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Original Research

Joint effect of highly-sensitive cardiac troponin T and ankle-brachial index on incident cardiovascular events: The MESA and CHS

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ABSTRACT

Background: Elevated highly-sensitive cardiac troponin-T (hs-cTnT≥14 ng/L) and low ankle-brachial index (ABI<0.9) are risk factors for atherosclerotic cardiovascular diseases (ASCVD) but their joint effect on the risk of ASCVD events is unknown.

Methods: We used data from the two population-based cohort studies, the Multi-Ethnic study of Atherosclerosis (MESA) and Cardiovascular Heart Study (CHS) among 10,897 participants free of CVD events at baseline (mean age 66.3 years, 44.7% males). Incident ASCVD was defined as CHD (fatal/non-fatal MI or revascularization), transient ischemic attack, or stroke,. Hazard ratio (HR) and 95% CI was calculated from a Cox regression model. Interaction on the additive scale was assessed using relative excess risk due to interaction (RERI) and interaction on the multiplicative scale was assessed by Likelihood ratio (LR) test.

Results: At baseline (2000–2002 for MESA and 1989–1990 for CHS), 10.2% of participants had elevated hs-cTnT and 7.5% had low ABI. During a median follow-up of 13.6 years (interquartile range, 7.5–14.7 years), there were 2590 incident ASCVD and 1542 incident CHD events. The hazard of CHD and ASCVD was higher in participants with both elevated hs-cTnT and low ABI [HR(95% CI): CHD: 2.04 (1.45, 2.88), ASCVD: 2.05 (1.58, 2.66)] than those with only elevated hs-cTnT [CHD: 1.65 (1.37, 1.99), ASCVD: 1.67 (1.44, 1.99)] or only low ABI [CHD: 1.87 (1.52, 2.31), ASCVD: 1.67 (1.42, 1.97)]. Antagonistic multiplicative interaction was observed for CHD (LR test *p*-value=0.042) but not for ASCVD (LR test *p*-value =0.08). No significant additive interaction was detected for CHD and ASCVD (RERI *p*-value ≥0.23).

Conclusion: The observed joint effect of elevated cTnT and low ABI on ASCVD risk was smaller (i.e., antagonistic interaction) than that expected by the combined independent effects of each risk factor.

1. Introduction

Peripheral arterial disease (PAD) and elevated cardiac troponin-T (cTnT) have been interpedently associated with a twofold increase in the risk of vascular events [1–4]. cTnT is frequently elevated in PAD patients, and a significant proportion of patients (22–44%) with symptomatic PAD have a detectable cTnT [5,6] while the prevalence of detectable cTnT in the general population is as low as 0.7–4.1% using the third or fourth generation assays [3,7]. Some studies have suggested that elevated cTnT could be a predictor of adverse outcomes in patients with PAD [4-6,8]. Compared with patients who had undetectable cTnT, PAD patients with detectable cTnT were at 4.1 times higher risk for myocardial infarction [5] and 4.5 times higher risk of death [8]. These findings suggest that elevated cTnT may potentiate the risk that PAD confers on cardiovascular events. The objective of this study was to examine whether the joint effect of elevated highly-sensitive cTnT

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(hs-cTnT, ≥14 ng/L) and low ankle-brachial index (ABI <0.9) on incident coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) events is higher than the expected combined effect of each risk factor using data from two large prospective cohort studies [the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS)].

2. Materials and methods

The MESA and CHS are population-based cohort studies of risk factors for subclinical and clinical CVD [9,10]. In the MESA, 6814 men and women (aged 45–84) were recruited between July 2000 - Aug 2002 (baseline) from six field centers (Baltimore, Maryland; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; St. Paul, MN). In the CHS, 5201 men and women ≥65 years were recruited between June 1989 – June 1990 (baseline), and an additional 687 Black adults were enrolled between Nov 1992 - June 1993 (baseline) from four field centers (Forsyth County, NC; Sacramento County, CA; Washington County, Maryland; Pittsburgh, PA). For both cohort studies, the study protocol was approved by the institutional review boards at each field center, and written informed consent was obtained from all participants. Follow-up was conducted between July 2000 – Dec 2015 in the MESA and June 1989 – Dec 1999 in the CHS. For the current study, CHS participants with cardiovascular events at baseline and those with no measurement of hs-cTnT and ABI, and those with ABI >1.4 were excluded. In MESA, by design, individuals with clinical CVD were excluded at baseline.

