463,049 participants. After a median follow-up of 15.53 years, a total of 490 participants developed MPN, including 190 PV, 146 ET, 67 PMF and 87 unclassifiable/not otherwise specified MPN. Of these 490 MPN patients, most were male (65.5%), white (90.6%) and married (70.2%; Table 1).

As shown in Table 2, compared to males, female participants had a decreased risk of MPN overall (HR = 0.71, 95% CI: 0.57–0.88; $p < 0.01$), as well as PV (HR = 0.53, 95% CI: 0.37–0.76; $p < 0.01$). Self-reported stroke was positively associated with MPN risk (HR = 1.98, 95% CI: 1.20–3.27; $p < 0.01$). Additionally, male participants with a family history of cancer in first-degree relatives had a 33% increased MPN risk (95% CI: 1.06–1.68; $p = 0.01$), although no significant association was observed between family history of cancer and MPN risk in the overall cohort (i.e., males and females combined).

When we assessed lifestyle factors in relation to the risk of MPN, alcohol intake, cigarette smoking, BMI and frequency of physical activity did not appear to influence the risk of MPN overall or PV or ET in particular (Table 3). Compared to participants who had a low level of coffee consumption, those with a medium (HR = 0.60, 95% CI: 0.44–0.81; $p < 0.01$) or high (HR = 0.53, 95% CI: 0.33–0.84; $p < 0.01$) level of consumption had a significantly lower risk of PV ($p$-trend < 0.01). For ET patients, the HRs for both medium- and high-level coffee consumption was elevated, but there was no significant linear trend. No association with coffee consumption was observed for MPN overall.

Stratified analyses by sex revealed an increased MPN risk among female smokers. Compared to nonsmokers, both former (HR = 1.43, 95% CI: 1.03–2.00; $p = 0.03$) and current female smokers (HR = 1.71, 95% CI: 1.08–2.71; $p = 0.02$) had an increased risk for developing MPN. Other than this, we did not observe any significant associations between each of the five lifestyle factors (alcohol intake, cigarette smoking, coffee consumption, BMI and physical activity) and each of the three disease endpoints (MPN overall, PV and ET) in sex-specific analyses.

To further evaluate the role of coffee consumption in the etiology of MPN, we analyzed the relation of total caffeine intake to MPN risk (Table 4). Compared to participants who had a low level of caffeine intake, those with high intake had a significantly decreased risk of PV (HR = 0.55, 95% CI: 0.39–0.79), and there appeared to be a dose–response relationship ($p$-trend < 0.01). When we examined specific types of beverages, we found that the consumption of regular coffee was a protective factor against PV risk—participants who drank regular coffee had a significantly reduced risk of PV (lower consumption *vs.* none: HR = 0.74, 95% CI: 0.55–0.99; higher consumption *vs.* none: HR = 0.45, 95% CI: 0.25–0.81) with a linear trend ($p < 0.01$), whereas the consumption of decaffeinated coffee was associated with an elevated PV risk (HR = 1.40, 95% CI:1.04–1.87; $p = 0.03$). No significant associations were observed between the consumption of other caffeinated or decaffeinated beverages (tea, soft drinks and diet soft drinks) and the risk of PV, ET or MPN overall. Stratified analyses by sex did not reveal significant associations with regard to caffeine intake or the consumption of different types of beverages.

We also conducted a sensitivity analysis by additionally adjusting for smoking status and/or aspirin use in all statistical models for caffeine-related analyses and observed no differences (detailed results not shown).

## Discussion

Our study is the first to examine the relation of lifestyle factors to MPN risk in a prospective cohort including both men and women. The number of MPN patients ($n = 490$) included in this cohort is large despite the rarity of MPN. Our findings suggest that coffee consumption and caffeine intake are inversely associated with the development of PV. In addition, female smokers and male participants with a family history of cancer in first-degree relatives have an increased risk of MPN.

