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Constipation and Risk of Cardiovascular Disease among Post-Menopausal Women

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Abstract

Background—Constipation is common in Western societies, accounting for 2.5 million-physician visits/year in the US. Since many factors predisposing to constipation are also risk factors for cardiovascular disease, we hypothesized that constipation may be associated with increased risk of cardiovascular events.

Methods—We conducted a secondary analysis in 93,676 women enrolled in the observational arm of the Women's Health Initiative. Constipation was evaluated at baseline by a self-administered questionnaire. Estimates of the risk of cardiovascular events (cumulative endpoint including mortality from coronary heart disease, myocardial infarction, angina, coronary revascularization, stroke and transient ischemic attack) were derived from Cox proportional hazards models adjusted for demographics, risk factors and other clinical variables (median follow-up: 6.9 years).

Results—The analysis included 73,047 women. Constipation was associated with increased age, African American and Hispanic descent, smoking, diabetes, high cholesterol, family history of myocardial infarction, hypertension, obesity, lower physical activity levels, lower fiber intake, and depression. Women with moderate and severe constipation experienced more cardiovascular events (14.2 and 19.1 events/1000 person-years, respectively) compared to women with no constipation (9.6/1000 person-years). After adjustment for demographics, risk factors, dietary factors, medications, frailty and other psychological variables, constipation was no longer associated with an increased risk of cardiovascular events except for the severe constipation group, which had a 23% higher risk of cardiovascular events.

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Conclusion—In postmenopausal women, constipation is a marker for cardiovascular risk factors and increased cardiovascular risk. Since constipation is easily assessed, it may be a helpful tool to identify women with increased cardiovascular risk.

Keywords

cardiovascular disease; prevention; women's health; risk factors

INTRODUCTION

Constipation is common in Western societies, the prevalence varying between 2 and 28% depending on the definition adopted. [1–5] Between 1958–1986, constipation accounted for 2.5 million-physician visits/year in the United States,[6] but this number has doubled over the last decade, especially in women and in the elderly,[7] leading to considerable utilization of health-care resources with costs estimated to reach \$6.9 billion. Nevertheless, constipation has received limited attention in the modern scientific literature and its etiology and physiopathology are still poorly understood.[8, 9] On the contrary, in the 19th century constipation was considered “the disease of diseases” [10] and the notion of its dangerous consequences dates back to the 16th century BC, when an Egyptian papyrus presented for the first time the notion of poisoning of the body by substances produced from decomposing waste in the intestine.[11] In both Ayurvedic and Chinese medicine there is the belief that constipation may cause serious diseases[12] and bowel purgation has been a mainstay of medical therapy for centuries.

To date, there is limited information about the possible connection between constipation and chronic conditions, including cardiovascular disease. In cross-sectional studies, constipation has been linked with age and female gender; [1, 3, 4, 13, 14] use of non-steroid anti-inflammatory drugs, aspirin and other medications;[13, 15] diabetes; [13] lack of physical exercise [3, 16], and with race, low socio-economic status, and low education level.[1–4, 17] Multiple studies have associated constipation with low fiber intake, [14, 16, 18, 19] and some trials have shown that adding fiber to specific diets improves bowel function.[20, 21]

Since many of the factors that have been associated with constipation are also risk factors for cardiovascular disease, we hypothesized that women with symptoms of constipation may be at higher risk for cardiovascular events. The Women's Health Initiative (WHI) provided an ideal population to test this hypothesis, both because constipation is more frequent in older women, and because of the high quality of cardiovascular outcome ascertainment.

METHODS

Design and Population

The WHI consisted of a set of randomized clinical trials and an observational study. [22] The observational study was a large prospective cohort study conducted in 93,676 postmenopausal women ineligible or unwilling to participate in the WHI clinical trials. Recruitment (1994–1998) was conducted through mailings to eligible women from large mailing lists. The duration of follow-up was between 6 and 10 years, depending on when women enrolled in the study. In order to be eligible, women had to be 50 to 79 years old, postmenopausal, willing to provide written informed consent, and planning to be resident in the study recruitment area for at least 3 years following enrollment. Exclusion criteria included medical conditions predictive of a survival time of less than 3 years, conditions inconsistent with study participation such as alcoholism, drug dependency, mental illnesses, and dementia, and participation in another randomized controlled clinical trial.