Incident CHD was defined as fatal or non-fatal myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Incident ASCVD was defined as CHD and/or transient ischemic attack, or stroke. In both cohorts, in addition to their follow-up visits, participants were contacted every 6–12 months, and CVD event data were collected from telephone interviews, medical records from hospitalizations, death certificate, autopsy reports, and in the case of out-of-hospital deaths by interviewing or administering questionnaires to physicians or next of kin [9,10]. In the MESA, CVD event classification and assignment of incidence date were independently made by two physicians who were members of the MESA study events committee. The two reviewers adjudicated differences if disagreement occurred. If disagreement persisted, the full MESA events committee made the final classification [11]. In the CHS, provisional CVD events diagnoses were assigned by the Field Center principal investigator and then adjudicated by a study-wide Morbidity Review Committee. All fatal events were reviewed by a study-wide Mortality Review Committee [10]. hs-cTnT was measured from ethylenediaminetetraacetic acid plasma sample (previously unthawed or only thawed once) using the Cobas e601 (Roche Diagnostics) in the MESA [12]. In the CHS, hs-cTnT was measured from previously stored plasma sample (thawed just before laboratory assays) using a Roche highly- sensitivity Troponin T reagent kit on a Roche Elecsys 2010 Analyzer (Roche Diagnostics, Indianapolis, Indiana) [13]. For these instruments, the limit of detection was 3 ng/L. The intraassay coefficient of variations were 3.6% at hs-cTNT concentration of 28 ng/L and 2.0% at 2154 ng/L in MESA [12] and 6.0% at 25 ng/L and 3.7% at 1940 ng/L in the CHS [14]. hs-cTnT ≥14 ng/L is considered elevated [15,16].

Supine systolic blood pressure was taken in the MESA bilaterally from brachial, dorsalis pedis, and posterior tibial arteries using handheld Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, Colo) [17,18] and in the CHS from only the right brachial artery but bilaterally from the posterior tibial artery using a standard mercury sphygmomanometer and a Doppler stethoscope (8 MHz, Huntleigh Technology, Inc., PLC, Luton, UK) [2]. In the MESA, the highest of the dorsalis pedis or posterior tibial pressure was used as ABI numerator and the average of right and left brachial artery pressures as the ABI denominator. A duplicate ABI measurement was made in 384 MESA participants and showed excellent reproducibility with intraclass correlation coefficient (ICC) of 0.93, intra-technician ICC was 0.95 and the inter-technician ICC of 0.92 [14]. In the CHS, duplicate blood pressures were obtained and the average of the two measurements was used in the ABI calculation. The correlations for each duplicate blood pressure measurements were 0.97 for right and left leg, 0.95 for right arm [2]. In both cohorts, the lower of the leg-specific ABI was used as the index ABI. ABI was classified as "incompressible" if a pulse was detected after leg cuff was inflated to 300 mmHg. ABI <0.9 was considered low and ABI 0.9–1.4 was considered normal [1,2].

