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Impact of Modifiable Risk Factors on B-type Natriuretic Peptide and Cardiac Troponin T Concentrations

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Abstract

Alcohol use, physical activity, diet, and cigarette smoking are modifiable cardiovascular risk factors that have a substantial impact on the risk of myocardial infarction, stroke, and cardiovascular death. We hypothesized that these behaviors may alter concentrations of cardiac troponin, a marker of myocyte injury, and B-type natriuretic peptide, a marker of myocyte stress. Both markers have shown strong association with adverse cardiovascular outcomes. In 519 women with no evidence of cardiovascular disease, we measured circulating concentrations of cardiac troponin T, using a high-sensitivity assay (hsTnT), and the amino-terminal fragment of B-type natriuretic peptide (NT-proBNP). We used logistic regression to determine if these behaviors were associated with detectable hsTnT (>3 ng/L) or with NT-proBNP in the highest quartile (> 127.3 ng/L). The median (Q1-Q3) NT-proBNP of the cohort was 68.8 (40.3–127.3), and 30.8% (160/519) of the cohort had detectable circulating hsTnT. In adjusted models, women who drank 1–6 drinks per week had lower odds of having a detectable hsTnT (0.58, 95% CI: 0.34–0.96) and lower odds of having an elevated NT-proBNP (OR 0.55, 95% CI 0.32–0.96). We were subsequently able to validate the results for B-type natriuretic peptide in a large independent cohort. In conclusion, our results suggest that regular alcohol consumption is associated with lower concentrations of hsTnT and NT-proBNP, two cardiovascular biomarkers associated with

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cardiovascular risk, and raise the hypothesis that the beneficial effects of alcohol consumption may be mediated by direct effects on the myocardium.

Keywords

cardiovascular disease; risk factors; troponin; BNP

Introduction

A substantial portion of the worldwide population attributable risk for myocardial infarction is due to potentially modifiable risk factors, including alcohol consumption, physical activity, diet, and cigarette smoking.¹ The mechanisms by which these behaviors modify cardiovascular risk, however, remain incompletely understood. Prospective studies in the general population have reported strong associations between circulating concentrations of natriuretic peptides (markers of myocyte stress) and cardiac troponin (a marker of myocyte injury) and adverse cardiovascular outcomes.^{2–9} Published data on the effects of alcohol consumption, physical activity, diet, and cigarette smoking on these two markers of myocardial stress and injury are scarce. While alcohol consumption has been associated with a significant increase in baseline B-type natriuretic peptide (BNP) in binge drinkers, other studies have reported no relationship, and we are not aware of any published studies on the relationship between alcohol consumption and cardiac troponin.^{10,11} Regular physical activity appears to blunt the age-associated increases observed in cardiac troponin T and the amino-terminal fragment of B-type natriuretic peptide (NT-proBNP).¹² Data for cigarette smoking and diet are similarly scarce. We sought to systematically examine the effects of alcohol consumption, regular physical activity, diet, and smoking on a marker of myocardial stress (NT-proBNP) and a marker of myocardial injury (troponin T) in a cohort of 519 apparently healthy women from the Women's Health Study.

Methods

Women included in this study were enrolled in the Women's Health Study (WHS), a completed, randomized, double-blind, placebo-controlled 2×2 factorial trial of aspirin and vitamin E in the prevention of cardiovascular disease and cancer. The WHS enrolled 39,876 female health professionals without coronary heart disease, cerebrovascular disease, or cancer, 19,871 of whom provided a fasting blood sample before randomization. The 519 white women included in this study were an age-stratified sample of these 19,871 women who had adequate blood sample volume available for measurement of NT-proBNP and cardiac troponin T. This sample is part of a larger WHS substudy that is described in detail elsewhere.^{5,9,13}

Both NT-proBNP and cardiac troponin T were measured using an electrochemiluminescent immunoassay from Roche Diagnostics. The assay used to measure NT-proBNP is commercially available and has day-to-day variability of 3.2%, 2.4%, and 2.2%, at concentrations of 175,434, and 6781 ng/L. We used a novel, high-sensitivity assay for cardiac troponin T (hsTnT) that has a lower limit of detection of 3 ng/L. The 99th percentile

in a healthy population is < 14 ng/L, and the concentration at which the assay has a 10% coefficient of variation is reported to be less than this value.^{14,15}

