Cardiac troponin-I and risk of heart failure: a community-based cohort study

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Aims
We examined if circulating levels of cardiac troponin-I (cTnI) predict subsequent heart failure in the community.

Methods and results
Using Cox proportional hazards models, we examined the risk of a first hospitalization for heart failure during a maximum of 11.4 years in a community-based sample of 1089 70-year-old men without heart failure, valvular disease, or electrocardiographic left ventricular hypertrophy. Adjusting for smoking, systolic blood pressure, antihypertensive medication use, diabetes, body mass index, serum cholesterol, and myocardial infarction before baseline or during follow-up, 0.01 μg/L higher cTnI conferred a hazard ratio (HR) of 1.26 (95% confidence interval 1.15–1.38) for subsequent heart failure. Persons with cTnI >0.03 μg/L had an HR of 5.25 (2.00–13.77) compared with persons with cTnI <0.01 μg/L. Adjusting additionally for serum NTproBNP attenuated the estimates somewhat [HR 1.22 (1.11–1.34) per 0.01 μg/L of cTnI]. Excluding persons with myocardial infarction before baseline and censoring at time of myocardial infarction during follow-up, 0.01 μg/L higher cTnI was associated with a multivariable-adjusted HR of 1.31 (1.16–1.47) for heart failure.

Conclusion
In a community-based sample, a direct measure of cardiomyocyte damage, cTnI, indicated a substantially increased risk of heart failure, accounting for other risk factors. Studies investigating the clinical utility of measuring cTnI in asymptomatic individuals are warranted.

Keywords
Heart failure • Risk factors • Epidemiology • Population

Introduction
Cardiac troponins are thin filaments in the sarcomere, which, activated by Ca2+, generate the contractile force of the heart. Cardiac troponins circulating in peripheral blood have a widespread clinical use as a tool for diagnosing myocardial damage, mainly that from myocardial infarctions. The new universal definition of myocardial infarction relies heavily on increased circulating cardiac troponin levels.1

It has recently been demonstrated that also in the absence of an acute myocardial infarction, myocardial damage identified by circulating cardiac troponins may be of prognostic importance.2 This has led to a shift in the view of cardiac troponins, from specific identifiers of myocardial infarction to general indicators of myocardial damage.3 Elevated levels of circulating cardiac troponins may have a variety of substrates, such as left ventricular hypertrophy4,5 or myocarditis,6 conditions that may be asymptomatic and are known precursors of heart failure.7–9 Circulating troponin levels have been demonstrated to predict mortality in samples of patients with acute decompensated heart failure,10–12 in chronic stable heart failure,13–16 as well as in apparently healthy people.2 The predictive value of cardiac troponins for incident heart failure is not known, and their role in risk evaluation in healthy persons remains to be identified.

We hypothesized that subclinical cardiomyocyte damage precedes the development of heart failure. Accordingly, we investigated whether circulating levels of cardiac troponin I (cTnI) are associated with incident heart failure independently of other risk factors for heart failure in a community-based sample of 70-year-old men free from heart failure at baseline.
Methods

Study sample

We used data from the Uppsala Longitudinal Study of Adult Men (www.pubcare.uu.se/ULSAM), a health survey focused on identifying risk factors for cardiovascular disease. All 50-year-old men living in Uppsala in 1970–73 were invited, and 82% (*n* = 2322) participated in the first investigation. The cohort was re-investigated 20 years later, in 1991–95 (the baseline of the present study). Seventy-three percent (*n* = 1221) of the 1681 invited 70-year-old men participated.

For the present study, we excluded participants who lacked cTnI measurements (*n* = 16) or had extreme outlier values (>3× inter-quartile range + 75th percentile) of ln[cTnI], corresponding to cTnI >0.13, *n* = 10, or who had been hospitalized for heart failure (*n* = 17) or valvular disease (*n* = 14) before the baseline investigation. We also excluded participants with electrocardiographic (ECG) left ventricular hypertrophy (defined as high amplitude R-waves according to the Minnesota code17 together with a left ventricular strain pattern) at baseline (*n* = 75), because of a statistically significant interaction between that variable and cTnI in the main models, and we only had power to analyse the stratum without left ventricular hypertrophy. This also had to be done for another study of heart failure prediction in this sample.18 These exclusions rendered a sample of 1089 men for analysis.

