CLINICAL RESEARCH STUDY

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Patterns of Cardiac Troponin I Concentrations as Risk Predictors of Cardiovascular Disease and Death: The Trøndelag Health Study

Magnus Nakrem Lyngbakken, MD, PhD,[a,b] Dorien M. Kimenai, PhD,[c] Kristian Hveem, MD, PhD,[d,e] Håvard Dalen, MD, PhD,[e,f,g] Helge Røsjø, MD, PhD,[b,h] Torbjørn Omland, MD, PhD, MPH[a,b]

[a]Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway; [b]K.G. Jebsen Center for Cardiac Biomarkers, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway; [c]BHF Centre for Cardiovascular Science, University of Edinburgh, United Kingdom; [d]HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway; [e]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway; [f]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway; [g]Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway; [h]Division of Research and Innovation, Akershus University Hospital, Lørenskog, Norway.

ABSTRACT

BACKGROUND: Concentrations of cardiac troponin predict risk of cardiovascular disease and death in the general population. There is limited evidence on changing patterns of cardiac troponin in the years preceding cardiovascular events.

METHODS: We analyzed cardiac troponin I (cTnI) with a high-sensitivity assay in 3272 participants in the Trøndelag Health (HUNT) Study at study visit 4 (2017-2019). Of these, 3198 had measurement of cTnI at study visit 2 (1995-1997), 2661 at study visit 3, and 2587 at all 3 study visits. We assessed the trajectories of cTnI concentrations in the years prior to cardiovascular events using a generalized linear mixed model, with adjustment for age, sex, cardiovascular risk factors, and comorbidities.

RESULTS: At HUNT4 baseline, median age was 64.8 (range 39.4-101.3) years, and 55% were women. Study participants who were admitted because of heart failure or died from cardiovascular cause on follow-up had a steeper increase in cTnI compared with study participants with no events ($P < .001$). The average yearly change in cTnI was 0.235 (95% confidence interval, 0.192-0.289) ng/L for study participants with heart failure or cardiovascular death, and −0.022 (95% confidence interval, −0.022 to −0.023) ng/L for study participants with no events. Study participants who experienced myocardial infarction, ischemic stroke, or noncardiovascular mortality exhibited similar cTnI patterns.

CONCLUSIONS: Fatal and nonfatal cardiovascular events are preceded by slowly increasing concentrations of cardiac troponin, independently of established cardiovascular risk factors. Our results support the use of cTnI measurements to identify at-risk subjects who progress to subclinical and later overt cardiovascular disease.

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KEYWORDS: Cardiac disease; Cardiac markers; Epidemiology studies; Troponin

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Requests for reprints should be addressed to Magnus Nakrem Lyngbakken, MD, PhD, Associate Professor of Medicine, University of Oslo/Division of Medicine, Akershus University Hospital, Postboks 1000, 1478 Lørenskog, Norway.

E-mail address: magnus.lyngbakken@medisin.uio.no

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INTRODUCTION

Low-grade elevations in cardiac troponin strongly associate with incident cardiovascular disease and death, both in patients with established cardiovascular disease[1] and in apparently healthy individuals recruited from the general population.[2] Despite being well within the limits of normality, such low-grade elevations are commonly referred to as subclinical myocardial injury. The associations with subclinical myocardial injury are particularly strong for cardiovascular mortality and incident heart failure admissions,[3] but cardiac troponins may additionally predict risk of incident myocardial infarction,[4] atrial fibrillation,[5] and ischemic stroke.[6] Development of cardiovascular disease is considered a chronic and multifactorial process, and heart failure, especially, is a clinical entity that takes years before symptoms occur. Cardiac troponins associate with left ventricular remodeling[7] and fibrosis,[8] and are considered sensitive indicators of the pathophysiological cardiac processes that ultimately will present as overt clinical disease such as heart failure.

CLINICAL SIGNIFICANCE

- In a general population cohort, cardiovascular events were preceded by increasing cardiac troponin I concentrations over 25 years.
- Persons who experienced cardiovascular events had consistently higher concentrations of cardiac troponin I on several occasions over a 25-year period prior to overt disease.
- These associations were independent of age, sex, and cardiovascular risk factors.
- Patterns of cardiac troponin may serve as risk markers of incident cardiovascular morbidity and death in the general population.

There are considerable data documenting the prognostic implications of longitudinal changes in cardiac troponin concentrations and risk of clinical outcomes.[9,10] Previous investigations have predominantly used cardiac troponin measured at 2 time points and focused on improvement in risk-prediction models and the clinical interpretation of temporal changes in biomarkers concentrations. More strongly pertaining to the pathomechanisms behind subclinical myocardial injury and the progression to overt cardiovascular disease in the general population, recent data have demonstrated that concentrations of cardiac troponin I (cTnI) slowly increase in the years preceding cardiovascular death.[11] There is limited evidence documenting such trends for nonfatal cardiovascular events. Accordingly, using a large cohort of community dwellers with several assessments of cTnI over a time-span of 25 years, we aimed to describe the temporal trends in cTnI concentrations prior to the development of cardiovascular morbidity and death (Figure 1).

METHODS

Study Overview

The Trøndelag Health (HUNT) Study is the largest population-based cohort in Norway, with more than 150,000 participants from Trøndelag County. Four study visits have so far been conducted; HUNT1 (n = 77,212, 1984-1986), HUNT2 (n = 65,237, 1995-1997), HUNT3 (n = 50,807, 2006-2008), and HUNT4 (n = 56,078, 2017-2019).[12] The HUNT Study was approved by the Regional Committee for Medical Research Ethics (REC 2012/859 and REC 2016/801) and the Norwegian Data Inspectorate Board, and all participants provided informed written consent.