At enrollment, women were asked to estimate the time per week during the past year they spent on walking, jogging, running, biking, aerobic exercise or dance, racquet sports, lap swimming, weight lifting, and yoga or stretching. The questionnaire used to collect this information has shown to be reliable and valid.^{16,17} A metabolic equivalent (MET) task score was assigned to each activity and the energy expended was determined by multiplying the MET score by the hours spent on the physical activity. The sum of these energies represented total energy expenditure and was used to calculate the total energy expended by the patient per week (MET hours/week) during the year prior to study entry.

A validated semiquantitative food frequency questionnaire was used to collect consumption (frequency and type) of dairy foods, fruits and vegetables, eggs and meat, breads, cereals and starches, sweets and baked goods, and beverages over the past year.^{18,19} The diet data was utilized to calculate an Alternative Healthy Eating Index-2010 (AHEI-2010) score. The calculation of the AHEI-2010 score has been described previously.²⁰ We excluded alcohol use in our calculation as we decided a priori to include alcohol as a separate modifiable risk factor. AHEI scores both including and excluding alcohol have shown to inversely associate with risk of coronary heart disease.^{20,21} Cigarette consumption and alcohol use were also collected via questionnaire.

Based on the data collected, physical activity was split into quartiles (<3.5 MET hours/week, 3.5–<10.8 MET hours/week, 10.8–<23.4 MET hours/week, 23.4 MET hours/week). AHEI-2010 score was split into quintiles (<42.4, 42.4–<48.2, 48.2–<53.0, 53.0–<57.5, 57.5). Alcohol was split into categories of “Rarely/Never”, “1–3 drinks/month”, “1–6 drinks/week”, or “1 drink/day”. Smoking status was coded as “Never/Past” or “Current”.

NT-proBNP concentrations were divided into increasing quartiles and continuous and categorical baseline characteristics were compared across NT-proBNP quartile using Jonckheere-Terpstra and Cochran-Armitage tests, respectively. Baseline characteristics for women with detectable hsTnT concentrations were compared to those without detectable hsTnT using Wilcoxon Rank-Sum and Chi-Square tests for continuous and categorical variables, respectively. Our primary analysis used logistic regression to test for associations between the four modifiable behaviors and either a prospectively-defined abnormal NT-proBNP (> 127.3 ng/L) or the presence of a detectable hsTnT (hsTnT > 3 ng/L). An abnormal NT-proBNP was prospectively defined as the top quartile (> 127.3 ng/L) of the distribution in our population of initially healthy middle-aged women. Thresholds lower than this have been associated with adverse cardiovascular outcome in this cohort.⁹ Logistic regression models were adjusted for age (Model 1); age, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of hypertension, triglycerides, postmenopausal status, and estimated glomerular filtration rate (Model 2); and the Model 2 covariables plus physical activity, alcohol use, smoking status, and AHEI-2010 score (Model 3).

We validated our observations in a subcohort of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study. The JUPITER subcohort contains 12,951 men and women with high-sensitivity cardiac troponin I (hsTnI) and 11,052 men and women with B-type natriuretic peptide (BNP) measurements available. All participants in the cohort were initially free of cardiovascular disease. Baseline characteristics of the cohort have been previously described.⁸ In JUPITER, we calculated tertiles separately in men and women, and used logistic regression to test for associations between alcohol use and odds of having a BNP in the highest tertile (28.6 ng/L for men, 44.4 ng/L for women) or hsTnI in the highest tertile (4.6 ng/L in men, 3.9 ng/L in women). BNP and hsTnI values in the highest tertile have been shown to associate with increased risk of first major cardiovascular event in this cohort.⁸ Models were adjusted for age, race and sex (Model 1), age, race, sex, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of hypertension, triglycerides, and estimated glomerular filtration rate (Model 2), and the covariables in Model 2 plus alcohol use, physical activity, and smoking status (Model 3).