In order to investigate cTnI as a predictor for ‘non-ischaemic’ heart failure, we also investigated a subsample of 950 men without myocardial infarction before baseline (either from the hospital discharge register or ECG Q-wave or left bundle branch block at baseline; *n* = 139).

All participants gave written informed consent and the study was approved by Uppsala University Ethics Committee.

Baseline examinations

At the baseline of the present study, participants underwent a medical examination, a questionnaire, office blood pressure measurement, an overnight collection of urine, blood sampling after an overnight fast for glucose, lipid, and other biomarker determinations, and anthropometric measurements, as previously described.19–21

Determinations of the cTnI method has been described in detail previously.22 Briefly, analyses were performed using the AccuTnI assay (Beckman Coulter Inc., USA) in August 2004 on serum that had been stored at −70°C since baseline and thawed ≤1 time since baseline. According to the manufacturer, the minimum detectable concentration was <0.01 µg/L. The coefficient of variation was 10% at a concentration of 0.03 µg/L in the lab used for the present study.

Office blood pressure was measured after 10 min supine rest in the right arm with a sphygmomanometer using the appropriate cuff size, and the mean of two measurements was used. Coding of smoking was based on interview reports and data on use of antihypertensive medication were obtained from the questionnaire. Diabetes at baseline was defined as fasting plasma glucose ≥7.0 mmol/L and/or the use of oral hypoglycaemic agents or insulin. Plasma N-terminal pro-brain natriuretic peptide (NTproBNP) was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). Urinary albumin excretion rate was analysed on urine collected during the night using a radioimmunoassay kit (Albumin RIA 100, Pharmacia, Uppsala, Sweden). Cystatin C measurements were performed with a latex-enhanced reagent using a Behring BN ProSpec analyser (Dade Behring, Deerfield, IL, USA). Insulin sensitivity was determined using the euglycaemic insulin clamp technique, according to DeFronzo et al.,23 with a slight modification [insulin was infused at a constant rate of 56 mU/(min×m²)]. Glucose disposal rate, representing insulin sensitivity, was calculated as the amount of glucose taken up during the last 60 min of the 2 h clamp. High-sensitivity C-reactive protein measurement was performed using a latex-enhanced reagent (Dade Behring). The presence of valvular disease (International Classification of Disease [ICD]-9 codes 394–397 and 424 or ICD-10 codes I05–I08 and I14–I17) and prior and interim myocardial infarction (ICD-9 code 410 or ICD-10 code I21) were assessed from the hospital discharge register. The precision of the myocardial infarction diagnosis in the Swedish hospital discharge register is high.24 Men with a Q-wave or left bundle branch block in their baseline ECG (Minnesota codes 1:1 or 7:1) were also classified as having had a previous myocardial infarction.

Follow-up and outcome parameter

Participants were followed for a maximum of 11.4 years [median 9.0 years, 9139 person-years at risk (PYAR)], between baseline in 1991–95 and 31 December 2002. Two hundred and fifty three men died during follow-up.

The primary endpoint, a first hospitalization for heart failure, was defined through a chart review process by two physicians (E.I. and LL) among all hospital records containing the ICD heart failure codes 428 (ICD-9) and IS0 (ICD-10) and the hypertensive heart disease with congestive heart failure code I11.0 (ICD-10). The classification relied on the definition proposed by the European Society of Cardiology25 and the review process has been described in detail previously.26 The secondary endpoint was a first hospitalization for non-ischaemic heart failure. For the analyses of this endpoint, participants who had experienced a myocardial infarction before baseline were excluded, and those who suffered a myocardial infarction during follow-up were censored at time of the myocardial infarction. Follow-up for this endpoint was 7775 PYAR.

In order to investigate a possible competing risk by death, we also investigated a combined endpoint of death or heart failure in the total sample in a secondary analysis.

None of the participants were lost to follow-up.

Statistical analyses

All primary analyses were defined a priori. Initially, distributional properties of all variables were examined, and non-normally distributed variables (C-reactive protein, cystatin C, urinary albumin excretion rate, NTproBNP, and cTnI) were logarithmically transformed. Thereafter, Cox proportional hazards models were used, modelling time to first hospitalization for heart failure. Proportional hazards assumptions were confirmed by Schoenfeld’s tests, and linearity assumptions were confirmed by inspecting Martingale residuals.