A Cox proportional hazards model was used to estimate Hazard ratios (HR) and their 95% confidence intervals (CI) [19]. Time at risk was calculated from baseline until the date for ASCVD event, death, lost to follow-up, or end of the study, whichever came first. Adjusted survival curve (by direct standardization) and log-rank test were used to examine differences in survival time [20–22]. Proportional-hazards assumption was examined graphically by plotting log-log of survival versus log-transformed time [23]. The joint effect of elevated hs-cTnT and low ABI on the risk of ASCVD and CHD was investigated on the additive scale using the relative excess risk caused by interaction (RERI) [24]. and on the multiplicative scale using the log-likelihood-ratio test by assessing models with and without an interaction term [25]. RERI was calculated as (HR11-HR10-HR01)+1, where HR11 is the hazard ratio for both risk factors present, HR10 is the hazard ratio for elevated hs-cTnT but normal ABI, and HR01 is the hazard ratio for non-elevated hs-cTnT but low ABI. Variables know to be risk factors for CVDs and are associated with hs-cTnT or PAD were included in the adjusted models (see result section). All analyses were performed using Stata 16 (StataCorp, College Station, TX) [26]. A 2-tailed $P < .05$ was considered statistically significant.

3. Results

There were 10,897 participants, mean age at baseline was 66.3 years (ranged 44–95 years), 44.7% were males, and 55.9% were White, 23.2% Black, 13.4% Hispanic, 7.3% Chinese race/ethnicity (Table 1). Individuals with both elevated hs-cTnT and low ABI compared to those with either risk factor alone were older, more likely to have hypertension, diabetes, higher triglyceride concentration, lower eGFR, to use antihypertensive medications, and less likely to exercise and to take statins.

Mean ABI and hs-cTnT were 1.1 ± 0.1 (range: 0.3–1.4) and 7.6 ± 18.5 ng/L (range: <3–1299), respectively, at baseline (Table 1). Among 10,897 participants, 84.5% had non-elevated hs-cTnT (<14 ng/L) and normal ABI (0.9–1.4), 8.0% had elevated hs-cTnT (>14 ng/L) but normal ABI, 5.3% had non-elevated hs-cTnT but low ABI (<0.9), and 2.2% had both elevated hs-cTnT and low ABI (Table 2). Between June 1989 – Dec 2015 (median follow-up 13.6 years, interquartile range, 7.5–14.7 years), there were 2590 incident ASCVD cases during 126,706.1 person-years of follow-up (crude incidence rate, 2.04 per 100 person-years) and 1542 incident cases CHD during 131,681.6 person-years of follow-up (crude incidence rate 1.17 per 100 person-years) (Table 2).

The multivariable-adjusted hazard of CHD and ASCVD was higher, as expected, in participants with both elevated hs-cTnT and low ABI [CHD HR: 2.04 (1.45, 2.88), ASCVD HR: 2.05 (1.58, 2.66)], only elevated hs-cTnT [CHD HR: 1.65 (1.37, 1.99), ASCVD HR: 1.67 (1.44, 1.99)], and only low ABI [CHD HR: 1.87 (1.52, 2.31), ASCVD HR: 1.67 (1.42, 1.97)] than individuals with non-elevated hs-cTnT and normal ABI (Table 2 and Fig. 1). Models were adjusted for age (years), sex (male, female), race (White, Black, Hispanic, Asian, other), education (<high school, high school complete, some college, college complete, graduate), pack years of smoking (continuous), alcohol drinks/week (continuous), exercise (met-hr/wk continuous), body mass index (continuous), hypertension (yes/no), diabetes (yes/no), glomerular filtration rate (continuous), total cholesterol (continuous), HDL cholesterol (continuous), triglyceride (continuous), hypertension medication (yes/no),

Table 1
Baseline participant characteristics by categories of elevated hs-cTnT and low ABI.