Participants

The present analysis includes 3272 participants with measurements of cTnI at HUNT4. Of these, 3198 had measurements of cTnI at HUNT2, 2661 had measurements of cTnI at HUNT3, and 2587 had measurements of cTnI at all 3 study visits. Information on demographics and medical history was acquired from questionnaires completed at HUNT4 study baseline. Higher education was defined as more than 12 years of formal education equaling college or university level. Cardiovascular disease was defined as self-reported history of angina pectoris, myocardial infarction, heart failure, atrial fibrillation, or ischemic stroke. Clinical examinations including waist and hip circumference and blood pressure were performed at study baseline.

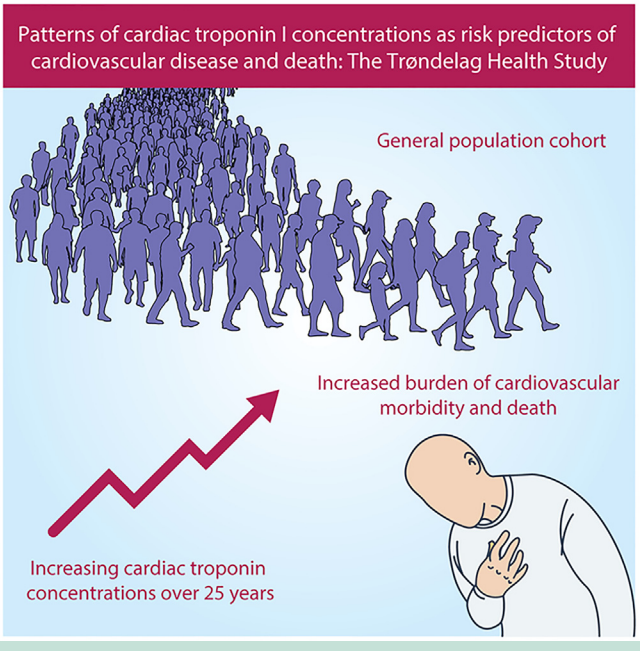

Figure 1 Temporal patterns of cTnI associate with future cardiovascular mobidity and death in persons recruited from the general population. cTnI = cardiac troponin I.

Blood Sampling Procedures and Biochemical Assays

We measured cTnI with a high-sensitivity assay from Abbott Diagnostics (Abbott Park, Ill; ARCHITECT STAT High Sensitive Troponin) from serum samples collected at HUNT2, HUNT3, and HUNT4. Details on sample analyses and coefficients of variations from the laboratory runs have been described in previous reports.[9,13,14] The limit of quantification for this assay is reported to be 3.5 ng/L, and limit of detection 1.2 ng/L. Concentrations below the limit of detection were assigned a value of 0.6 ng/L. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[15] C-reactive protein, total cholesterol, and high-density lipoprotein cholesterol were measured from fresh, nonfasting serum samples and hemoglobin A1c from fresh, nonfasting whole blood samples on the Architect ci8200 (Abbott Diagnostics, Abbott Park, Ill).

Outcomes

Data on fatal incident events after HUNT4 were acquired from the Cause of Death Registry of Statistics Norway, and data on nonfatal incident events from the Norwegian Patient Registry. We primarily assessed the associations of measurements of cTnI from HUNT2, HUNT3, and HUNT4 with first event of hospital admission for heart failure (International Statistical Classification of Diseases, 10th Revision codes I50.x) or cardiovascular mortality (codes I00.x-I99.x and R960). We separately assessed the associations with hospital admission for myocardial infarction (codes I21.x), atrial fibrillation (codes I48.x), heart failure (codes I50.x), or ischemic stroke (codes I63.x). Lastly, we assessed the associations with cardiovascular and noncardiovascular mortality. All clinical events were obtained after the date of the HUNT4 baseline examinations through December 31, 2021.

Statistical Methods

Baseline data are reported as absolute numbers (proportion) or median (interquartile range) unless otherwise stated. Continuous variables were analyzed using the Mann-Whitney *U* test, and categorical variables with the Fisher exact test.

For the cTnI trajectories, we classified study subjects according to incident clinical events during follow-up. We assessed the trajectories of cTnI concentrations from each study visit (HUNT2, HUNT3, HUNT4) using a generalized linear mixed model, with subject-specific random intercept and slope. We calculated time from each study visit and the time scale was entered into the fixed- and random-effects part of the model, with fixed effects for outcomes and time as a continuous variable with outcome × time interactions. Missing data are managed implicitly in mixed models under the assumption of missing at random. We defined subclinical myocardial injury as concentrations of cTnI above sex-specific cut-offs at 4 ng/L for women and 6 ng/L for men, as these values, despite being well within the limits of normality, associate with inferior prognosis in the general population.[16,17] We performed all analyses for cTnI as a continuous variable transformed by a $\log_2$ logarithm and according to these cut-offs. All regression models were adjusted for age, sex, and history of cardiovascular disease (ie, self-reported history of angina pectoris, myocardial infarction, heart failure, atrial fibrillation, or stroke), as well as a priori selected variables influencing cardiovascular risk (higher education, history of diabetes mellitus, current smoking, systolic blood pressure, treatment for hypertension, statin therapy, serum total cholesterol, serum high-density lipoprotein cholesterol, and estimated glomerular filtration rate). For all models, trajectories of cTnI were compared between study participants who experienced specific events and study participants who experienced no events at all on follow-up. We performed sensitivity analyses, excluding study participants with history of cardiovascular disease at baseline. Statistical significance was assumed at $P < .05$. The analyses were performed with Stata 17 (StataCorp LP, College Station, Texas).

