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Water, Other Fluids, and Fatal Coronary Heart Disease

The Adventist Health Study

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Whole blood viscosity, plasma viscosity, hematocrit, and fibrinogen are considered independent risk factors for coronary heart disease and can be elevated by dehydration. The associations between fatal coronary heart disease and intake of water and fluids other than water were examined among the 8,280 male and 12,017 female participants aged 38–100 years who were without heart disease, stroke, or diabetes at baseline in 1976 in the Adventist Health Study, a prospective cohort study. A total of 246 fatal coronary heart disease events occurred during the 6-year follow-up. High daily intakes of water (five or more glasses) compared with low (two or fewer glasses) were associated with a relative risk in men of 0.46 (95% confidence interval (CI): 0.28, 0.75; *p* trend = 0.001) and, in women, of 0.59 (95% CI: 0.36, 0.97). A high versus low intake of fluids other than water was associated with a relative risk of 2.47 (95% CI: 1.04, 5.88) in women and of 1.46 (95% CI: 0.7, 3.03) in men. All associations remained virtually unchanged in multivariate analysis adjusting for age, smoking, hypertension, body mass index, education, and (in women only) hormone replacement therapy. Fluid intake as a putative coronary heart disease risk factor may deserve further consideration in other populations or using other study designs. *Am J Epidemiol* 2002;155:827–33.

blood viscosity; coronary disease; dehydration; fluids and secretions; hemorheology; men; water; women

Whole blood viscosity (1–3), plasma viscosity (4), fibrinogen (1–5), and hematocrit (2–6) levels are positively correlated with coronary heart disease. Even in the high "normal" range, they have been considered independent risk factors (2, 4–7). In some reports, the magnitudes of their effects are comparable with those of smoking, diastolic blood pressure, and low density serum cholesterol (2, 4, 6). These hemorheologic factors are found to be elevated years before manifestation of acute ischemic events (4) and are implicated in the early stages (6), acceleration (8), and extent (9) of atherosclerosis, as well as prognosis in patients with arteriosclerotic disease (5, 10). They are also associated with hypertension (11) and intermittent claudication (12). Additionally, a higher hematocrit level has been associated with tachycardia (13), infarct size (14), reduced oxygen transport (15), and reduced myocardial perfusion (5).

Elevation of hemorheologic factors can result from chronic hypohydration (16, 17). They also respond acutely to circadian changes in hydration (18, 19), normal daily activities (20), and use of medications such as diuretics (21). Moreover, an increased risk of coronary heart disease has been associated with circadian increases in hematocrit and fibrinogen (22). This may result in part from an increased risk of coronary thrombosis (4, 21).

Because of these reported relations, the authors prospectively examined the associations between fluid intake and risk of fatal coronary heart disease, using data from the Adventist Health Study, a large cohort study. The effects of plain water and fluids other than water were examined separately because both composition and volume may affect a fluid's impact on acute and chronic hydration (23, 24).

MATERIALS AND METHODS

Study design and participants

The Adventist Health Study is a cohort study designed to test the effects of lifestyle on the risk of coronary heart disease, cancer, and all-cause mortality. Details have been described elsewhere (25). Briefly, in 1976, persons aged 25 years or more living in California Seventh-day Adventist households were sent a detailed lifestyle questionnaire that was completed by 34,192 White, non-Hispanic persons (75 percent response rate). Analyses are confined to the 8,280 males and 12,017 females who reported no physician-diagnosed heart disease, stroke, or diabetes and were 38 years of age or more at baseline (because no fatal coronary heart disease events occurred in younger subjects).

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Abbreviation: CI, confidence interval.

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The lifestyle questionnaire included information on traditional and dietary risk factors of coronary heart disease and intake of all types of beverages. Intake of water was reported as the number of glasses consumed daily (less than one, from one to two, from three to four, from five to six, and more than six), whereas intake of other fluids was reported as the frequency of intake per day, week, or month.

The cohort was followed for 6 years. Follow-up data for coronary heart disease events were complete for 97 percent of the participants (25). The criteria for diagnosing fatal coronary heart disease in this study have been described in detail elsewhere (26). Briefly, fatal coronary heart disease defined as either "definite fatal myocardial infarction" or "other definite fatal coronary heart disease" required death within 30 days of a myocardial infarction confirmed by hospital records, electrocardiogram and cardiac enzymes, or fresh myocardial infarction recorded at autopsy. Deaths were found by computer-assisted linkage with the California death certificate files, the National Death Index, use of church records, contact with relatives, and, when available, autopsy reports.