Because the relation of cTnI to heart failure incidence was hypothesized to be potentially non-linear, we investigated cTnI in two ways: as an ordinal variable and as a continuous variable. For the non-linear models, the cTnI assay used provided values rounded to the nearest 1/100 µg/L, and because of this rounding, quantile subdivisions were unsatisfactory. We therefore chose to construct four cTnI groups with as equal size as possible: <0.01 µg/L (*n* = 147); 0.01 µg/L (*n* = 669); 0.02 µg/L (*n* = 184); and ≥0.03 µg/L (*n* = 89); respectively. The cumulative incidences of heart failure in these cTnI groups, as well as for corresponding groups in the sample without myocardial infarction before baseline (*n* = 132, 597, 146, and 75, respectively), are illustrated in Figures 1 and 2, with log-rank *P*-values for differences between groups.

Linear models were also examined, investigating the effect of a 0.01 µg/L higher cTnI. Covariates were examined either on the continuous scale or dichotomized, depending on their character.
Four sets of models were considered, in a hierarchical fashion: (a) unadjusted models; (b) adjusting for established risk factors for heart failure [smoking, systolic blood pressure, antihypertensive medication use, diabetes, body mass index, serum cholesterol, previous myocardial infarction, and myocardial infarction during follow-up (modelled as a time-dependent covariate)]; (c) covariates as in Model B plus NTproBNP; (d) covariates as in Model B plus more recently described risk factors for heart failure (urinary albumin excretion rate, euglycaemic insulin clamp glucose disposal rate, cystatin C, and C-reactive protein).

In order to rule out an effect modification by established risk factors on the relation of cTnI to heart failure, we investigated interaction terms between each of those covariates and cTnI in Model B. The covariate ECG left ventricular hypertrophy was also tested in this respect, and because of significant interaction with cTnI, further analyses had to be restricted to participants without that trait, as described above.

Differences between cTnI groups regarding baseline characteristics were examined using \( \chi^2 \) tests and analyses of variance. To investigate independent relations of baseline variables to cTnI, partial correlation coefficients from a multiple linear regression model with cTnI as dependent variable and all other variables in Table 1 as independent variables were examined.

In order to examine the clinical utility of cTnI measurement for prediction of subsequent heart failure, we used the method described by Pencina et al.\textsuperscript{27} The integrated discrimination improvement (IDI) calculated is the mean of increments and decrements in the estimated probabilities of subsequent heart failure for cases and non-cases, respectively, comparing a model with the cTnI variable (our Model B) to a model with the same covariates but without the cTnI variable; the corresponding \( P \)-value for test of the null hypothesis of no discrimination improvement for the larger model is also presented.

We examined IDI for a continuous cTnI variable, but also extended the IDI method to identify the optimal cut-off point of cTnI to achieve optimal discrimination. The following criteria was used: all cut-off points between percentile 1 and percentile 99 of cTnI using step length (percentile 99–percentile 1)/98 defined binary variables (0 = below cut-off point/1 = above or equal to cut-off point). For each cut-off point, IDI was calculated for the comparison of discrimination improvement from a small model (including the covariates in Model B) to a larger model = small model + the binary cTnI variable. The optimal cut-off point of cTnI was defined as the cut-off point related to the maximum achieved IDI. The relation between all examined cTnI cut-off points and IDI are shown in a figure.

Two-tailed 95% confidence intervals (CI) and \( P \)-values are given, with \( P < 0.05 \) regarded as significant. Analyses were performed by J.S. using Stata 10.1 (Stata Corporation, College Station, USA) and by L.B. using SAS 9 (SAS Institute Inc., Cary, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

During follow-up, 87 of the 1089 men in the total sample experienced a first hospitalization for heart failure; rendering an incidence rate of 9.5 (95% CI 7.7–11.7) per 1000 PYAR. In the subsample of 950 participants without myocardial infarction, 52 experienced a first hospitalization for non-ischaemic heart failure [incidence rate 6.7 (5.1–8.8)/1000 PYAR]. In a secondary analysis in the
total sample, 298 participants experienced the combined endpoint of death or heart failure [incidence rate 32.6 (29.1–36.5)/1000 PYAR].

