International Journal of Cardiology Cardiovascular Risk and Prevention 11 (2021) 200109

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention

The association between serum high-sensitivity cardiac troponin T and acute myocardial infarction in patients with suspected chronic coronary syndrome is modified by body mass index☆,☆☆

Vegard Vavik [a,*], Kristin Moberg Aakre [a,b,c], Eva Kristine Ringdal Pedersen [a], Gard Frodahl Tveitevåg Svingen [a], Grethe Seppola Tell [d], Ottar Nygård [a,b], Kjell Vikenes [a,b]

[a] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[b] Department of Clinical Science, University of Bergen, Bergen, Norway
[c] Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway
[d] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

ARTICLE INFO

Keywords:
Cardiac troponin T
Body mass index
Inflammation
Acute myocardial infarction

ABSTRACT

Background: Higher systemic concentrations of cardiac troponins and biomarkers of inflammation and endothelial dysfunction as well as obesity are associated with increased risk of cardiovascular disease (CVD) and may share pathophysiological pathways. We sought to explore the association between serum high sensitive cardiac troponin T (hs-cTnT) and future acute myocardial infarction (AMI) according to body mass index (BMI) among patients with suspected chronic coronary syndrome (CCS), as well as interactions with C-reactive protein (CRP) and asymmetric dimethylarginine (ADMA).

Methods: A total of 3879 patients with baseline hs-cTnT ≤ 30 ng/L who underwent elective coronary angiography due to chronic coronary syndrome (CCS) were followed to subsequent AMI or end of 2009. Risk associations between hs-cTnT and incident AMI were explored with Cox regression according to BMI categories <25 kg/m 2, 25–30kg/m2 and >30kg/m2 and quartiles of serum CRP and plasma ADMA.

Results: Median (25 th −75 th percentile) age was 62 (54–69) years and 2773 (77.5%) were men. During median 7.5 (25 th −75 th percentile) (6.9–9.2) years of follow-up, 460 (11.9%) patients experienced an AMI. The risk relationship between hs-cTnT and incident AMI was stronger among patients in the higher vs lower BMI categories, HR 1.087 (1.055–1.119), P for interaction 0.043. A similar interaction was not found in categories of CRP or ADMA.

Conclusion: The risk relationship of hs-cTnT with incident AMI was stronger in patients with higher BMI. Our results motivate further studies into potential pathophysiological mechanisms connecting hs-cTnT with increased cardiovascular risk.

1. Introduction

Troponins are regulatory myocyte proteins of which the cardiac specific forms (cTn) have been proven very sensitive markers of myocardial injury. Chronically elevated systemic high-sensitivity cardiac troponin T (hs-cTnT) concentrations are strong predictors of future cardiovascular events [1] as well as mortality in general [2]. The prevailing theory suggests that chronic hs-cTnT elevations reflect low-grade myocardial damage which may eventually result in structural heart disease and heart failure, although the inducers, release mechanisms and prognostic impact of troponin increase in the non-ischemic setting are not fully understood.

Inflammation is recognized as a pivotal component in the pathogenesis of atherosclerosis. Obesity is closely linked to increased inflammatory load and is believed to increase risk of cardiovascular disease (CVD) through multiple inflammatory pathways [3]. Accordingly, the inflammation marker C-reactive protein (CRP) has been established as a strong predictor for impaired prognosis of

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.☆☆ The research is funded by the Department of Heart Disease, Haukeland University Hospital.

* Corresponding author. Haukeland University Hospital, Department of Heart Disease, Postbox 1400, 5021, Bergen, Norway.
E-mail address: vegard.vavik@helse-bergen.no (V. Vavik).

https://doi.org/10.1016/j.ijcrp.2021.200109
Received 30 April 2021; Received in revised form 5 August 2021; Accepted 30 August 2021
Available online 6 October 2021

Table 1
Baseline characteristics of the study population of patients with suspected chronic coronary syndrome in Western Norway according to BMI groups.