RESULTS

At HUNT4 baseline, median age was 64.8 (range 39.4-101.3) years, and 55% were women. Baseline characteristics at HUNT4 according to hospital admission for heart failure or cardiovascular mortality on follow-up are outlined in Table 1. Study participants who were admitted because of heart failure or died from cardiovascular cause (n = 67) were more frequently older men with diabetes mellitus and with cardiovascular disease. They had, less frequently, higher education, higher concentrations of C-reactive protein, impaired renal function, and higher concentrations of cTnI at all study visits.

Trajectories of cTnI and Incident Heart Failure or Cardiovascular Mortality

Study participants who were admitted because of heart failure or died from cardiovascular causes on follow-up had a steeper increase in cTnI compared with study participants with no events (*P* compared with no events < .001; Figure 2). The average yearly change in cTnI was 0.235 (95% confidence interval [CI], 0.192-0.289) ng/L for study participants with heart failure or cardiovascular death and −0.022 (95% confidence interval, −0.022 to −0.023) ng/L for study participants with no events (Table 2).

Trajectories of cTnI and Incident Nonfatal Cardiovascular Clinical Endpoints

When we examined first event for individual nonfatal cardiovascular endpoints, the trends were comparable with that of the primary outcome. The trajectory of cTnI was steepest for incident heart failure hospitalization (*P* compared with no events < .001; Figure 3A), followed by incident ischemic stroke (*P* compared with no events < .001; Figure 3B), and myocardial infarction (*P* compared with no events < .001; Figure 3C). For atrial fibrillation, the

Table 1 Baseline Characteristics According to Admission for Heart Failure or Cardiovascular Mortality

	n	No Events (n = 2961)	n	Heart Failure or Cardiovascular Mortality (n = 67)	*P* Value
Male sex, n (%)	2961	1296 (43.8%)	67	39 (58.2%)	.024
Age, years	2961	63.6 (55.3-72.3)	67	81.0 (72.1-88.6)	< .001
Current smoking, n (%)	2934	261 (8.9%)	63	9 (14.3%)	.18
Higher education, n (%)	2940	1086 (36.9%)	64	12 (18.8%)	.002
Body mass index	2944	27.0 (24.4-30.0)	59	27.1 (24.2-30.2)	.95
Waist-to-hip ratio	2809	0.96 (0.91-1.02)	46	0.97 (0.89-1.05)	.56
Heart rate, bpm	2878	69 (63-78)	51	75 (64-86)	.042
Systolic blood pressure, mm Hg	2950	132 (120-146)	64	139 (122-158)	.08
Diastolic blood pressure, mm Hg	2950	74 (68-81)	64	72 (63-83)	.21
History of:					
Diabetes mellitus, n (%)	2917	210 (7.2%)	63	17 (27.0%)	< .001
Angina pectoris, n (%)	2780	79 (2.8%)	55	14 (25.5%)	< .001
Myocardial infarction, n (%)	2803	153 (5.5%)	50	7 (14.0%)	.020
Heart failure, n (%)	2763	54 (2.0%)	54	15 (27.8%)	< .001
Atrial fibrillation, n (%)	2753	156 (5.7%)	53	15 (28.3%)	< .001
Stroke, n (%)	2772	101 (3.6%)	50	9 (18.0%)	< .001
Any cardiovascular disease, n (%)	2961	416 (14.0%)	67	39 (58.2%)	< .001
Antihypertensive therapy, n (%)	2961	900 (30.4%)	67	41 (61.2%)	< .001
Statin therapy, n (%)	2961	599 (20.2%)	67	23 (34.3%)	.008
Total cholesterol, mg/dL	2961	213 (186-244)	67	197 (155-244)	.07
HDL cholesterol, mmol/L	2961	54 (43-66)	67	50 (39-58)	.011
Hemoglobin A1c, %	2955	5.3 (5.1-5.5)	65	5.5 (5.2-6.0)	< .001
eGFR, mL/min/1.73 m^2	2961	86.0 (74.0-95.0)	67	67.0 (52.0-80.0)	< .001
CRP, mg/L	2961	1.3 (0.7-2.6)	67	2.5 (1.0-5.6)	< .001
Cardiac troponin I, ng/L (HUNT2)	2893	2.7 (1.9-3.8)	65	4.5 (3.2-5.9)	< .001
Cardiac troponin I, ng/L (HUNT3)	2417	1.6 (0.6-2.6)	53	4.0 (2.2-6.6)	< .001
Cardiac troponin I, ng/L (HUNT4)	2961	2.1 (0.6-4.0)	67	8.9 (4.3-18.4)	< .001

CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HUNT = Trøndelag Health Study.
Data are presented as numbers (proportion) or median (interquartile range). To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

trajectory of cTnI was comparable with that of study participants with no events (*P* compared with no events = .10; Figure 3D). The yearly increase in cTnI ranged from 0.002 (95% CI, 0.001-0.002) ng/L for incident hospitalization for atrial fibrillation to 0.155 (95% CI, 0.114-0.209) ng/L for incident heart failure hospitalization (Table 2).

Trajectories of cTnI and Mortality

Trajectories of cTnI associated with both cardiovascular and noncardiovascular mortality in a similar fashion as for the primary outcome. The trajectory of cTnI was steepest for cardiovascular mortality (*P* compared with no events < .001; Figure 4), with a trajectory approximately twice as steep as for noncardiovascular mortality (*P* compared with no events < .001; Figure 4). The yearly increase in cTnI was 0.280 (95% CI, 0.218-0.359) ng/L for cardiovascular mortality and 0.145 (95% CI, 0.126-0.166) ng/L for noncardiovascular mortality (Table 2).