Characteristics	All participants (N = 10,897)	hs-cTnT (<14 ng/L) & ABI (0.9 – 1.4) (n = 9206)	hs-cTnT (≥14 ng/L) & ABI (0.9 – 1.4) (n = 876)	hs-cTnT (<14 ng/L) & ABI (<0.9) (n = 577)	hs-cTnT (≥14 ng/L) & ABI (<0.9) (n = 238)
Age in years, mean (SD)	66.3(10.1)	64.9 (9.9)	73.1 (8.4)	73.1 (7.4)	76.6 (7.2)
Male (%)	44.7	42.1	70.8	37.8	68.1
Race/Ethnicity (%)					
White	55.9	54.9	61.0	60.5	61.8
Black	23.2	21.8	29.7	33.1	31.1
Hispanic	13.4	14.8	6.7	3.8	5.0
Asian	7.3	8.3	1.7	1.9	1.3
Other race	0.3	0.2	0.9	0.7	0.8
Pack years of smoking	13.7(23.6)	12.4 (22.3)	17.6 (27.4)	25.1 (29.9)	21.1 (29.4)
Alcohol (drinks/ week)	2.4(6.1)	2.4(5.6)	2.3(5.8)	2.6 (11.4)	2.2(5.4)
Exercise (met-hr/ wk)	27.1(37.2)	27.9 (38.1)	26.3 (35.6)	19.2 (28.0)	18.9 (25.7)
BMI (kg/m^2)	27.7(5.2)	27.7 (5.2)	27.9 (5.1)	26.8 (5.1)	26.5 (4.7)
eGFR (ml/min/ 1.73m^2)	80.1(19.1)	81.8 (18.1)	68.2 (20.7)	76.5 (20)	59.3 (22.1)
Total cholesterol (mg/dL)	201.0(37.9)	201.0 (37.1)	193.6 (40.8)	211.6 (42.8)	202.3 (40.1)
HDL cholesterol (mg/dL)	52.3(15.3)	52.6 (15.1)	49.9(16)	52.2 (16)	49.6 (16.8)
Triglycerides (mg/ dL)]	135.0(85.9)	133.7 (81.6)	142.8 (120.8)	139.0 (74.8)	146.8 (111.6)
Hypertension (%)	55.5	51.3	76.6	76.6	89.9
Diabetes mellitus (%)	14.3	11.8	29.0	24.2	34.5
Antihypertensives (%)	41.3	37.7	58.9	56.7	75.2
Statins (%)	9.9	10.0	8.9	10.7	6.7
Family history of CHD (%)	38.6	38.8	33.7	42.3	37.8
Family history of ASCVD (%)	51.7	52.3	45.5	52.9	49.3
ABI†	1.1(0.1)	1.1(0.1)	1.1(0.1)	0.7 (0.1)	0.7(0.1)
hs-cTnT (ng/L)†	7.6(18.5)	5.3(2.8)	25.6 (32.5)	6.8 (3.4)	35.1 (96.7)

Abbreviations: ABI, ankle-brachial index; ASCVD, Atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; hs-cTnT, highly-sensitive cardiac troponin; MET, Metabolic Equivalent of Task; SD, standard deviation. †Median (interquartile range) for hs-cTnT 4.7(2.99–8.46) and for ABI 1.1 (1.0–1.2). * p-value is from a one-way anova comparing characteristics across categories of hs-cTnT and ABI.

statin (yes/no), family history of ASCVD (yes/no), and cohort indicator (MESA/CHS). Adjusted cumulative survival free of ASCVD (log-rank p-value <0.001) and CHD (log-rank p-value <0.001) were significantly lower in participants with both or either risk factors than individuals with non-elevated hs-cTnT and normal ABI (Fig. 1).

In a stratified analysis, low ABI was associated with a higher hazard of CHD and ASCVD only in individual with non-elevated hs-cTnT [CHD HR: 1.85 (1.50, 2.28), ASCVD HR: 1.67 (1.4`, 1.97)] but not in those with elevated hs-cTnT [CHD HR: 1.15 (0.79, 1.68), ASCVD HR: 1.22 (0.92, 164)]. Similarly, elevated hs-cTnT was associated with a higher hazard of CHD and ASCVD in individuals with normal ABI [CHD HR: 1.62 (1.34, 1.96), ASCVD HR: 1.64 (1.41, 1.90)] but not in participants with low ABI [CHD HR: 1.29 (0.82, 2.02), ASCVD HR: 1.31 (0.93, 1.84)] (Table 3).