	Total		BMI <25 kg/m2		BMI 25–30 kg/m2		BMI >30 kg/m2		P[b]
	N[a]		N		N		N		
BMI, kg/m2									
Women	1106	26 (23–29)	437	22 (21–23)	479	27 (26–28)	190	33 (31–35)	–
Men	2773	26 (24–28)	873	23 (21–23)	1561	27 (26–28)	339	32 (29–35)	–
Age, years	3879	62 (54–69)	1310	63 (56–71)	2040	61 (54–69)	529	59 (53–67)	<0.001
Female sex, n (%)	3879	1106 (28.5)	1310	437 (33.4)	2040	479 (23.5)	529	190 (35.9)	<0.001
hs-cTnT, ng/L	3879	4 (3–9)	1310	4 (3–9)	2040	4 (3–9)	529	5 (3–10)	0.027
CRP, mg/L	3878	1.7 (0.9–3.6)	1310	1.4 (0.7–2.8)	2039	1.8 (0.9–3.6)	529	2.7 (1.4–5.2)	0.008
ADMA, μmol/L	3873	0.57 (0.48–0.61)	1308	0.57 (0.48–0.63)	2036	0.55 (0.47–0.60)	529	0.56 (0.48–0.61)	<0.001
Previous AMI, n (%)	3879	1519 (39.2)	1310	505 (38.5)	2040	791 (38.8)	529	223 (42.2)	0.313
Previous PCI, n (%)	3879	741 (19.1)	1310	229 (17.5)	2040	401 (19.7)	529	111 (21.0)	0.146
Previous CABG, n (%)	3879	431 (11.1)	1310	134 (10.2)	2040	231 (11.3)	529	66 (12.5)	0.346
Previous PAD, n (%)	3879	333 (8.6)	1310	139 (10.6)	2040	147 (7.2)	529	47 (8.9)	0.003
Left ventricular ejection fraction	3879	66 (60–70)	1310	67 (60–70)	2040	67 (60–70)	529	65 (60–70)	0.04
Diabetes mellitus, n (%)	3879	439 (11.3)	1310	109 (8.3)	2040	209 (10.2)	529	121 (22.9)	<0.001
Hypertension, n (%)	3879	1790 (46.1)	1310	474 (36.2)	2040	982 (48.1)	529	334 (63.1)	<0.001
Current smoker, n (%)	3879	1170 (30.2)	1310	450 (34.4)	2040	576 (28.2)	529	144 (27.2)	<0.001
Blood pressure, mmHg									
Systolic	3832	140 (126–154)	1295	139 (124–152)	2016	140 (128–155)	521	140 (129–155)	0.001
Diastolic	3829	80 (75–88)	1293	80 (73–85)	2015	80 (75–89)	521	84 (77–90)	<0.001
eGFR	3873	91 (79–100)	1308	90 (79–98)	2036	92 (80–100)	529	93 (78–101)	0.001
Serum lipid parameters									
Total cholesterol, mmol/L	3877	4.9 (4.3–5.7)	1309	4.9 (4.2–5.7)	2039	5.0 (4.3–5.7)	529	5.0 (4.3–5.8)	0.219
LDL cholesterol, mmol/L	3876	2.9 (2.4–3.7)	1308	2.9 (2.3–3.7)	2039	3.0 (2.4–3.7)	529	3.0 (2.3–3.7)	0.144
HDL cholesterol, mmol/L	3878	1.2 (1.0–1.5)	1310	1.4 (1.1–1.6)	2039	1.2 (1.0–1.4)	529	1.1 (0.9–1.4)	<0.001
Triglycerides, mmol/L	3875	1.5 (1.1–2.2)	1310	1.2 (0.9–1.7)	2037	1.6 (1.2–2.3)	528	2.0 (1.4–2.7)	<0.001
Serum apo A1, g/L	3878	1.3 (1.1–1.5)	1310	1.4 (1.2–1.6)	2039	1.3 (1.1–1.4)	529	1.3 (1.1–1.5)	<0.001
Serum B100, g/L	3879	0.9 (0.7–1.0)	1310	0.8 (0.7–1.0)	2040	0.9 (0.8–1.0)	529	0.9 (0.8–1.1)	<0.001
Medications at discharge, n (%)									
Aspirin	3879	3112 (80.2)	1310	1048 (80.0)	2040	1659 (81.3)	529	405 (76.6)	0.048
Beta blocker	3879	2850 (73.5)	1310	929 (70.9)	2040	1524 (74.4)	529	397 (75.0)	0.036
ACE-inhibitor or ARB	3879	1180 (30.4)	1310	317 (24.2)	2040	631 (30.9)	529	232 (43.9)	<0.001
Statin	3879	2816 (72.6)	1310	906 (69.2)	2040	1523 (74.7)	529	387 (73.2)	0.002
CCB	3879	871 (22.5)	1310	268 (20.5)	2040	450 (22.1)	529	153 (28.9)	<0.001
Loop diuretic	3879	359 (9.3)	1310	98 (7.5)	2040	172 (8.4)	529	89 (16.8)	<0.001

BMI = Body mass index; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; PAD = peripheral artery disease; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.

