Cardiac Troponins and Cardiovascular Disease Risk Prediction

Cardiac Troponins and Cardiovascular Disease Risk Prediction: An Individual-Participant-Data Meta-Analysis

Brief title: Cardiac troponins and cardiovascular disease risk prediction

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Summary

Background: The extent to which high-sensitivity cardiac troponin can predict cardiovascular disease (CVD) is uncertain.

Objectives: We aimed to quantify the potential advantage of adding information on cardiac troponins to conventional risk factors in the prevention of CVD.

Methods: We meta-analysed individual-participant-data from 15 cohorts, comprising 62,150 participants without prior CVD. We calculated hazard ratios (HR), measures of risk discrimination, and reclassification after adding cardiac troponin T (cTnT) and I (cTnI) to conventional risk factors. The primary outcome was first-onset CVD (i.e., coronary heart disease or stroke). We then modelled the implications of initiating statin therapy using incidence rates from 2.1 million individuals from the UK.

Results: Among participants with cTnT or cTnI measurements, 8,133 and 3,749 incident CVD events occurred during a median follow-up of 11.8 and 9.8 years, respectively. HRs for CVD per 1-SD higher concentration were 1.31 (95% CI 1.25-1.37) for cTnT and 1.26 (1.19–1.33) for cTnI. Addition of cTnT and cTnI to conventional risk factors was associated with C-index increases of 0.015 (0.012–0.018) and 0.012 (0.009–0.015) and continuous net reclassification improvements of 5% and 6% in cases and 17% and 22% in non-cases. If cTnT or cTnI were assessed among individuals at intermediate 10-year CVD risk, one additional CVD event would be prevented for every 408 and 473 individuals screened, respectively.

Conclusions: Measurement of cardiac troponin results in a modest improvement in the prediction of first-onset CVD that may translate into population health benefits if used at scale.

Introduction

Guidelines recommend measurement of cardiac troponins – structural proteins released into the circulation following myocardial injury – for the assessment of patients with suspected acute coronary syndrome, during which circulating troponins are significantly elevated.[1-5] However, because assays for cardiac troponins (including cardiac troponin T [cTnT] and troponin I [cTnI]) are now highly sensitive and specific, they can quantify even very low circulating concentrations among apparently healthy individuals.[6,7]

A key strategy in the prevention of cardiovascular disease (CVD) is the use of risk prediction algorithms that integrate conventional risk factors to identify individuals who could benefit most from preventive interventions, such as statin therapy.[8-10] Current clinical guidelines also recommend incorporating additional biomarkers when an individual's risk level does not meet a clear decision threshold, providing opportunities for enhanced risk stratification.[9,10] However, the population health utility of cardiac injury biomarkers such as troponins in improving CVD risk prediction remains uncertain.[8] Previous studies have focused only on measures of risk discrimination and recalibration but lacked modelling of the clinical implications of initiating guideline-recommended interventions (e.g. statin therapy).[6,7,11,12] This limitation has hindered the evaluation of the potential clinical benefits of routinely measuring cardiac troponins in apparently healthy individuals for the prevention of CVD.

To address these gaps, our study aimed to answer two key questions. First, what is the improvement in CVD risk prediction when cardiac troponins are added to risk factors used in conventional risk algorithms? We analyzed data from 62,150 participants in 15 prospective longitudinal general population cohorts to assess the value of adding cardiac

troponins to several conventional risk factors. Second, what is the estimated population health impact of incorporating cardiac troponins into CVD risk assessment? Using data from 2.1 million individuals in the UK Clinical Practice Research Datalink (CPRD),[13] we modeled the potential clinical benefit of initiating statin therapy in accordance with current guidelines.[8-10] To contextualize our findings, we compared the incremental predictive gains afforded by cardiac troponins with those provided by C-reactive protein (CRP), a plasma biomarker recommended for risk prediction in some CVD primary prevention guidelines[9,10], estimated glomerular filtration rate (eGFR), a biomarker of kidney function that estimates how well the kidneys filter waste and excess fluid from the blood[14], and N-terminal-pro-B-type natriuretic peptide (NT-proBNP), a biomarker of neurohormonal activation that could also serve as an adjunct in the prediction of first-onset CVD.[15]

Methods

Data sources

To evaluate the role of cardiac troponins in the primary prevention of CVD, we established the CArdiac troponin in the PReventIon of Cardiovascular Events (CAPRICE) collaboration, an international consortium of longitudinal cohort studies including individuals without a history of CVD at baseline which agreed to share individual-participant data. Details of the initial search strategy and methods used to collect and harmonise data are detailed in **Supplementary Text 1**. Studies were eligible if they had: (i) assayed cTnT[6,16-26] or cTnI[21,22,25,27-29] using a high-sensitivity assay[5,30]; (ii) recorded baseline information on age, sex, smoking status (current versus other [former and never]), history of diabetes, systolic blood pressure, total and high-density lipoprotein cholesterol concentration (henceforth, "conventional risk factors"); (iii) included participants without a known history

of cardiovascular disease (i.e. coronary heart disease, stroke, transient ischaemic attack, peripheral vascular disease, or cardiovascular surgery) at entry into the study; and (iv) and recorded cause-specific deaths and major cardiovascular morbidity (non-fatal myocardial infarction or stroke) over at least 1 year of follow-up.

Contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause) based on International Classification of Diseases coding, revisions 8–10, to at least three digits, or according to study-specific classification systems. We based ascertainment of fatal outcomes on death certificates, supplemented in 10 cohorts by additional data, and of non-fatal outcomes on WHO (or similar) criteria for myocardial infarction and for stroke (**Supplementary Table 1**). The Newcastle-Ottawa scale was used to assess the quality of the included cohorts (**Supplementary Table 2**).[31] This study follows the TRIPOD reporting guidelines (**Supplementary Text 2**).[32]

To estimate the potential for disease prevention in a general population setting, we used data from the CPRD, a primary care database of anonymized medical records covering over 20 million individuals opting into data linkage from over 675 general practices in the UK.[13] Individual-level data from consenting practices in the CPRD have been linked to HES and the national death registry. Details of the CPRD data used and endpoint definition are provided in **Supplementary Text 1**. The present analysis involved records of 2.1 million patients, a random sample of all CPRD data, working under the assumption that individuals in this database should be broadly representative of the UK general population.

The study was conducted by the CAPRICE independent coordinating centre at the University of Cambridge and the London School of Hygiene and Tropical Medicine. All cohorts were approved by the institutional review boards of the participating institutions

with participants providing written informed consent. The current study proposal was reviewed and approved by the Research Ethics Committee at the University of Cambridge.

Data analysis

The analysis involved four interrelated components. First, we characterized cross-sectional associations of cardiac troponin concentrations with established and emerging risk factors. Second, we assessed associations of cardiac troponin concentrations with subsequent risk of first-onset coronary heart disease (defined as fatal and non-fatal myocardial infarction) and stroke, considering these outcomes singly and in combination. Third, we quantified the incremental value of information on cardiac troponin concentrations, beyond that of conventional risk factors, for predicting major CVD outcomes. Fourth, we assessed the population health relevance of adding cardiac troponins to conventional risk factors, by generalising our analyses to the context of a UK population eligible for CVD risk assessment.

The primary outcome was a first-onset CVD event defined as the composite of any fatal or non-fatal coronary heart disease (CHD) or any stroke.[33] Secondary outcomes included CHD and stroke separately. Participants contributed only the first CVD outcome (whether non-fatal or fatal) recorded during follow-up (ie, we did not include deaths preceded by non-fatal CVD events). We censored outcomes if a participant was lost to follow-up, died from causes other than CVD, or reached the end of the follow-up period. Individuals with cTnT and cTnI values at or below the limit of detection (3.00 ng/L for cTnT or 1.20 ng/L for cTnI) were assigned a value of 2.99 ng/L for cTnT or 1.19 ng/L for cTnI.[21,22] All continuous analyses were based on log-transformed cTnT and cTnI concentrations.

Cross-sectional correlates were estimated using linear fixed-effects regression of cTnT and cTnI on quintiles of continuous variables and categorical variables adjusted for age and sex.[34] To evaluate associations between cTnT and cTnI with primary and secondary outcomes, hazard ratios (HRs) were calculated separately within each study using Cox proportional hazards regression models stratified by sex, using time-on-study as a timescale. The proportional hazards assumption was assessed using Schoenfeld residuals. HRs were adjusted for conventional risk factors (age, sex, smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol concentrations) and pooled across cohorts using a random-effects meta-analysis.[35] We investigated effect modification by individual characteristics with formal tests of interaction.[35] To characterise shapes of associations, we calculated pooled hazard ratios within overall fifths of cardiac troponin concentrations and plotted them against the pooled geometric mean of cardiac troponins concentration within each fifth. Additional analyses used martingale residuals, fractional polynomials, restricted maximum likelihood models, Fine and Gray[36] competing risk-adjusted models.

We used CVD risk prediction models containing information about conventional risk factors first without and then with cardiac troponins. We quantified improvements in predictive ability using measures of risk discrimination and reclassification.[37,38] We calculated Harrell's C-indices and C-index changes within each study before pooling results weighted by the number of outcomes contributed. To avoid overestimation of the model's ability to predict risk, we applied a cross-validation approach.[39] We examined the change in C-index after adding cardiac troponins and other circulating biomarkers as both linear and quadratic terms. We calculated the continuous net reclassification improvement using data

from studies in which both fatal and non-fatal CVD events had been recorded and separately among stroke and CHD cases and non-cases.

To assess the population health relevance of adding cardiac troponins to conventional risk factors, we generalized our reclassification analyses to the context of a UK population eligible for CVD risk assessment (**Supplementary Text 1**). Using CPRD data, we recalibrated the risk prediction models from our analysis to give 10-year risks that would be expected in a UK primary care setting, employing methods previously described.[40] We modelled a population of 100,000 adults aged 40–89 years in CPRD, with an age and sex structure matching that of the standard UK general population, and CVD incidence rates observed in individuals without previous CVD or diabetes, and not taking statins.[41] We then modelled the population health impact of additional assessment of troponin for individuals at intermediate 10-year CVD risk based on conventional risk factors alone. The intermediate risk group was defined by European Society of Cardiology (ESC) 2021 guidelines as a risk of 2.5 to <7.5% in those aged <50 years old, 5 to <10% in those aged 50 to <69 years old, and 7.5 to 15% in those aged 70 years or older.[8] We also modelled the potential population health impact for the intermediate risk group defined by the National Institute for Health and Care Excellence (NICE) guidelines.[41] Assuming a policy of statin allocation for people in the highest 10-year risk category, we estimated the potential that treatment allocation would reduce incident CVD. We assumed that statin allocation would result in a proportional reduction of ~20% in CVD risk across different individual level characteristics.[42] Additional analyses assumed larger reductions in risk with statin treatment. The number needed to screen to prevent one CVD event was quantified from this modelling procedure and included 95% confidence intervals calculated using 200 bootstrap standard errors.

Findings are based on complete case analysis. Stata/SE version 17 was used for all analyses, with 2-sided p-values and 95% confidence intervals (CI).

Results

Baseline characteristics and association with CVD outcomes

Individual participant data were available on 62,150 participants without a history of cardiovascular disease from 15 prospective studies. 30,144 (48.5%) of participants were women and the mean age was 61 years (standard deviation [SD] 12). Most participants were enrolled in either Europe (65%) or North America (33%). cTnT was measured in 50,592 participants from 11 studies,[6,16-26] cTnI in 28,090 participants from 6 studies, [21,22,25,27-29] and two studies measured both.[21,25,43] Across all cohorts, cardiac troponin was measured using either the Elecsys Troponin T high-sensitive (Roche Diagnostics, Basel, Switzerland) or ARCHITECT$_{STAT}$ high-sensitivity troponin I (Abbott Diagnostics, Chicago, IL, United States of America) assays.[44] Median (interquartile range [IQR]) concentrations were 5.0 ng/L (3.0-9.0) and 3.3 ng/L (2.1-5.2) for cTnT and cTnI, respectively. Details of the contributing studies are provided in **Table 1**, **Supplementary Tables 3-4**, and **Supplementary Figure 1**.[6,16-29] cTnT and cTnI concentrations increased with age and were lower in women, but were only weakly associated with several other characteristics, including history of diabetes, systolic and diastolic blood pressure, body mass index, total and HDL cholesterol concentration, and creatinine (**Supplementary Figures 2-4**).

Among participants with an assessment of cTnT or cTnI, the median follow-up was 11.8 years (25th-75th percentile: 8.7-17.7 years) and 9.8 years (8.3-12.4), during which 8,133 and 3,749 incident CVD events occurred, respectively (**Table 1** and **Supplementary Tables 3-4**). cTnT and cTnI concentrations were approximately linearly associated with CVD

risk (**Figure 1** and **Supplementary Figure 5**). HR for the composite CVD outcome (per 1 SD higher log-transformed concentration) adjusted for conventional risk factors were 1.31 (95% confidence interval [CI] 1.25–1.37) and 1.26 (1.19–1.33) for cTnT and cTnI, respectively (**Figure 2** and **Supplementary Figures 6-7**). Corresponding HRs for NT-proBNP, eGFR, and CRP for the composite CVD outcomes were 1.37 (1.30–1.44), 1.12 (1.02–1.22), and 1.16 (1.12–1.20), respectively (**Figure 2** and **Supplementary Figures 8-9**). HRs were similar for CHD and stroke outcomes, but slightly higher for fatal CVD outcomes (**Figure 3**). HRs were somewhat higher for females compared to males, but did not vary substantially with levels of other conventional risk factors or in other clinically relevant subgroups (**Supplementary Figures 10-11**). Similar results were found using competing risk-adjusted and restricted maximum likelihood models (**Supplementary Figure 12** and **Supplementary Figure 13**).

Incremental value in risk prediction

We assessed the incremental predictive ability of cardiac troponins using measures of risk discrimination and reclassification, adding cTnT or cTnI to models containing conventional CVD risk factors. For CVD outcome, the C-index increased by 0.015 (95%CI 0.012–0.018), from 0.673 (0.667-0.679) to 0.688 (0.682-0.691) for cTnT, and by 0.012 (95%CI 0.009–0.015), from 0.715 (0.706-0.723) to 0.727 (0.718-0.735) for cTnI (**Figure 4**). Similar results were observed using cross-validation analyses (**Supplementary Figure 14**). Continuous NRI were 6% (3%–9%) among CVD cases and 22% (20%–23%) among non-cases for cTnT, and 5% (2%–9%) among CVD cases and 17% (15%–18%) among non-cases for cTnI (**Table 2** and **Supplementary Figure 15**). **Supplementary Table 5** shows continuous NRI among stroke and CHD cases and non-cases.

Incremental risk prediction demonstrated by cardiac troponins was similar to that of NT-proBNP but greater than CRP and eGFR (**Figure 4, Supplementary Figure 16 and Supplementary Figure 17**). The addition of cardiac troponins to CRP demonstrated incremental risk discrimination. In contrast, the addition of cardiac troponins to NT-proBNP or eGFR did not substantially improve risk discrimination, with overlapping confidence intervals. Improvements in C-index with information on cardiac troponin concentrations were possibly greater among older individuals and people with a history of diabetes (**Supplementary Figures 18-19**). Models including cardiac troponins showed good calibration, with good agreement between the observed and predicted CVD risks (**Supplementary Figure 20**).

Estimate for the potential of disease prevention

For cTnT, and using a conventional cardiovascular risk factor model alone, 35,675 (36%) of 100,000 individuals would be classified as having intermediate 10-year according to the 2021 ESC Prevention Guidelines risk who were not already taking or eligible for statin treatment (i.e., people without a history of diabetes or CVD; **Figure 5**). Assessment of cTnT in these individuals (i.e., a "targeted" approach focusing only on people judged to be at intermediate 10-year risk of CVD after initial screening with conventional risk factors alone) would re-classify 2,754 intermediate-risk individuals as high-risk, of whom approximately 437(16%) would be expected to have a CVD event within 10 years. This would correspond to an increase of about 4.6% (437/9,487) of the CVD events already classified at high risk using conventional risk predictors alone.