Coffee has been popular in North America and is the main source of caffeine for adults in the United States.[15] In 2016, after reviewing more than 1,000 studies, a Working Group convened by the International Agency for the Research on Cancer concluded that there was inadequate evidence for the potential carcinogenicity of coffee drinking while noting the protective effects of coffee against at least two types of cancer (endometrial and liver cancers).[16] To the best of our knowledge, no study had evaluated the role of coffee consumption in the etiology of MPN.

In our study, we observed an inverse relationship between coffee consumption and the risk of PV. The magnitude of association was larger among participants whose caffeine intake fell in the highest intake group and who consumed more regular coffee. When MPN was analyzed as a single group, there was also a suggestive inverse trend between the consumption of regular coffee and MPN risk. These findings are consistent with the results from recent studies looking at caffeine-containing beverages and development of other types of cancer, including head and neck cancer,[17] endometrial cancer,[18,19] liver cancer,[20] colorectal cancer,[19,21] breast cancer,[18,22] ovarian cancer[23] and prostate cancer.[24] In some studies, this association was only observed among individuals who drank caffeinated coffee.[17,25]

There are multiple biologically plausible mechanisms behind the inverse relationship that we observed between coffee consumption and MPN risk. Roasted coffee is a complex mixture of over 1,000 bioactive compounds including caffeine and polyphenols,[26] which are known to have anti-inflammatory effects and may prevent carcinogenesis by inhibiting the inflammatory processes.[18,27-29] Emerging evidence suggests that chronic inflammation plays an important role in clone initiation and evolvement in MPN,[30,31] with animal study[32] and clinical studies[33-35] reporting inflammation caused by both malignant clone and surrounding non-malignant cells. Additionally, caffeine can promote antitumor immune response through the adenosine A2A receptor[36] and induce apoptosis by increasing the apoptotic inducer (c-Fos, c-Myc) and decreasing the apoptotic repressors (Bcl-2, c-N-Ras) in many types of cancer cells.[37-40] Future research is needed to confirm our findings and clarify underlying mechanisms.

Consistent with the IWHS[6] and the Million Women Study,[7] we observed no association between alcohol consumption and risk of MPN. In the IWHS, compared to nonsmokers, both former and current smokers had increased risks of PV ($p$-trend = 0.006). The Million Women Study did not separate patients with MPN and myelodysplastic syndromes. They reported that female smokers had a 42% increased risk of myeloproliferative/myelodysplastic disease compared to nonsmokers. In our study, both former (HR = 1.43, 95% CI: 1.03–2.00) and current (HR = 1.71, 95% CI: 1.08–2.71) female smokers had an elevated risk of developing MPN, although we did not observe significant associations in analyses of PV or ET, which had smaller sample sizes and reduced statistical power. The IWHS reported a trend of increased risk of ET with higher BMI, as well as a trend of decreased ET risk with a higher level of physical activity, while we did not find any significant association between BMI or physical activity and MPN risk, regardless of sex.

We observed a positive association between self-reported stroke and the risk of MPN. The interpretation of this finding can be challenging, as stroke (a thrombotic event) might be a consequence of undiagnosed MPN,[41,42] in which case the observed association would be an example of reverse causality.

Our study has several strengths. It is a large, prospective cohort that includes both men and women. Detailed information on lifestyle factors as well as other participant characteristics were collected before cancer diagnosis, minimizing the potential for recall bias and reverse causality. The availability of data on demographic factors, history of selected chronic diseases and family history of cancer enabled the adjustment of these covariates in multivariable Cox models, reducing the likelihood of confounding. The large cohort size and the extended duration of follow-up allowed the identification of 490 MPN cases, which represented the largest number of MPN patients included in any epidemiological studies to date. In addition to analyzing MPN as a single entity, we were able to conduct separate analyses for PV ($n$ = 190) and ET ($n$ = 146), as well as stratified analyses by sex.