Antagonistic (negative) multiplicative interaction was observed between elevated hs-cTnT and low ABI on the hazard of CHD in both the unadjusted (LR-test p-value =0.002) and adjusted (LR-test p-value =0.042) models (Table 2 and Fig. 1). When the outcome was ASCVD, a significant negative multiplicative interaction was observed in unadjusted model (LR test p-value =0.001) and a borderline significant negative multiplicative interaction in the fully adjusted model (LR test p-value =0.08). No evidence of additive interaction was observed between elevated hs-cTnT and low ABI for the risk of CHD [unadjusted RERI 0.06 (−1.36, 1.48); adjusted RERI −0.49 (−1.28, 0.31)] and ASCVD [unadjusted RERI 0.38 (−0.74, 1.49); adjusted RERI −0.29 (−0.89, 0.31)]. We found similar results for the joint association of detectable hs-cTnTn (≥3 ng/L) and low ABI (<0.9) with incident CHD and ASCVD (Supplemental Table 1).

4. Discussion

Using data from two large prospective cohort studies (MESA and CHS), we showed that there was antagonistic multiplicative interaction between elevated hs-cTnT and low ABI, indicating that the observed joint effect of elevated hs-cTnT and low ABI on ASCVD risk was smaller than the expected combined effects of each risk factor.

Elevated hs-cTnT and low ABI have each been consistently shown to be associated with higher risk of cardiovascular event in previous studies [27–31]. Clinically significant PAD (ABI <0.9) was associated with *a* >2-fold higher risk of vascular events in the getABI study [1] and with a twofold higher prevalence of CVD in the CHS study [2]. In OPUS-TIMI 16 trial, PAD was a predictor of worse and more extensive coronary artery disease in patients who had acute coronary syndromes [32]. The risk of cardiovascular events in individuals with elevated cTnT (compared to those with non-elevated cTnT) was two times higher in the Atherosclerosis Risk in Communities (ARIC) study [27,28], 1.7 times higher in the Dallas Heart Study [33]. The risk of cardiovascular death was also 2.9 times higher in the CHS [15] in individual with elevated cTnT.

Inflammatory mediators, impaired flow-mediated vasodilation, functional limitations in exercising, abnormal peripheral vasodilation and paradoxical vasoconstriction that can lead to increased systemic afterload and impaired cardiac output, have been suggested as the pathophysiologic mechanisms underlying the associations between PAD and cardiovascular events [29–31]. Chronic hs-cTnT elevation is also believed to reflect ongoing myocardial damage, because it has been found to be associated with subclinical myocardial injury, left ventricular hypertrophy, heart failure, and microvascular disease, all of which are likely to result in the development of cardiovascular events [34–36].

Interaction in epidemiology tests whether the observed joint effect of two or more risk factors on an outcome is greater (synergism or positive) or lower (antagonism or negative) than the sum (interaction on the additive scale) or product (Interaction on the multiplicative scale) of individual risks [24,37]. We expanded previous findings on the association of hs-cTnT and ABI with ASCVD by showing that the joint effect of elevated hs-cTnT and low ABI is an antagonistic multiplicative interaction.

Using the sufficient-cause framework, Szklo and Nieto [38], VanderWeele and Robins [39,40] and Greenland et al. [41] elucidated that antagonism is expected if two dichotomous risk factors can cause a disease outcome in the absence of the other risk factor but not in the presence of both risk factors, suggesting that when both are present, the risk factors effectively compete to cause the outcome. In our study we also observed that each of the risk factors (elevated hs-cTnT and low ABI) was associated with higher hazard of CHD and ASCVD in the absence the other risk factor whereas in the presence of both risk factors the association was attenuated and became non-significant (Table 3). Bjørnevik et al. [42] also suggested that antagonistic interaction is expected to occure if two risk factors share some common pathways in the pathogenesis of the disease outcome, and some of the specific pathways are saturated by either risk factor. It has previously been noted that

Table 2
Cox-regression for the joint association of elevated highly-sensitive cardiac troponin-T and low ankle-brachial index with cardiovascular events.