Assuming statin allocation as per current ESC guidelines and statin treatment conferring a 20% relative risk reduction[42,45], such targeted assessment of cTnT among the

intermediate-risk group would help prevent 87 events over the next 10-year period, equating to the screening of 408 participants to prevent one event. Similar findings were observed with the targeted assessment of cTnI, with 473 participants needing to be screened to prevent one event (**Figure 5**), and when analysis involved cutoffs for clinical risk categories defined by NICE guidelines (**Supplementary Table 6**). For comparison, the numbers needed to screen to prevent one event with targeted assessment of NT-proBNP and CRP would be 468 and 593, respectively (**Supplementary Table 7**). Assuming a larger relative risk reduction from statin treatment of 30 or 40%,[46] the numbers needed to screen to prevent one event with targeted assessment of cTnT and cTnI would be between 205-273 and 237-316, respectively (**Supplementary Table 8**).

Discussion

In an analysis comprising individual participant data on over 60,000 participants from 15 prospective cohort studies, we studied the potential value of adding information on cardiac troponins to conventional cardiovascular risk factors used to predict first-onset CVD risk. We then modelled a scenario using data from 2.1 million people from general practices in the UK, in which cardiac troponins were assessed in people considered to be at intermediate risk by current prevention guidelines after initial screening with the use of conventional risk factors alone. Overall, our results suggest that the addition of cardiac troponins to conventional risk factors can provide a modest improvement in the prediction of first-onset CVD, which, if applied at scale, could help prevent ~5% more CVD events than the use of conventional risk factors alone. Our results have potential implications for CVD risk prediction and for the evaluation of the potential population health utility of cardiac troponins for disease.

First, our modelling suggests that, if applied to the standard UK general population aged 40–89 years, additional use of cardiac troponins could help detect and prevent additional CVD events over the next 10 years beyond the assessment of conventional risk factors alone. In a modelled scenario in which cardiac troponins were assessed in a primary care setting among individuals considered at intermediate CVD risk after initial screening with conventional risk predictors alone, our data suggest 1 extra CVD outcome could be prevented over a period of 10 years for approximately every 400 people in whom cardiac troponins are assessed if coupled with initiation of statin therapy in accordance with current guidelines.[8]

Second, to provide clinical context, we compared the incremental predictive gains afforded by information on cardiac troponins with those provided by CRP, eGFR, and NT-proBNP. Our results demonstrated that cardiac troponins provided a greater gain in predictive accuracy compared to CRP and eGFR, whereas using NT-proBNP showed similar results. While cardiac troponins potentially offered additional improvements in risk discrimination beyond those provided by CRP—suggesting these biomarkers might capture distinct aspects of CVD risk—the improvements from cardiac troponins and NT-proBNP or eGFR were not additive. This suggests that cardiac troponins and NT-proBNP provide somewhat overlapping information about myocardial damage in the context of primary prevention. We also found that improvements in risk discrimination with cardiac troponins were greater than those provided by total and HDL cholesterol, even though our evaluation was skewed in favour of lipid measurements since we added total and HDL cholesterol only to other conventional risk factors (and omitted cardiac troponins), whereas we added cardiac troponins to all conventional risk factors, including total and HDL cholesterol. We

restricted comparisons of cardiac troponins with other circulating biomarkers to participants who had complete information on these measurements, thereby avoiding potential bias.

Third, we found that cTnT and cTnI provide similar predictive information for CVD risk prediction, indicating that either biomarker can be effectively utilized in clinical settings for the assessment of first-onset CVD risk. This equivalence in predictive ability suggests that the choice between cTnT and cTnI can be flexible, depending on availability and specific clinical scenarios. Our findings align with previous studies that have demonstrated comparable diagnostic and prognostic capabilities of these biomarkers in various populations and clinical conditions.[3,7,47]

Fourth, our main model assumed that information on cardiac troponins would provide similar predictions of CVD risk across population subgroups. However, an exploratory analysis suggested that these biomarkers could provide more accurate risk prediction in older individuals and in those with a history of diabetes. These findings require cautious interpretation because they could arise, at least to some extent, due to the play of chance from the conduct of multiple statistical tests (since we explored interactions of cardiac troponins with several characteristics). Nevertheless, the potential for more accurate risk prediction in these subgroups raises the possibility that subclinical CVD may be more prevalent among these individuals[48], warranting further investigation to determine whether targeting the assessment of cardiac troponins in older individuals and in those with diabetes enhances screening efficiency.

Our study had major strengths. In all cohorts, cardiac troponin concentrations were measured using commonly used diagnostic assays, with potential for clinical use. We recorded information about the incidence of various CVD outcomes using well-validated

endpoint definitions. We centrally analysed individual-participant data, which were harmonized from prospective studies with extended follow-up, enabling time-to-event analyses, exclusion of people with a baseline history of CVD, and adoption of a uniform approach to statistical analyses. Because of its considerable statistical power, we could provide precise estimates, even for analyses that involved categorisation of cardiac troponin concentrations. To enhance validity further, we restricted analyses to people with complete information about a set of relevant risk factors. We used multiple complementary metrics of risk discrimination and reclassification, as well as different absolute risk thresholds used in different clinical guidelines. The broadly concordant results we observed across these metrics supported the validity of our main conclusions. To extend the relevance of our findings to a primary care population, we also conducted modelling using the UK CPRD, adapting (recalibrating) our findings to be more representative of the general population. The generalisability of our findings was enhanced by the inclusion of data from 10 countries and by the robustness of results to various sensitivity analyses.

Our study had potential limitations. We used a convenience sample of cohorts derived from middle- to older-aged individuals of European continental ancestry, which may limit the generalizability of our findings to other populations. Only two contributing cohorts measured both cTnT and cTnI, preventing reliable head-to-head comparison of cardiac troponins.[21,25,43] We used a conventional 10-year timeframe and standard clinical risk categories, acknowledging that reclassification analyses are intrinsically sensitive to choices of follow-up interval and clinical risk categories. A somewhat greater population health impact than suggested by our main analysis would be estimated if we had used less conservative modelling assumptions (e.g., more effective statin regimens, additional medications lowering CVD risk for example antihypertensives, and longer time horizons).

Conversely, our models could have overestimated the potential benefits of assessing cardiac troponins because not all people eligible for statins will receive them or be willing and able to take them and be adherent. Additionally, if competing risks are not adequately accounted for, population health benefits could be overestimated.[36] Data were unavailable to assess the added value of incorporating cardiac troponin measurements into the risk prediction tools currently recommended by US and UK guidelines (i.e., QRISK3[49] and PREVENT[50]), as well as when using additional risk modifiers such as coronary calcium scores or polygenic risk scores.[51] Finally, a comprehensive health economic evaluation or analyses of the feasibility of widespread troponin screening were beyond the scope of the present analysis.

We conclude that measurement of cardiac troponin in addition to conventional risk factors results in a modest improvement in the prediction of first-onset CVD that may translate into population health benefits if used at scale.

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Figure 1: Associations of cardiac troponin T and cardiac troponin I with first-onset fatal or non-fatal cardiovascular disease

Hazard ratios were adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and HDL-C concentration (HDL-C concentration only for NT-proBNP concentration analysis) and models were stratified by sex. The first cardiac troponin group represents measurements at or below the LOD and measurements higher than the LOD were grouped using quartiles of values. The cardiac troponin values were (natural) log-transformed and the x-axis was plotted on the log-scale and refers to the average levels of cardiac troponin calculated as the geometric mean. The size of the boxes is proportional to the inverse of the variance of the respective estimate. Error bars are 95% CIs, estimated from floated variances.

Figure 2. Adjusted hazard ratios of conventional cardiovascular risk factors and biomarkers for comparison with cardiac troponin T and cardiac troponin I.

Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. For categorical variables, HRs are shown for patients with diabetes versus without, and for current smokers versus others. For continuous variables, HRs are shown per standard deviation higher of each predictor to facilitate comparison, except for high-density lipoprotein cholesterol, where the HR is shown per standard deviation lower. All circulating cardiac-related biomarkers were transformed using the natural log of the original scale. The standard deviation for the continuous variables are systolic blood pressure = 21.6, total cholesterol = 1.11, high-density lipoprotein = 0.42, ln of C-reactive protein = 1.18, ln of N-

terminal pro B-type natriuretic peptide = 1.13, cardiac troponin T = 0.68, and cardiac troponin I = 0.85.

Figure 3: Associations of cardiac troponin T and cardiac troponin I concentrations with several incident first-onset cardiovascular outcomes.

Hazard ratios adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and HDL-C and stratified by sex and cohort. Cardiac troponin values were (natural) log-transformed and left as continuous values. Hazard ratios represent one standard deviation increase in cardiac troponin value. Error bars are 95% CIs and box sizes are unweighted. Individuals only needed at least one component outcome to be defined as a case for the composite outcome. The standard deviation is 0.68 for cardiac troponin T and 0.85 for cardiac troponin I.

Figure 4: Improvement in risk discrimination for first-onset fatal or non-fatal cardiovascular disease by addition of information about cardiac troponin-T (left) and cardiac troponin-I (right) concentration compared with that about HDL-C and total cholesterol (top), CRP (middle), or NT-proBNP concentration (bottom).

Cardiac troponin, CRP, and NT-proBNP values were all (natural) log-transformed. The change in C-index is in reference to the model which included information about age, smoking status, systolic blood pressure, history of diabetes, HDL-C, and concentration of total cholesterol, where relevant. Note that the reference model has a higher C-index for the studies measuring cardiac troponin-I compared to cardiac troponin-T. * indicates a p-value <0.05, ** indicates a p-value<0.01, and *** indicates a p-value <0.001.

Figure 5: Estimated population health impact with targeted assessment of cardiac troponin T (left) or cardiac troponin I (right) among 100,000 UK adults in a primary care setting using thresholds from ESC 2021 guidelines

Reclassification analyses was contextualized to a UK population eligible for CVD screening which did not include people with a history of diabetes. Those with a history of diabetes were excluded from the calculations of screening benefit because people with diabetes are eligible for statin treatments irrespective of baseline risk. The conventional risk factors model included baseline age, smoking status, systolic blood pressure, total cholesterol, and high-density lipoprotein.

Central Illustration. Cardiac troponin in the prevention of cardiovascular events (CAPRICE) - A collaborative individual patient data meta-analysis

Table 1. Baseline characteristics of participants from cohorts with measured cardiac troponin T and troponin I

	Participants with assessment of cardiac troponin T	Participants with assessment of cardiac troponin I
Baseline characteristics		
No of participants	50,523	28,090
No of cohorts	11	6
Age, years	61 (11)	60 (12)
Female sex	26,292 (52%)	13,881 (49%)
Cardiovascular risk factors		
Current smoker	9,735 (19%)	5,461 (20%)
History of diabetes	4,154 (8%)	1,317 (5%)
Body mass index, kg/m^2	27.4 (5.0)	26.9 (4.5)
Systolic Blood Pressure, mmHg	134 (22)	139 (20)
Total cholesterol, mmol/l	5.47 (1.09)	5.76 (1.13)
HDL cholesterol, mmol/l	1.41 (0.42)	1.46 (0.42)
Biomarkers of cardiac injury, inflammation, and renal function		
Cardiac troponin T, ng/L*	5.0 (3.0-9.0)	-
Cardiac troponin I, ng/L*	-	3.3 (2.1-5.2)
NT-proBNP, ng/mL*	63 (33-121)	51 (26-94)
C-reactive protein, mg/L *	1.89 (0.89-4.00)	1.50 (0.70-3.20)
Creatinine, µmol/l*	81 (71-97)	81 (70-93)
Primary outcomes		
No. of CVD cases	8,133	3,749
Follow-up, years*	11.80 (8.67-17.74)	9.75 (8.25-12.42)

Data are shown as mean (SD), or N(%); * median (IQR); cTnT, cardiac troponin T; cTnI, cardiac troponin I; NT-proBNP, N-terminal-pro-B-type natriuretic peptide

Table 2: Continuous net reclassification index (NRI) and 95% confidence interval for 10-year fatal or non-fatal cardiovascular disease (generalised to a primary prevention population).

Conventional risk factors plus cardiac troponin T	
No. cohorts/participants/events	11/49405/7966
Non-cases	22 (20, 23)
Cases	6 (3, 9)
Conventional risk factors plus cardiac troponin I	
No. cohorts/participants/events	6/27384/3634
Non-cases	17 (15, 18)
Cases	5 (2, 9)
Conventional risk factors plus CRP	
No. cohorts/participants/events	14/39826/7037
Non-cases	19 (17, 20)
Cases	-2 (-5, 1)
Conventional risk factors plus NT-proBNP	
No. cohorts/participants/events	11/31836/3948
Non-cases	21 (19, 23)
Cases	-5 (-8, 0)

Conventional risk factors included age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein.
NRI is expressed as a percentage
Calculations were performed by cohort and sex.

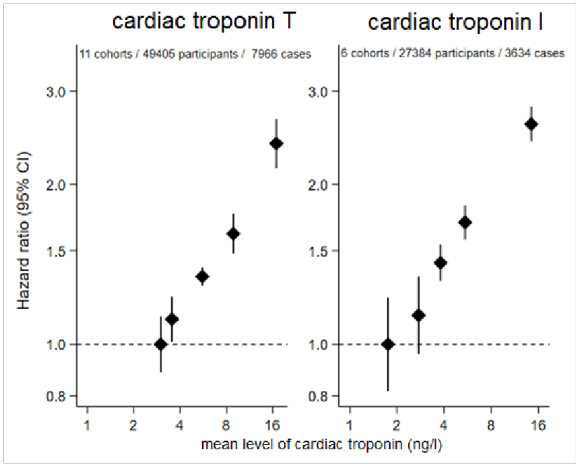


Figure 1: Associations of cardiac troponin T and cardiac troponin I with first-onset fatal or non-fatal cardiovascular disease

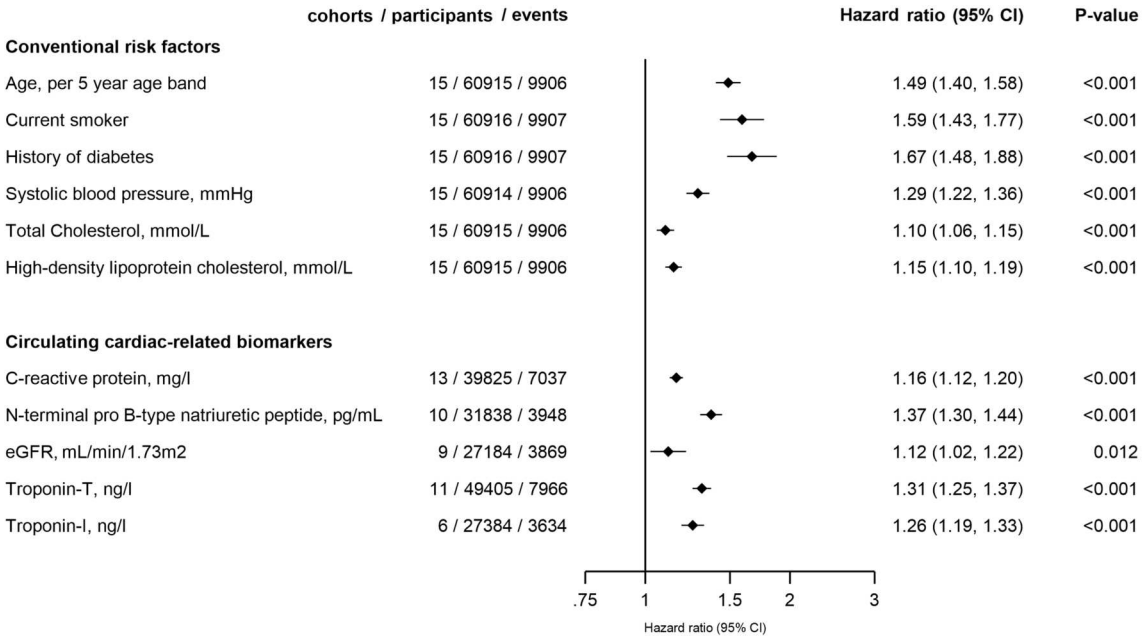


Figure 2: Adjusted hazard ratios of conventional cardiovascular risk factors and biomarkers for comparison with cardiac troponin T and cardiac troponin I.