Statistical analysis

For analysis, intake of all types of fluids was recoded to monthly intakes. A validity study on a subset of 147 participants of the Adventist Health Study found that the average serving size of fluids other than water was close to one 8-ounce (240 ml) glass (range, 0.94–1.28 glasses) (26). Alcoholic beverages were not included as part of the total fluid intake because they were consumed by less than 11 percent of this special population and then in very small amounts.

Participants with a total fluid intake of less than once per day ($n = 55$) or with a daily milk intake greater than seven times daily ($n = 206$) were considered outliers and excluded from analysis. However, including them in a sensitivity analysis of the final model did not significantly change the results. The use of three exposure categories allowed for analysis of dose-response relations. For water, these categories were obtained by collapsing the two lowest and the two highest intake levels. Similar categories for intake of fluids other than water were formed using average portion size data. This formed low intake comparison categories that were biologically reasonable with sufficient numbers of events to provide stability in multivariate analysis.

The Statistical Package for the Social Sciences (SPSS for Windows: Advanced Statistics Release 7.0, 1995, and 9.0.0, 1998; SPSS, Inc., Chicago, Illinois) was used for all analyses, including gender-specific Cox proportional hazard models (27). Subjects with missing values in any of the variables included in a model were excluded from the analysis. The assumption of proportional hazards was not violated as tested by the log-minus-log survival plots (27). In addition to the age-adjusted model (model 1), eight other models were examined. Model 2 adjusted for age and several conventional coronary heart disease risk factors (smoking, hypertension, educational level, body mass index, and, in women, estrogen replacement therapy). Models 3–8, in addition, adjusted for other variables one at a time: fluid other than that being tested, energy intake, exercise, and dietary factors found to be related to coronary heart disease in the Adventist Health Study (nuts, type of bread, and, in men, meat intake) (26, 28, 29), respectively. This kept the number of variables in a particular model in reasonable proportion to the number of events (27). In model 9, weight replaced body mass index as a variable in model 2.

The consistency of the association between water intake and risk of fatal coronary heart disease was further explored in age- and sex-adjusted models applied to subgroups of the population defined by dichotomization of 11 different coronary heart disease risk factors.

RESULTS

During follow-up, 246 fatal coronary heart disease events (128 in men, 118 in women) were reported. Baseline characteristics of the study population are shown in table 1. The subjects were well educated, 37 percent of men and 19 percent of women being college graduates. Overall, the population adhered to a lifestyle that is commonly held to be healthy, as assessed by their diet and level of exercise. Very few subjects drank alcoholic beverages or were current smokers, and these were usually non-Adventists living in Adventist households (8.7 percent of the total Adventist Health Study population). The mean daily intake of beverages among the study population and the general population is shown in table 2. Water was the fluid consumed in greatest amounts. Compared with the national averages (30), the Adventist Health Study population drank more water, milk, and fruit juices and less coffee, tea, and carbonated and alcoholic beverages.

Water intake and risk of coronary heart disease

The clearest and most consistent association with fatal coronary heart disease was found with water intake (table 3). Among men, univariate analysis showed a dose-response relation ($p < 0.001$). Compared with those drinking two or fewer glasses of water daily (low), subjects drinking from three to four glasses (medium) and five or more glasses (high) had relative risks of 0.65 (95 percent confidence interval (CI): 0.40, 1.05) and 0.46 (95 percent CI: 0.28, 0.75), respectively. Among women, the relative risks of drinking medium and high levels of water were 0.54 (95 percent CI: 0.32, 0.90) and 0.59 (95 percent CI: 0.36, 0.97), respectively. The associations remained virtually unchanged when adjusting for traditional risk factors as well as for fluids other than water, energy intake, diet, exercise, and when weight replaced body mass index in model 2. Therefore, we have included the results for only models 1–4.

The negative association between risk of fatal coronary heart disease and water intake was seen consistently when further tested within subgroups defined by 11 coronary heart disease risk factors. The relative risks then ranged from 0.34 to 0.73 for the highest level of water intake (table 4).