Joint effects of exposures	End points					
	Participants	Events	Person-years	Incidence rate (100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Outcome CHD						
Non-elevated hs-cTnT (<14 ng/L) & normal ABI (0.9 – 1.4)	9197	1144	117,564.3	0.97	1 (reference)	1 (reference)
Elevated hs-cTnT (≥14 ng/L) & normal ABI (0.9 – 1.4)	876	203	7433.1	2.73	2.98 (2.56, 3.46)§	1.65 (1.37, 1.99)§
Non-elevated hs-cTnT (<14 ng/L) & low ABI (<0.9)	574	140	5358.6	2.61	2.79(2.34, 3.33)§	1.87 (1.52, 2.31)§
Elevated hs-cTnT (≥14 ng/L) & low ABI (<0.9)	238	55	1325.6	4.15	4.82 (3.67, 6.34)§	2.04 (1.45, 2.88)§
Trend *p*-value					<0.001	<0.001
Joint expected HR (multiplicative model)					8.30	3.09
Joint expected HR (additive model)					4.77	2.52
LR test *p*-value for multiplicative interaction					0.002	0.042
RERI (95% CI) test for additive interaction					0.06 (−1.36, 1.48)	−0.49 (−1.28, 0.31)
Outcome ASCVD						
Non-elevated hs-cTnT (<14 ng/L) & normal ABI (0.9 – 1.4)	9206	1958	113,501.9	1.73	1 (reference)	1 (reference)
Elevated hs-cTnT (≥14 ng/L) & normal ABI (0.9 – 1.4)	876	322	7008.5	4.60	2.83 (2.52, 3.19)§	1.67 (1.44, 1.93)§
Non-elevated hs-cTnT (<14 ng/L) & low ABI (<0.9)	577	220	4965.9	4.43	2.67 (2.32, 3.07)§	1.67 (1.42, 1.97)§
Elevated hs-cTnT (≥14 ng/L) & low ABI (<0.9)	238	90	1229.8	7.32	4.88 (3.94, 6.04)§	2.05 (1.58, 2.66)§
Trend *p*-value					<0.001	<0.001
Joint expected HR (multiplicative model)					7.56	2.79
Joint expected HR (additive model)					4.50	2.34
LR test *p*-value for multiplicative interaction					0.001	0.08
RERI (95% CI) test for additive interaction					0.38 (−0.74, 1.49)	−0.29 (−0.89, 0.31)

p-value: †<0.05, ‡<0.01, §<0.001.
Abbreviations: ABI, ankle-brachial index; ASCVD, Atherosclerotic cardiovascular disease; hs-cTnT, highly-sensitive cardiac troponin-T; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; LR, likelihood ratio; RERI, relative excess risk due to interaction.
Models were adjusted for age (years), sex (male, female), race/ethnicity (White, Black, Hispanic, Asian, other), education (<high school, high school complete, some college, college complete, graduate), pack years of smoking (continuous), alcohol drinks/week (continuous), exercise (met-hr/wk continuous), body mass index (continuous), hypertension (yes/no), diabetes (yes/no), glomerular filtration rate (continuous), total cholesterol (continuous), HDL cholesterol (continuous), triglyceride (continuous), hypertension medication (yes/no), statin (yes/no), family history of CVD (yes/no) and cohort indicator (MESA/CHS).
Expected HR for additive model was calculated as $HR_{10} + HR_{01}–1$, where HR_{10} is the hazard ratio for elevated hs-cTnT but normal ABI, and HR_{01} is the hazard ratio for non-elevated hs-cTnT but low ABI. Expected HR for multiplicative model was calculated as $HR_{10}*HR_{01}$.