Probability of Subclinical Myocardial Injury and Incident Clinical Endpoints

We assessed the probability of subclinical myocardial injury, defined as concentrations of cTnI ≥4 ng/L for women and ≥6 ng/L for men, in the years prior to all incident clinical endpoints. The slopes of predicted probability for subclinical myocardial injury were steepest for admission for heart failure or cardiovascular mortality (*P* compared with no events < .001; Supplementary Table 1 and Supplementary Figure 1, available online) and

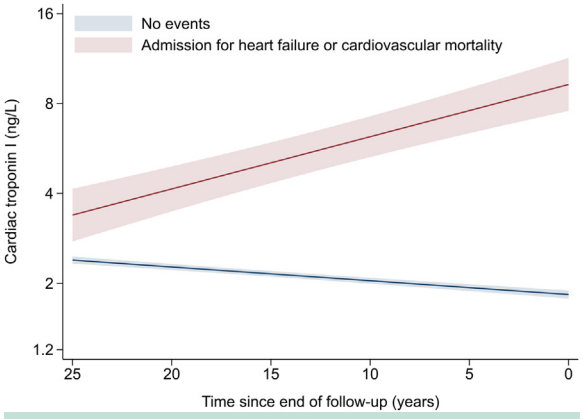

Figure 2 Trajectories of cardiac troponin I in the years prior to admission for heart failure, or cardiovascular mortality.

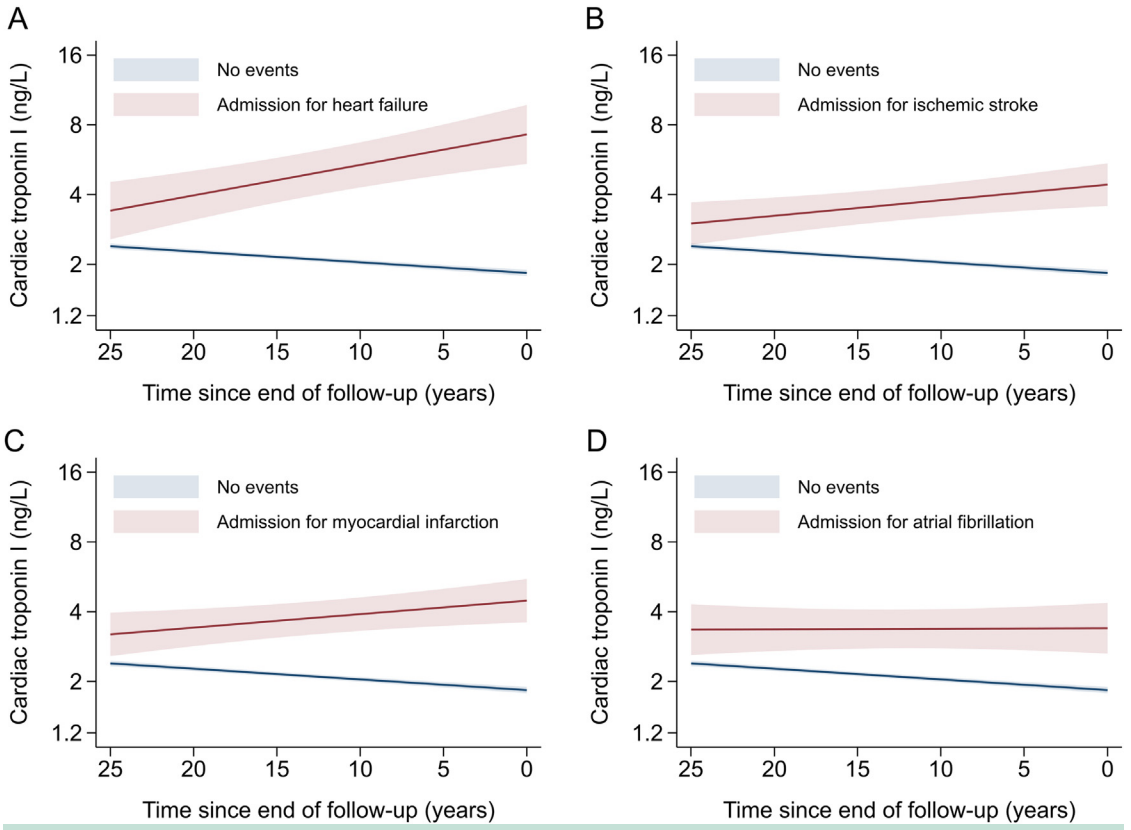

Figure 3 Trajectories of cardiac troponin I in the years prior to admission for nonfatal cardiovascular events. (**A**) Heart failure; (**B**) ischemic stroke; (**C**) myocardial infarction; (**D**) atrial fibrillation.

cardiovascular mortality alone (*P* compared with no events < .001; Supplementary Table 1 and Supplementary Figure 2, available online). For the nonfatal outcomes, the results were comparable with those from the trajectory analyses, with steeper slopes for all outcomes compared with study participants with no events, apart from no differences according to hospitalization for atrial fibrillation (Supplementary Table 1 and Supplementary Figures 2 and 3, available online).

In the sensitivity analyses, we excluded study participants with established cardiovascular disease at baseline from the models. Overall, the patterns of associations were unchanged, but with weaker effect estimates for the slopes of cTnI and wider confidence intervals (Supplementary Tables 2 and 3, Supplementary Figures 4 and 5, available online).