In the total sample, persons with cTnI ≥ 0.03 μg/L had an incidence rate of any heart failure of 25.5 (15.6–41.7) per 1000 PYAR, and persons with cTnI < 0.01 μg/L an incidence rate of 4.6 (2.1–10.3) per 1000 PYAR. Baseline characteristics of the sample are displayed in Table 1.

In the total sample, baseline cTnI level was consistently related to subsequent incidence of any heart failure in all models. In the continuous models, 0.01 μg/L higher cTnI was associated with a 22–33% higher risk of heart failure, as seen in Table 2.

The most marked risk increase was observed in the highest cTnI group (≥ 0.03 μg/L), which had a striking three- to nearly six-fold risk increase compared with the lowest cTnI group (< 0.01 μg/L) in all models, see Table 2. A statistically significant risk increase was also observed in the 0.02 μg/L group compared with the lowest group in the unadjusted Model A, with statistically non-significant increases in the other models.

The excess risk in the highest cTnI group was most pronounced during the first 2 years of follow-up, see Figure 1.

In models investigating non-ischaemic heart failure, the pattern was very similar to the any heart failure models (Figure 2 and Table 2), although the estimates for the highest cTnI group were lower in multivariable-adjusted non-ischaemic heart failure models, and statistically non-significant in Model C.

In secondary analyses investigating the combined outcome of death or heart failure in the total sample, 0.01 μg/L higher cTnI was associated with a Cox proportional hazard ratio (HR) of 1.18 (95% CI 1.11–1.25) in the continuous Model B, and the highest cTnI group (≥ 0.03 μg/L) had an HR of 2.85 (95% CI 1.77–4.58) compared with the lowest cTnI group (< 0.01 μg/L) in Model B. The two middle cTnI groups had statistically non-significant 26–32% risk increases compared with the lowest group in Model B. Results were similar in Models C and D (data not shown).

No deviations from the proportional hazards assumptions were detected by Schoenfeld’s tests and no deviations from linearity were observed in Model B in both investigated samples. Interaction terms between cTnI and all covariates in Model B were tested one at a time; no interactions other than the one described between ECG left ventricular hypertrophy and cTnI were observed.

Investigating the discriminatory value of cTnI for subsequent heart failure, the addition of a continuous cTnI variable to the covariates in Model B improved discrimination borderline significantly (IDI = 0.022, P = 0.05). The optimal cut-off level from a discriminatory point of view was a cTnI of 0.04 μg/L, which corresponded to an IDI of 0.027; P = 0.03; see Figure 3.
## Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n = 1089)</th>
<th>Cardiac troponin-I groups</th>
<th>P for difference between groups</th>
<th>Partial correlation coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;0.01 μg/L (n = 147)</td>
<td>0.01 μg/L (n = 669)</td>
<td>0.02 μg/L (n = 184)</td>
<td>≥0.03 μg/L (n = 89)</td>
</tr>
<tr>
<td>Cardiac troponin-I</td>
<td>0.01 (0.01)</td>
<td>0.005 (0.0)</td>
<td>0.01 (0.0)</td>
<td>0.02 (0.0)</td>
<td>0.03 (0.02)</td>
</tr>
<tr>
<td>Smoking</td>
<td>223 (21.1)</td>
<td>28 (19.6)</td>
<td>129 (19.8)</td>
<td>42 (23.7)</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>146 (18)</td>
<td>144 (17)</td>
<td>146 (18)</td>
<td>149 (19)</td>
<td>146 (20)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84 (9)</td>
<td>82 (10)</td>
<td>84 (9)</td>
<td>85 (10)</td>
<td>83 (8)</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>355 (32.8)</td>
<td>53 (36.1)</td>
<td>201 (30.2)</td>
<td>67 (36.8)</td>
<td>34 (39.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>198 (18.2)</td>
<td>25 (17.0)</td>
<td>113 (16.9)</td>
<td>39 (21.2)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 (3.4)</td>
<td>26.3 (3.7)</td>
<td>26.2 (3.3)</td>
<td>26.4 (3.5)</td>
<td>26.6 (3.8)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.8 (1.0)</td>
<td>5.7 (1.0)</td>
<td>5.8 (1.0)</td>
<td>5.8 (0.9)</td>
<td>5.8 (1.1)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.43 (0.76)</td>
<td>1.38 (0.69)</td>
<td>1.43 (0.79)</td>
<td>1.46 (0.70)</td>
<td>1.54 (0.74)</td>
</tr>
<tr>
<td>Previous myocardial infarction (by hospital discharge register or ECG)</td>
<td>139 (12.8)</td>
<td>15 (10.2)</td>
<td>72 (10.8)</td>
<td>38 (20.7)</td>
<td>14 (15.7)</td>
</tr>
<tr>
<td>Urinary albumin excretion rate, μg/min</td>
<td>5.1 (3.7)</td>
<td>5.0 (5.3)</td>
<td>4.9 (6.6)</td>
<td>5.5 (10.6)</td>
<td>7.6 (9.6)</td>
</tr>
<tr>
<td>Clamp glucose disposal rate, mg/kg/min</td>
<td>5.2 (2.1)</td>
<td>5.2 (2.1)</td>
<td>5.2 (2.0)</td>
<td>5.1 (2.2)</td>
<td>4.8 (1.8)</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>1.20 (0.26)</td>
<td>1.19 (0.24)</td>
<td>1.20 (0.25)</td>
<td>1.21 (0.30)</td>
<td>1.26 (0.33)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.85 (3.01)</td>
<td>1.76 (3.56)</td>
<td>1.80 (2.67)</td>
<td>1.96 (3.67)</td>
<td>2.17 (4.63)</td>
</tr>
</tbody>
</table>