On the other hand, due to the rarity of MPN, the numbers of patients with specific types of MPN were small, which probably compromised the statistical power of our study and could have contributed to some of the null findings. In addition, the NIH-AARP study population only comprised of participants aged 50 years or older, so our findings may not be applicable to a broader age group. Furthermore, although we adjusted for a number of covariates in the analysis, residual confounding by unknown or unmeasured risk factors may have persisted. For the evaluation of different types of beverages, we did not have information on the exact method for coffee brewing (e.g., espresso, boiled and filtered) or specific types of tea (e.g., green and black). Finally, given a large number of factors being tested, consideration must be given to the possibility of false positives findings due to multiple testing.

In conclusion, our study is the first to report an inverse association between coffee consumption, caffeine intake and the risk of MPN. We also found that female smokers and male participants with a family history of cancer in first-degree relatives had an increased risk of developing MPN. Prospective studies with a larger number of patients are needed to further examine the pathogenesis of MPN and inform potential preventive strategies.

## Acknowledgements

This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute and the Frederick A. Deluca Foundation. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia. Cancer incidence data from California were collected by the California Cancer Registry, California Department of Public Health's Cancer Surveillance and Research Branch, Sacramento, California. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, Lansing, Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (Miami, Florida) under contract with the Florida Department of Health, Tallahassee, Florida. The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, The Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, North Carolina. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from

Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Division of Public and Behavioral Health, State of Nevada Department of Health and Human Services, Carson City, Nevada. We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

## Abbreviations:

| | |
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| **BMI** | body mass index |
| **CI** | confidence interval |
| **ET** | essential thrombocythemia |
| **HR** | hazard ratio |
| **IQR** | interquartile range |
| **IWHS** | Iowa Women's Health Study |
| **MPN** | myeloproliferative neoplasms |
| **NIH** | National Institutes of Health |
| **PMF** | primary myelofibrosis |
| **PV** | polycythemia vera |

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## What's new?

Risk of Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) is associated with various environmental and familial factors. These factors, however, remain understudied, resulting in significant gaps in knowledge of MPN pathogenesis. In this investigation, drawing on data from the NIH-AARP Diet and Health Study, the authors elaborate on specific factors linked to MPN risk in men and women. In particular, coffee consumption and caffeine intake were found to be inversely associated with the development of polycythemia vera, one of three major MPN types. MPN risk was elevated among women who smoked and among men with a familial cancer history in first-degree relatives.

**Table 1.**

Demographic factors, medical history and family history of cancer among patients diagnosed with myeloproliferative neoplasms in the National Institutes of Health-AARP Diet and Health Study, United States, 1995–2011

| | All participants | | MPN | | PV | | ET | |
|---|---|---|---|---|---|---|---|---|
| **Characteristics** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| Total | 463,049 | | 490 | | 190 | | 146 | |
| *Age groups (years)* | | | | | | | | |
| <55 | 63,337 | 13.68 | 44 | 8.98 | 17 | 8.95 | 14 | 9.59 |
| 55–59 | 105,564 | 22.80 | 80 | 16.33 | 37 | 19.47 | 24 | 16.44 |
| 60–64 | 130,284 | 28.14 | 146 | 29.80 | 55 | 28.95 | 46 | 31.51 |
| ≥65 | 163,864 | 35.37 | 220 | 44.90 | 81 | 42.63 | 62 | 42.47 |
| *Sex* | | | | | | | | |
| Male | 278,349 | 60.11 | 321 | 65.51 | 141 | 74.21 | 76 | 52.05 |
| Female | 184,700 | 39.89 | 169 | 34.49 | 49 | 25.79 | 70 | 47.95 |
| *Ethnic* | | | | | | | | |
| White | 423,931 | 91.55 | 444 | 90.61 | 178 | 93.68 | 131 | 89.73 |
| Non-white | 33,377 | 7.21 | 39 | 7.96 | 12 | 6.32 | 13 | 8.90 |
| Unknown | 5,741 | 1.24 | 7 | 1.43 | 0 | 0.00 | 2 | 1.37 |
| *Education (years)* | | | | | | | | |
| <12 | 25,929 | 5.60 | 26 | 5.31 | 15 | 7.89 | 5 | 3.42 |
| 12–15 | 242,603 | 52.39 | 246 | 50.20 | 89 | 46.84 | 77 | 52.74 |
| ≥16 | 181,644 | 39.23 | 207 | 42.24 | 80 | 42.11 | 61 | 41.78 |
| Unknown | 12,873 | 2.78 | 11 | 2.24 | 6 | 3.16 | 3 | 2.05 |
| *Marital status* | | | | | | | | |
| Married | 320,124 | 69.13 | 344 | 70.20 | 148 | 77.89 | 88 | 60.27 |
| Not married | 139,529 | 30.13 | 142 | 28.98 | 41 | 21.58 | 57 | 39.04 |
| Unknown | 3,396 | 0.73 | 4 | 0.82 | 1 | 0.53 | 1 | 0.68 |
| *Self-reported heart disease* | | | | | | | | |
| No | 402,213 | 86.86 | 421 | 85.92 | 157 | 82.63 | 131 | 89.73 |
| Yes | 60,836 | 13.14 | 69 | 14.08 | 33 | 17.37 | 15 | 10.27 |
| *Self-reported emphysema* | | | | | | | | |