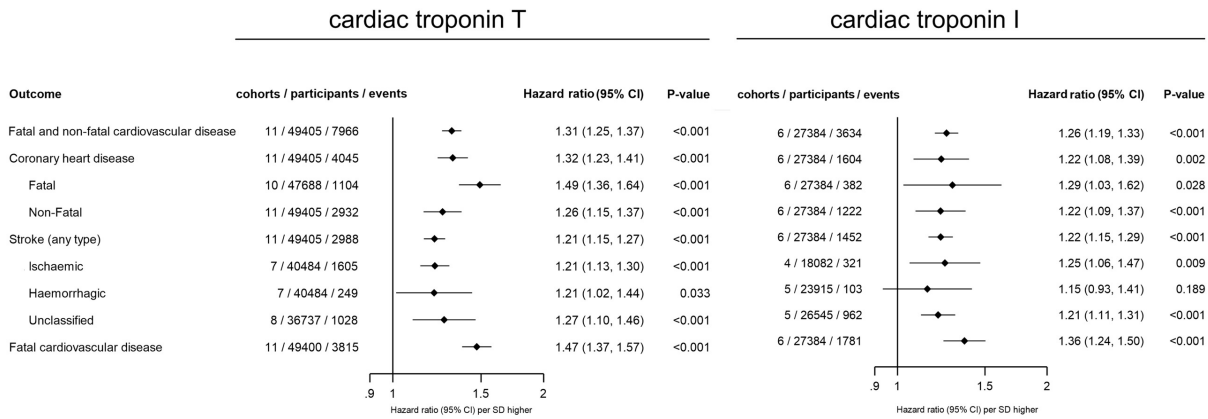
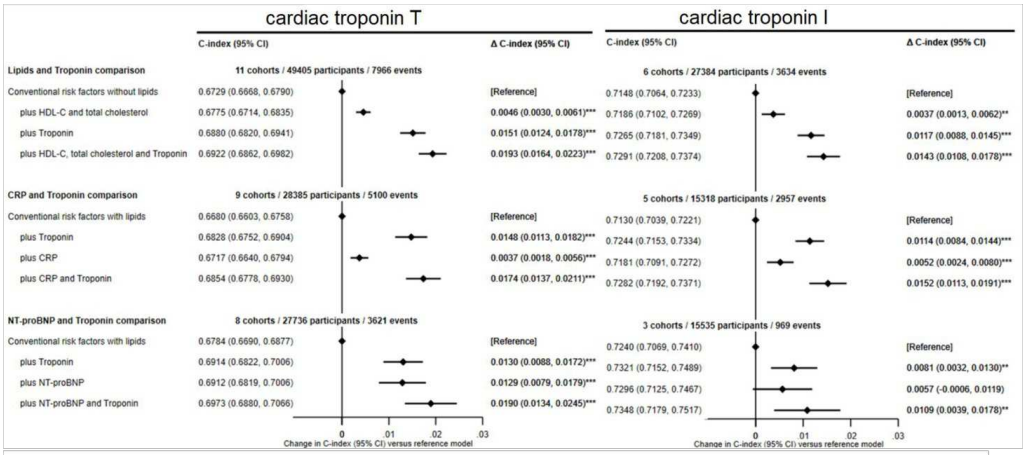


Figure 3: Associations of cardiac troponin T and cardiac troponin I concentrations with several incident first-onset cardiovascular outcomes.



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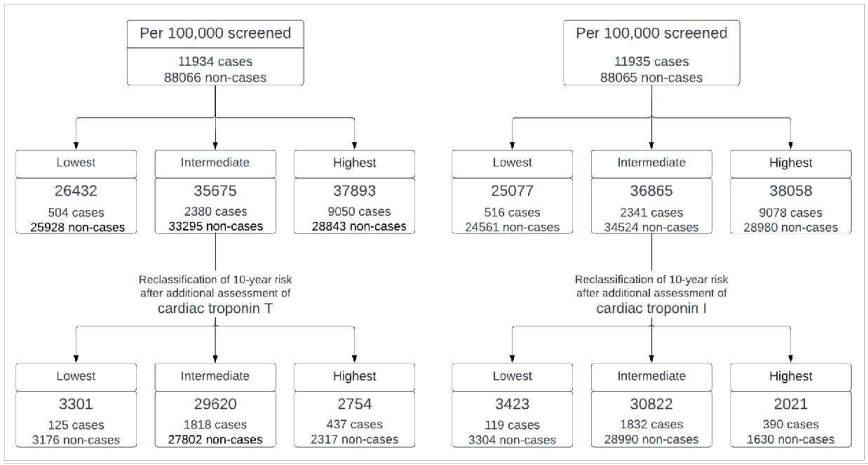

Figure 5: Estimated population health impact with targeted assessment of cardiac troponin T (left) or cardiac troponin I (right) among 100,000 UK adults in a primary care setting using thresholds from ESC 2021 guidelines

Supplementary Material

Cardiac troponins and cardiovascular disease risk prediction: an individual-participant-data meta-analysis

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Supplementary Methods

Supplementary Text 1: Description of cohort selection and statistical analysis

Study selection

Studies eligible for inclusion in CAPRICE were identified by systematic searches of multiple databases, including PubMed/Medline, Scientific Citation Index Expanded, and EMBASE. Our primary choice of databases was in line with the previous evidence synthesis.[1] The literature search was conducted up to October 2019, did not apply language restrictions, and combined terms related to high-sensitivity cardiac troponin (cTn) and the primary outcomes of interest. In addition, the reference lists of identified articles (including review articles and the previously published meta-analysis) were scanned for additional relevant studies. Prospective cohort studies were eligible if they met the following criteria: (i) had assayed cTnT or cTnI using a high-sensitivity assay; (ii) recorded baseline information on conventional risk factors (ie, age, sex, smoking status, blood pressure, history of diabetes, total and HDL-cholesterol); (iii) included participants without a recorded baseline history of cardiovascular disease (CVD); and (iv) recorded cause-specific deaths or cardiovascular events (nonfatal myocardial infarction or stroke) or both during more than 1 year of follow-up using well-defined criteria. Only prospective cohort studies with accessible and shareable individual participant data, enabling standardized and detailed analyses using a common protocol, were included in the collaboration.

Cardiac troponin values

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) values were summarised in their original scale for reporting baseline characteristics but, due to their right-skewed distribution, were natural log-transformed for all subsequent analyses. Individuals with values at or below the limit of detection were given a value of 2.99 ng/L for cTnT or 1.19 ng/L for cTnI.[2,3] For each cohort, individuals were followed from baseline until the earliest occurrence of the first cardiovascular outcome, loss to follow-up, death, or the end of the follow-up period.

Cross-sectional analysis

Cross-sectional correlates of cTnI and cTnT were estimated as hypothesis-generating analyses using linear fixed effect models and were presented as levels of baseline correlates by quintile of cTnT and

cTnI, separately for men and women. Individuals with values at or below the limit of detection for cTnT (3.0 ng/L) and cTnI (1.2 ng/L) formed the first group. The fixed effects in each model were: study, age, age^2, sex, age x sex, age^2 x sex, risk-factor fifth, risk-factor fifth x sex, and risk-factor fifth x age (where x denotes an interaction). From each fitted model, overall adjusted geometric mean values and 95% confidence intervals for cTnT or cTnI concentration by sex within fifths of continuous markers were obtained with age fixed at 60 years. Inverse-variance weighted polynomials were superimposed across the adjusted means to help judge whether the overall association was consistent with a linear or quadratic shape.

Modelling procedure used in subsequent analyses

To evaluate associations between cTnT and cTnI with our primary outcome (fatal or non-fatal cardiovascular events, henceforth called 'CVD') and secondary outcomes (components of the primary outcome), HRs were calculated separately within each study using Cox proportional hazards regression models stratified by sex. We used a cohort-stratified Cox regression model in our individual patient data meta-analysis to account for both heterogeneity between cohorts (e.g. potential differences in baseline hazards or follow-up periods between cohorts) and other study-level variations (e.g. recruitment criteria, period, patient characteristics). HRs were adjusted for conventional risk factors which included age, smoking status, diabetes status, systolic blood pressure, and lipid profiles. These risk factors reflect the variables included in SCORE2 prediction models for primary prevention of cardiovascular disease.[4] The strength of associations between cTnT or cTnI and CVD were compared with the associations of conventional risk factors.

Where available, Cox model results from associations between cTnI and cTnT and CVD were directly compared with other circulating biomarkers including N-terminal pro-B-type natriuretic peptide (NT-proBNP), estimated Glomerular Filtration Rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP). Z-scores were used for better comparison of different circulating biomarkers. These comparisons were restricted only to participant data where additional circulating biomarker data, in addition to cTnT or cTnI, were available.

Association between cardiac troponin and incident CVD

We pooled cohort-specific HRs using a random-effects meta-analysis for our main results. The proportional hazards assumption was assessed using Schoenfeld residuals. We performed a sensitivity analysis to test if our pooled estimates differed after using restricted maximum likelihood models, which are less susceptible to errors from including a small number of studies.[5] The HR for cTnT or cTnI was evaluated by subgroups according to age, sex, body mass index (BMI), smoking status, history of diabetes, and, tertiles of total cholesterol, triglycerides, creatinine, systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Finally, five groups were, again, created from continuous cTnT and cTnI values to assess the linearity of the associations with CVD. The linearity assumption underlying the Cox regression model was further evaluated using martingale residual plots[6] and fractional polynomial analyses.

Discrimination and calibration

Incremental improvement in predictive ability (change in Harrell's C-index[7]) was estimated after adding cTnT and cTnI to the same set of conventional risk factors and compared with other biomarkers. To avoid overestimation of the model's ability to predict risk, we applied a cross-validation approach by validating within one cohort the prediction model that included the remaining cohorts. During cross-validation, the same model is used during each iteration when calculating risk in the cohort left out, as previously described.[8,9] This approach was performed separately for cohorts with cTnT and cTnI measurements. Results were then meta-analyzed using the number of events as weights for each cohort. The rationale for using the number of events rather than the inverse variance for weights has been described previously[10] and includes 1) it gives consistency between pooled absolute C-indices and pooled differences between C-indices and 2) it avoids studies with few events but many non-events getting disproportionate weight. Overoptimism was also accounted for when checking the calibration of the models by using a similar cross-validation approach. Supplementary analyses compared C-index change results after adding quadratic terms (factor + factor2) for cardiac troponins and other biomarkers due to some prior evidence of non-linear associations with CVD[4] and to enable a fairer comparison between biomarkers. The change in C-index was evaluated by the same subgroups described above.

The continuous net reclassification index (NRI) was calculated after adding cTnT or cTnI (or other markers for comparison) to models with conventional risk factors. This summarises the appropriate directional change in risk predictions for those who do and do not experience an event during follow-up (with increases in predicted risk being appropriate for cases and decreases being appropriate for non-cases).

Population modelling

We generalised our analysis of reclassification to the context of a United Kingdom (UK) population eligible for CVD screening by recalibrating the risk prediction models to give 10-year risks in line with those observed in such a UK primary care setting using Clinical Practice Research Datalink (CPRD) data.[11] CPRD collects de-identified patient data from a network of primary care practices across the UK with linkage to clinical outcomes.

The general process taken to estimate the potential public health impact of using different risk models for population screening involved three pieces of information:

(1) Predicted 10-year CVD risk in CAPRICE participants using models including conventional risk predictors and with or without additional information on cardiac troponin I or cardiac troponin T.

(2) Incidence rates of CVD by sex and 5-year age-at-risk among individuals without prior history of CVD, and not on statin treatment at baseline in CPRD.

(3) UK population structure by sex and 5-year age groups in mid-2017, from UK office of national statistics.

Recalibration of 10-year CVD risk in CAPRICE participants

Given that CAPRICE participants are likely less healthy than the UK general population, absolute risk estimates derived from CAPRICE participants are higher than those estimated by deriving and applying risk models in a general population. This can be attributed to the lower baseline survival probability, generally higher values of risk factors, and potentially longer follow-up periods in CAPRICE. Crude reclassification statistics relying on clinically relevant risk thresholds, calculated

within the CAPRICE dataset are, therefore, not generalizable to a broader UK primary prevention setting. To correct for this, we adapted (i.e., recalibrated) the predicted 10-year CVD risk for each CAPRICE participant, using incidence rates estimated in CPRD. The general recalibration process involves a simple rescaling of the participants' risk predictions without affecting the ability of the model to discriminate risk. For the current analysis, recalibration was undertaken separately for each model, using the following steps:

(1) In CAPRICE, we estimated the 10-year CVD risk ($\widehat{\text{risk}}_{\text{pred},i}(10)$) for individual i using a Cox model including the relevant set of risk predictors.

(2) In CAPRICE, we calculated the mean of the predicted 10-year CVD risks for each sex and 5-year age group ($\widehat{\text{risk}}_{\text{pred,agegrp}}(10)$).

(3) In CPRD, among individuals without prior history of CVD, and not on statin treatment at registration, we calculated the incidence rates of CVD for each sex and 5-year age-at-risk group. Assuming exponential survival (i.e., constant hazard) within each 5-year age group, the expected 10-year CVD risk was estimated as follows:

$$\widehat{\text{risk}}_{\text{expected}}(10) = 1 - \exp(-IR_{\text{mid}} \times 10) \qquad (1)$$

where IR_{mid} is the annual incidence at the mid-point of the 10-year interval ahead, i.e., for the 40 to 44 year age-group the incidence rate for 45 to 49 years was used.

(4) The following recalibration model was fitted relating the expected risk to the means of predicted risks by age group, for each sex, with transformation applied.

$$g\left(1 - \widehat{\text{risk}}_{\text{expected}}(10)\right) = \alpha + \beta g\left(1 - \widehat{\text{risk}}_{\text{pred}}(10)\right) \quad (2)$$

where $g(.)$ is the link function $\ln(-\ln(.))$

(5) $\hat{\alpha}$ and $\hat{\beta}$ from the fitted recalibration model are then used to adjust the original 10-year risk prediction $\widehat{\text{risk}}_{\text{pred},i}(10)$ for each participant i in the CAPRICE dataset, yielding a recalibrated 10-year risk prediction $\widehat{\text{risk}}_{\text{recal},i}(10)$ using the relation:

$$\widehat{\text{risk}}_{\text{recal},i}(10) = 1 - g^{-1}\left(\hat{\alpha} + \hat{\beta} g\left(1 - \widehat{\text{risk}}_{\text{pred},i}(10)\right)\right) \qquad (3)$$

Estimation of reclassification and translation to 100,000 UK individuals

To express our findings in a more clinically accessible manner, we used the information observed in reclassification tables to generalise our findings to the context of population screening. We modelled a hypothetical UK population of 100,000 individuals aged 40-89 years old and without a previous cardiovascular disease in CPRD, with sex- and age-specific structure the same as that of the standard UK population (2017 mid-year population, https://www.ons.gov.uk/), and CVD incidence rates.[9] We used the recalibrated predicted CVD risk $\widehat{\text{risk}}_{\text{recal},i}(10)$ to estimate the up- or down-classification of risk after additional assessment of troponin among individuals at intermediate 10-year cardiovascular risk calculated using conventional risk factors alone.