Data are n (%), means (standard deviations) for normally distributed variables, and medians (interquartile ranges) for non-normally distributed variables. C-reactive protein, cystatin C, urinary albumin excretion rate, N-terminal pro-brain natriuretic peptide (NTproBNP), and cardiac troponin-I. P for differences between groups are from χ² tests and analyses of variance. Rightmost columns are partial correlation coefficients and corresponding P-values from a model with cardiac troponin-I as dependent variable and all other variables in the table as independent variables. ECG, electrocardiogram.
Table 2 Risk of heart failure by cardiac troponin-I levels

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted (Model A)</th>
<th>Adjusting for established risk factors (Model B)</th>
<th>Adjusting for established risk factors plus NTproBNP (Model C)</th>
<th>Adjusting for established and recent risk factors (Model D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of any heart failure in the total sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 0.01 μg/L of cTnI</td>
<td>1.33 (1.23–1.43), P &lt; 0.001</td>
<td>1.26 (1.15–1.38), P &lt; 0.001</td>
<td>1.22 (1.11–1.34), P &lt; 0.001</td>
<td>1.26 (1.15–1.38), P &lt; 0.001</td>
</tr>
<tr>
<td>By cTnI groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.01 μg/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.01 μg/L</td>
<td>1.86 (0.80–4.36), P = 0.15</td>
<td>1.94 (0.82–4.56), P = 0.13</td>
<td>1.62 (0.68–3.83), P = 0.28</td>
<td>2.15 (0.84–5.49), P = 0.11</td>
</tr>
<tr>
<td>0.02 μg/L</td>
<td>2.66 (1.05–6.70), P = 0.04</td>
<td>2.09 (0.81–5.38), P = 0.13</td>
<td>1.53 (0.58–4.03), P = 0.39</td>
<td>2.01 (0.71–5.71), P = 0.19</td>
</tr>
<tr>
<td>≥0.03 μg/L</td>
<td>5.89 (2.30–15.08), P &lt; 0.001</td>
<td>5.25 (2.00–13.77), P = 0.001</td>
<td>3.47 (1.28–9.41), P = 0.02</td>
<td>5.95 (2.09–16.92), P = 0.001</td>
</tr>
</tbody>
</table>