| Characteristics | All participants | | MPN | | PV | | ET | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| No | 452,666 | 97.76 | 481 | 98.16 | 186 | 97.89 | 143 | 97.95 |
| Yes | 10,383 | 2.24 | 9 | 1.84 | 4 | 2.11 | 3 | 2.05 |
| *Self-reported diabetes* | | | | | | | | |
| No | 423,854 | 91.54 | 454 | 92.65 | 178 | 93.68 | 133 | 91.10 |
| Yes | 39,195 | 8.46 | 36 | 7.35 | 12 | 6.32 | 13 | 8.90 |
| *Self-reported stroke* | | | | | | | | |
| No | 454,448 | 98.14 | 474 | 96.73 | 184 | 96.84 | 141 | 96.58 |
| Yes | 8,601 | 1.86 | 16 | 3.27 | 6 | 3.16 | 5 | 3.42 |
| *Family history of cancer in first-degree relatives* | | | | | | | | |
| No | 214,184 | 46.26 | 206 | 42.04 | 84 | 44.21 | 58 | 39.73 |
| Yes | 225,466 | 48.69 | 254 | 51.84 | 93 | 48.95 | 78 | 53.42 |
| Unknown | 23,399 | 5.05 | 30 | 6.12 | 13 | 6.84 | 10 | 6.85 |

Abbreviations: ET, essential thrombocythemia; MPN, myeloproliferative neoplasms; PV, polycythemia vera.

**Table 2.**

Demographic factors, medical history, family history and risk of myeloproliferative neoplasms in the National Institutes of Health-AARP Diet and Health Study

| | | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Person-years of follow-up** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** |
| *Age groups at baseline* | | | | | | | | | | |
| <55 years | 849,647 | 44 | 1.00 | | 17 | 1.00 | | 14 | 1.00 | |
| 55–59 years | 1,362,761 | 80 | 1.15 (0.79–1.65) | 0.47 | 37 | 1.35 (0.76–2.40) | 0.31 | 24 | 1.10 (0.57–2.13) | 0.78 |
| 60–64 years | 1,603,302 | 146 | 1.80 (1.28–2.52) | <0.01 | 55 | 1.71 (0.99–2.95) | 0.05 | 46 | 1.84 (1.01–3.34) | 0.05 |
| ≥65 years | 1,706,653 | 220 | 2.33 (1.68–3.23) | <0.01 | 81 | 2.14 (1.26–3.62) | <0.01 | 62 | 2.17 (1.21–3.89) | <0.01 |
| *p*-trend | | | | <0.01 | | | <0.01 | | | <0.01 |
| *Sex* | | | | | | | | | | |
| Male | 3,323,065 | 321 | 1.00 | | 141 | 1.00 | | 76 | 1.00 | |
| Female | 2,380,005 | 169 | 0.71 (0.57–0.88) | <0.01 | 49 | 0.53 (0.37–0.76) | <0.01 | 70 | 1.10 (0.75–1.59) | 0.63 |
| *Ethnicity* | | | | | | | | | | |
| White | 5,209,450 | 444 | 1.00 | | 178 | 1.00 | | 131 | 1.00 | |
| Non-white | 424,193 | 39 | 1.14 (0.82–1.59) | 0.42 | 12 | 0.91 (0.50–1.63) | 0.75 | 13 | 1.20 (0.68–2.13) | 0.53 |
| Unknown | 69,427 | 7 | 1.24 (0.57–2.69) | 0.60 | 0 | - | - | 2 | 1.18 (0.28–5.00) | 0.83 |
| *Education* | | | | | | | | | | |
| <12 years | 307,407 | 26 | 1.00 | | 15 | 1.00 | | 5 | 1.00 | |
| 12–15 years | 2,996,516 | 246 | 1.08 (0.72–1.63) | 0.70 | 89 | 0.67 (0.38–1.15) | 0.14 | 77 | 1.74 (0.70–4.30) | 0.23 |
| ≥16 | 2,244,467 | 207 | 1.19 (0.79–1.80) | 0.40 | 80 | 0.73 (0.42–1.28) | 0.27 | 61 | 1.97 (0.79–4.94) | 0.15 |
| Unknown | 154,680 | 11 | 0.87 (0.42–1.77) | 0.69 | 6 | 0.96 (0.37–2.47) | 0.93 | 3 | 1.21 (0.28–5.14) | 0.80 |
| *Marital status* | | | | | | | | | | |
| Married | 3,929,244 | 344 | 1.00 | | 148 | 1.00 | | 88 | 1.00 | |
| Not married | 1,732,808 | 142 | 1.08 (0.87–1.34) | 0.50 | 41 | 0.85 (0.58–1.24) | 0.39 | 57 | 1.37 (0.94–1.99) | 0.10 |
| Unknown | 41,017 | 4 | 1.17 (0.42–3.26) | 0.77 | 1 | 1.06 (0.15–7.62) | 0.95 | 1 | 1.04 (0.14–7.96) | 0.97 |
| *Self-reported heart disease* | | | | | | | | | | |
| No | 5,022,469 | 421 | 1.00 | | 157 | 1.00 | | 131 | 1.00 | |
| Yes | 680,600 | 69 | 1.05 (0.81–1.37) | 0.69 | 33 | 1.30 (0.89–1.91) | 0.18 | 15 | 0.81 (0.47–1.40) | 0.45 |
| *Self-reported emphysema* | | | | | | | | | | |

| | | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Person-years of follow-up** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** |
| No | 5,601,273 | 481 | 1.00 | | 186 | 1.00 | | 143 | 1.00 | |
| Yes | 101,797 | 9 | 1.01 (0.52–1.95) | 0.99 | 4 | 1.11 (0.41–3.01) | 0.83 | 3 | 1.21 (0.38–3.81) | 0.75 |
| *Self-reported diabetes* | | | | | | | | | | |
| No | 5,265,615 | 454 | 1.00 | | 178 | 1.00 | | 133 | 1.00 | |
| Yes | 437,454 | 36 | 0.90 (0.64–1.27) | 0.56 | 12 | 0.73 (0.41–1.32) | 0.30 | 13 | 1.22 (0.69–2.17) | 0.50 |
| *Self-reported stroke* | | | | | | | | | | |
| No | 5,612,491 | 474 | 1.00 | | 184 | 1.00 | | 141 | 1.00 | |
| Yes | 90,578 | 16 | 1.98 (1.20–3.27) | <0.01 | 6 | 1.86 (0.82–4.23) | 0.14 | 5 | 2.24 (0.91–5.50) | 0.08 |
| *First-degree family history* | | | | | | | | | | |
| No | 2,646,816 | 206 | 1.00 | | 84 | 1.00 | | 58 | 1.00 | |
| Yes | 2,771,939 | 254 | 1.19 (0.99–1.43) | 0.007 | 93 | 1.08 (0.80–1.45) | 0.62 | 78 | 1.27 (0.90–1.78) | 0.18 |
| Unknown | 284,315 | 30 | 1.35 (0.92–1.98) | 0.13 | 13 | 1.48 (0.83–2.66) | 0.19 | 10 | 1.61 (0.82–3.15) | 0.17 |