TABLE 1. Selected baseline characteristics of study participants 38 years of age or more who reported no physician-diagnosed heart disease, stroke, or diabetes at baseline (1976–1977), Adventist Health Study

Selected characteristic	Men (n = 8,280)	Women (n = 12,017)
Age (mean years (SD*))	57.6 (12.5)	59.2 (12.9)
Hypertensive (%)†	17	24
Smoking (%)		
Never smoked	61	86
Smoked in the past	33	12
Currently smokes	6	2
Body mass index (tertiles)‡		
Low	<23.4	<21.8
Medium	23.4–25.9	21.8–25.2
High	>25.9	>25.2
Education level (%)		
High school	34	39
Some college	30	43
College graduate	37	19
Exercise level (%)§		
None to low	31	39
Moderate	23	20
High	46	41
Energy intake (kcal quintiles)		
1	<2,100	<1,588
2	2,100–<2,268	1,588–<1,743
3	2,268–<2,401	1,743–<1,876
4	2,401–<2,562	1,876–<2,028
5	≥2,562	≥2,028
Weight (lb¶ quintiles)		
1	<150	<120
2	150–<165	120–<132
3	165–<178	132–<145
4	178–<195	145–<160
5	≥195	≥160
Menopausal females (%)	Not applicable	72
Current estrogen users among menopausal females (%)	Not applicable	30
Vegetarian status (%)		
Eats meat <1 time/week	48	56
Nut intake (%)		
Never	5	6
≤2 times/week	53	52
≥3 times/week	42	42
Type of bread (%)		
Whole wheat only	64	62
Mixed	23	29
White only	13	9
Alcohol intake (%)		
None	84	93

* SD, standard deviation.
† Self-reported, physician diagnosed.
‡ Body mass index = self-reported weight (kg)/height (m)^2.
§ Occupational and leisure exercise index.
¶ One pound = 0.454 kg.

Fluids other than water and risk of coronary heart disease

In univariate analysis, intake of fluids other than water was associated with increased risk of fatal coronary heart disease (table 5). The association was statistically significant in women who drank five or more compared with two or fewer servings daily, with a relative risk of 2.47 (95 percent CI: 1.04, 5.88). When adjusting for traditional risk factors, as well as for water and caloric intake, exercise, diet, and replacing body mass index with weight, the point estimates remained virtually unchanged and significance was retained. However, the confidence intervals around these estimates were quite wide.

We were unable to determine the degree to which juices or sugared drinks (including soda) might individually contribute to the increased risk of fatal coronary heart disease in women, because too few of this study population consumed any of these beverages individually more than once a day. After adjustment for water intake, the association with intake of milk (omitting soy milk) was close to the null and with caffeinated beverages (coffee, tea, and caffeinated sodas), positive but not statistically significant.

DISCUSSION

We have found a strong negative multivariate association between intake of water and risk of fatal coronary heart disease and, in contrast, a positive association between intake of fluids other than water and risk. These results were consistent between the sexes, although the negative association with water was stronger in men and the positive association with fluids other than water was stronger in women. Moreover, formal tests of the differences between the opposite-signed linear trends of water and fluids other than water were significant ($p < 0.01$) in both sexes independently.

Our study has strengths and limitations. As an observational study, potential confounding always needs to be considered. Could fluid consumption be a marker of other risk factors not included in the model? Few candidate confounding variables are obvious. Those subjects who drink more water may be more health conscious in other less clearly defined ways. Drinking more water may be a marker of higher physical activity or those with higher energy intake. However, a two-tailed Pearson's correlation test showed no correlation between water and energy intakes ($r = 0.08$, $p < 0.01$ and $r = 0.06$, $p < 0.01$ for males and females, respectively) and, when exercise and energy consumption are included in the multivariate model, the effect of water consumption remained. Diabetics, who may drink more fluids, are excluded from these analyses. That the negative association with water intake was relatively consistent across many subgroups of the population makes confounding less likely as an explanation for this effect.

The study population is large and relatively well educated, includes men and women with a broad range of ages, and provides detailed baseline information on the intake of fluids of different kinds. Data were missing for males and females, respectively, on between 1.7 and 6.6 percent and on between 1.3 and 9.0 percent of the various items included in the measurements of fluid intake. If the associations between fluid intake and coronary heart disease were markedly different for those who did not provide all the relevant data, then associations in the remainder may differ from those in the whole population. However, we have no reason to suspect this.