Participants in the observational study had a baseline visit that included physical measurements (height, weight, blood pressure, heart rate, waist and hip circumferences), collection of blood specimens, a medication/supplement inventory, and completion of questionnaires related to medical history, family history, reproductive history, lifestyle/behavioral factors, and quality of life. Routine follow-up activities consisted of mailings sent annually and a visit 3 years after enrollment to update selected baseline data and obtain additional risk factor data. The annual mailing included a medical history update and questionnaires about lifestyle habits, demographics, hormone therapy, dietary habits, and psychosocial variables. However, except for the medical history update, such information was not collected at each year of follow-up. For internal consistency, we used only baseline variables for this analysis.

The study outcomes were coronary heart disease, stroke, breast and colorectal cancer, osteoporotic fractures, diabetes, and total mortality. Outcomes were identified by self-report on the medical history update or by reporting directly to clinic staff in the intervals between questionnaires. Centrally trained physicians adjudicated cardiovascular and mortality outcomes. [23]

Variables definition

Information about constipation was collected at baseline by means of a self-administered questionnaire. Constipation, defined as “difficulty having bowel movements” over the previous four weeks, was rated using a scale ranging from none (symptom did not occur), mild (symptom did not interfere with usual activities), moderate (symptom interfered somewhat with usual activities), or severe (symptom was so bothersome that usual activities could not be performed).

We considered covariates that may affect constipation and/or cardiovascular events, such as age, risk factors for coronary heart disease, diet, medications, and depression. Frailty,[24] optimism,[25] white blood cell count,[26] and resting heart rate,[27] which have been previously associated with unfavorable mortality and cardiovascular outcomes in WHI were included in the analysis as additional confounders.

Demographics (race/ethnicity, age at screening, marital status and education), and information about hypertension, diabetes, high cholesterol, previous cardiovascular events, smoking status (ever, never, current), family history of coronary heart disease were collected at baseline by means of self-administered questionnaires. Body-mass index (BMI: weight in kilograms/(height in meters)² was calculated from direct measurements of height and weight performed at baseline. Since baseline cholesterol levels were not measured in the entire sample, a proxy was used (history of high cholesterol requiring pills). Because of the high percentage of missing data in the question inquiring about age of first-degree relatives at the time of the heart attack, we used a yes/no question about the occurrence of myocardial infarction in any first-degree relative. Dietary variables (water, alcohol, fiber and total fiber intake) were derived from a self-administered food-frequency questionnaire designed for the WHI. [28] Energy expenditure (total MET-hours per week, kcal/week/kg) from recreational physical activity (walking, mild, moderate and strenuous physical activity) was computed from self-reported questionnaires. Information about ongoing medications was collected from study participants who were required to bring their medication bottles at the baseline visit. Depression was assessed using the shortened version of the Center for Epidemiological Studies Depression Scale [29]. Frailty was calculated using the criteria described by LaCroix and colleagues:[30] optimism was measured using the Life Orientation Test-Revised.[31] Trained study staff measured the baseline resting heart rate by palpating the radial pulse for 30 seconds; white blood cells count was obtained from baseline fasting blood specimens.

Outcome

The study outcome was a composite of death from coronary heart disease, non-fatal myocardial infarction, angina, coronary revascularization, stroke and transient ischemic attack. WHI definitions for each of the cardiovascular outcomes are provided in the WHI manuals.[32]

Fatal events were confirmed by death certificates, autopsy reports, hospital discharge summaries/death summaries, and coroner's report for deaths occurring out of hospital. Non-fatal events were documented by discharge summaries, hospital face sheet with ICD-9-CM codes, and/or physician attestation.