Risk of non-ischaemic heart failure in sample without myocardial infarction before baseline, censoring at time of myocardial infarction

|                                |                      |                                               |                                                 |                                                  |
| Per 0.01 μg/L of cTnI          | 1.36 (1.23–1.50), P < 0.001 | 1.31 (1.16–1.47), P < 0.001               | 1.26 (1.11–1.45), P < 0.001               | 1.34 (1.18–1.52), P < 0.001               |
| By cTnI groups                 |                      |                                               |                                                 |                                                  |
| <0.01 μg/L                     | 1                    | 1                                             | 1                                               | 1                                               |
| 0.01 μg/L                      | 1.49 (0.52–4.31), P = 0.46  | 1.53 (0.52–4.44), P = 0.44            | 1.24 (0.42–3.64), P = 0.70            | 1.24 (0.42–3.68), P = 0.70            |
| 0.02 μg/L                      | 3.43 (1.11–10.54), P = 0.03  | 2.97 (0.95–9.31), P = 0.06            | 2.30 (0.72–7.31), P = 0.16            | 2.03 (0.62–6.70), P = 0.24            |
| ≥0.03 μg/L                     | 6.30 (2.00–19.84), P = 0.002 | 4.85 (1.47–15.98), P = 0.009          | 3.00 (0.86–10.44), P = 0.08          | 4.53 (1.36–15.07), P = 0.01          |

Cardiac troponin-I was investigated as a continuous variable (per 0.01 of cardiac troponin-I) and in four groups (the lowest group being the reference level) in separate models. Data are Cox proportional hazard ratios (95% confidence intervals), and P-values.

Figure 3 Discrimination of risk of any heart failure by cardiac troponin-I cut-offs in the total sample.
Discussion

Primary observations
In this community-based sample of 70-year-old men free from previous heart failure, valvular disease, or ECG left ventricular hypertrophy, higher cTnI levels were associated with a higher risk of subsequent heart failure. This relation was independent of established and more recently described risk factors for heart failure. Furthermore, cTnI predicted heart failure in individuals without a myocardial infarction before baseline, censoring at time of myocardial infarction during follow-up, suggesting that cTnI also predicts subsequent non-ischaemic heart failure. The best cut-off level in this sample for discriminating those who subsequently suffered heart failure from those who did not was a cTnI of 0.04 μg/L.

Comparisons with previous studies
Circulating troponin levels have been demonstrated to predict mortality in patients with manifest heart disease, such as acute coronary syndromes, acute decompensated heart failure, and chronic stable heart failure, and chronic stable renal disease without overt heart disease, as well as in patients with end-stage renal disease without overt heart disease, as well as in apparently healthy people in the community.

The association of cTnI levels with subsequent heart failure incidence is less studied. In patients with acute coronary syndromes, circulating troponin levels a few days after onset of symptoms predict subsequent left ventricular systolic dysfunction, but no previous study has reported the predictive value of circulating troponin levels for incident heart failure in apparently healthy individuals in a community-based setting.

In heart failure patients, persistently increasing or increasing troponin levels on serial measurements predict worse outcome than decreasing levels. As only one single measurement of cTnI was available in the present study, the value of serial troponin measurements in healthy individuals needs to be investigated in future studies.

Potential mechanisms
Numerous sources of elevated cTnI levels have been identified in persons angiographically free from coronary artery disease. Most involve an oxygen supply/demand mismatch, such as in tachycardia, physical exertion, severe aortic stenosis, left ventricular hypertrophy, severe heart failure, or anaemia, whereas the cardiomyocyte damage mechanism may be less obviously ischaemia-related in other cases, such as sepsis, myocarditis, pericarditis, diabetic ketoacidosis, or myocardial contusion. Many of these scenarios will be defined as Type 2 (secondary) myocardial infarctions according to the new universal definition of myocardial infarction. Several of these sources of elevated cTnI are likely to be present in or cohort, and may explain part of the associations observed. However, it should be noted that for the present study of apparently healthy individuals, we a priori excluded participants who had been hospitalized for heart failure or with valvular disease before the baseline investigation, and due to interaction subsequently also participants with ECG left ventricular hypertrophy at baseline, thereby diminishing the influence of some of these sources of elevated cTnI.

In our a priori-defined models, we investigated other explanations for the observed relations, including NTproBNP or more recently proposed heart failure risk factors (urinary albumin excretion rate, euglycaemic insulin clamp glucose disposal rate, cystatin C, and C-reactive protein). The covariate which attenuated the cTnI estimates the most was serum NTproBNP (in Model C), implying that myocardial strain may explain part, but not all, of the relation between cTnI and subsequent heart failure in our study.