The results can strictly be applied only to the California Adventist population. Moreover, because they drink more water and less caffeinated and alcoholic beverages than the US averages, it could be that, unlike some other findings in this population, this specific finding may apply only to this

TABLE 2. Daily fluid intake in 8-oz (240 ml) servings per day of the US population aged 20 years or more in 1977–1978* and of study participants aged 38 years or more who reported no physician-diagnosed heart disease, stroke, or diabetes at baseline (1976–1977), Adventist Health Study

Fluids	Study participants						US population*	
	Men (*n* = 8,280)			Women (*n* = 12,017)			Men + women (*n* = 14,273)	
	Mean (SD†)	Range	% missing	Mean (SD)	Range	% missing	Mean (SD)	99th percentile
Water	4.7 (2.2)	0–>6	1.7	4.4 (2.1)	0–>6	1.8	2.9 (2.3)	10.6
Fluids other than water (nonalcoholic)	3.9 (2.2)	0–19		3.6 (2.1)	0–16.1		3.8	
Coffee	0.7 (1.5)	0–7	4.4	0.4 (1.0)	0–7	7.0	1.6 (1.9)	7.9
Hot chocolate	0.1 (0.2)	0–7	6.3	0.1 (0.2)	0–4.5	8.6	Included with milk	
Black tea	0.1 (0.5)	0–7	6.6	0.1 (0.4)	0–7	9.0	0.6 (1.1)	4.5
Other hot drinks‡	0.4 (0.8)	0–7	4.7	0.6 (1.0)	0–7	5.9	0.0 (0.1)	0.2
Milk	1.7 (1.3)	0–7	0.9	1.7 (1.3)	0–7	1.3	0.7 (0.8)	4.4
Juice, unsweetened	0.5 (0.5)	0–2	3.7	0.5 (0.5)	0–2	4.7	0.3 (0.3)§	2.1§
Juice, sweetened	0.1 (0.2)	0–2	5.3	0.07 (0.2)	0–2	8.2		
Fruit drinks	0.1 (0.3)	0–2	5.4	0.1 (0.3)	0–2	7.2	0.1 (0.4)	1.6
Carbonated soft drinks (noncaffeinated)¶	0.1 (0.2)	0–2	3.3	0.1 (0.2)	0–2	4.7	0.4 (0.8) (regular)#	3.4
Carbonated soft drinks (caffeinated)¶	0.1 (0.3)	0–2	3.3	0.1 (0.3)	0–2	5.4	0.1 (0.5) (low calorie)#	2.2
Alcoholic beverages	0.08 (0.34)	0–4	3.1	0.02 (0.14)	0–4	4.3	0.3 (0.9)	5.1

* 1977–1978 Nationwide Food Consumption Survey of the United States (A. G. Ershow and K. P. Cantor. Tables 62 and 63. In: Total water and tap water intake in the United States: population-based estimates of quantities and sources. Bethesda, MD: National Cancer Institute, 1989).
† SD, standard deviation.
‡ Including postum, herbal tea (except black tea), decaffeinated coffee, etc.
§ The Adventist Health Study differentiated between "juice, unsweetened" and "juice, sweetened," but the US population study did not.
¶ Regular + low calorie.
# Caffeinated + noncaffeinated.

population alone. However, California Adventists probably do not differ biochemically or physiologically from others. If these results describe causal associations, they will probably also be found in the general population. The traditional risk factors for coronary heart disease operate with their usual force in California Adventists (31). Associations

TABLE 3. Relative risk of fatal coronary heart disease according to water intake among study participants 38 years of age or more who reported no physician-diagnosed heart disease, stroke, or diabetes at baseline (1976–1977), Adventist Health Study

	8-oz (240 ml) glasses of water/day	Model 1*,†		Model 2*,‡		Model 3*,§		Model 4*,¶	
		RR#	95% CI#	RR	95% CI	RR	95% CI	RR	95% CI
Men (*n* = 8,280)	≤2	1.00		1.00		1.00		1.00	
	3–4	0.65	0.40, 1.05	0.60	0.36, 0.99	0.64	0.36, 1.16	0.67	0.40, 1.13
	≥5	0.46	0.28, 0.75	0.38	0.23, 0.64	0.33	0.17, 0.62	0.39	0.22, 0.67
		Trend *p* = 0.001		Trend *p* = 0.0002		Trend *p* = 0.0003		Trend *p* = 0.0003	
Women (*n* = 12,017)	≤2	1.00		1.00		1.00		1.00	
	3–4	0.54	0.32, 0.90	0.57	0.32, 1.00	0.44	0.21, 0.91	0.41	0.20, 0.85
	≥5	0.59	0.36, 0.97	0.61	0.35, 1.06	0.57	0.29, 1.11	0.52	0.27, 1.03
		Trend *p* = 0.08		Trend *p* = 0.1		Trend *p* = 0.17		Trend *p* = 0.17	