[1]Hazard ratios and 95% confidence interval were generated by Cox regression models. All models adjusted for age (<55, 55–59, 60–64, 65–69 and ≥70 years), gender, ethnic (white, nonwhite and unknown), education (<12, 12–15 and 16 years and up, known), material status (married, not married and unknown) and self-reported chronic disease (heart disease, emphysema, diabetes and stroke as four binary variables).

Abbreviations: CI, confidence interval; ET, essential thrombocythemia; HR, hazard ratio; MPN, myeloproliferative neoplasms; No., number; PV, polycythemia vera.

**Table 3.**

Selected lifestyle factors and risk of myeloproliferative neoplasms in the National Institutes of Health-AARP Diet and Health Study, United States, 1995–2011

| | | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Person-years of follow-up** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** |
| *Alcohol intake (g/day)* | | | | | | | | | | |
| Nondrinker | 407,676 | 40 | 1.00 | | 19 | 1.00 | | 14 | 1.00 | |
| 0–1.90 | 2,461,754 | 203 | 0.85 (0.61–1.20) | 0.36 | 74 | 0.62 (0.38–1.04) | 0.05 | 58 | 0.72 (0.40–1.29) | 0.26 |
| ≥1.91 | 2,833,640 | 247 | 0.84 (0.59–1.18) | 0.31 | 97 | 0.61 (0.37–1.01) | 0.07 | 74 | 0.85 (0.47–1.52) | 0.58 |
| *p*-trend | | | | 0.44 | | | 0.17 | | | 0.90 |
| *Cigarette smoking* | | | | | | | | | | |
| Nonsmoker | 2,108,338 | 161 | 1.00 | | 68 | 1.00 | | 45 | 1.00 | |
| Former smoker | 2,774,867 | 263 | 1.17 (0.96–1.44) | 0.12 | 94 | 0.91 (0.66–1.25) | 0.55 | 78 | 1.43 (0.98–2.07) | 0.06 |
| Current smoker | 612,748 | 49 | 1.18 (0.85–1.63) | 0.32 | 20 | 1.12 (0.67–1.86) | 0.67 | 19 | 1.67 (0.97–2.87) | 0.07 |
| Unknown | 207,116 | 17 | 1.02 (0.62–1.69) | 0.93 | 8 | 1.13 (0.54–2.37) | 0.74 | 4 | 1.43 (0.98–2.07) | 0.94 |
| *Total coffee (g/day)* | | | | | | | | | | |
| ≤373.86 | 1,987,444 | 181 | 1.00 | | 87 | 1.00 | | 41 | 1.00 | |
| 373.87–957.53 | 2,830,039 | 238 | 0.90 (0.74–1.09) | 0.27 | 81 | 0.60 (0.44–0.81) | <0.01 | 84 | 1.50 (1.03–2.19) | 0.04 |
| ≥957.54 | 885,586 | 71 | 0.90 (0.68–1.19) | 0.46 | 22 | 0.53 (0.33–0.84) | <0.01 | 21 | 1.29 (0.76–2.20) | 0.35 |
| *p*-trend | | | | 0.31 | | | <0.01 | | | 0.15 |
| *BMI (kg/m$^2$)* | | | | | | | | | | |
| 18.5–24.9 | 2,023,178 | 165 | 1.00 | | 63 | 1.00 | | 52 | 1.00 | |
| 25–29.9 | 2,468,749 | 222 | 1.06 (0.86–1.30) | 0.59 | 83 | 0.95 (0.68–1.33) | 0.78 | 62 | 1.13 (0.78–1.64) | 0.51 |
| ≥30 | 1,211,142 | 103 | 1.10 (0.85–1.41) | 0.47 | 44 | 1.18 (0.80–1.74) | 0.41 | 27 | 0.93 (0.58–1.49) | 0.75 |
| *p*-trend | | | | 0.45 | | | 0.48 | | | 0.89 |
| *Physical activity (times/week)* | | | | | | | | | | |
| <1 | 1,711,717 | 154 | 1.00 | | 51 | 1.00 | | 47 | 1.00 | |
| 1–2 | 1,251,508 | 108 | 0.93 (0.72–1.18) | 0.54 | 54 | 1.36 (0.93–2.00) | 0.12 | 32 | 0.94 (0.60–1.48) | 0.79 |
| 3–4 | 1,565,368 | 125 | 0.81 (0.64–1.03) | 0.09 | 49 | 0.94 (0.63–1.39) | 0.74 | 35 | 0.80 (0.51–1.24) | 0.31 |
| ≥5 | 1,119,715 | 98 | 0.87 (0.67–1.12) | 0.28 | 35 | 0.89 (0.58–1.38) | 0.61 | 30 | 0.96 (0.60–1.52) | 0.85 |
| Unknown | 54,761 | 5 | 0.90 (0.33–2.44) | 0.84 | 1 | 0.73 (0.09–5.74) | 0.77 | 2 | 1.43 (0.30–6.74) | 0.65 |