[a] Number of patients with valid measurements.

[b] Adjusted for age and gender.

cardiovascular disease (CVD), both in patients with established CVD and in the general population [4,5]. However, CRP *per se* is probably not a causal mediator in disease progression [6]. Notably, endothelial dysfunction has been suggested as a link between inflammation and CVD [7]. Asymmetric dimethylarginine (ADMA) inhibits nitric oxide synthase [8] and is suggested as a marker of endothelial dysfunction [9]. We previously reported that higher plasma ADMA was associated with CVD risk only in patients with low body-mass index (BMI) [10], again suggesting an interplay between inflammation, endothelial dysfunction and body weight in terms of CVD risk.

In sum, increased body weight as well as markers of chronic myocardial injury, inflammation and endothelial dysfunction all predict future acute myocardial infarction (AMI), but the pathophysiologic mechanisms and interactions between these are unknown. In this study we investigated the prospective association between hs-cTnT and incident AMI in a large cohort of patients with presumed stable coronary disease and whether this risk association was modified by BMI or blood concentrations of CRP or ADMA.

2. Methods

2.1. Study design, enrollment and data collection

The WEstern Norway Coronary Angiography Cohort (WECAC) study population has been described previously [11]. In short it consists of 4164 patients who underwent planned coronary angiography for suspected chronic coronary syndrome (CCS) at either Haukeland (Bergen, Norway) or Stavanger (Stavanger, Norway) university hospitals during 2000–2004. About 2/3 were enrolled in the Western Norway B vitamin Intervention Trial (WENBIT), and randomized to receive B-vitamin treatment or placebo for secondary CVD prevention [12].

All patients provided written, informed consent. The study was approved by the regional ethics committee and was carried out according to the Declaration of Helsinki.

Patients with baseline serum troponin of >30 ng/L were excluded in order to minimize the risk of including patients with acute myocardial disease. This left 3879 participants available for the final analyses. Information on patients' lifestyle and medical history was obtained from self-administered questionnaires and verified by comparing to hospital records as has previously been described [13]. Coronary catheterization and angiography were performed by invasive cardiologists.

The biosampling and biochemical analyses have been described in detail in earlier reports [10,11]. Serum and plasma for study-specific analyses were immediately prepared and stored in 2 mL Vacutainer® tubes (Becton, Dickinson and Company, United States) at −80°, before later being thawed and analyzed by laboratory staff blinded to clinical outcomes. Serum hs-cTnT was analyzed with a high sensitive cardiac troponin T assay on Modular E170 from Roche diagnostics with a limit of blank of 3 ng/L, limit of detection of 5 ng/L and an upper 99th percentile of 14 ng/L. Troponin values below the limit of blank of 3 ng/L were set to 1.5 ng/L for the purposes of statistical analyses.

Table 2
Risk of incident acute myocardial infarction according to hs-cTnT, BMI, CRP and ADMA.

Variable	Model 1[a]		Model 2[b]	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* Value
Hs-cTnT	1.055 (1.041–1.068)	<0.001	1.038 (1.024–1.052)	<0.001
BMI	1.034 (1.011–1.058)	0.004	1.030 (1.006–1.055)	0.013
CRP	1.010 (1.001–1.020)	0.026	1.006 (0.996–1.016)	0.234
ADMA	1.747 (0.830–3.676)	0.141	1.964 (0.923–4.180)	0.080

Abbreviations: Hs-cTnT = High-sensitive cardiac troponin T, BMI = Body Mass Index, CRP = C-reactive protein, ADMA = Asymmetric DiMethylArginine.
[a] Model adjusted for age and sex.
[b] Model adjusted for age, sex, hypertension, diabetes mellitus, smoking, left ventricular ejection fraction (%) and number of stenosed coronary arteries at baseline (0–3).

2.2. Endpoints

The endpoint was incident fatal and nonfatal AMI defined according to the International Classification on Diseases (ICD) 10th edition; I21–I22. Information on endpoints was obtained from the Cardiovascular Disease in Norway (CVDNOR; https://cvdnor.b.uib.no/) project [14], which provided information on discharge diagnoses from Norwegian hospitals, and from the Norwegian Cause of Death Registry (www.ssb.no) during 1994–2009, and linked to each patient's unique 11-digit national identification number.