* Excluding subjects with unknown values for model variables.
† Adjusted for age.
‡ Adjusted for traditional coronary heart disease risk factors age, smoking, hypertension, body mass index, and education level for men, plus estrogen replacement therapy in menopausal women.
§ Adjusted for traditional coronary heart disease risk factors plus intake of fluids other than water.
¶ Adjusted for energy in addition to traditional coronary heart disease risk factors.
# RR, relative risk; CI, confidence interval.

TABLE 4. Relative risk of fatal coronary heart disease in dichotomized groupings of 10 coronary heart disease risk factors, among study men and women 38 years of age or more who reported no physician-diagnosed heart disease, stroke, or diabetes at baseline (1976–1977), Adventist Health Study

Risk factor for coronary heart disease	High vs. low water intake		Risk factor for coronary heart disease	High vs. low water intake	
	RR*,†	95% CI*		RR†	95% CI
Gender‡			Exercise		
Women	0.60	0.36, 0.98	High	0.60	0.34, 1.07
Men	0.46	0.28, 0.75	Low	0.55	0.35, 0.87
Age, years§			Meat consumption		
<80	0.68	0.43, 1.06	<1/week	0.46	0.28, 0.75
≥80	0.59	0.34, 1.02	≥1/week	0.54	0.34, 0.96
Smoker			Bread		
Never	0.45	0.30, 0.69	Whole wheat	0.38	0.25, 0.60
Ever	0.61	0.33, 1.16	Not whole wheat only	0.73	0.42, 1.28
Blood pressure			Nut intake		
Normotensive	0.52	0.33, 0.81	>1, 2/week	0.45	0.19, 1.04
Hypertensive	0.50	0.30, 0.85	≤1, 2/week	0.54	0.36, 0.80
Body mass index¶			Intake of fluids other than water		
≤23.7	0.34	0.14, 0.83	<3 times/day	0.60	0.24, 1.52
>23.7	0.52	0.32, 0.85	≥3 times/day	0.38	0.23, 0.62
Education					
>High school	0.56	0.31, 1.02			
≤High school	0.50	0.33, 0.77			

* RR, relative risk; CI, confidence interval.
† Relative risk comparing those with intake of five or more 8-oz (240 ml) glasses of water daily versus two or fewer, excluding unknowns and adjusted for age and sex except ‡ and §. RR = 1.00 for intake of two or fewer glasses of water daily. Results for medium level of water intake were omitted to conserve space.
‡ Adjusted for age only.
§ Adjusted for sex only.
¶ Body mass index = weight (kg)/height $(m)^2$.

TABLE 5. Relative risk of fatal coronary heart disease according to intake of "fluids other than water" among study participants 38 years of age or more who reported no physician-diagnosed heart disease, stroke, or diabetes at baseline (1976–1977), Adventist Health Study

	8-oz (240 ml) glasses of "fluids other than water"/ day	Model 1*,†		Model 2*,‡		Model 3*,§		Model 4*,¶	
		RR#	95% CI#	RR	95% CI	RR	95% CI	RR	95% CI
Men (n = 8,280)	≤2	1.00		1.00		1.00		1.00	
	>2–<5	1.44	0.75, 2.76	1.34	0.75, 2.76	1.29	0.65, 2.52	1.46	0.73, 2.92
	≥5	1.46	0.70, 3.03	1.07	0.48, 2.35	1.00	0.45, 2.22	1.34	0.59, 3.04
		Trend p = 0.4		Trend p = 0.9		Trend p = 0.9		Trend p = 0.7	
Women (n = 12,017)	≤2	1.00		1.00		1.00		1.00	
	>2–<5	2.02	0.90, 4.50	2.14	0.83, 5.50	2.01	0.78, 5.18	2.25	0.87, 5.80
	≥5	2.47	1.04, 5.88	2.98	1.10, 8.07	2.79	1.03, 7.62	3.32	1.18, 9.30
		Trend p = 0.06		Trend p = 0.03		Trend p = 0.04		Trend p = 0.02	