All statistical analyses were performed using SAS 9.2 (SAS Institute Inc.).

Results

The median (Q1-Q3) age of the study population was 57.2 years (51.2–64.5) and the median (Q1-Q3) NT-proBNP concentration was 68.8 ng/L (40.3–127.3 ng/L). Baseline characteristics of the women, stratified by quartile of NT-proBNP concentration, are displayed in Table 1. As can be seen, higher concentrations of NT-proBNP are associated with older age and higher high-density lipoprotein cholesterol concentrations as well as lower body mass index, total cholesterol, triglycerides, and low-density lipoprotein cholesterol. Women with detectable hsTnT were older, had a higher prevalence of hypertension, and a lower prevalence of current smoking than women without a detectable hsTnT (Table 2).

The associations between alcohol consumption and an elevated NT-proBNP or a detectable hsTnT are presented in Figure 1A and Supplementary Table 1. In adjusted models (Model 3), we observed that women who drank 1–6 drinks/week had 45% lower odds of having an elevated NT-proBNP compared to women who rarely or never drink. Additionally, women who drank 1–6 drinks/week had 42% lower odds of having a detectable hsTnT, while women who drank 1 drink/day had 68% lower odds of having a detectable hsTnT compared to women who rarely or never drink (P-trend: 0.004; Figure 1A and Supplementary Table 1).

In sensitivity analyses controlling additionally for income and education level, we did not observe any significant attenuation of these effect estimates (data not shown). In exploratory analyses, we separated women who drank 1 drink/day into those who drank 1 to 2 drinks per day and those who drank 2 drinks/day. In total 28 women drank 1 to 2 drinks per day, and 14 women drank 2 drinks/day. In adjusted models (Model 3), those who drank 1–2 drinks/day had a 78% decreased odds of having a detectable hsTnT compared to women who drank rarely/never. No significant association was seen with this group and odds of an

elevated NT-proBNP. Neither biomarker was significant in the 2 drinks per day group (data not shown). Finally, when compared to women who drank only rarely or never, women who drank any alcohol had 43% decreased odds of having an elevated NT-proBNP and had 47% decreased odds of having a detectable hsTnT (data not shown). We were able to validate the association between alcohol consumption and BNP in 11,052 participants from the JUPITER trial. In adjusted models (Model 3), men and women who drank 1 drink per day had 15% lower odds of having a BNP in the highest tertile (Table 3).

In age-adjusted models, current smoking was associated with 54% decreased odds of a detectable hsTnT. This relationship remained significant after adjustment for other cardiovascular risk factors as well as for alcohol use and AHEI-2010 score but became non-significant after physical activity was added to the model (Figure 1B and Supplementary Table 2). In a validation dataset from the JUPITER trial, current smoking was associated with 15% increased odds of a detectable cardiac troponin I (Supplementary Table 3).

We did not observe any clear associations between physical activity or the AHEI-2010 score and the odds of either a detectable hsTnT or an elevated NT-proBNP (Figure 1C and 1D; Supplementary Tables 4 and 5).

Discussion

In this cross-sectional study of 519 women without diabetes mellitus or cardiovascular disease, we observed a statistically significant association between regular alcohol consumption and lower concentrations of 2 myocardial-derived markers of adverse cardiovascular risk. Consumption of 1–6 drinks/week was associated with lower odds of having elevated concentrations of NT-proBNP, a marker of myocardial stress, and lower odds of having detectable concentrations of cardiac troponin T, a marker of myocardial injury. Furthermore, we were able to validate the association between alcohol consumption and natriuretic peptide concentrations in men and women enrolled in the JUPITER trial.