2.3. Statistical analysis

Categorical variables are reported as counts (percentages), means (SD) and medians (25th −75th percentiles) as appropriate. Differences in baseline characteristics according to different BMI categories were tested with Chi-squared test and analysis of variance (ANOVA) for categorical and continuous variables, respectively. Correlations between BMI, ADMA and CRP were calculated using Spearman's correlations.

Risk associations between hs-cTnT, BMI, CRP and ADMA and later AMI was explored with Cox regression using two different models (one adjusting for age and gender, the second adjusting for age, sex, hypertension, diabetes mellitus, smoking, left ventricular ejection fraction (%) and number of stenosed coronary arteries at baseline). Subgroup analyses were performed for the hs-cTnT-AMI relationships according to BMI categories (<25 kg/m^2, 25–30 kg/m^2 and >30 kg/m^2) and quartiles of CRP and ADMA. We further investigated any non-linear interactions according to BMI as continuous variables using generalized additive modelling (GAM).

A 2-sided P value of less than 0.05 was considered statistically significant. The statistical analyses were carried out in R version 3.0.2 (the R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 26.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study population are described in Table 1. In short, the median (25th-75th percentile) age of the patients was 62 (54–69) and 71.5% were male. 39.2% had a history of AMI, and 19.1% and 11.1% had prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), respectively. Systolic function was in general preserved with an average left ventricular ejection fraction (LVEF) of 66% (60%–70%). Near half had a diagnosis of hypertension (46.1%) and 11.3% of diabetes mellitus. A third (30.2%) were smoking at the time of inclusion. Most patients were treated with aspirin (80.2%), beta blockers (73.5%) and statins (72.6%).

CRP was significantly positively correlated with BMI, r- = 0.199, p < 0.001, while ADMA was negatively correlated with BMI,r = −0.053, p = 0.001. CRP and ADMA were also weakly positively correlated to each other, r = 0.048, p = 0.003.

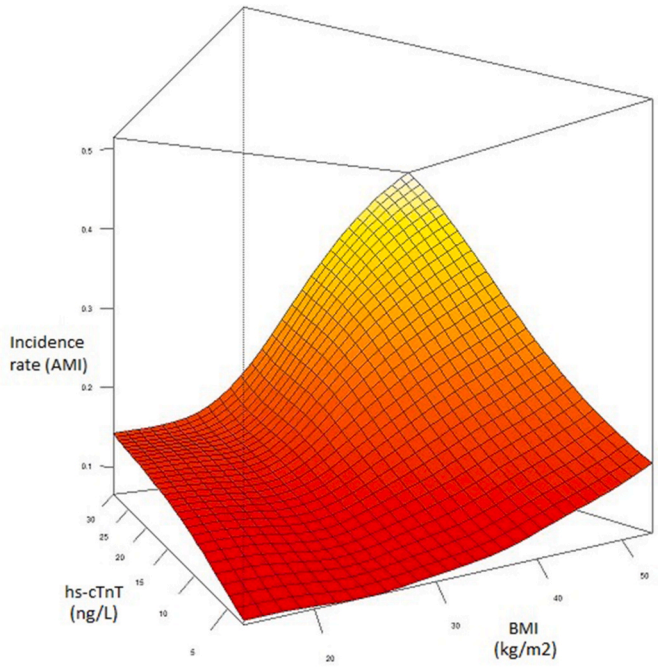

Fig. 1. Smooth surface spline estimate for AMI incidence rate according to hs-cTnT and BMI.

Table 3
Risk of incident acute myocardial infarction according to hs-cTnT in categories of BMI, CRP and ADMA.

	Model 1[a]		
BMI kg/m2	Hazard Ratio for AMI per SD increment of hs-cTnT (95% CI)	P value	P for interaction
<25	1.047 (1.025–1.071)	<0.001	0.043
25–30	1.047 (1.026–1.068)	<0.001	
>30	1.087 (1.055–1.119)	<0.001	
CRP mg/L	Hazard Ratio for AMI per SD increment of hs-cTnT (95% CI)	P value	P for interaction
Quartile 1 <0.86	1.021 (0.980–1.063)	0.315	0.980
Quartile 2 0.86–1.73	1.064 (1.035–1.093)	<0.001	
Quartile 3 1.74–3.57	1.070 (1.042–1.099)	<0.001	
Quartile 4 >3.57	1.049 (1.027–1.071)	<0.001	
ADMA µmol/L	Hazard Ratio for AMI per SD increment of hs-cTnT (95% CI)	P value	P for interaction
Quartile 1 <0.48	1.048 (1.017–1.081)	0.002	0.186
Quartile 2 0.48–0.54	1.060 (1.030–1.090)	<0.001	
Quartile 3 0.55–0.61	1.049 (1.021–1.078)	0.001	
Quartile 4 >0.61	1.062 (1.038–1.086)	<0.001	