Statistical analysis

Baseline characteristics according to different constipation categories were compared using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Survival curves were generated by the Kaplan-Meier method. Log-rank statistics were used to compare failure curves among different constipation categories. Estimates of the risk of cardiovascular events between categories of constipation relative to women reporting no symptoms (reference group) were derived from Cox proportional hazards regression models, adjusting for covariates in Tables 1 and 2. Time to event was computed in years as time from entry in the study to event, death or last follow-up interview and survivors were censored at the date of the last follow-up interview, or loss to follow-up. The validity of the proportional hazards assumption was confirmed by plotting $\log(-\log(S(t)))$ versus time on study, where $S(t)$ indicates the estimated survivorship function, and noting that lines for different covariate values were parallel.[33]

The univariate model was adjusted for potential baseline confounders using three different models. The first model adjusted for demographic variables; the second model included model 1 covariates plus previous history of cardiovascular disease, coronary risk factors, and baseline heart rate. The third and final model adjusted for all previous covariates plus dietary factors, use of calcium channel blockers and diuretics, white blood cells count, depression, optimism and frailty scores. The continuous variables age and BMI were categorized as in Table 1, for consistency with previous WHI analyses. To handle non-linear associations in Cox proportional hazards models, total calories and alcohol were categorized using quartiles, and white blood cells count, energy expenditure and resting heart rate were log-transformed.

Results are presented as unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals. P values <0.05 were considered significant. All statistical analyses were performed using SAS statistical software version 9.1. [34]

RESULTS

Of the 93,676 women initially available for the analysis, 22.0% were excluded for missing data on the exposure indicator or major confounders leaving 73,047 women for the final analysis. Higher rates of exclusion were seen in African-Americans and Hispanics compared with non-Hispanic Caucasians and in women with lower educational levels. Compared with women included in the analyses, women omitted due to missing data were slightly more likely to report constipation (37.8% versus 34.7%), and were slightly older on average (64.2 versus 63.4 years). All other comparisons between groups were statistically significant because of the large number of observations, but the magnitude of the differences was small.

Table 1 shows the baseline prevalence of selected characteristics by constipation severity. At baseline, 34.7% of women reported having constipation: 25.7% reported having mild

constipation, and 7.4% and 1.6 % reported moderate and severe constipation, respectively. The mean duration of follow up was 6.4 ± 1.4 years (median, 6.9 years).

Demographic characteristics and risk factor profile of women with constipation

The population's age ranged from 50 to 79 (median, 63.0). Women reporting constipation tended to be older, were more likely of African American or Hispanic descent, were less educated, and had greater frailty. They also more frequently reported one or more risk factors for cardiovascular disease: being diabetic, obese, hypertensive or current smokers; using cholesterol-lowering medications; having lower levels of physical activity; or reporting that a family relative had a myocardial infarction. Baseline prevalence of previous cardiovascular disease was higher in women with complaints of constipation. A higher proportion of women with constipation took calcium channel blockers and/or diuretics. Finally, the prevalence of depression was higher in women with constipation.

Women reporting moderate or severe constipation had a slightly lower intake of dietary fiber, alcohol and water, while differences among caloric intake were minimal. (Table 2)

Univariate and multivariate models

Overall, women with moderate and severe constipation had a higher number of cardiovascular events (14.3 and 19.1 events/1000 person-years, respectively) compared to women with no constipation (9.6/1000 person-years). The cumulative incidence of cardiovascular events by constipation category is shown in figure 1. Constipation was associated with an increased risk of cardiovascular events [unadjusted HR, mild vs. none: 1.09; (95% confidence interval: 1.02, 1.17); moderate vs. none, 1.49 (1.35, 1.64); severe vs. none, 2.00 (1.68, 2.38)—Table 3].

The association of constipation with increased risk of cardiovascular events was reduced with adjustment for age, race/ethnicity, and education (Table 3, Model 1), and for risk factors and previous history of cardiovascular disease (Model 2). With further adjustment for dietary factors, use of diuretics and calcium-channel blockers, depression, optimism and frailty scores, and while blood cells count (Model 3), constipation was no longer associated with an increased risk of cardiovascular events, except for women with severe constipation, who still had a 23% higher risk of cardiovascular events compared to women with no symptoms of constipation. Results were overall consistent upon excluding women with baseline cardiovascular disease (data not shown).