The intermediate risk group was defined by European Society of Cardiology (ESC) 2021 guidelines as a risk of 2.5 to <7.5% in those <50 years old, 5 to <10% in those 50 - <69 years old, and 7.5 to 15% in those 70 or older. In supplementary analyses, 5% to <10% was the intermediate risk group as defined by National Institute for Health and Care Excellence (NICE) guidelines.[9] The lowest and highest risk groups were defined as risks that are lower and higher than the intermediate risk category. The primary focus was on up-classification into the high-risk category after adding cardiac troponins since the safety of not using statins in down-classified individuals is unknown. We assumed an initial policy of statin allocation for people in the highest 10-year risk category according to the recalibrated risk for the same guidelines. We also assumed that treatment with statins would reduce the risk of CVD by 20%.[12,13] Those who had a history of diabetes were assumed to be treated regardless of their risk and so these individuals were excluded from the population health modelling procedure. The number needed to screen to prevent one CVD event was quantified from this modelling procedure and included 95% confidence intervals calculated using 200 bootstrap standard errors.

Supplementary text 2: Funding details for individuals and cohorts

Generation Scotland: Troponin measurements and analysis were supported by a Stratified Medicine Grant from the Chief Scientist Office of the Scottish Government Health Directorates (ASM/14/1). Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates (CZD/16/6) and the Scottish Funding Council (HR03006). AGES-RS: The Age/Gene-Environment Susceptibility study was funded by the NIA (grants N01-AG-12100 and HHSN27120120022C), Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament), with contributions from the Intramural Research Programs at the NIA.

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Supplementary Text 3: TRIPOD reporting checklist

Section/Topic	Itemm		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction, paragraphs 1-2
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction, paragraph 3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods, paragraph 1; Supplementary Tables 1-4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods, paragraphs 1-3
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods, paragraphs 1-3; Supplementary Tables 3-4
	5b	D;V	Describe eligibility criteria for participants.	Methods, paragraph 1
	5c	D;V	Give details of treatments received, if relevant.	n/a
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods, paragraph 6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	n/a
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Methods, paragraph 1
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	n/a
Sample size	8	D;V	Explain how the study size was arrived at.	Methods, paragraph 1; Results paragraph 1
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Methods, last paragraph
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods, Data analysis section
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods, “Data analysis” subsection
	10c	V	For validation, describe how the predictions were calculated.	n/a
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods, “Data analysis” subsection
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Methods, “Data analysis” section; Suppl Text 1
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Methods, last

				paragraph
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	n/a
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Results, paragraph 1, 2; Table 1; Suppl Table 3, 4
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results, paragraph 1-2; Table 1; Suppl Table 1, 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Results, paragraph 3; Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Fig 2
	15b	D	Explain how to the use the prediction model.	Methods, “Data analysis” section, paragraph 4
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Results, “Incremental value in risk prediction” subsection
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion, paragraph 5
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	n/a
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion, all paragraphs
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Discussion, paragraph 3, 4
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	n/a
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Funding Statement

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Supplementary Table 1: Ascertainment of fatal and non-fatal outcomes by cohort

	Ascertainment of incident outcomes			Classification of incident outcomes						
				MI			Stroke			
	Death	Non-fatal MI	Non-fatal stroke	Definite	Probable	Silent	Ischemic	Hemorrhagic	SAH	Unclassified

AGES[14]	**	++	++	X	X	o	X	X	X	NS
ARIC[15]	**	++	++	X	X	o	X	X	X	X
BRHS[16]	**	++	NS	X	o	o	o	o	o	X
CHS[17]	**	++	++	X	o	o	X	X	o	X
DHS[18]	**	++	++	X	o	o	X	X	X	X
GS[19]	*	++	++	X	X	o	X	NS	NS	NS
HIMS[20]	*	++	++	X	NS	NS	X	X	NS	NS
HUNT[21]	*	++	NS	X	NS	NS	X	NS	NS	NS
MESA[22]	**	++	++	X	NS	X	X	X	X	X
MPP-RES[23]	*	++	++	X	o	o	X	X	X	NS
PIVUS[24]	**	++	++	X	o	o	o	o	o	X
PREVEND[25]	**	NS	NS	NS	NS	NS	NS	NS	NS	NS
PROSPER[26]	**	++	++	X	o	o	o	o	o	X
ULSAM[27]	**	++	++	X	o	o	X	X	X	X
WOSCOPS[28]	**	++	++	X	X	o	o	o	o	X

+, self-report only; ++, self-report supplemented by objective criteria; X, yes; o, no; NA, not available; NS, not stated; *, based on death certificate only; **, based on death certificate supplemented by medical record;

Supplementary Table 2: Quality of included cohorts as assessed by the Newcastle-Ottawa (NOS) quality assessment scale[29]

Cohort	Selection	Comparability	Outcome	Quality*
	★★★★	★★	★★★	
GS	★★★★	★★	★★★	high
AGES	★★★	★★	★★★	high
CHS	★★★★	★★	★★	high
BRHS	★★★	★★	★★★	high
DHS	★★★★	★★	★★	high
HIMS	★★★	★★	★★★	high
HUNT	★★★★	★★	★★★	high
MESA	★★★★	★★	★★★	high
MPP-RES	★★★★	★★	★★★	high
ULSAM	★★★	★★	★★★	high
PIVUS	★★★	★★	★★★	high
PREVEND	★★★★	★★	★★★	high
PROSPER	★★★	★★	★★★	high
WOSCOPS	★★★	★★	★★★	high
ARIC	★★★★	★★	★★★	high

*While not explicitly stated in the NOS rating guidance, we used the following score ranges to qualitatively categorize the overall quality of the included studies: 0 to 4=poor quality; 5 to 7=fair quality; 8 to 9=high quality

Supplementary Table 3: Baseline characteristics of participants from cohorts with measured cardiac troponin T by individual cohort

	Total	ARIC[15]	BRHS[16]	CHS[17]	DHS[18]	GS[19]	MESA[22]	MPP-RES[23]	PREVEND[25]	PROSPER[26]	AGES[14]	ULSAM[27]
	N=50,523	N=8,841	N=3,072	N=3,241	N=1,721	N=12,489	N=6,767	N=1,314	N=5,388	N=2,962	N=3,978	N=750
Country		USA	UK	USA	USA	UK	USA	Sweden	Netherlands	Scotland, Ireland, Netherlands	Iceland	Sweden
Cohort period		1996-1998	1998-2000	1989-1993	2000-2002	2006-2010	2000-2002	2002-2006	1997-1998	1998	2002-2006	1991-1995
Patient demographics												
Age, years**	61 (11)	54 (6)	68 (5)	72 (5)	50 (7)	55 (9)	62 (10)	67 (6)	55 (10)	76 (3)	76 (5)	71 (1)
Female, n (%)	26,292 (52%)	4,811 (54%)	0 (0%)	2,053 (63%)	977 (57%)	7,512 (60%)	3,575 (53%)	412 (31%)	2,701 (50%)	1,730 (58%)	2,521 (63%)	0 (0%)
Cardiovascular risk factors												
Current smoker, n (%)	9,735 (19%)	2,174 (25%)	407 (13%)	375 (12%)	484 (28%)	1,662 (14%)	1,027 (15%)	195 (15%)	1,808 (34%)	920 (31%)	493 (13%)	190 (25%)
Known diabetes, n (%)	4,154 (8%)	798 (9%)	186 (6%)	490 (15%)	220 (13%)	392 (3%)	762 (11%)	312 (24%)	101 (2%)	376 (13%)	412 (10%)	105 (14%)
Body mass index, kg/m2**	27.4 (5.0)	27.3 (5.0)	26.7 (3.5)	26.7 (4.7)	30.6 (7.2)	27.2 (5.1)	28.3 (5.5)	28.1 (4.2)	26.6 (4.2)	NA	27.1 (4.5)	26.0 (3.2)
Haemodynamics												
Systolic Blood Pressure, mmHg**	134 (22)	120 (17)	150 (24)	136 (21)	129 (17)	135 (18)	126 (21)	148 (20)	132 (21)	156 (22)	143 (21)	147 (19)
Diastolic Blood Pressure, mmHg**	75 (11)	73 (11)	86 (11)	71 (11)	80 (9)	NA	72 (10)	85 (10)	76 (10)	NA	74 (10)	84 (9)
Biochemistry												
Cardiac troponin T, ng/L*	5.0 (3.0-9.0)	5.0 (3.0-8.0)	11.3 (8.5-15.5)	4.6 (3.0-9.0)	3.0 (3.0-3.8)	3.8 (3.0-6.5)	4.4 (3.0-7.5)	8.0 (5.0-11.0)	3.0 (3.0-5.0)	6.0 (4.0-11.0)	9.8 (6.8-14.2)	8.0 (5.6-11.8)
Creatinine, µmol/l*	81 (71-97)	97 (88-106)	94 (86-104)	88 (71-106)	80 (62-88)	72 (63-83)	81 (72-99)	NA	71 (61-80)	84 (80-99)	84 (73-98)	91 (84-100)
C-reactive protein, mg/L*	1.9 (0.9-4.0)	NA	1.5 (0.8-3.2)	2.4 (1.2-4.3)	3.0 (1.3-7.0)	NA	1.9 (0.8-4.3)	1.9 (0.9-4.0)	1.4 (0.6-3.1)	2.2 (1.1-4.3)	1.9 (1.0-3.8)	1.8 (0.9-3.6)
N-terminal pro B-type naturietic peptide, ng/L*	63 (33-121)	NA	NA	96 (51-185)	31 (14-63)	62 (35-108)	46 (24-89)	86 (42-161)	39 (18-75)	127 (70-235)	NA	95 (55-175)
Lipid profile												
Total cholesterol, mmol/l**	5.47 (1.09)	5.54 (1.06)	6.08 (1.06)	5.51 (1.00)	4.81 (1.04)	5.39 (1.04)	5.02 (0.92)	5.60 (1.07)	5.87 (1.11)	5.04 (1.08)	5.82 (1.09)	5.77 (0.99)
High-density lipoprotein-C, mmol/l**	1.41 (0.42)	1.35 (0.44)	1.34 (0.34)	1.44 (0.41)	1.31 (0.39)	1.50 (0.43)	1.32 (0.38)	1.34 (0.41)	1.32 (0.40)	1.40 (0.39)	1.63 (0.45)	1.30 (0.36)
Low-density lipoprotein-C, mmol/l**	3.55 (1.01)	NA	3.94 (0.96)	3.38 (0.91)	2.86 (0.92)	NA	NA	3.62 (0.97)	NA	NA	3.66 (0.99)	
Triglycerides, mmol/l*	1.24 (0.90-1.76)	1.22 (0.87-1.71)	1.56 (1.12-2.19)	1.33 (1.03-1.80)	1.14 (0.79-1.72)	NA	1.25 (0.88-1.82)	1.20 (0.90-1.70)	1.24 (0.90-1.79)	NA	1.04 (0.78-1.42)	1.21 (0.89-1.64)
Primary outcome												
No. of CVD cases (%)	8133 (16)	2191 (25)	682 (22)	1516 (47)	137 (7.9)	706 (5.6)	580 (8.6)	133 (10)	455 (8.4)	309 (10)	1055 (27)	369 (49)
Follow-up, years*	11.8 (8.67, 17,7)	28.2 (20.2 29.4)	14.5 (8.3, 15.3)	12.5 (7.1, 18.9)	12.1 (11.6, 12.7)	9.4 (8.7, 10.8)	16.6 (10.7, 17.5)	8.8 (8.3, 9.7)	18.4 (13.5, 18.8)	2.8 (2.5, 3)	10.6 (6.8, 11.7)	13.9 (7.6, 18.1)
Secondary outcomes												
No. of any stroke cases (%)	3055 (6.1)	724 (8.2)	262 (8.5)	552 (17)	57 (3.3)	296 (2.4)	297 (4.4)	70 (5.3)	158 (2.9)	94 (3.2)	420 (11)	125 (17)
No. of coronary heart disease cases (%)	4120 (8.2)	1280 (14)	331 (11)	863 (27)	65 (3.8)	251 (2.0)	257 (3.8)	47 (3.6)	218 (4.1)	202 (6.8)	451 (11)	155 (21)
No. of fatal CVD cases (%)	3901 (7.7)	734 (8.3)	396 (13)	949 (29)	37 (2.2)	247 (2.0)	297 (4.4)	44 (3.4)	202 (3.8)	83 (2.8)	657 (17)	255 (34)

We summarized variables using the median (IQR) if a variable was not normally distributed and the mean if it was normally distributed. *median (IQR) **mean (SD); Number of participants censored at <10-years, n (%) = 14,296 (28). Reasons for censoring include a combination of non-cardiovascular death and loss of follow-up

Supplementary Table 4: Baseline characteristics of participants from cohorts with measured cardiac troponin I by individual cohort

	Total	GS[19]	HIMS[20]	HUNT[21]	PIVUS[24]	AGES[14]	WOSCOPS[28]
	N=28,090	N=12,489	N=1,275	N=5,915	N=847	N=4,095	N=3,469
Country		Scotland	Australia	Norway	Sweden	Iceland	Scotland
Cohort period		2006-2010	2001-2004	1998-1997	2001	2002-2006	1989-1995
Patient demographics							
Age, years**	60 (12)	55 (9)	75 (2)	57 (12)	70 (0)	76 (5)	55 (6)
Female, n (%)	13,881 (49%)	7,512 (60%)	0 (0%)	3,316 (56%)	450 (53%)	2,603 (64%)	0 (0%)
Cardiovascular risk factors							
Current smoker, n (%)	5,461 (20%)	1,662 (14%)	76 (6%)	1,671 (29%)	87 (10%)	501 (13%)	1,464 (42%)
Known diabetes, n (%)	1,317 (5%)	392 (3%)	155 (12%)	192 (3%)	88 (10%)	440 (11%)	50 (1%)
Body mass index, kg/m2**	26.9 (4.5)	27.2 (5.1)	26.5 (3.6)	26.7 (4.0)	26.9 (4.2)	27.0 (4.5)	25.9 (3.1)
Haemodynamics							
Sytolic Blood Pressure, mmHg**	139 (20)	135 (18)	150 (19)	142 (22)	150 (23)	142 (21)	136 (17)
Diastolic Blood Pressure, mmHg**	80 (12)	NA	77 (10)	84 (12)	79 (10)	74 (10)	84 (10)
Biochemistry							
Cardiac troponin I, ng/L*	3.3 (2.1-5.2)	2.2 (1.4-3.4)	5.4 (4.0-7.5)	3.6 (2.6-5.2)	3.3 (2.4-4.8)	5.7 (4.1-8.8)	3.8 (3.0-5.2)
Creatinine, µmol/l*	81 (70-93)	72 (63-83)	89 (79-99)	86 (78-95)	77 (65-89)	84 (73-98)	95 (88-102)
C-reactive protein, mg/L*	1.5 (0.7-3.2)	NA	1.9 (1.0-3.5)	1.2 (0.5-2.6)	1.2 (0.6-2.3)	1.9 (1.0-3.8)	1.8 (0.8-3.6)
N-terminal pro B-type naturietic peptide, ng/L*	51 (26-94)	62 (35-108)	NA	NA	10 (6-16)	NA	30 (14-57)
Lipid profile							
Total cholesterol, mmol/l**	5.76 (1.13)	5.39 (1.04)	5.12 (0.93)	6.19 (1.17)	5.52 (0.97)	5.82 (1.09)	6.53 (0.79)
High density lipoprotein-C, mmol/l**	1.46 (0.42)	1.50 (0.43)	1.44 (0.37)	1.43 (0.41)	1.54 (0.42)	1.63 (0.45)	1.20 (0.26)
Low density lipoprotein-C, mmol/l**	3.97 (0.96)	NA	NA	NA	3.45 (0.84)	3.66 (0.99)	4.47 (0.69)
Triglycerides, mmol/l*	1.36 (0.98-1.91)	NA	1.20 (0.80-1.60)	1.53 (1.08-2.17)	1.11 (0.86-1.49)	1.04 (0.78-1.43)	1.64 (1.26-2.17)
Primary outcome							
No. of CVD cases (%)	3,749 (13.3)	706 (5.7)	327 (26)	1280 (22)	168 (20)	1096 (27)	172 (5)
Follow-up, years*	9.8 (8.2, 12.4)	9.4 (8.7, 10.8)	12.9 (7.8, 15.1)	20.9 (14.5, 21.2)	15.0 (10.9, 15.1)	10.5 (6.52, 11.7)	5.0 (4.6, 5.3)
Secondary outcomes							
No. of any stroke cases (%)	1493 (5.3)	296 (2.4)	136 (11)	509 (8.6)	82 (9.7)	433 (11)	37 (1.1)
No. of coronary heart disease cases (%)	1654 (5.9)	251 (2.0)	155 (12)	578 (9.8)	67 (7.9)	469 (11)	134 (3.9)
No. of fatal CVD cases (%)	1,848 (6.6)	247 (2.0)	152 (12)	664 (11)	53 (6.3)	696 (17)	36 (1.0)

We summarized variables using the median (IQR) if a variable was not normally distributed and the mean if it was normally distributed.*median (IQR) **mean (SD); Censored at <10-years, n (%) = 11893 (42). Reasons for censoring include a combination of non-cardiovascular death and loss of follow-up

Supplementary Table 5: Continuous net reclassification index (NRI) and 95% confidence interval for 10-year coronary heart disease and any stroke (generalised to a primary prevention population).