Abbreviations: Hs-cTnT = High-sensitive cardiac troponin T, BMI = Body Mass Index, CRP = C-reactive protein, ADMA = Asymmetric DiMethylArginine.
[a] Model adjusted for age and sex.

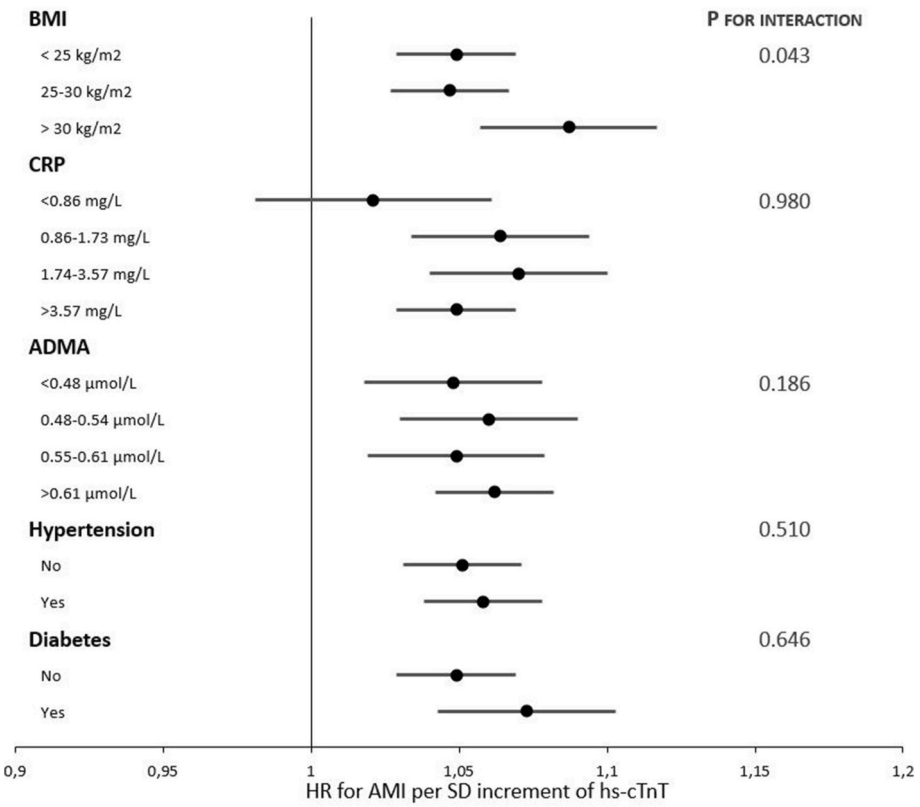

Fig. 2. Hazard rate for AMI per SD increment of hs-cTnT according to subgroups.

3.2. The association between hs-cTnT, BMI, ADMA and CRP and later acute myocardial infarction

During median 7.5 (6.9–9.2) years of follow-up, 460 (11.9%) patients experienced an AMI. In a model adjusted for age and sex, serum hs-cTnT and CRP, as well as BMI were all significantly associated with incident AMI (Table 2), whereas plasma ADMA was not. After correction in a multivariate model, hs-cTnT and BMI were significantly associated with future AMI, while CRP was not. Fig. 1 shows a smooth surface spline estimate for AMI incidence rate according to hs-cTnT and BMI.

The results from subgroup analyses are provided in Table 3 and depicted in Fig. 2. Hs-cTnT was more strongly associated with later AMI among patients with higher BMI (P for interaction = 0.043), and the results suggest that hs-cTnT was particularly strongly related to AMI among patients with BMI >30 kg/m^2. There was no significant interaction in subgroups of patients with or without history of diabetes or hypertension. Although we observed a trend towards a weaker risk relationship between hs-cTnT and AMI among patients with serum CRP in the lowest quartile, we did not observe any overall interactions for CRP or ADMA quartiles.