Table 4 shows the unadjusted and adjusted hazard ratios by constipation severity for each cardiovascular event composing the main study outcome. Constipation was associated with an increased risk of myocardial infarction, stroke, coronary revascularization, and angina (moderate and severe vs. none). For most cardiovascular events, the confidence interval widened compared to the cumulative outcome due to the low number of events, but the direction of the association was generally consistent with an increased risk of events in most constipation categories compared with the no constipation group.

DISCUSSION

In this analysis of a prospective cohort of community dwelling, post-menopausal women, constipation was significantly associated with all the major risk factors for cardiovascular disease and with an increased risk of cardiovascular events. However, constipation was not an independent predictor of cardiovascular risk.

At baseline, the prevalence of all major cardiovascular risk factors was higher in women with more severe self-reported constipation. Consequently, the finding of an association

between constipation and increased incidence of cardiovascular events was not surprising and confirmed our hypothesis that constipation is a marker for cardiovascular risk in women who are post-menopausal. When cardiovascular risk factors were added into the multivariate model (Model 2), they reduced the strength of the associations between constipation and cardiovascular events. Further adjustment for diet, constipation-causing medications, depression, optimism and frailty scores, and leukocyte count had a more modest impact on the association. In the final model, women with severe constipation still had a 23% higher risk of cardiovascular events compared with women who do not describe constipation. Our first hypothesis is that this independent association is due to residual confounding. Since information about risk factors and previous medical history in the observational arm of the WHI was self-reported, residual confounding could result if women had under-reported coronary risk factors such as high cholesterol levels that were not measured at baseline. Second, it has been suggested that food frequency questionnaires may underestimate fiber intake, thus resulting in inadequate adjustment for fiber consumption.[35] However, fiber intake is more likely to be under-reported in men than in women[35] and the instrument used in the WHI showed good correlations with dietary recalls. [28] A purely speculative explanation is that severe constipation might trigger an inflammatory process that in turn accelerates the development of atherosclerosis and cardiovascular events. Inflammation, with release of cytokines by activated macrophages, could be caused by excessive or abnormal bacterial proliferation. Bacterial overgrowth with movement of gut bacteria from the lumen across the intestinal mucosa and immune activation has been described in patients with irritable bowel syndrome, [36] and there is preliminary evidence of an association between infections and coronary heart disease. [37, 38]

This study presents some limitations. First, information about constipation was self-reported and limited to the previous four weeks. It has been suggested that self-reported constipation is not as specific and sensitive as symptom-based criteria [4] such as the number of bowel movements or the Rome II criteria.[39] The prevalence of constipation in our population was in fact higher (34%) than that reported in studies using objective criteria. If women in our study reported constipation that would not otherwise be confirmed by objective criteria, this would result in an underestimation of the associations between constipation and cardiovascular risk. Furthermore, the definition used in the WHI – “difficulty having bowel movements”- is similar to how primary care providers ask their patients about constipation.

Second, because of the particular population studied, including women who are post-menopausal, mostly white and educated beyond high school, these results may not be generalizable to younger age groups, and less educated women and men. The limitations however should not detract from the strengths of the study; that is, a large cohort of community-dwelling, older women who were prospectively followed for outcomes over 6–10 years.

In conclusion, in post-menopausal women constipation is a marker for the major risk factors for cardiovascular disease and for increased cardiovascular risk. We did not find evidence for an independent association or for a causal association between constipation and cardiovascular disease. Since constipation is easily assessed in a primary care setting, it may be a helpful tool to identify women who may present several risk factors for cardiovascular disease and who may be at increased cardiovascular risk. Considering the prevalence of constipation, further research is needed to confirm whether it may be a marker of cardiovascular risk in both men and women and in younger age groups.