	Coronary heart disease	Stroke
Conventional risk factors plus cardiac troponin T		
No. cohorts/participants/events	11/49405/4045	11/49405/2988
Non-cases	21 (20, 22)	16 (15, 17)
Cases	6 (2, 11)	8 (1, 14)
Conventional risk factors plus cardiac troponin I		
No. cohorts/participants/events	6/27384/1604	6/27384/1452
Non-cases	16 (14, 18)	10 (8, 11)
Cases	6 (0, 12)	5 (0, 11)
Conventional risk factors plus CRP		
No. cohorts/participants/events	14/39826/3444	14/39826/2746
Non-cases	16 (14, 17)	21 (20, 22)
Cases	0 (-5, 4)	-7 (-12, -2)
Conventional risk factors plus NT-proBNP		
No. cohorts/participants/events	11/31836/1994	11/31836/1477
Non-cases	18 (16, 20)	17 (15, 18)
Cases	-8 (-14, -1)	3 (-4, 10)

Conventional risk factors included age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein.
NRI is expressed as a percentage
Calculations were performed by cohort and sex.

Supplementary Table 6: Estimated public health impact with targeted assessment of circulating cardiac-related biomarkers among 100,000 UK adults in a primary care setting using thresholds from NICE guidelines

Conventional risk factors	*plus* cardiac troponin T alone			*plus* cardiac troponin I alone			*plus* CRP alone			*plus* NT-proBNP alone		
	0-<5%	5-<10%	≥10%	0-<5%	5-<10%	≥10%	0-<5%	5-<10%	≥10%	0-<5%	5-<10%	≥10%
Cases (n=11,934)												
0-<5%	670	105	6	653	136	6	763	57	0	755	109	22
5-<10%	129	1318	305	176	1262	294	61	1411	196	82	1434	248
≥10%	0	311	9090	4	318	9085	0	138	9308	0	296	8988
Non-cases (n=88,066)												
0-<5%	33,523	1864	22	32,724	1913	11	33,689	1374	0	34,434	1957	19
5-<10%	3078	16,684	1805	3215	17,491	1696	1740	18,875	1347	2415	17,652	1474
≥10%	8	2975	28,107	11	2725	28,280	0	1368	29,673	0	2937	27,178
CVD events prevented	61			59			39			50		
Number needed to screen to identify one additional CVD case with 95% CI	382 (318, 446)			410 (264, 556)			603 (473, 733)			470 (354, 586)		

Supplementary Table 7: Estimated public health impact with targeted assessment of circulating cardiac-related biomarkers among 100,000 UK adults in a primary care setting using thresholds from ESC 2021 guidelines

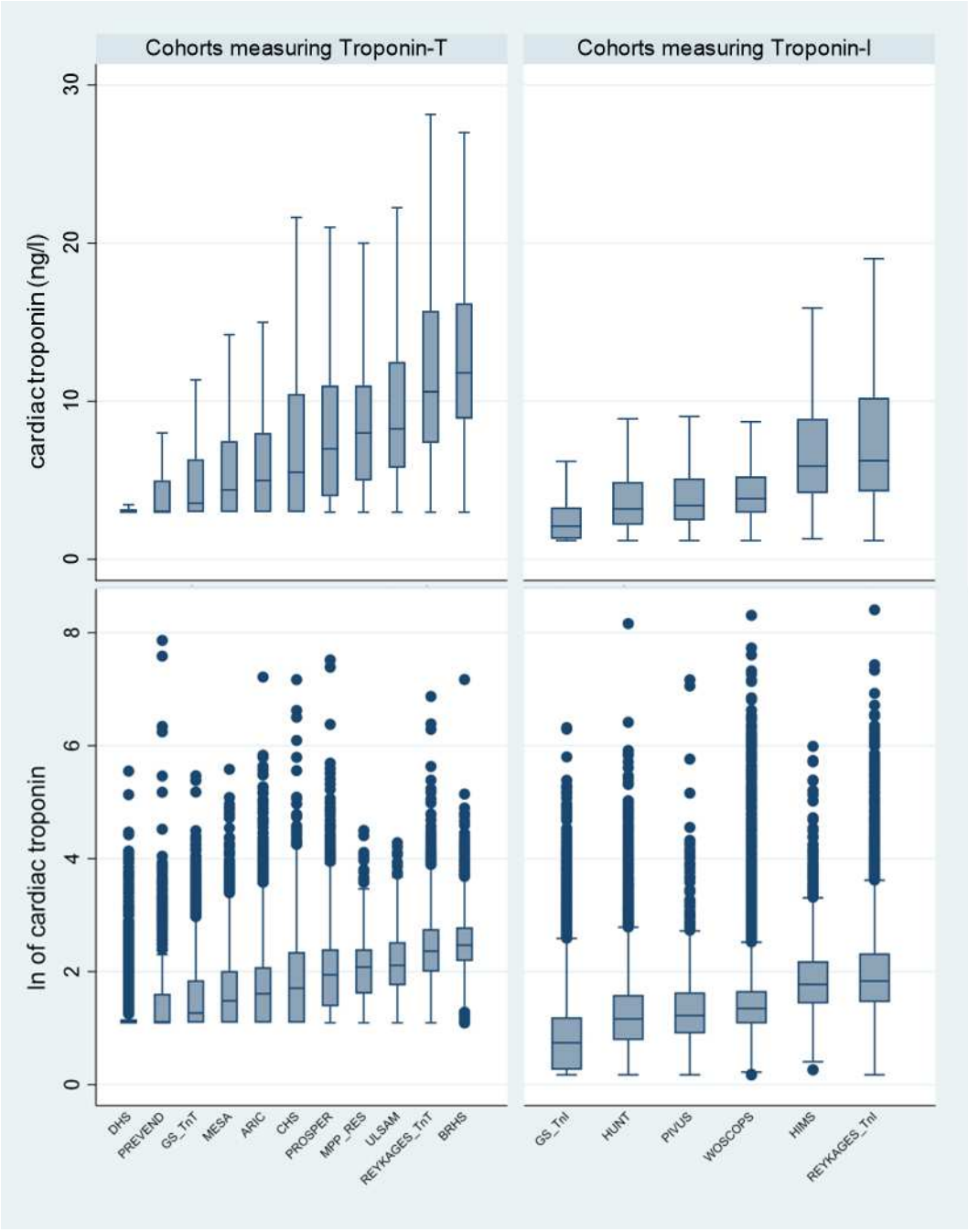
Conventional risk factors	*plus* cardiac troponin T alone			*plus* cardiac Troponin I alone			*plus* CRP alone			*plus* NT-proBNP alone		
	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest
Cases (n=11,934)												
Lowest	425	73	6	430	80	6	464	60	0	518	74	12
Intermediate	125	1818	437	119	1832	390	55	1924	305	89	1940	381
High	0	440	8610	0	424	8654	0	205	8921	0	429	8492
Non-cases (n=88,066)												
Lowest	24,329	1586	13	23,225	1325	11	23,896	1396	2	24,890	2163	15
Intermediate	3176	27,802	2317	3304	28,990	2230	1920	30,355	1633	2987	28,351	1880
High	6	3680	25,157	7	3315	25,658	0	1798	27,066	0	3654	24,125
CVD events prevented	87			78			61			76		
Number needed to screen to identify one additional CVD case with 95% CI	408 (344, 472)			473 (327, 619)			593 (463, 723)			468 (352, 584)		

Supplementary Table 8: Sensitivity analysis assuming different reductions in risk with statin treatment.

Decrease in LDL-C with statin and approximate equivalent decrease in risk*		CVD events prevented		Number needed to screen to prevent one CVD event (95% CI)	
		cardiac troponin T	cardiac troponin I	cardiac troponin T	cardiac troponin I
1 mmol/L	20%	88	78	408 (344, 472)	473 (327, 619)
1.5 mmol/L	30%	132	117	273 (209, 337)	316 (170, 462)
2 mmol/L	40%	175	156	205 (141, 269)	237 (91, 383)

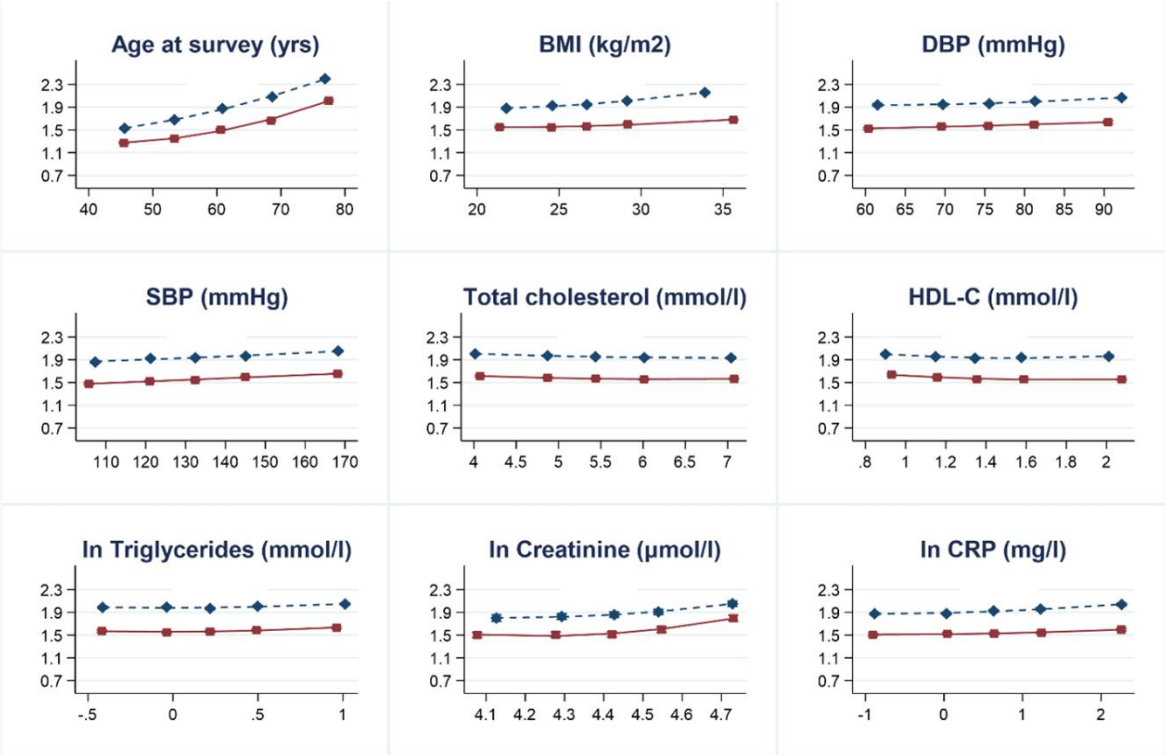
*Evidence from the Cholesterol Treatment Trialists' Collaboration has shown that a 2 mmol/L reduction in LDL-C by statin treatment is associated with a 40% lower risk of CVD within 5 years.[30] Assuming this relationship is linear the above sensitivity shows that our 20% estimate used in the main analysis gives more conservative estimates of the impact of cardiac troponins.

Supplementary Figure 1: Box and whisker plot for levels of cardiac troponin T and cardiac troponin I by cohort.



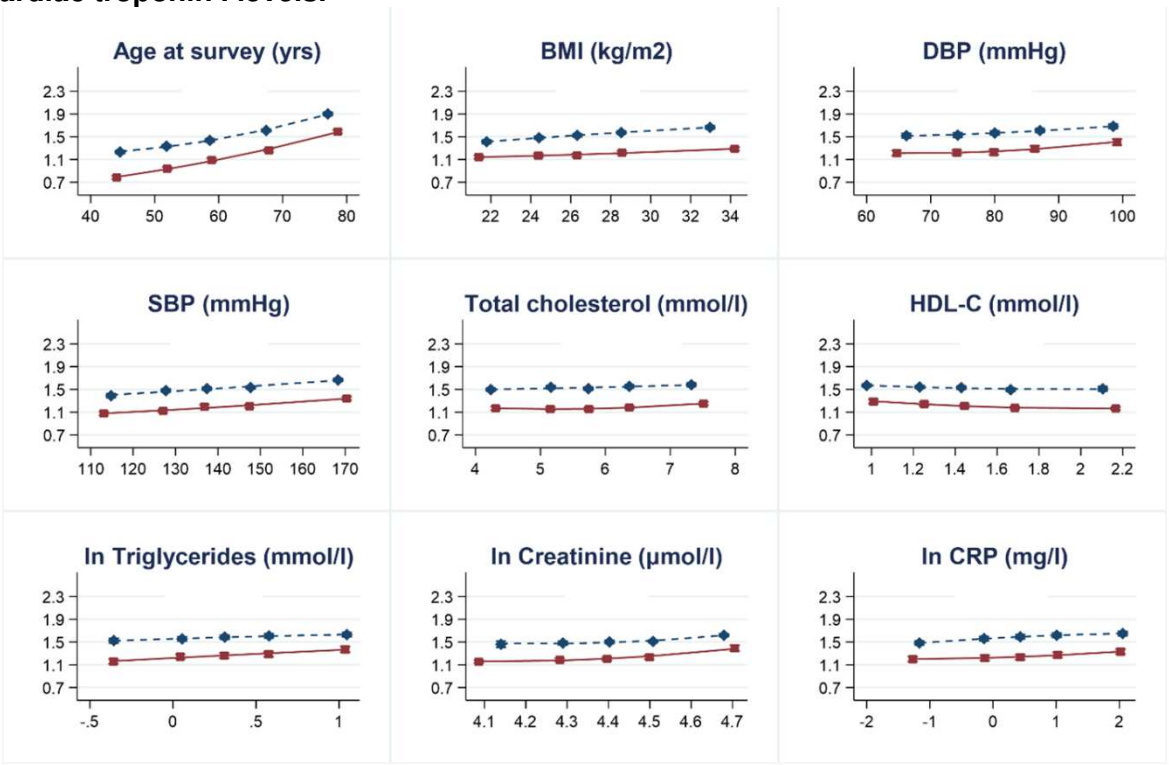
The middle of the box represents the median and the top and bottom of the box represent the 75th and 25th percentiles. The top and bottom of the whiskers represent the maximum and minimum values. The minimum values are lower for cardiac troponin I than for cardiac troponin T because the limit of detection for cardiac troponin I assay is lower than that of cardiac troponin T. Outliers were all values above the 99th centile and these are shown for log transformed cardiac troponin values (bottom panels)

Supplementary Figure 2: Correlations between continuous covariates (x-axis) and cardiac troponin T levels.