| Variable | Person-years of follow-up | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | HR (95% CI)[1] | *p*-value | No. of cases | HR (95% CI)[1] | *p*-value | No. of cases | HR (95% CI)[1] | *p*-value |
| *p*-trend | | | | 0.21 | | | 0.32 | | | 0.89 |

[1]Hazard ratios and 95% confidence intervals were derived from multivariable Cox proportional hazards regression models. All models adjusted for age (<55, 55–59, 60–64, 65–69 and ≥70 years), sex, ethnic (white, non-white and unknown), education (<12, 12–15 and ≥16 years, unknown), material status (married, not married and unknown) and self-reported chronic diseases (heart disease, emphysema, diabetes and stroke as four binary variables).

Abbreviations: CI, confidence interval; ET, essential thrombocythemia; HR, hazard ratio; MPN, myeloproliferative neoplasms; PV, polycythemia vera.

**Table 4.**

Consumption of caffeinated beverages and risk of myeloproliferative neoplasms in the National Institutes of Health-AARP Diet and Health Study, United States, 1995–2011

| | | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Person-years of follow-up** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** | **No. of cases** | **HR (95% CI)[1]** | ***p*-value** |
| *Caffeine (mg/day)* | | | | | | | | | | |
| ≤70.97 | 1,903,076 | 187 | 1.00 | | 84 | 1.00 | | 49 | 1.00 | |
| 70.98–531.58 | 1,912,893 | 156 | 0.85 (0.69–1.06) | 0.14 | 58 | 0.72 (0.51–1.01) | 0.05 | 48 | 0.97 (0.65–1.45) | 0.89 |
| >531.58 | 1,887,101 | 147 | 0.81 (0.65–1.01) | 0.06 | 48 | 0.55 (0.39–0.79) | <0.01 | 49 | 1.11 (0.74–1.66) | 0.62 |
| *p*-trend | | | | 0.06 | | | <0.01 | | | 0.63 |
| *Regular coffee with no sugar or cream (g/day)* | | | | | | | | | | |
| None | 2,287,083 | 219 | 1.00 | | 94 | 1.00 | | 63 | 1.00 | |
| 0–957.53 | 2,726,497 | 223 | 0.86 (0.71–1.03) | 0.11 | 83 | 0.74 (0.55–0.99) | 0.04 | 67 | 0.91 (0.64–1.28) | 0.57 |
| >957.53 | 689,490 | 48 | 0.77 (0.56–1.05) | 0.10 | 13 | 0.45 (0.25–0.81) | <0.01 | 16 | 0.93 (0.54–1.62) | 0.80 |
| *p*-trend | | | | 0.05 | | | <0.01 | | | 0.65 |
| *Decaffeinated coffee with no cream or sugar* | | | | | | | | | | |
| No | 3,986,059 | 324 | 1.00 | | 117 | 1.00 | | 94 | 1.00 | |
| Yes | 1,717,011 | 166 | 1.14 (0.95–1.38) | 0.17 | 73 | 1.40 (1.04–1.87) | 0.03 | 52 | 1.24 (0.88–1.75) | 0.21 |
| *Regular tea with no sugar or cream (g/day)* | | | | | | | | | | |