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Figure 1.
Cumulative incidence of cardiovascular events by baseline constipation

Table 1

Baseline characteristics according to self-reported symptoms of constipation

Characteristic, % (n)	Total Sample 100 (73047)	Constipation severity			p-value [†]
		None 65.3 (47699)	Mild 25.7 (18790)	Moderate 7.4 (5391)	
Age					<0.001
50–59	32.4 (23634)	31.8 (15156)	34.7 (6514)	29.9 (1610)	30.3 (354)
60–69	44.3 (32377)	44.8 (21377)	43.7 (8216)	43.0 (2319)	39.9 (465)
70+	23.3 (17036)	23.4 (11166)	21.6 (4060)	27.1 (1462)	29.8 (348)
Race/ethnicity					<0.001
American Indian	0.4 (264)	0.3 (149)	0.4 (82)	0.5 (26)	0.6 (7)
Asian-Pacific Islander	2.8 (2054)	3.0 (1406)	2.8 (526)	1.9 (104)	1.5 (18)
Black	6.5 (4769)	5.8 (2747)	7.0 (1306)	10.2 (548)	14.4 (168)
Hispanic	3.1 (2238)	2.7 (1306)	3.3 (617)	4.5 (245)	6.0 (70)
White	86.2 (62998)	87.3 (41631)	85.6 (16074)	81.6 (4401)	76.4 (892)
Other/unknown	1.0 (724)	1.0 (460)	1.0 (185)	1.2 (67)	1.0 (12)
Education					<0.001
< High school	4.1 (2991)	3.5 (1660)	4.2 (793)	7.2 (387)	12.9 (151)
High school diploma	16.0 (11690)	15.2 (7262)	16.7 (3136)	19.3 (1039)	21.7 (253)
School after HS	36.3 (26533)	35.9 (17121)	36.6 (6875)	39.4 (2125)	35.3(412)
College degree	11.8 (8585)	12.2 (5811)	11.4 (2135)	9.6 (518)	10.4 (121)
School after college	31.8 (23248)	33.2 (15845)	31.1 (5851)	24.5 (1322)	19.7 (230)
Marital status					<0.001
Never married	4.7 (3412)	4.8 (2282)	4.5 (838)	4.4 (238)	4.6 (54)
Previously married	31.8 (23227)	32.5 (15516)	29.6 (5559)	32.3 (1739)	35.4 (413)
Currently married	63.5 (46408)	62.7 (29901)	66.0 (12393)	63.3 (3414)	60.0 (700)
Diabetes	4.0 (2882)	3.5 (1653)	4.3 (808)	6.3 (339)	7.0 (82)
BMI (kg/m²):					<0.001
Normal (<25)	41.5 (30297)	41.7 (19872)	42.4(7973)	37.5 (2022)	36.9 (430)
Overweight (25–29.9)	34.0 (24853)	34.0 (16200)	33.9 (6366)	35.4 (1906)	32.7 (381)
Obesity (30+)	24.5 (17897)	24.4 (11627)	23.7 (4451)	27.1 (1463)	30.5 (356)
Use of cholesterol-lowering medications	14.5 (10617)	13.6 (6495)	15.3 (2865)	18.5 (997)	22.3 (260)