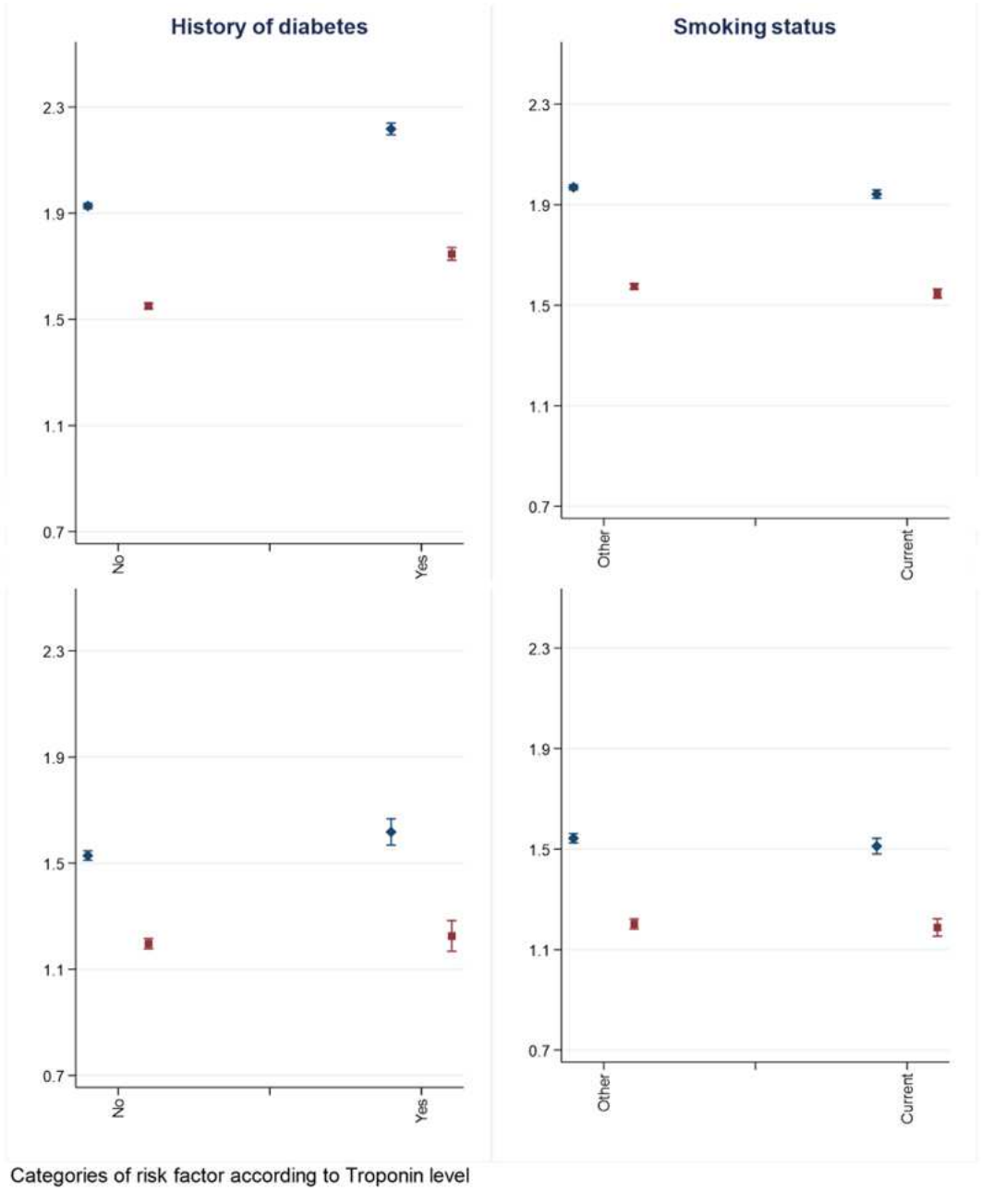
Cardiac troponin T was (natural) log-transformed. Levels are presented for males (blue) and females (red), separately for each factor. First, quintiles of each factor are formed and then troponin levels predicted for each quintile. Error bars refer to the 95% CIs.

Supplementary Figure 3: Correlations between continuous covariates (x-axis) and cardiac troponin I levels.



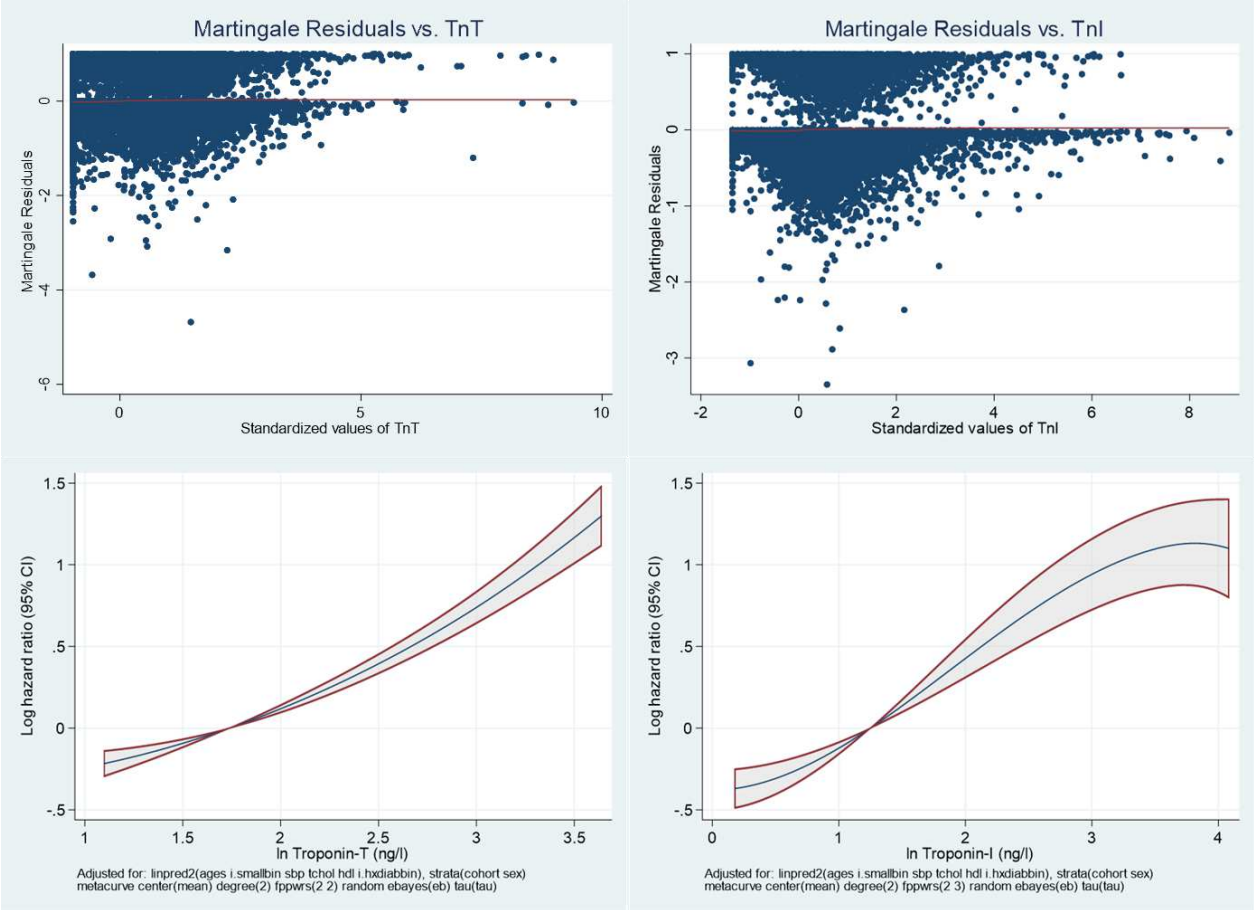
Cardiac troponin I was (natural) log-transformed. Levels are presented for males (blue) and females (red), separately for each factor. First, quintiles of each factor are formed and then troponin levels predicted for each quintile. Error bars refer to the 95% CIs.

Supplementary Figure 4: Correlations between categorical covariates and cardiac troponin T and cardiac troponin I.



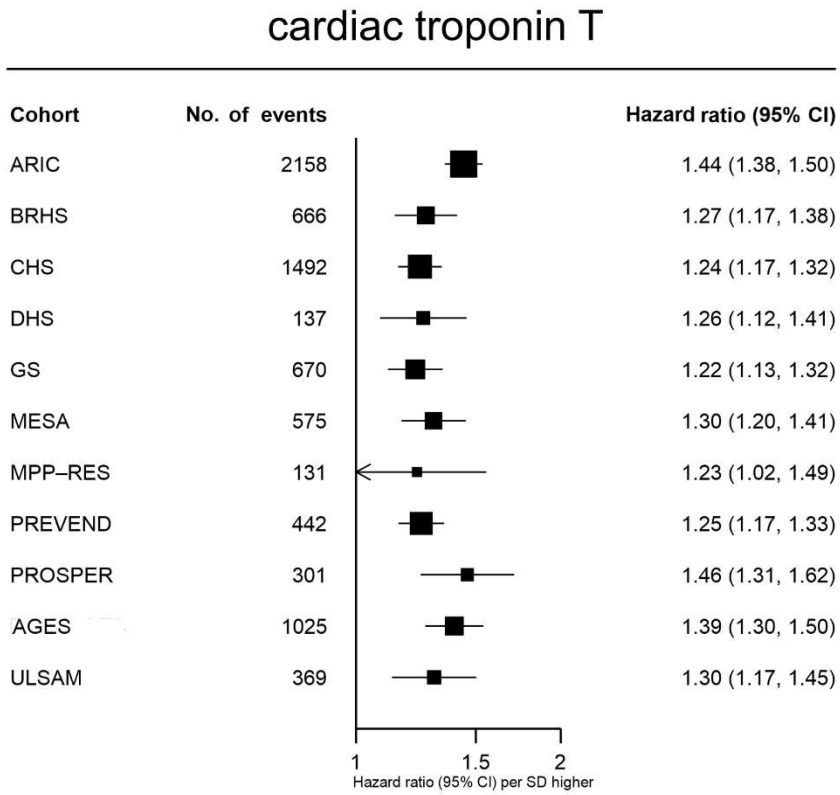
Cardiac troponin T (top two panels) and cardiac troponin I (bottom two panels) were (natural) log-transformed. Levels are presented for males (blue) and females (red), separately for each factor. Error bars refer to the 95% CIs.

Supplementary Figure 5: Martingale residual and fractional polynomial plots for the association between cardiac troponins and first-onset CVD.



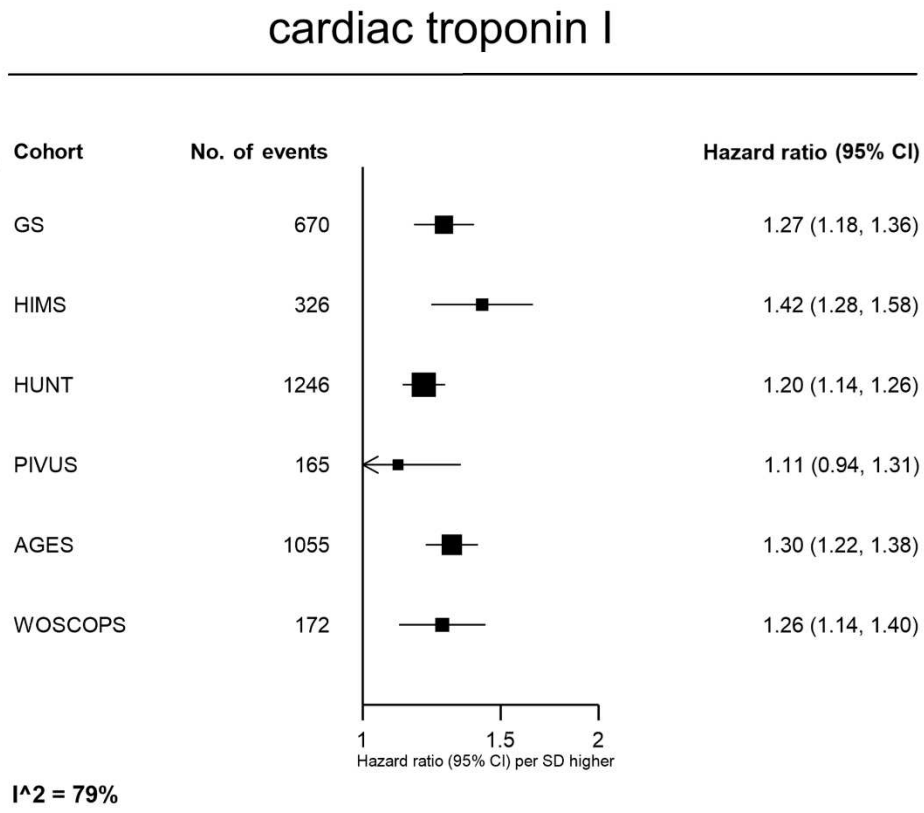
The left panels are for cardiac troponin T and the right panels are for cardiac troponin I. Martingale residual plots (top) have a running mean smoother. Fractional polynomial plots were produced in an individual participant data meta-analysis context to show non-linear associations.[31]

Supplementary Figure 6: Hazard ratios for first-onset CVD for cardiac troponin T by cohort.



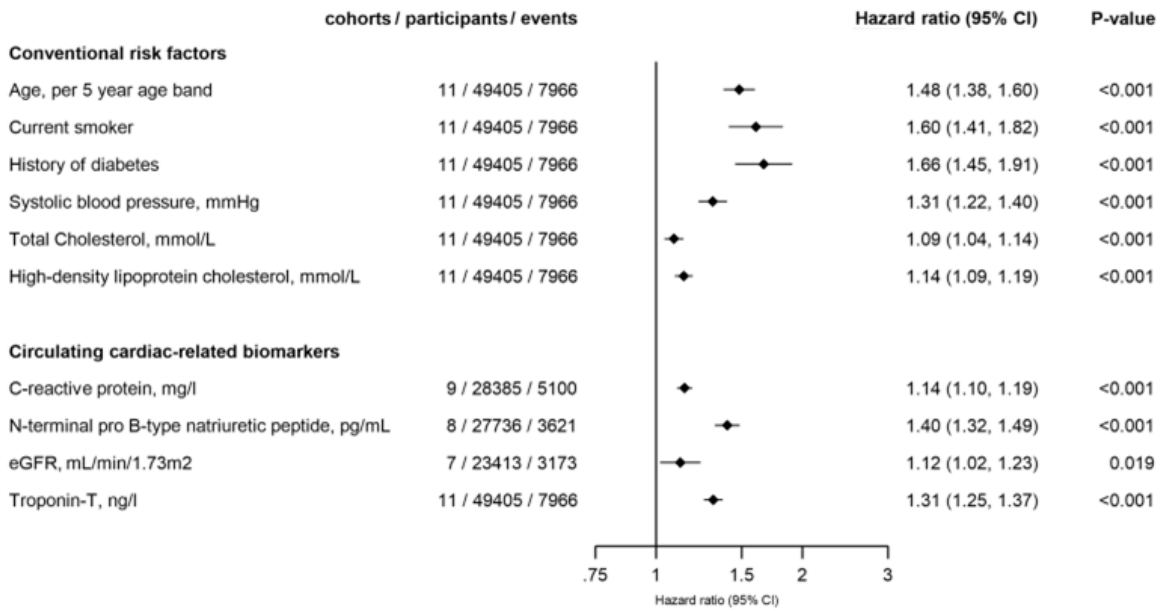
Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels.