DISCUSSION

Using data from a large population cohort with repeated measurements of cTnI, we have demonstrated associations of slowly increasing concentrations of cTnI in the years prior to incident fatal and nonfatal cardiovascular outcomes. The slope of change for both continuous

Table 2 Yearly Change in cTnI from HUNT2 to HUNT4 According to Incident First Event After HUNT4

Outcome	Yearly Change in cTnI (95% CI), ng/L	*P* Compared with No Events
Heart failure or cardiovascular death (n = 67)	0.235 (0.192-0.289)	< .001
Heart failure (n = 30)	0.155 (0.114-0.209)	< .001
Myocardial infarction (n = 53)	0.051 (0.041-0.063)	< .001
Atrial fibrillation (n = 39)	0.002 (0.001-0.002)	.10
Ischemic stroke (n = 60)	0.057 (0.046-0.070)	< .001
Cardiovascular death (n = 47)	0.280 (0.218-0.360)	< .001
Noncardiovascular death (n = 125)	0.101 (0.086-0.120)	< .001
No events (n = 2961)	−0.022 (−0.022 to −0.023)	

CI = confidence interval; cTnI = cardiac troponin I; HUNT = Trøndelag Health Study.

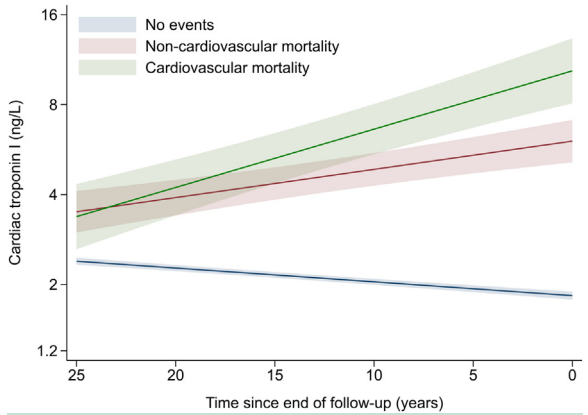

Figure 4 Trajectories of cardiac troponin I in the years prior to death.

concentrations of cTnI and concentrations of cTnI defined as subclinical myocardial injury (cTnI ≥4 ng/L for women and ≥6 ng/L for men) were steepest for heart failure hospitalizations and cardiovascular mortality. The slopes for atherosclerotic events (hospitalizations for myocardial infarction or ischemic stroke) were less pronounced and the cTnI slopes did not associate with hospitalization for atrial fibrillation, the latter contrasting our results to recent investigations from the Atherosclerosis Risk in Communities study.[18]

Cardiac Troponin Trajectories and Incident Heart Failure

Low-grade elevations in cardiac troponin strongly associate with incidence of most cardiovascular outcomes, but especially heart failure hospitalizations and cardiovascular mortality.[2] Most previous investigations have focused on the prognostic associations between cardiac troponin measured at single time-points or at 2 time-points with calculation of simple or proportional differences.[9,19] Cardiovascular disorders usually develop over years, and for heart failure, the condition progresses from at-risk subjects with predisposing conditions such as coronary heart disease, nonischemic myocardial disease, valvular heart disease, hypertension, or diabetes mellitus, through asymptomatic stages with objective evidence of cardiac dysfunction, to symptomatic and ultimately, refractory heart failure.[20] Through all these stages of heart failure progression, cardiac troponins are expected to be elevated, as cardiovascular risk factors,[3] comorbidities, and alterations in cardiac structure and function[7] all associate with increased concentrations of cardiac troponin in the general population. In the current investigation, we demonstrate the insidious increase in concentrations of cTnI in the years prior to overt disease in need of hospital admission. In this regard, concentrations of cardiac troponin accurately reflect the overall burden of risk factors contributing to cardiac remodeling and hypertrophy, ultimately culminating in symptomatic disease.

Cardiac Troponin Trajectories and Incident Atherosclerotic Events

Atherosclerotic events such as myocardial infarction and ischemic stroke share many risk factors with heart failure, but the immediate pathogenesis is less chronic, as the precipitating event commonly is rupture of atherosclerotic plaques or cardioembolism. Despite being considered as more acute occurrences, both admission for myocardial infarction and ischemic stroke were preceded by low-grade progression of subclinical myocardial injury in our study. Two of the strongest risk factors for atherosclerotic disease, arterial hypertension and diabetes mellitus, are highly chronic conditions. Blood pressure and particularly, high blood pressure, associates with subclinical myocardial injury,[21] and correspondingly, community dwellers with minor elevations in cardiac troponin are at increased risk of developing clinical hypertension.[22] As for arterial hypertension, prevalent diabetes mellitus associates with increased risk of subclinical myocardial injury. More interestingly, glycated hemoglobin A1c, one of the biomarkers essential for the diagnosis of diabetes mellitus, associates with increasing concentrations of cardiac troponin even in the absence of established diabetes mellitus.[23] Compared with heart failure, atherosclerotic cardiovascular disease is less frequently preceded by alterations in cardiac structure and function, but concentrations of cardiac troponin would still be expected to increase parallel to increase in the cumulative burden of modifiable risk factors.

Cardiac Troponin Trajectories and Mortality

Concentrations of cardiac troponin associate strongly with mortality in the general population, and cTnI and cardiac troponin T exhibit equally strong associations with death from cardiovascular cause. For noncardiovascular mortality, the associations appear stronger for cardiac troponin T and less pronounced for cTnI.[3] In the current investigation, we found similar patterns in the slopes of cTnI in the years prior to death, with a steeper cTnI slope for cardiovascular mortality compared with noncardiovascular mortality. The association of increasing concentrations of cTnI with cardiovascular death is not entirely surprising. However, the notion that concentrations of cTnI increase also in the years prior to noncardiovascular death raises some interesting questions to the pathophysiology of low-grade cardiac troponin release. In this context, the pattern of slowly increasing concentrations of cardiac troponin could reflect overall frailty, with accumulation of risk factors and deterioration of normal physiology ultimately leading to death. Cardiovascular comorbidities could obviously have contributed to acceleration of the process toward noncardiovascular death, but despite adjustment for established cardiovascular disease and risk factors, cTnI remained associated with both cardiovascular and noncardiovascular fatal outcomes. Whatever the cause, increasing concentrations of cardiac troponin should be viewed as a pathophysiological response with increased risk of symptomatic disease.