Elevated concentrations of natriuretic peptides and cardiac troponin have shown strong association with adverse cardiovascular outcomes, including cardiovascular death, in this cohort and in others,^{5,7–9} raising the possibility that some of alcohol's benefits are mediated by reductions in myocardial stress and injury. Indeed, a number of studies have demonstrated an association between low to moderate alcohol consumption (1 drink/day in women and 1–2 drinks/day in men) and a reduction in the risk of heart disease and myocardial infarction.^{1,22–24}

Moderate alcohol consumption has been shown to have beneficial effects on lipid levels, oxidative stress, insulin sensitivity, coagulation, and coronary blood flow.²² Further, animal models have shown that moderate consumption promotes survival signaling through up-regulation of AKT, pAKT, pBCL2, and AMPK while down regulating apoptosis through decreased expression of TNF α , BAD, FOXO3, and caspase 9 in both ischemic and normal myocardium.²⁵ Our observations support the possibility that moderate alcohol consumption has direct impacts on myocardial metabolism and turn over through reductions in myocardial stress and myocardial injury. While alcohol consumption may be acting through

other pathways known to alter myocardial stress and injury, such as blood pressure or sodium and water retention, the association between alcohol and NT-proBNP and hsTnT concentrations remained significant after including many of these possible pathways in our model.

Alternative explanations for our findings could include alcohol-induced alterations in the breakdown and metabolism of both circulating hsTnT and NT-proBNP. NT-proBNP is mostly passively cleared through organs with high blood flow rates such as the muscles, liver, and kidney.²⁶ Thus, alcohol-induced changes in the cytochrome P-450 system in the liver seem unlikely to alter NT-proBNP clearance. Recent evidence suggests that hsTnT is broken down into smaller fragments in the blood within the first 12 hours of release.²⁷ How these smaller fragments are degraded and cleared is poorly understood.²⁷ The diagnostic kit used in this study has been shown to bind to both intact hsTnT and its degradation fragments.²⁸

While de Fillipi *et al.* were able to demonstrate blunting of age-associated increases in concentrations of cardiac troponin T and NT-proBNP among those with regular physical activity,¹² we were unable to find a significant association between physical activity and either of these biomarkers. We may have failed to observe an association due to differences in sample size, in the timing of the collection of blood, differences in intensity of the physical activity, or because our study only included women. Interestingly, current smoking was associated with decreased odds of detectable hsTnT. While this relationship was attenuated and no longer significant after adjusting for physical activity, the reasons for this observation are unclear. One possible explanation is that chronic exposure to tobacco smoke may alter the production and release of cardiac troponin to the circulation, or speed the degradation of the circulating protein.

The strengths of our study include the standardized and well-validated collection of dietary patterns, physical activity, alcohol consumption, and cigarette use in a large number of healthy women. While we controlled for a wide variety of possible confounders, residual unmeasured confounding could still exist. Unfortunately, we are unable to address whether changes in healthy behaviors might alter these biomarkers on serial examinations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Modifiable Risk Factors (A: Alcohol, B: Smoking, C: Leisure Time Physical Activity, D: Alternative Healthy Eating Index-2010 Score,) and the Odds of Having an Elevated NT-proBNP Concentration(●) or a Detectable Cardiac Troponin T (■). Models adjusted for age, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of hypertension, triglycerides, postmenopausal status, estimated glomerular filtration rate, physical activity, alcohol use, smoking status, Alternative Healthy Eating Index-2010 score. Abbreviations: MET, Metabolic Equivalent; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; hsTnT, High-Sensitivity Cardiac Troponin T.

Table 1

Baseline characteristics of the cohort, stratified by N-terminal pro-B-type natriuretic peptide. Categorical variables presented as n (%) and continuous variables presented as median (25th–75th percentile).