	Total Sample	None	Constipation severity		p-value [†]
			Mild	Moderate	
Characteristic, % (n)	100 (73047)	65.3 (47699)	25.7 (18790)	7.4 (5391)	1.6 (1167)
Relative with MI	52.7 (38489)	51.9 (24773)	53.2 (9998)	56.4 (3039)	58.2 (679)
Smoking					
Never	50.7 (37013)	50.7 (24195)	50.5 (9488)	50.9 (2745)	50.1 (585)
Past	43.3 (31639)	43.2 (20626)	43.8 (8228)	42.7 (2299)	41.7 (486)
Current	6.0 (4395)	6.0 (2878)	5.7 (1074)	6.4 (347)	8.2 (96)
Physical activity (MET-hours/week)	10.0 (3.5, 20.2)	10.5 (3.8, 21.0)	9.5 (3.0, 19.0)	8.0 (2.3, 17.3)	6.3 (1.5, 5.5)
Past history of CHD	22.3 (16291)	20.6 (9817)	23.6 (4442)	30.0 (1615)	35.7 (417)
Depression	10.9 (7947)	9.0 (4280)	12.4 (2327)	19.1 (1031)	26.5 (309)
CES-D ≥0.06					
Optimism	23.0 (21.0, 26.0)	24.0 (22.0, 26.0)	23.0 (21.0, 25.0)	22.0 (20.0, 24.0)	22.0 (19.0, 24.0)
Frailty score					
0	56.4 (41167)	60.4 (28810)	52.7 (9899)	39.4 (2122)	28.8 (336)
1	30.2 (22029)	28.4 (13541)	32.4 (6094)	36.8 (1981)	35.4 (413)
2	13.5 (9851)	11.2 (5348)	14.9 (2797)	23.9 (1288)	35.8 (418)
White blood cell count	5.6 (4.7, 6.7)	5.6 (4.8, 6.7)	5.6 (4.7, 6.7)	5.7 (4.8, 6.8)	5.7 (4.8, 6.9)
Resting pulse (30 sec)	34.0 (31.0, 37.0)	34.0 (31.0, 37.0)	34.0 (31.0, 37.0)	34.0 (31.0, 37.0)	34.0 (31.0, 37.0)
Calcium channel blockers	9.6 (7035)	8.3 (3962)	10.9 (2042)	14.7 (794)	20.3 (237)
Diuretics	7.2 (5277)	6.7 (3177)	7.5 (1417)	9.8 (526)	13.5 (157)

* Observations reported as % (n) or Median (25th–75th percentile); observations with any missing data were omitted

[†] Chi-square or Kruskal-Wallis

Abbreviations: BMI= body mass index; MI= myocardial infarction; MET= Metabolic Equivalent of Task;

CHD=coronary heart disease; CES-D = Center for Epidemiological Studies Depression scale

Table 2

Dietary characteristics by constipation severity

Characteristic	Total sample	Severity of constipation			p [†]	
		None	Mild	Moderate		
Dietary fiber (g)	16.3 (12.1, 21.4)	16.5 (12.2, 21.6)	16.1 (12.0, 21.0)	15.6 (11.5, 20.8)	15.3 (11.0, 20.3)	<0.001
Dietary water(g)	1410.6 (1081.1, 1788.4)	1425.5 (1096.6, 1800.2)	1392.9 (1069.2, 1769.2)	1353.8 (1020.9, 1758.6)	1310.0 (985.9, 1758.6)	<0.001
Dietary alcohol (g) [‡]	5.08 (1.23, 12.79)	5.50 (1.34, 13.23)	4.16 (1.19, 12.45)	3.65 (1.05, 12.00)	2.71 (1.00, 10.54)	<0.001
Total calories (kcal)	1474.0 (1145.9, 1871.8)	1474.2 (1148.9, 1869.4)	1473.9 (1147.5, 1869.9)	1472.9 (1123.2, 1896.1)	1467.1 (1114.0, 1898.4)	0.0011

* Observations reported as median (25th–75th percentile); observations with any missing data omitted

[†] Kruskal-Wallis[‡] Drinkers only

Table 3

Adjusted and unadjusted hazard ratios (95% CI) of cumulative cardiovascular events by constipation severity

Outcome	Constipation severity			
	None	Mild	Moderate	Severe
All cardiovascular events				
<i>Full sample: n=72,628</i>				
# events	2891	1233	467	131
Events/1000 person-yrs	9.59	10.48	14.24	19.13
Unadjusted	Reference	1.09 (1.02, 1.17)	1.49 (1.35, 1.64)	2.00 (1.68, 2.38)
Model 1	Reference	1.13 (1.05, 1.20)	1.37 (1.24, 1.51)	1.77 (1.48, 2.11)
Model 2	Reference	1.05 (0.99, 1.13)	1.14 (1.03, 1.26)	1.38 (1.15, 1.64)
Model 3	Reference	1.02 (0.95, 1.09)	1.07 (0.97, 1.18)	1.23 (1.03, 1.47)

Model 1: adjusted for demographics (baseline age group, race/ethnicity, education, marital status). Age categorized as 50–59, 60–69, and 70–79. Marital status categorized as never married, previously married (widowed, divorced, or separated), and currently married or in marriage-like relationship). Education categorized as: < high school, high school or equivalent, some college, college degree, and post-graduate.