Clinical Outlooks

Measurement of cardiac troponin is fundamental in the clinical work-up of suspected acute coronary syndromes, but evidence is accruing that cardiac troponins also have strong prognostic properties in patients with coronary heart disease,[1] heart failure,[24] and in the general population.[2] Most cardiovascular risk factors influence concentrations of cardiac troponin measured in community dwellers,[25] and specific preventive therapies such as lipid-lowering medication attenuate concentrations of cardiac troponin and cardiovascular risk in parallel.[26] Furthermore, moderate physical activity[27] and weight loss[28] may delay the progression of subclinical myocardial injury. In the current investigation, all fatal and most nonfatal cardiovascular events were preceded by slowly increasing concentrations of cTnI in years prior to overt disease. In light of these results and the growing evidence that pharmacological and nonpharmacological interventions may concurrently reduce concentrations of cardiac troponin and cardiovascular risk, assessment of cardiac troponin patterns could identify patients appropriate for risk-factor-directed preventive measures. Prospective trials are needed to test whether this sentiment would translate to improved personalized patient management.

Strengths and Limitations

One of the principal strengths of the current investigation is repeated measurements of cTnI over >20 years in a large population cohort recruited from the general population, allowing detailed assessment of trajectories of cTnI in the years prior to incident morbidity and death. Outcome data were acquired from national quality registries, largely ruling out missing information on clinical outcomes. The use of registry data and not adjudicated diagnoses do, however, increase the risk of diagnostic misclassification, especially for heart failure.[29] However, the associations with heart failure were convincing, and more accurate diagnostication would most likely have strengthened our results. The diagnostic criteria for the clinical endpoints did not change during the follow-up period of the study, making this a less likely source of misclassification. We do not have information on incident clinical events happening abroad, but this number is most likely negligible. Information on demographics and medical history were acquired from questionnaires, and we cannot exclude some degree of reporting or recall bias. Most of the study participants attended all 3 specified waves of the HUNT Study (HUNT2, HUNT3, HUNT4), and the cohort may not entirely represent the general population due to healthy user bias. We assessed annual change in cTnI over 25 years of follow-up on group levels, and our finding may, as such, be less applicable on an individual person basis. We do not have measurement of other cardiac biomarkers such as natriuretic peptides, barring us from assessing the potentially additive prognostic properties of such biomarkers. Due to significant differences in demographic and baseline risk-burden, our results may not be generalizable to a general US population. Lastly, due to the homogenous population of Trøndelag County, our results may not be generalized to ethnicities other than northern European Caucasian.

CONCLUSIONS

Fatal and nonfatal cardiovascular events are preceded by slowly increasing concentrations of cardiac troponin, independently of established cardiovascular risk factors. Our results support a model where cTnI could identify subjects in the general population with subclinical myocardial injury, possibly progressing to overt cardiovascular disease and mortality over time. Whether serial assessment of cardiac troponin could identify patients appropriate for risk-factor-directed preventive measures needs to be assessed in prospective trials.

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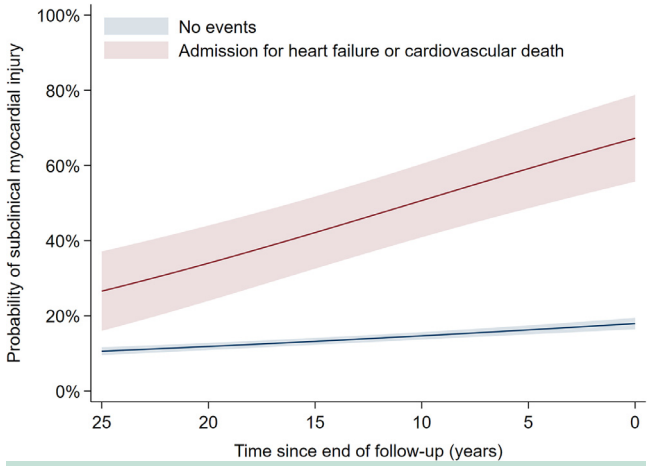
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2023.05.009.

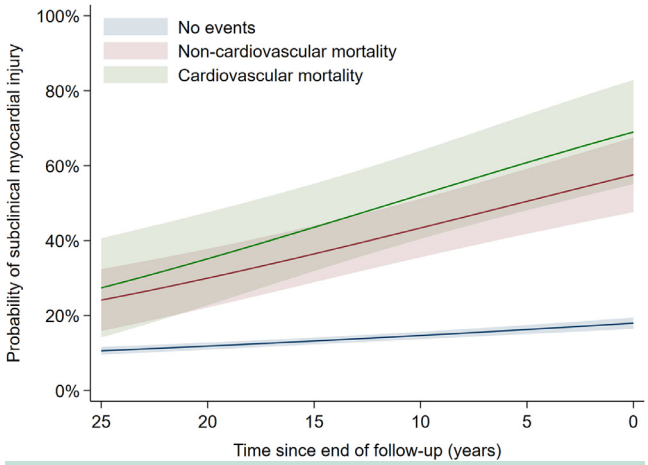
Supplementary Table 1 Yearly Change in Probability of Subclinical Myocardial Injury from HUNT2 to HUNT4 According to Incident First Event After HUNT4