4. Discussion

In this study, hs-cTnT and BMI were both associated with incident AMI during approximately 8 years of follow up, and our results suggest that the predictive value of hs-cTnT may be stronger among patients with obesity.

Obesity and overweight are established risk factors for CVD, and elevated cTnT levels have been observed in subjects from the general population with the metabolic syndrome [15] as well as in the general population [16]. The association between BMI and troponins is not quite consistent as one study found increased troponin levels correlated with lower BMI, albeit in a population of patients with hypertensive crisis [17]. Arteriosclerosis and chronic myocardial injury often co-exist and are associated with similar risk factors [18]. Current knowledge indicates that epicardial adipose tissue in obese individuals might induce injury on the adjacent myocardium through paracrine mediators [19]. Indeed, in patients who underwent bariatric surgery profound weight loss was associated with a small but significant reduction in troponin concentrations [20]. Our finding of an interaction between BMI and hs-cTnT supports that adipose tissue could be involved in the mechanisms by which circulating hs-cTnT is associated to the development of myocardial injury and AMI.

Obesity and BMI is strongly linked to the development of diabetes mellitus [21] which is also associated with elevated troponin levels [22]. Troponins in diabetics has in turn been shown to predict increased risk of major cardiovascular events [23] and CVD mortality [24], an association also found in prediabetic patients [25]. We did not, however, find that the presence of diabetes had a significant effect on the hs-cTnT-AMI relationship.

Inflammation likely plays a pivotal role in atherogenesis and atherothrombosis [26]. This theory has recently been fueled by the findings of decreased risk of cardiovascular events from receiving anti-inflammatory treatment [27]. Obesity is associated with increased inflammation [18] and in the current study, hs-cTnT was positively associated with CRP. Unlike BMI, we did not observe any significant interaction with CRP on the risk relationship between hs-cTnT and future AMI.

Increased systemic concentrations of ADMA have been suggested as a marker of endothelial dysfunction [9], and higher ADMA concentrations have been observed among obese subjects, possibly linked to insulin resistance [28]. We previously reported that ADMA predicted atherosclerosis development in a sub study of WENBIT patients [29]. However, in the current study, while baseline hs-cTnT was inversely related to plasma ADMA, ADMA status did not influence the future hs-cTnT-AMI relationship. Also, among WENBIT patients, plasma ADMA was predictive of adverse cardiovascular prognosis among patients with low BMI only [9]. Hence, any effect modification by ADMA on the

hs-cTnT-AMI association could be attenuated due to BMI and may have influenced the findings in the current study.

Although single biomarkers provide limited information about complex biological processes in multifactorial diseases such as atherothrombosis, our investigation suggests that the potential effect modification by BMI on the hs-cTnT-AMI relationship may not be explained solely by inflammation or endothelial dysfunction.

The strengths of the current study include the large, well-defined cohort, and while the diagnosis of chronic coronary syndrome is a clinical one, all patients were evaluated with coronary angiography. A limitation is the use of BMI as a marker of obesity as it does not necessarily reflect body composition. CRP and ADMA have a similar limitation in that they do not alone represent the complexity of inflammatory processes and endothelial function. The population was predominantly Caucasian middle-aged men with presumed CCS and the results may not be generalizable to other populations.

In conclusion, in this study of 3879 patients with presumed chronic coronary syndrome undergoing coronary angiography, the risk of incident AMI according to hs-cTnT was modified by BMI but not by CRP or ADMA. This suggests a linkage between circulating troponin and the underlying mechanisms responsible for developing coronary artery disease that may be mediated by local adipose paracrine effects. Future studies should explore the association and effects of adipose tissue on chronic myocardial injury and coronary artery disease.

Author statement

Vegard Vavik: Writing – original draft, Formal analysis, Methodology **Kristin Moberg Aakre:** Writing – review & editing **Eva Kristine Ringdal Pedersen:** Writing – review & editing **Gard FT Svingen:** Writing – review & editing **Grethe S. Tell:** Investigation, Resources **Ottar Nygård:** Conceptualization, Project administration **Kjell Vikenes:** Supervision.

Acknowledgements

We thank all the recruiting study personnel, as well as the staff performing the laboratory analyses at Bevital AS, Bergen, Norway (www.bevital.no). We are also grateful to Tomislav Dimoski at the Norwegian Institute of Public Health, Oslo, Norway, for his contribution by developing the software necessary for obtaining data from Norwegian public hospitals, conducting the data collection and quality assurance of data in this project.

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