Variable	NT-proBNP Quartile				P-Value
	1 (n=129)	2 (n=130)	3 (n=130)	4 (n=130)	
NT-pro BNP (ng/L)	<40.3	40.3 – < 68.8	68.8 – <127.3	127.3	
Age (years)	54.3 (49.0–58.9)	54.7 (49.4–61.5)	59.7 (53.0–66.2)	63.3 (55.5–68.8)	<0.001
Hypertension	40 (31.0%)	29 (22.3%)	39 (30.0%)	51 (39.2%)	0.07
Systolic Blood Pressure (mm Hg)	125 (115–135)	125 (115–135)	125 (115–135)	125 (115–145)	0.18
Body Mass Index (kg/m ²)	26.6 (23.9–30.6)	25.5 (22.5–27.4)	25.0 (22.8–28.3)	24.6 (22.1–27.1)	<0.001
Hypercholesterolemia	51 (39.5%)	43 (33.1%)	35 (26.9%)	45 (34.6%)	0.26
Total Cholesterol (mg/dl)	221.0 (202.0–250.0)	217.5 (187.0–246.0)	211.0 (186.0–238.0)	209.0 (186.0–233.5)	0.003
Low-Density Lipoprotein Cholesterol (mg/dl)	133.5 (115.2–159.6)	127.5 (102.1–153.0)	124.2 (101.9–144.4)	123.2 (101.5–145.3)	0.002
High-Density Lipoprotein Cholesterol (mg/dl)	46.6 (41.0–56.0)	52.9 (43.4–63.2)	56.4 (44.5–65.0)	52.2 (44.1–61.7)	<0.001
Triglycerides (mg/dl)	138.0 (98.0–211.0)	127.5 (83.0–174.0)	114.0 (81.0–169.0)	114.5 (82.5–158.5)	0.005
Postmenopausal	78 (60.5%)	84 (65.0%)	99 (76.2%)	103 (79.2%)	<0.001
Estimated Glomerular Filtration Rate (ml/min/1.73m ²)	100.0 (82.7–128.5)	94.9 (77.4–110.8)	87.6 (75.8–106.2)	87.1 (70.1–101.6)	<0.001
Alcohol Consumption					0.17
Rarely/Never	65 (50.4%)	57 (43.9%)	53 (40.8%)	71 (54.6%)	
1–3 Drinks/Month	19 (14.7%)	18 (13.9%)	13 (10.0%)	14 (10.8%)	
1–6 Drinks/Week	39 (30.2%)	46 (35.4%)	48 (36.9%)	34 (26.2%)	
1 Drink/Day	6 (4.7%)	9 (6.9%)	16 (12.3%)	11 (8.5%)	
Alcohol (drinks/day)	0.0 (0.0–0.2)	0.1 (0.0–0.4)	0.1 (0.0–0.5)	0.0 (0.0–0.2)	0.99

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Variable	NT-proBNP Quartile				P-Value
	1 (n=129)	2 (n=130)	3 (n=130)	4 (n=130)	
Alcohol (grams/day)	0.0 (0.0–2.9)	1.1 (0.0–4.6)	1.2 (0.0–5.9)	0.0 (0.0–2.3)	0.99
Physical Activity (Metabolic Equivalent hours/week)	8.4 (2.5–23.1)	13.0 (4.4–22.6)	10.2 (5.0–24.2)	11.4 (3.5–24.0)	0.42
Alternate Healthy Eating Index-2010 Score	51.4 (44.4–56.4)	50.0 (42.3–57.2)	51.0 (44.7–55.9)	49.2 (42.9–55.9)	0.72
Current Smoker	14 (10.9%)	17 (13.1%)	9 (6.9%)	11 (8.5%)	0.25

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide

* Continuous variables compared across quartiles of NT-proBNP using Jonckheere-Terpstra test. Categorical variables compared across quartiles of NT-proBNP using Cochran-Armitage test.

Table 2

Baseline characteristics of the cohort, stratified by the presence of a detectable Cardiac Troponin T by high-sensitivity assay. Categorical variables presented as n (%) and continuous variables presented as median (25th–75th percentile).