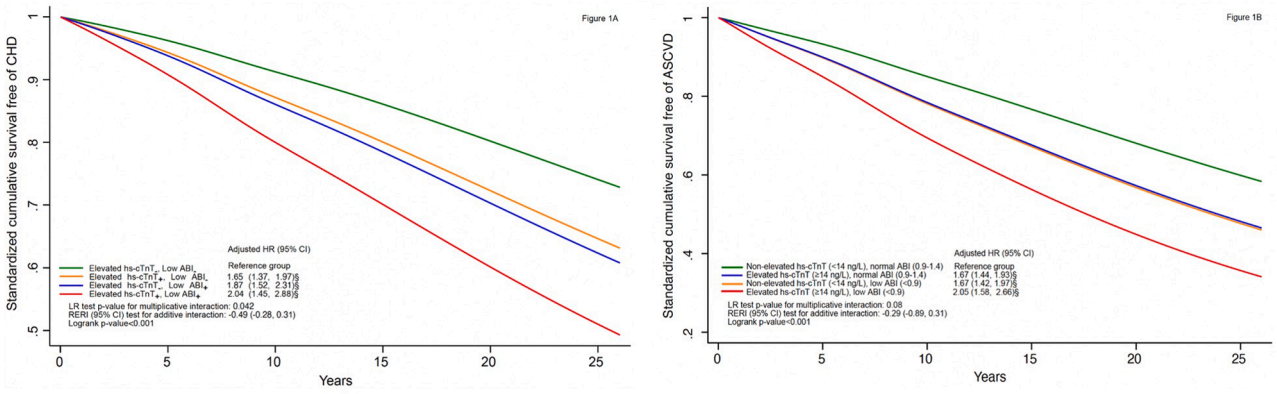

Fig. 1. Adjusted (by direct standardization) cumulative survival free of CHD (Fig. 1A) and free of ASCVD (Fig. 1B) by categories of elevated hs-cTnT and low ABI. Model adjusted for age (years), sex (male, female), race/ethnicity (White, Black, Hispanic, Asian, other), education (<high school, high school complete, some college, college complete, graduate), pack years of smoking (continuous), alcohol drinks/week (continuous), exercise (met-hr/wk continuous), body mass index (continuous), hypertension (yes/no), diabetes (yes/no), glomerular filtration rate (continuous), total cholesterol (continuous), HDL cholesterol (continuous), triglyceride (continuous), hypertension medication (yes/no), statin (yes/no), family history of CVD (yes/no), and cohort indicator (MESA/CHS). Abbreviations: ABI, ankle-brachial index; ASCVD, Atherosclerotic cardiovascular disease; hs-cTnT, highly-sensitive cardiac troponin; CHD, coronary heart disease; CI, confidence interval; LR, likelihood ratio; RERI, relative excess risk due to interaction. *p*-value: †<0.05, ‡<0.01, §<0.001.

elevated hs-TnT and low ABI share some common pathways, such as left ventricular dysfunction and hypertrophy [43,44], that were shown to subsequently lead to the development of cardiovascular events [45,46]. Additive interaction is relevant in translating findings to disease prevention [24,37,47]; however, it was found to be absent in the present study.

A major strength of this study is that it was conducted using data from two large prospective cohort studies from ten field centers throughout the United and this is likely to increase generalizability. To our knowledge, our study is also the first to examine the joint effect of elevated hs-cTnT and low ABI on the risk of ASCVD events. Interaction tests are prone to insufficient power [48]; however, our study had a bigger sample size (N = 10,897) and this is another strength of our study. A highly sensitive assay was used to measure cardiac troponin T,

Table 3
Stratified analysis of highly-sensitive cardiac troponin-T and ankle-brachial index with cardiovascular events in a Cox proportional hazards model.