| 0 | 2,446,601 | 233 | 1.00 | | 91 | 1.00 | | 67 | 1.00 | |
| 0–34.27 | 1,627,001 | 128 | 0.83 (0.67–1.03) | 0.09 | 49 | 0.80 (0.56–1.13) | 0.21 | 37 | 0.83 (0.56–1.25) | 0.38 |
| >34.27 | 1,629,468 | 129 | 0.84 (0.68–1.04) | 0.11 | 50 | 0.85 (0.60–1.20) | 0.36 | 42 | 0.91 (0.62–1.34) | 0.63 |
| *p*-trend | | | | 0.08 | | | 0.29 | | | 0.57 |
| *Decaffeinated tea with no cream or sugar* | | | | | | | | | | |
| No | 4,427,032 | 376 | 1.00 | | 148 | 1.00 | | 105 | 1.00 | |
| Yes | 1,276,037 | 114 | 1.11 (0.90–1.37) | 0.35 | 42 | 1.10 (0.78–1.56) | 0.59 | 41 | 1.29 (0.89–1.86) | 0.18 |
| *Caffeinated soft drinks* | | | | | | | | | | |
| No | 3,928,788 | 327 | 1.00 | | 124 | 1.00 | | 101 | 1.00 | |
| Yes | 1,774,282 | 163 | 1.07 (0.89–1.30) | 0.47 | 66 | 1.10 (0.81–1.50) | 0.52 | 45 | 1.05 (0.73–1.50) | 0.80 |
| *Caffeinated diet soft drinks* | | | | | | | | | | |
| No | 4,518,249 | 393 | 1.00 | | 154 | 1.00 | | 116 | 1.00 | |

| Variable | Person-years of follow-up | MPN | | | PV | | | ET | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | HR (95% CI)[1] | *p*-value | No. of cases | HR (95% CI)[1] | *p*-value | No. of cases | HR (95% CI)[1] | *p*-value |
| Yes | 1,184,821 | 97 | 1.01 (0.81–1.27) | 0.98 | 36 | 0.96 (0.67–1.38) | 0.82 | 30 | 1.01 (0.67–1.51) | 0.97 |
| *Decaffeinated soft drinks* | | | | | | | | | | |
| No | 5,148,608 | 442 | 1.00 | | 170 | 1.00 | | 133 | 1.00 | |
| Yes | 554,461 | 48 | 0.99 (0.73–1.33) | 0.93 | 20 | 1.06 (0.66–1.68) | 0.81 | 13 | 0.92 (0.52–1.62) | 0.77 |
| *Decaffeinated diet soft drinks* | | | | | | | | | | |
| No | 4,117,485 | 359 | 1.00 | | 141 | 1.00 | | 105 | 1.00 | |
| Yes | 1,585,585 | 131 | 0.95 (0.78–1.16) | 0.62 | 49 | 0.91 (0.65–1.26) | 0.56 | 41 | 0.99 (0.69–1.42) | 0.94 |

[1]Hazard ratios and 95% confidence intervals were derived from multivariable Cox proportional hazards regression models. All models adjusted for age (<55, 55–59, 60–64, 65–69 and ≥70 years), sex, ethnic (white, nonwhite and unknown), education (<12, 12–15 and ≥16 years, unknown), material status (married, not married and unknown) and self-reported chronic diseases (heart disease, emphysema, diabetes and stroke as four binary variables).

Abbreviations: CI, confidence interval; ET, essential thrombocythemia; HR, hazard ratio; MPN, myeloproliferative neoplasms; PV, polycythemia vera.