Supplementary Figure 7: Hazard ratios for first-onset CVD for cardiac troponin I by cohort



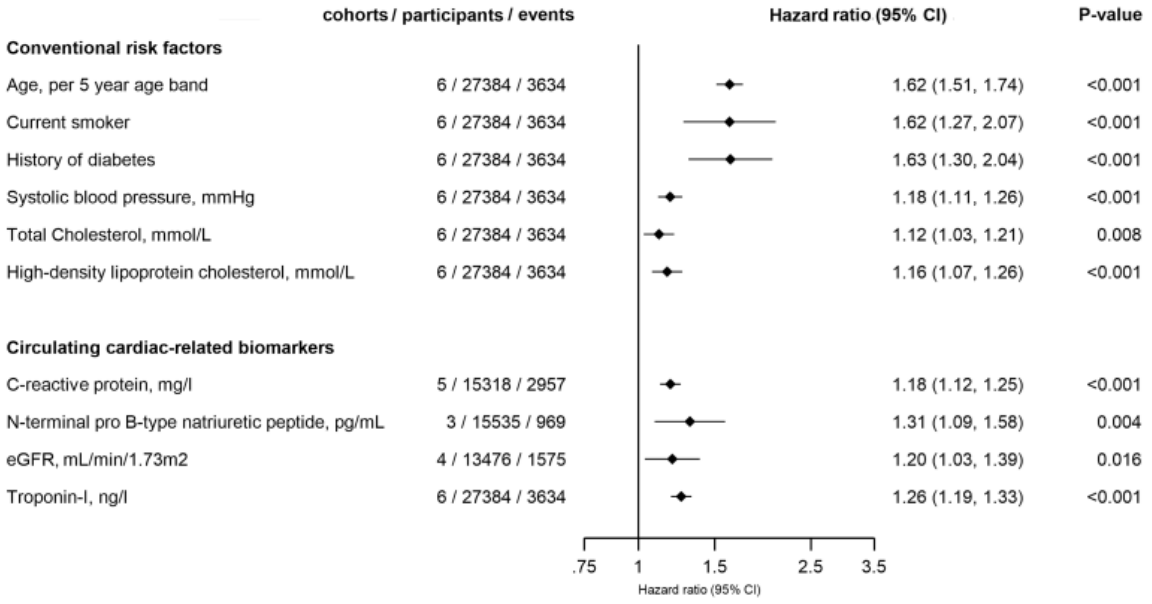
Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels.

Supplementary Figure 8. Hazard ratios for first-onset CVD of conventional cardiovascular risk factors and biomarkers for comparison with cardiac troponin T.



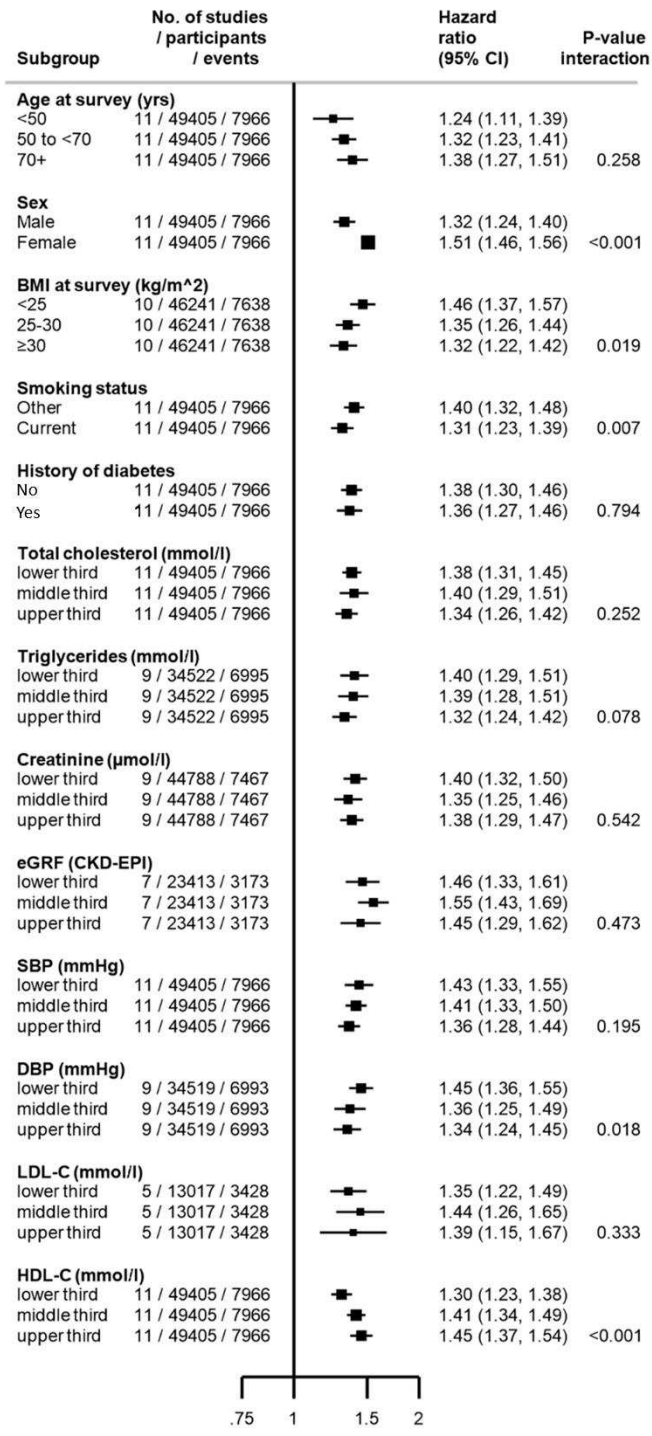
All factors are only measured in those participants from the cohorts with cardiac troponin T measurements. Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. For categorical variables, HRs are shown for patients with diabetes versus without, and for current smokers versus others. For continuous variables, HRs are shown per standard deviation higher of each predictor to facilitate comparison, except for age (per 5 years) and high-density lipoprotein cholesterol, where the HR is shown per standard deviation lower. C-Reactive protein, N-terminal pro B-type natriuretic peptide and cardiac troponin T were transformed using the natural log of the original scale. The standard deviation for the continuous variables are systolic blood pressure = 22.2 mmHg, total cholesterol = 1.09 mmol/L, high-density lipoprotein = 0.42 mmol/L, eGFR = 16.4 mL/min/1.73 m^2, ln of C-reactive protein = 1.12, ln of N-terminal pro B-type natriuretic peptide = 1.10, and ln cardiac troponin T = 0.68.

Supplementary Figure 9. Hazard ratios for first-onset CVD of conventional cardiovascular risk factors and biomarkers for comparison with cardiac troponin I.



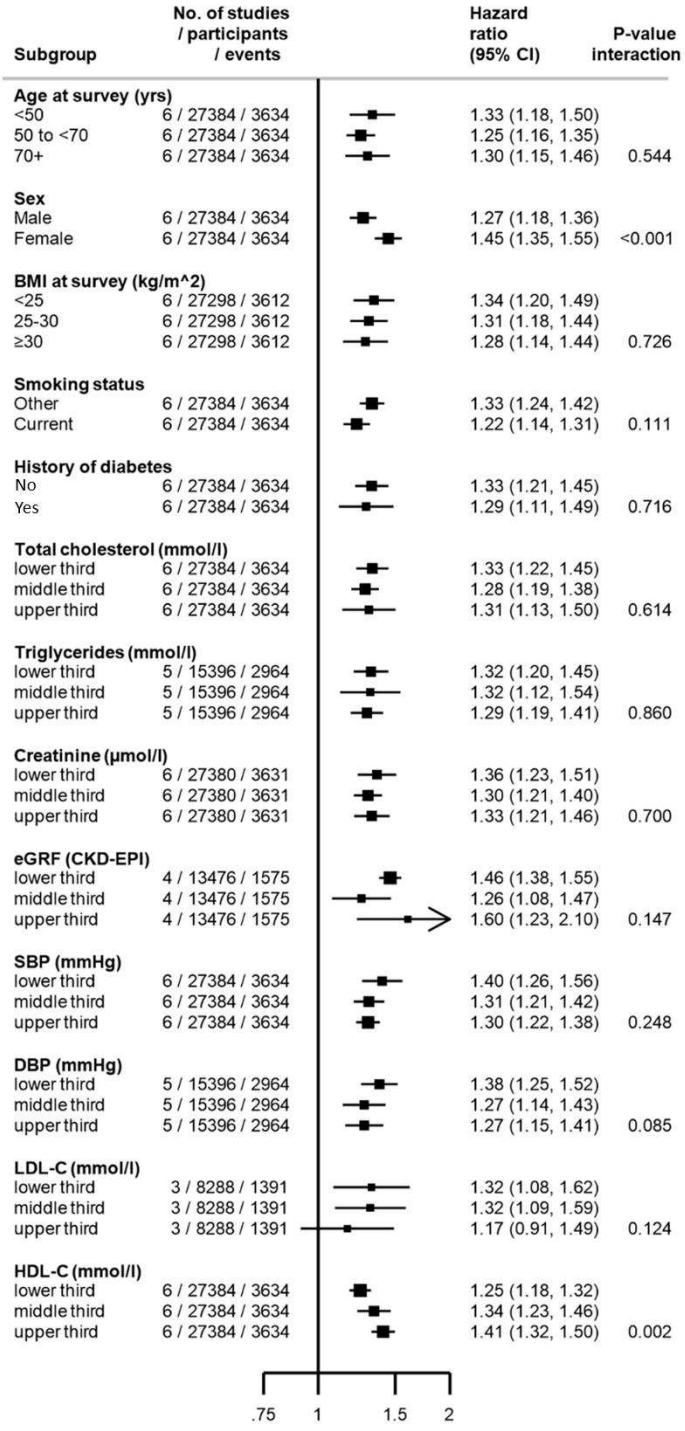
All factors are only measured in those participants from the cohorts with cardiac troponin I measurements. Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. For categorical variables, HRs are shown for patients with diabetes versus without, and for current smokers versus others. For continuous variables, HRs are shown per standard deviation higher of each predictor to facilitate comparison, except for age (per 5 years) and high-density lipoprotein cholesterol, where the HR is shown per standard deviation lower. C-Reactive protein, N-terminal pro B-type natriuretic peptide and cardiac troponin I were transformed using the natural log of the original scale. The standard deviation for the continuous variables are systolic blood pressure = 20 mmHg, total cholesterol = 1.13 mmol/L, high-density lipoprotein = 0.42 mmol/L, eGFR = 15.8 mL/min/1.73 m^2, ln of C-reactive protein = 1.18, ln of N-terminal pro B-type natriuretic peptide = 1.00, and cardiac troponin I = 0.85.

Supplementary Figure 10: HR and 95% CI by subgroups for association between cardiac troponin T and first-onset CVD after adjustment for conventional risk factors



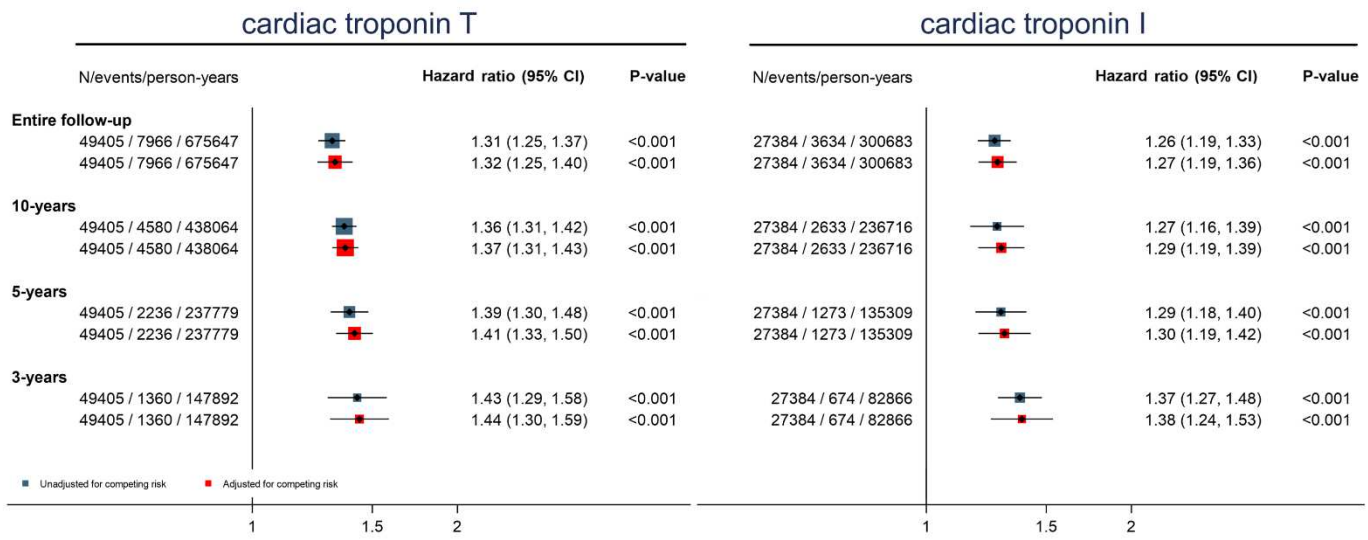
Cardiac troponin T was (natural) log-transformed. Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. Hazard ratios represent one standard deviation increase in cardiac troponin T value. Given multiple testing, we consider statistically significant effect modification to have an interaction threshold <0.001.

Supplementary Figure 11: HR and 95% CI by subgroups for association between cardiac troponin I and first-onset CVD after adjustment for conventional risk factors



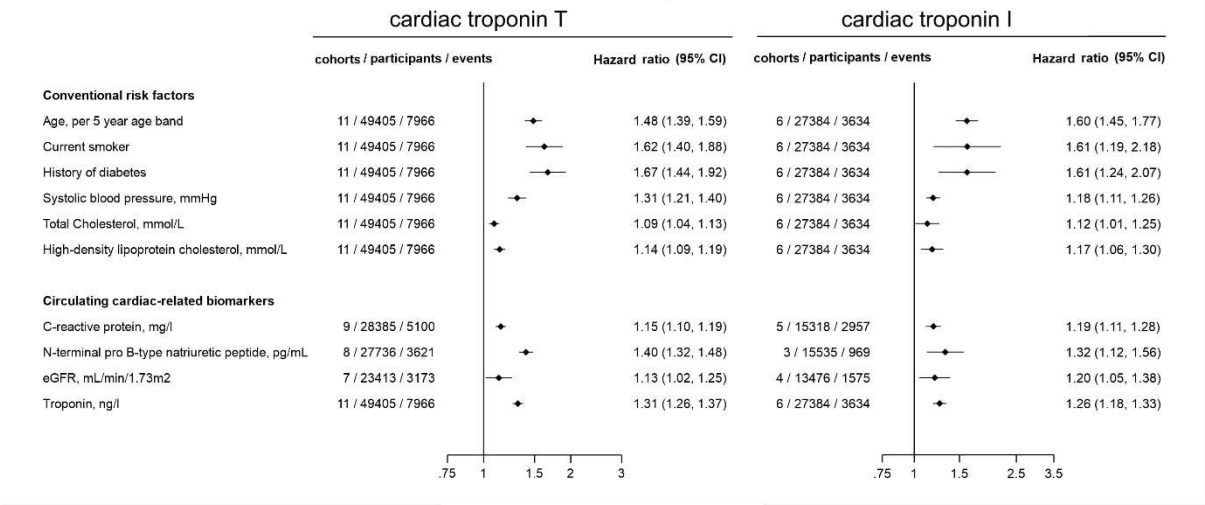
Cardiac troponin I was (natural) log-transformed. Hazard ratios (HRs) were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. Hazard ratios represent one standard deviation increase in cardiac troponin I value. Given multiple testing, we consider statistically significant effect modification to have an interaction threshold <0.001

Supplementary Figure 12: Forest plot showing the cohort-startified Cox regression analysis alongside Fine and Gray model results adjusting for competing risk.