Model 2: adjusted for Model 1 covariates plus cardiovascular risk factors (previous history of cardiovascular disease, family history of MI, BMI, diabetes, high cholesterol, smoking, physical activity, hypertension) and log baseline heart rate. BMI categorized as underweight/normal (<25 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30 kg/m²).

Model 3: adjusted for Model 2 covariates plus dietary factors (water, fiber, alcohol, total calories), medications (calcium channel blockers, diuretics), log depression score, optimism score, frailty score, log WBC count. Dietary variables categorized by quartile in order to allow for non-linear associations.

Table 4

Adjusted and unadjusted hazard ratios (95% CI) of each cardiovascular event by constipation severity

	Constipation severity			
	None	Mild	Moderate	Severe
Death, CHD				
<i>Full sample: n=72,688</i>				
# events	145	43	17	11
Events/1000 person-yrs	0.47	0.35	0.50	1.52
Unadjusted	Reference	0.76 (0.54, 1.06)	1.06 (0.64, 1.76)	3.25 (1.76, 6.01)
Model 1	Reference	0.81 (0.58, 1.14)	0.94 (0.57, 1.55)	2.63 (1.42, 4.89)
Model 2	Reference	0.73 (0.52, 1.03)	0.69 (0.42, 1.15)	1.84 (0.99, 3.43)
Model 3	Reference	0.65 (0.46, 0.92)	0.58 (0.35, 0.97)	1.32 (0.70, 2.48)
Death, possible CHD				
<i>Full sample: n=72,688</i>				
# events	90	41	16	6
Events/1000 person-yrs	0.29	0.34	0.47	0.83
Unadjusted	Reference	1.17 (0.81, 1.69)	1.62 (0.95, 2.76)	2.90 (1.27, 6.62)
Model 1	Reference	1.22 (0.85, 1.77)	1.34 (0.78, 2.28)	2.18 (0.95, 5.01)
Model 2	Reference	1.15 (0.79, 1.66)	1.11 (0.65, 1.90)	1.65 (0.71, 3.81)
Model 3	Reference	1.04 (0.72, 1.51)	0.93 (0.54, 1.59)	1.24 (0.53, 2.89)
MI				
<i>Full sample: n=72,620</i>				
# events	663	299	103	31
Events/1000 person-yrs	2.16	2.49	3.05	4.34
Unadjusted	Reference	1.15 (1.01, 1.32)	1.41 (1.15, 1.74)	2.02 (1.41, 2.89)
Model 1	Reference	1.19 (1.04, 1.37)	1.29 (1.04, 1.58)	1.76 (1.22, 2.52)
Model 2	Reference	1.12 (0.98, 1.29)	1.07 (0.87, 1.32)	1.38 (0.96, 1.98)
Model 3	Reference	1.10 (0.96, 1.26)	1.04 (0.84, 1.28)	1.28 (0.89, 1.99)
Stroke				
<i>Full sample: n=72,615</i>				