Outcome	Yearly Change (95% CI), %	*P* Compared with No Events
Heart failure or cardiovascular death (n = 67)	1.27 (0.79-1.76)	< .001
Heart failure (n = 30)	1.02 (0.37-1.68)	.028
Myocardial infarction (n = 53)	1.11 (0.64-1.58)	< .001
Atrial fibrillation (n = 39)	0.10 (−0.45-0.65)	.50
Ischemic stroke (n = 60)	0.82 (0.38-1.27)	.020
Cardiovascular death (n = 47)	1.32 (0.63-1.39)	< .001
Noncardiovascular death (n = 125)	1.01 (0.71-1.92)	.001
No events (n = 2961)	0.29 (0.22-0.35)	

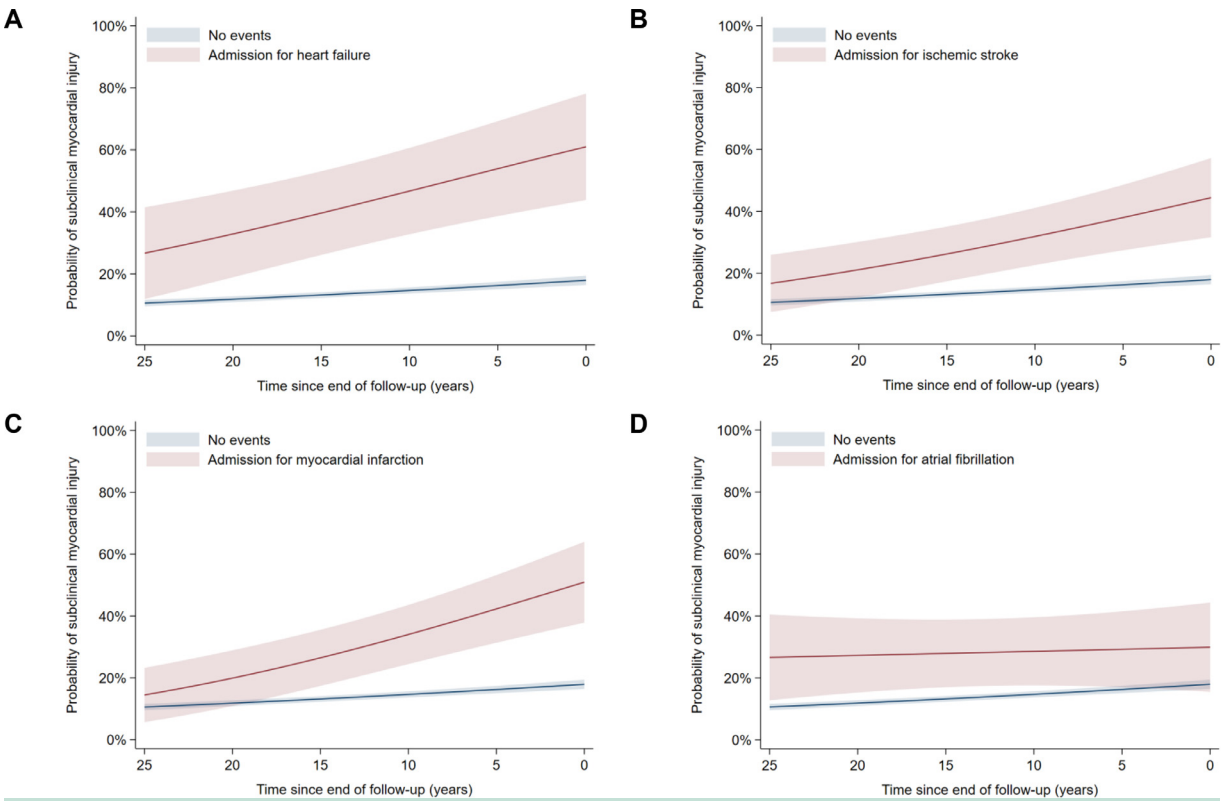
CI = confidence interval; HUNT = Trøndelag Health Study.



Supplementary Figure 1 Probability of subclinical myocardial injury in the years prior to admission for heart failure or cardiovascular mortality.



Supplementary Figure 2 Probability of subclinical myocardial injury in the years prior to death.



Supplementary Figure 3 Probability of subclinical myocardial injury in the years prior to admission for non-fatal cardiovascular events. (**A**) Heart failure; (**B**) ischemic stroke; (**C**) myocardial infarction; (**D**) atrial fibrillation.

Supplementary Table 2 Yearly Change in cTnI from HUNT2 to HUNT4 According to Incident First Event After HUNT4, Participants with Baseline Cardiovascular Disease Excluded