	Outcome CHD			Outcome ASCVD		
	Incidence rate (100 person-years)	Adjusted HR (95% CI)	*p*-value	Incidence rate (100 person-years)	Adjusted HR (95% CI)	*p*-value
Stratified analysis						
Non-elevated hs-cTnT (<14 ng/L)						
Normal ABI (0.9 - 1.4)	0.97	1 (reference)		1.73	1 (reference)	
Low ABI (<0.9)	2.61	1.85 (1.50, 2.28)	<0.001	4.43	1.67 (1.41, 1.97)	<0.001
Elevated (≥14 ng/L)						
Normal ABI (0.9 - 1.4)	2.73	1 (reference)		4.59	1 (reference)	
Low ABI (<0.9)	4.15	1.15 (0.79, 1.68)	0.47	7.32	1.22 (0.92, 1.64)	0.17
Normal ABI (0.9 - 1.4)						
Non-elevated hs-cTnT (<14 ng/L)	0.97	1 (reference)		1.73	1 (reference)	
Elevated (≥14 ng/L)	2.73	1.62 (1.34, 1.96)	<0.001	4.59	1.64 (1.41, 1.90)	<0.001
Low ABI (<0.9)						
Non-elevated hs-cTnT (<14 ng/L)	2.61	1 (reference)		4.43	1 (reference)	
Elevated (≥14 ng/L)	4.15	1.29 (0.82, 2.02)	0.27	7.32	1.31 (0.93, 1.84)	0.13
Model output						
Elevated (≥14 ng/L) vs. non-elevated (<14 ng/L) hs-cTnT		1.65 (1.37, 1.99)	<0.001		1.67 (1.44, 1.93)	<0.001
Low (<0.9) vs. normal (0.9 - 1.4) ABI		1.87 (1.52, 2.31)	<0.001		1.67 (1.42, 1.97)	<0.001
Interaction term of elevated (≥14 ng/L) and low ABI		0.66 (0.44, 0.99)	0.046		0.73 (0.54, 1.01)	0.06

Abbreviations: ABI, ankle-brachial index; ASCVD, Atherosclerotic cardiovascular disease; hs-cTnT, highly-sensitive cardiac troponin-T; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.
Models were adjusted for age (years), sex (male, female), race/ethnicity (White, Black, Hispanic, Asian, other), education (<high school, high school complete, some college, college complete, graduate), pack years of smoking (continuous), alcohol drinks/week (continuous), exercise (met-hr/wk continuous), body mass index (continuous), hypertension (yes/no), diabetes (yes/no), glomerular filtration rate (continuous), total cholesterol (continuous), HDL cholesterol (continuous), triglyceride (continuous), hypertension medication (yes/no), statin (yes/no), family history of CVD (yes/no) and cohort indicator (MESA/CHS).

and this allows measurement of concentrations that are lower by a factor of 10 than conventional assays [49]. Our study also had some limitations. Only baseline data of ABI and cTnT were used, and the incidence of these risk factors may have changed after baseline given the changes in health behaviors, disease awareness, and use of statins during the 25-year follow-up time. MESA and CHS data were collected at different time points and had slightly different measurement protocols for hs-cTnT [2,12,13,17,18], to account for the potential impact of these on the results, we adjusted cohort indicator (MESA or CHD) in all the adjusted models. In addition, we presented in supplemental Table 2 results stratified by cohort indicator (MESA and CHS), and we observed similar no additive interaction in both cohorts and multiplicative interaction only in the CHS cohort. Although we adjusted for many risk factors, residual confounding may also partially explain the observed associations.

In conclusion, our study revealed that the observed joint effect of simultaneously elevated cTnT and low ABI on ASCVD risk was smaller (i.e., negative multiplicative interaction) than the expected combined independent effects of each risk factor.

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CRediT authorship contribution statement

Yacob G. Tedla: Conceptualization, Writing – original draft, Formal analysis. **Steven Driver:** Conceptualization, Writing – review & editing. **Moyses Szklo:** Writing – review & editing. **Lewis Kuller:** Conceptualization, Writing – review & editing. **Joao AC Lima:** Writing – review & editing. **Erin D. Michos:** Writing – review & editing. **Hongyan Ning:** Writing – review & editing. **Christopher R. deFilippi:** Writing – review & editing. **Philip Greenland:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100471.

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