* Excluding subjects with unknown values for model variables.
† Adjusted for age.
‡ Adjusted for traditional coronary heart disease risk factors age, smoking, hypertension, body mass index, and education level for men, plus estrogen replacement therapy in menopausal women.
§ Adjusted for intake of water in addition to traditional coronary heart disease risk factors.
¶ Adjusted for energy in addition to traditional coronary heart disease risk factors.
# RR, relative risk; CI, confidence interval.

between coronary heart disease and certain foods (nuts and meats), which were first described in this population, have now been confirmed in several other populations (32–34).

An important question is whether there are known mechanisms that might underlie these results if the associations are causal. There is a small literature strongly suggesting that several factors related to blood viscosity are adversely affected by hypohydration (16–21, 35–39) and that these rheologic factors predict the risk of coronary heart disease (4, 6, 8, 9). Whole blood viscosity is determined mainly by hematocrit and fibrinogen levels, both of which have frequently been associated with coronary heart disease events (1–9).

It is interesting that, although percentage differences in blood viscosity-associated factors between those who do and do not experience coronary heart disease events are often statistically significant, they are quite small, often in the range of 2–7 percent (2, 6, 9, 18, 19, 21, 40, 41). Yet these are the kind of changes seen in mild, nonclinical hypohydration (16–20), within the presumed normal range.

There is a well-described circadian rhythm of hemorheologic factors that can be quite marked (18, 41), perhaps due to continued non-reabsorbed glomerular filtration at night in the absence of fluid intake (19, 42). One can speculate that relatively elevated blood viscosity in the morning could be one factor accounting for the well-known increased risk of coronary heart disease events at this time of the day (43).

Why may coronary heart disease risk be increased with a higher intake of fluids other than water? Several mechanisms can be postulated. Caffeinated beverages are mild diuretics and thus may raise blood viscosity (44). High energy drinks such as juices and regular sodas have osmolalities between 556 and 836 mOsm/kg (45). Their consumption causes a net movement of fluid from the vascular system into the intestinal lumen, resulting in a rapid elevation in blood viscosity after consumption (24). Perfusing the duodenum with a glucose solution that has an osmolality of 456 mOsm/kg, which is lower than that of juices and regular soda, was observed to reduce plasma volume by 3.3 percent within 105 minutes (46). Further, serum triglyceride levels may be raised by drinks containing high concentrations of sugar, including fruit juices (47–50). In subjects drinking 2.7 glasses (640 ml) of grape juice and three glasses (750 ml) of orange juice daily, triglyceride levels were seen to increase by 50 percent (51) and 30 percent (52), respectively. There is growing evidence that postprandial and fasting elevations of plasma triglycerides are independent coronary heart disease risk factors (53–58), even within the high normal range (59). Elevated triglyceride levels have been positively associated with coagulation factor VII (60), plasminogen activator inhibitor-1 (57), and thrombotic factors X (60) and IX (57) but inversely associated with antithrombin III (58) and plasma fibrinolytic activity (57). We hypothesize that higher intake of diuretic and high energy beverages results in more frequent and larger exposure to conditions that increase the risk of thrombosis and atherosclerosis.

The magnitudes of the apparent effects associated with greater intake of both types of fluid appeared to differ between the two sexes. Although these differences could easily be explained by chance, it may be relevant that women typically have lower blood viscosity than do men because of lower hematocrit levels, erythrocyte rigidity, and aggregability at all shear rates (7). They may also experience less reduction in plasma volume with dehydration (61) and regulate their body temperatures at lower sweat rates (62). Reduced water intake in women, therefore, may not produce high levels of blood viscosity as readily as in men. On the other hand, because men have larger blood volumes than do women, the same quantities of hyperosmolar fluids or caffeinated beverages (fluids other than water) would produce a lower proportionate decrease in intravascular volume and subsequently a smaller increase in blood viscosity.

In summary, we report intriguing associations between the intake of fluids and the risk of coronary heart disease that are not obviously explained by confounding. Further research in other populations, possibly including experimental study designs, is necessary to decide whether the associations are causal.

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