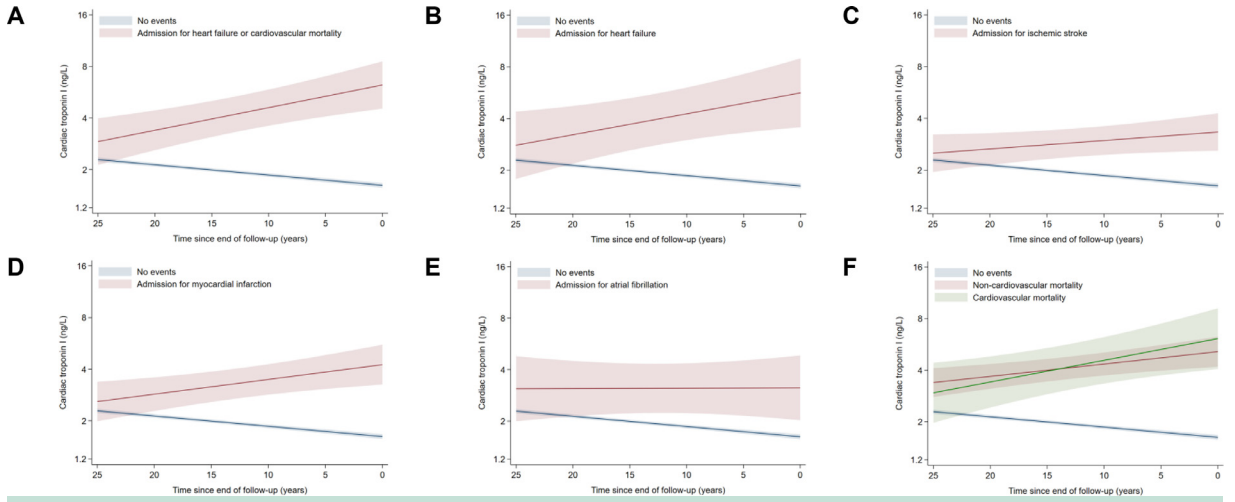
Outcome	Yearly Change in cTnI (95% CI), ng/L	*P* Compared with No Events
Heart failure or cardiovascular death (n = 28)	0.133 (0.096-0.184)	< .001
Heart failure (n = 12)	0.114 (0.071-0.183)	< .001
Myocardial infarction (n = 34)	0.066 (0.051-0.087)	< .001
Atrial fibrillation (n = 13)	0.002 (0.001-0.002)	.22
Ischemic stroke (n = 41)	0.033 (0.026-0.042)	< .001
Cardiovascular death (n = 18)	0.126 (0.084-0.191)	< .001
Noncardiovascular death (n = 87)	0.070 (0.056-0.086)	< .001
No events (n = 2545)	−0.027 (−0.026 to −0.027)	

CI = confidence interval; cTnI = cardiac troponin I; HUNT = Trøndelag Health Study.

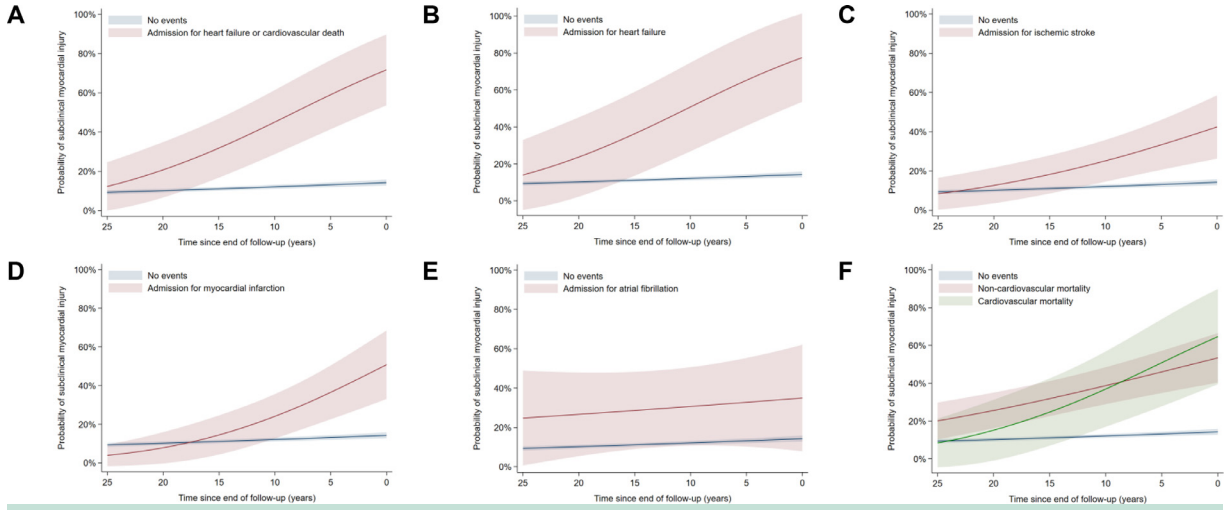
Supplementary Table 3 Yearly Change in Probability of Subclinical Myocardial Injury from HUNT2 to HUNT4 According to Incident First Event After HUNT4, Participants with Baseline Cardiovascular Disease Excluded

Outcome	Yearly Change (95% CI), %	*P* Compared with No Events
Heart failure or cardiovascular death (n = 28)	1.88 (1.15-2.62)	< .001
Heart failure (n = 12)	2.08 (1.07-3.09)	< .001
Myocardial infarction (n = 34)	1.44 (0.82-2.06)	< .001
Atrial fibrillation (n = 13)	0.35 (−0.77-1.46)	.79
Ischemic stroke (n = 41)	1.02 (0.48-1.57)	.003
Cardiovascular death (n = 18)	1.72 (0.77-2.67)	.002
Noncardiovascular death (n = 87)	1.04 (0.55-1.54)	< .001
No events (n = 2545)	0.19 (0.13-0.26)	

CI = confidence interval; HUNT = Trøndelag Health Study.



Supplementary Figure 4 Trajectories of cTnI in the years prior to incident clinical endpoints, participants with baseline CVD excluded. (**A**) Heart failure or cardiovascular mortality; (**B**) heart failure; (**C**) ischemic stroke; (**D**) myocardial infarction; (**E**) atrial fibrillation; (**F**) mortality. cTnI = cardiac troponin I; CVD = cardiovascular disease.



Supplementary Figure 5 Probability of subclinical myocardial injury in the years prior to incident clinical endpoints, participants with baseline CVD excluded. (**A**) Heart failure or cardiovascular mortality; (**B**) heart failure; (**C**) ischemic stroke; (**D**) myocardial infarction; (**E**) atrial fibrillation; (**F**) mortality. CVD = cardiovascular disease.