We cannot exclude that subclinical or mild ischaemia may partly explain our observations. In that context, it should be noted that elevated troponin levels have been demonstrated to predict adverse outcome and to be related to BNP levels also in heart failure patients angiographically free from coronary disease. This is supported by the observation in our study that cTnI levels also predicted non-ischaemic heart failure. Inevitably, some residual confounding may exist, but the observation that cTnI was a statistically significant predictor of heart failure also adjusting for or excluding myocardial infarctions before baseline and censoring at time of myocardial infarction during follow-up indicates that ischaemia is likely not the sole explanation for our observations.

Increased circulating troponin levels are generally assumed to reflect severe cardiomyocyte injury or death. Both cardiomyocyte necrosis and apoptosis have been documented in heart failure, with seven-fold higher necrosis than apoptosis rates reported in severe heart failure. The rates of these cell death are unknown in asymptomatic persons. In the absence of heart disease, men appear to lose 1 g of myocardium per year, corresponding to 64 million cells, but it is not known if this is due to necrosis or apoptosis. Furthermore, relations between apoptosis or necrosis and circulating troponin levels have not been documented.

In addition to reflecting cardiomyocyte death, increased circulating cTnI levels may signify leakage of unbound sarcoplasmatic cTnI through damaged membranes, or may be the result of cTnI assays detecting cleaved cTnI peptides, degraded as a result of a higher rate of normal cTnI turnover or because of acute cardiomyocyte injury. In ischaemia/reperfusion injury, two proteases suggested to be responsible for cTnI cleavage and contractile dysfunction are calpain (a Ca2+-activated protease) and the previously presumed extracellularly acting matrix metalloproteinase-2.

Strengths and limitations
The strengths of this study include the large, community-based sample, the long follow-up period, and the carefully characterized cohort allowing for adjustment for a large number of important covariates, and the fact that all heart failure cases were validated, limiting the inclusion of false-positive cases. Further, a causal relation is supported by the temporal relationship, the strength of the relation, the dose–response association, and the consistency of the results in analyses of three separate heart failure outcomes.

There are some limitations to this study. As we only examined men of the same age with a similar ethnic background, the generalizability to women or older age and ethnic groups is unknown. On the other hand, the powerful effects of age on heart failure...
incidence were circumvented. Because the heart failure diagnosis was based on chart review, we could not distinguish between systolic and diastolic heart failure, as echocardiography was not available at the time of diagnosis for many of the cases. Because we could only study heart failure of a degree that required hospitalization, some milder heart failure forms will most likely be found among the non-cases. More importantly, some included men may have had mild heart failure at baseline. In order to exclude reverse causation as a major explanation for our observations, we performed a secondary analysis repeating our main models in a subsample of men who answered ‘no’ to the questions ‘Does climbing two flights of stairs or the equivalent at the same speed as others of your age leave you out of breath?’ and ‘Do you usually get out of breath when walking on level ground?’ at baseline. Cardiac troponin-I remained a statistically significant predictor of any heart failure and non-ischaemic heart failure in these analyses (data not shown).

Another limitation of the study is that when studying ‘non-ischaemic’ heart failure cases, we could only censor at clinically recognized myocardial infarctions during follow-up. Even if this is an established method for examining ‘non-ischaemic’ heart failure, more specific ways of assessing coronary disease during follow-up, such as coronary angiography, would be desirable, but are unfeasible in a cohort study. Because of the evidence of an interaction between cTnl and ECG left ventricular hypertrophy, we had to restrict the study sample to participants without that trait for power reasons, which may be considered a limitation.

Conclusions

Our data suggest that subclinical cardiomyocyte damage, as indicated by elevated serum levels of cTnl, is an independent contributor to the development of heart failure in the community. Further studies are needed to validate our findings and to evaluate the clinical utility of measuring cTnl in other settings than acute chest pain.

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Conflict of interest: P.V. collaborates with several diagnostic companies (Abbott Diagnostics, Beckman Coulter, DPC, Roche, Dade Behring, and more) in the evaluation of assays of cardiac markers. He has also received honorarium for lectures from several of these companies. No perceived potential conflicts of interest exist for any of the other authors.

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