Variable	Detectable hsTnT*		P-Value [†]
	No (n=359)	Yes (n=160)	
Age (years)	55.8 (50.3–63.2)	61.0 (53.8–67.3)	<0.001
Hypertension	98 (27.3%)	61 (38.1%)	0.01
Systolic Blood Pressure (mm Hg)	125.0 (115.0–135.0)	125.0 (115.0–135.0)	0.02
Body Mass Index (kg/m ²)	25.1 (22.7–28.2)	25.8 (23.3–29.1)	0.06
Hypercholesterolemia	113 (31.5%)	61 (38.1%)	0.14
Total Cholesterol (mg/dl)	218.0 (189.0–246.0)	211.5 (187.0–233.0)	0.05
Low-Density Lipoprotein Cholesterol (mg/dl)	127.2 (107.6–151.9)	124.2 (106.5–144.7)	0.30
High-Density Lipoprotein Cholesterol (mg/dl)	52.0 (43.8–62.9)	49.3 (41.8–60.4)	0.06
Triglycerides (mg/dl)	124.0 (86.0–184.0)	116.0 (82.0–161.0)	0.19
Postmenopausal	240 (66.9%)	124 (78.0%)	0.01
Estimated Glomerular Filtration Rate (ml/min/1.73m ²)	92.5 (76.6–109.1)	92.5 (74.8–113.1)	0.98
Alcohol Consumption			0.05
Rarely/Never	156 (43.5%)	90 (56.3%)	
1–3 Drinks/Month	47 (13.1%)	17 (10.6%)	
1–6 Drinks/Week	123 (34.3%)	44 (27.5%)	
1 Drink/Day	33 (9.2%)	9 (5.6%)	
Alcohol (drinks/day)	0.1 (0.0–0.4)	0.0 (0.0–0.2)	0.003
Alcohol (grams/day)	1.1 (0.0–5.1)	0.0 (0.0–2.0)	0.003
Physical Activity (Metabolic Equivalent hours/week)	10.3 (3.8–22.5)	12.6 (2.9–26.3)	0.55
Alternative Healthy Eating Index-2010 Score	50.9 (43.1–56.1)	49.3 (43.9–57.0)	0.95
Current Smoker	42 (11.7%)	9 (5.6%)	0.03

Abbreviations: hsTnT, High-Sensitivity Cardiac Troponin T

* Detectable high-sensitivity cardiac troponin T is 3 ng/L.

[†] Continuous variables compared using Wilcoxon Rank-Sum test, and categorical variables compared using Chi-Square test.

Table 3

Validation in the JUPITER cohort. Alcohol use and the odds of having a B-type Natriuretic Peptide in the highest tertile or a high-sensitivity cardiac troponin I in the highest tertile*

Odds Ratio (95% Confidence Interval)						P-Value
Category of Alcohol Use	Rarely/Never	1–3 Drinks/Month	1–6 Drinks/Week	1 Drink/Day	Linear Trend	
BNP						
N normal/elevated	2926/1575	906/452	1839/854	1710/790	N/A	
Model 1	1.00	1.07 (0.93–1.23)	0.94 (0.84–1.05)	0.91 (0.81–1.03)	0.08	
Model 2	1.00	1.05 (0.92–1.21)	0.90 (0.80–1.01)	0.85 (0.74–0.96)	0.004	
Model 3	1.00	1.06 (0.92–1.22)	0.91 (0.81–1.02)	0.85 (0.75–0.96)	0.005	
hsTnI						
N normal/elevated	3448/1889	1136/531	2120/1011	1913/903	N/A	
Model 1	1.00	0.93 (0.82–1.06)	0.92 (0.83–1.02)	0.91 (0.81–1.01)	0.06	
Model 2	1.00	0.95 (0.84–1.08)	0.98 (0.88–1.09)	0.94 (0.84–1.06)	0.39	
Model 3	1.00	0.95 (0.83–1.07)	0.97 (0.87–1.08)	0.94 (0.83–1.05)	0.31	

*The sex-specific cutpoints for the highest tertile of B-type natriuretic peptide were 28.6 ng/L for men and 44.4 ng/L for women. The sex-specific cutpoints for high-sensitivity cardiac troponin I were 4.6 ng/L for men and 3.9 ng/mL for women.

Abbreviations: BNP, B-type Natriuretic Peptide; hsTnI, High-Sensitivity Cardiac Troponin I; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin;

Model 1: Adjusted for age, race and sex

Model 2: Adjusted for variables in Model 1 plus body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of hypertension, triglycerides, estimated glomerular filtration rate

Model 3: Adjusted for variables in Model 2 plus physical activity and smoking