Constipation severity				
	None	Mild	Moderate	Severe
# events	674	254	96	27
Events/1000 person-yrs	2.19	2.11	2.83	3.77
Unadjusted (p=0.0029)	Reference	0.96 (0.83, 1.11)	1.30 (1.05, 1.60)	1.73 (1.18, 2.54)
Model 1	Reference	1.01 (0.88, 1.17)	1.19 (0.96, 1.48)	1.53 (1.04, 2.26)
Model 2	Reference	0.97 (0.85, 1.12)	1.04 (0.84, 1.29)	1.28 (0.87, 1.88)
Model 3	Reference	0.94 (0.81, 1.08)	0.98 (0.78, 1.21)	1.15 (0.78, 1.70)
TIA				
<i>Full sample: n=72,614</i>				
# events	387	162	57	15
Events/1000 person-yrs	1.26	1.34	1.68	2.09
Unadjusted	Reference	1.07 (0.89, 1.29)	1.34 (1.01, 1.77)	1.67 (0.997, 2.80)
Model 1	Reference	1.10 (0.92, 1.32)	1.25 (0.94, 1.65)	1.51 (0.90, 2.54)
Model 2	Reference	1.05 (0.88, 1.26)	1.10 (0.83, 1.46)	1.23 (0.73, 2.07)
Model 3	Reference	1.02 (0.85, 1.22)	1.01 (0.76, 1.35)	1.07 (0.63, 1.80)
PTCA				
<i>Full sample: n=72,614</i>				
# events	768	344	120	36
Events/1000 person-yrs	2.50	2.87	3.56	5.06
Unadjusted	Reference	1.15 (1.01, 1.30)	1.42 (1.17, 1.72)	2.03 (1.45, 2.83)
Model 1	Reference	1.16 (1.03, 1.32)	1.32 (1.09, 1.60)	1.84 (1.31, 2.57)
Model 2	Reference	1.08 (0.95, 1.23)	1.08 (0.89, 1.31)	1.39 (0.99, 1.95)
Model 3	Reference	1.06 (0.93, 1.20)	1.03 (0.84, 1.25)	1.27 (0.91, 1.79)
CABG				
<i>Full sample: n=72,616</i>				
# events	461	211	80	23
Events/1000 person-yrs	1.50	1.75	2.36	3.22
Unadjusted	Reference	1.17 (0.994, 1.38)	1.58 (1.24, 2.00)	2.15 (1.41, 3.27)
Model 1	Reference	1.20 (1.02, 1.42)	1.46 (1.15, 1.85)	1.95 (1.28, 2.97)
Model 2	Reference	1.11 (0.94, 1.31)	1.15 (0.91, 1.46)	1.43 (0.94, 2.19)

Constipation severity					
	None	Mild	Moderate	Severe	
Model 3	Reference	1.08 (0.92, 1.28)	1.12 (0.88, 1.43)	1.34 (0.88, 2.05)	
Angina					
<i>Full sample: n=72,616</i>					
# events	1070	467	206	60	
Events/1000 person-yrs	3.50	3.91	6.17	8.61	
Unadjusted	Reference	1.12 (1.00, 1.24)	1.76 (1.51, 2.04)	2.45 (1.89, 3.17)	
Model 1	Reference	1.13 (1.02, 1.27)	1.62 (1.39, 1.88)	2.16 (1.67, 2.81)	
Model 2	Reference	1.04 (0.93, 1.16)	1.29 (1.11, 1.50)	1.60 (1.23, 2.07)	
Model 3	Reference	1.00 (0.90, 1.12)	1.20 (1.03, 1.40)	1.39 (1.07, 1.82)	

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; TIA, transient ischemic attack; PTCA, percutaneous coronary angioplasty; CABG, coronary artery bypass grafting.

Model 1: adjusted for demographics (baseline age group, race/ethnicity, education, marital status). Age categorized as 50–59, 60–69, and 70–79. Marital status categorized as never married, previously married (widowed, divorced, or separated), and currently married or in marriage-like relationship). Education categorized as: < high school, high school or equivalent, some college, college degree, and post-graduate.

Model 2: adjusted for Model 1 covariates plus cardiovascular risk factors (previous history of cardiovascular disease, family history of MI, BMI, diabetes, high cholesterol, smoking, physical activity, hypertension) and log baseline heart rate. BMI categorized as underweight/normal (<25 kg/m²), overweight (25.0 – 29.9 kg/m²), and obese (≥ 30 kg/m²).

Model 3: adjusted for Model 2 covariates plus dietary factors (water, fiber, alcohol, total calories), medications (calcium channel blockers, diuretics), log depression score, optimism score, frailty score, log WBC count. Dietary variables categorized by quartile in order to allow for non-linear associations.