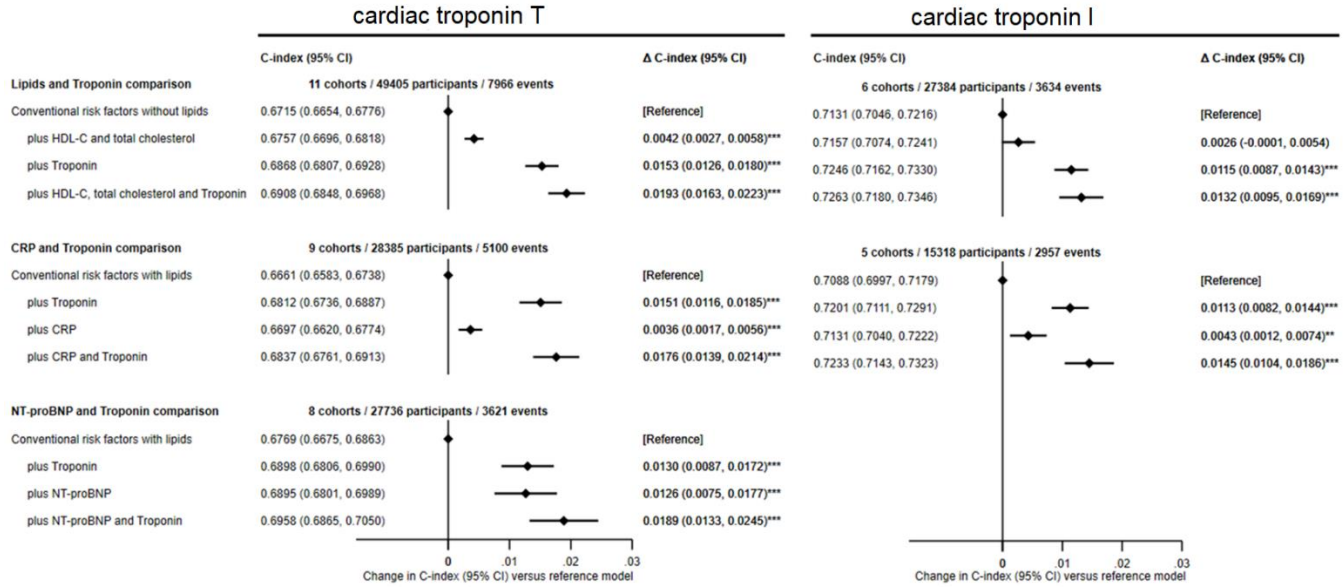
The outcome is first-onset CVD. The hazard ratios are shown for 3-, 5-, and 10-year time periods and show slightly stronger associations with shorter periods.

Supplementary Figure 13: Forest plot showing associations between biomarkers and conventional risk factors pooling results together using restricted maximum likelihood models.



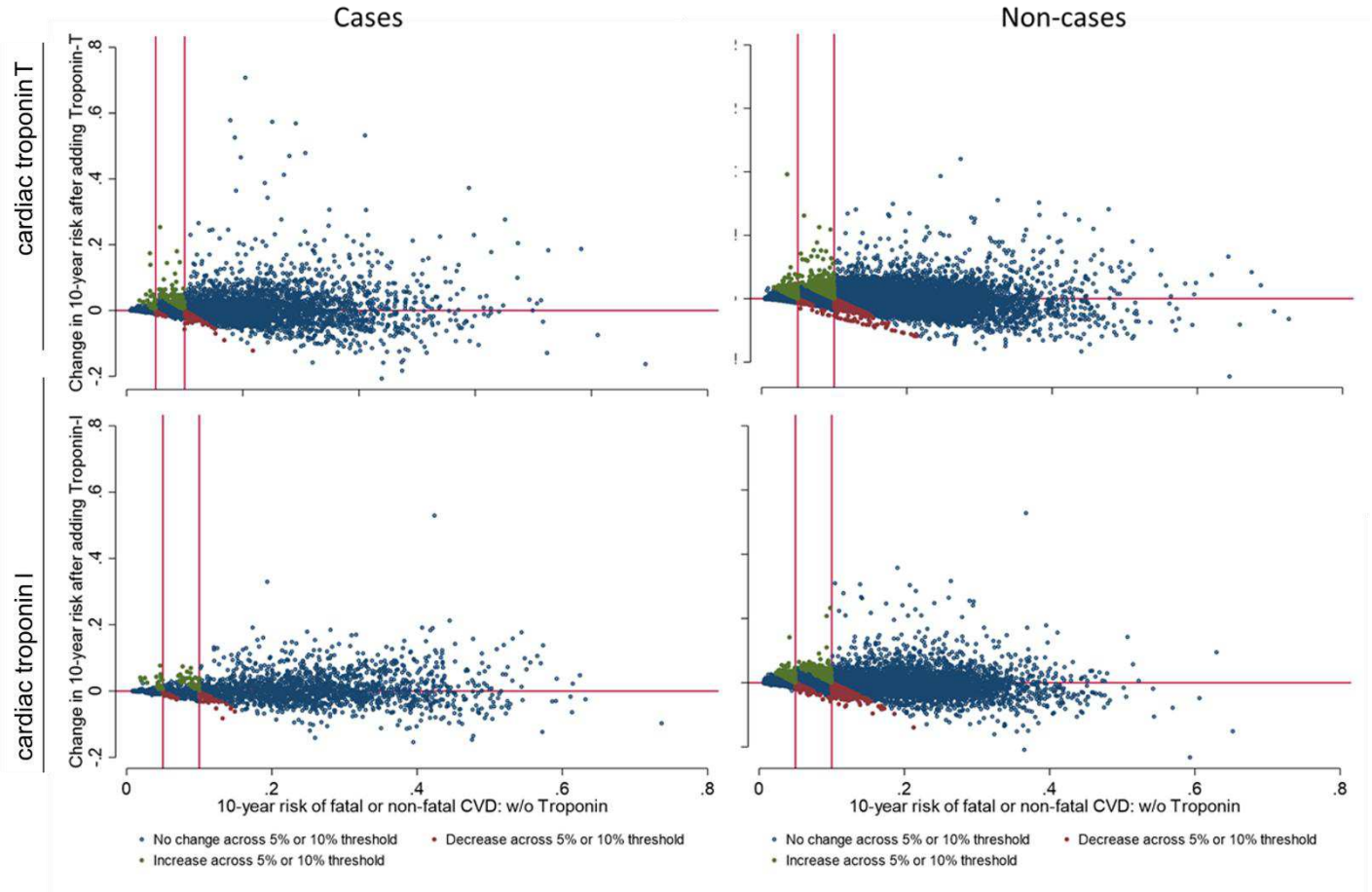
The outcome is first-onset CVD. Restricted maximum likelihood models are less sensitive to a low number of cohorts and more accurately reflect the imprecision in each analysis.[5]

Supplementary Figure 14: Improvement in risk discrimination for first-onset CVD after addition of cardiac troponin T or cardiac troponin I compared with other circulating biomarkers using a cross-validation approach to account for optimism.



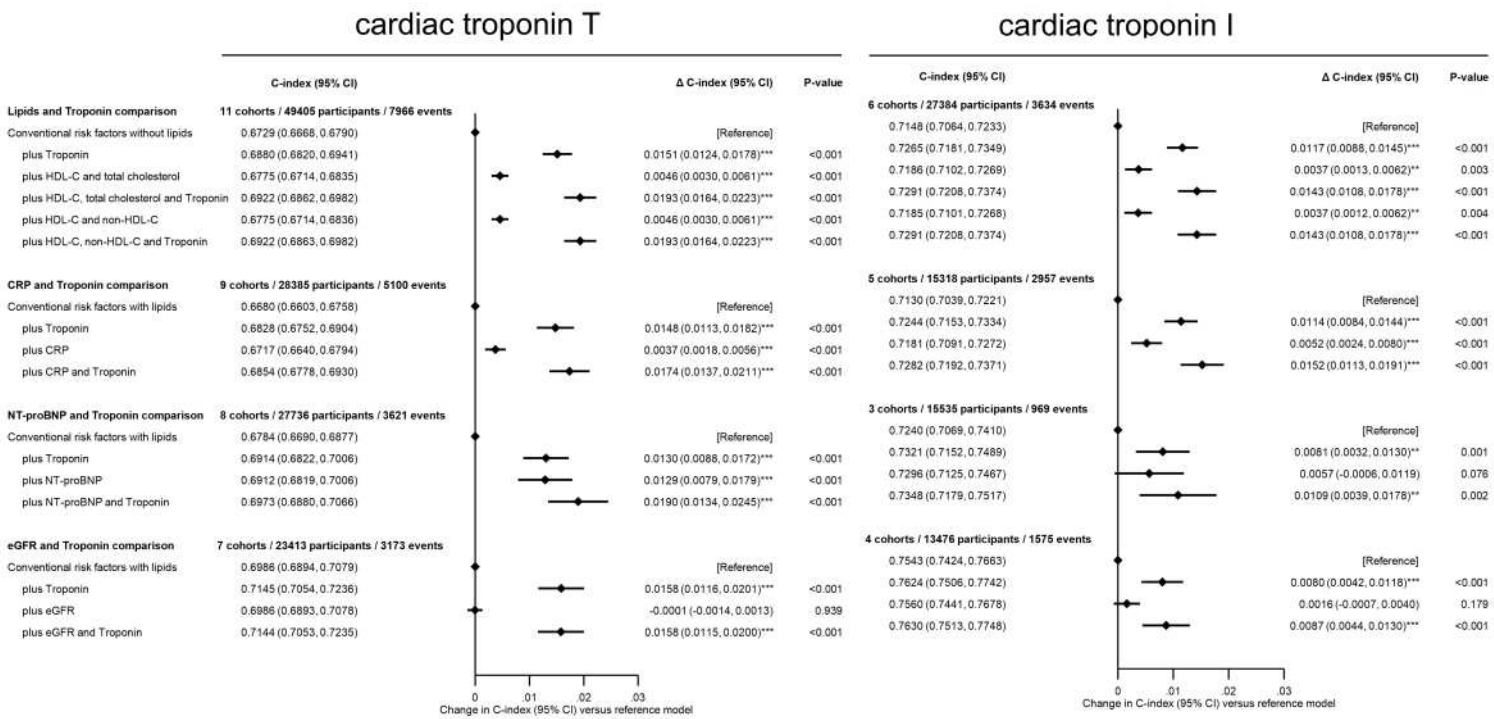
Cardiac troponins, NT-proBNP, and CRP values were all (natural) log-transformed. Δ C-index indicates the change in C-index with reference to the conventional risk factor model which included information about age, smoking status, systolic blood pressure, history of diabetes, and concentration of total cholesterol. HDL-C was included in the set of predictors in the conventional risk factor model before determining the change in C-index after adding CRP. Note that there were too few participants with complete NT-proBNP among the studies with measured cardiac troponin I for a cross validation approach to run successfully.

Supplementary Figure 15: Change in 10-year risk after adding cardiac troponin T or cardiac troponin I plotted against the 10-year risk before adding cardiac troponin isoforms in cases and non-cases.



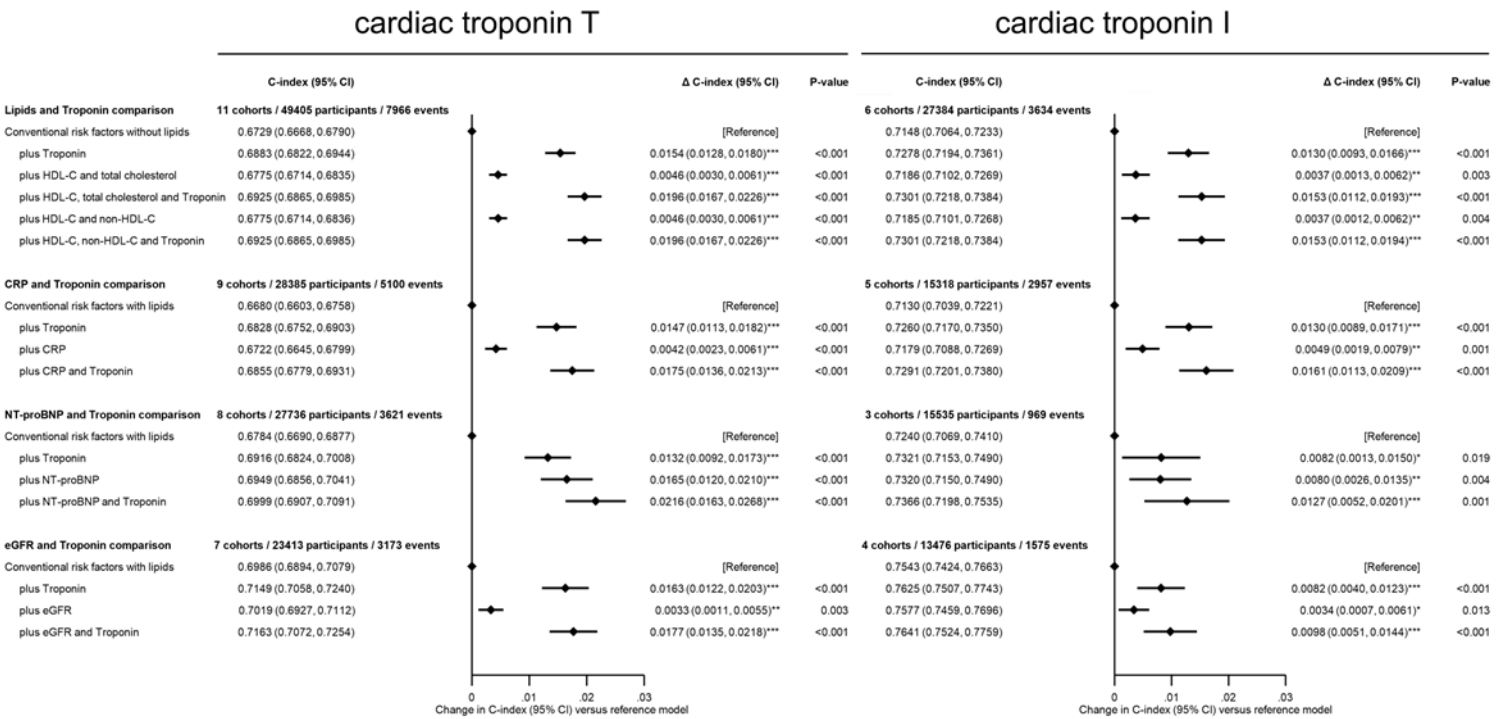
Plots show that a small number of participants have an increase (green) or decrease (red) in risk that crosses the 5 or 10% threshold (used in the NICE guidelines). In addition, large increases in risk were more common in those with high baseline risk and in cases.

Supplementary Figure 16: Improvement in risk discrimination for first-onset CVD after addition of cardiac troponin T or cardiac troponin I compared with other circulating biomarkers assuming linearity in the association.



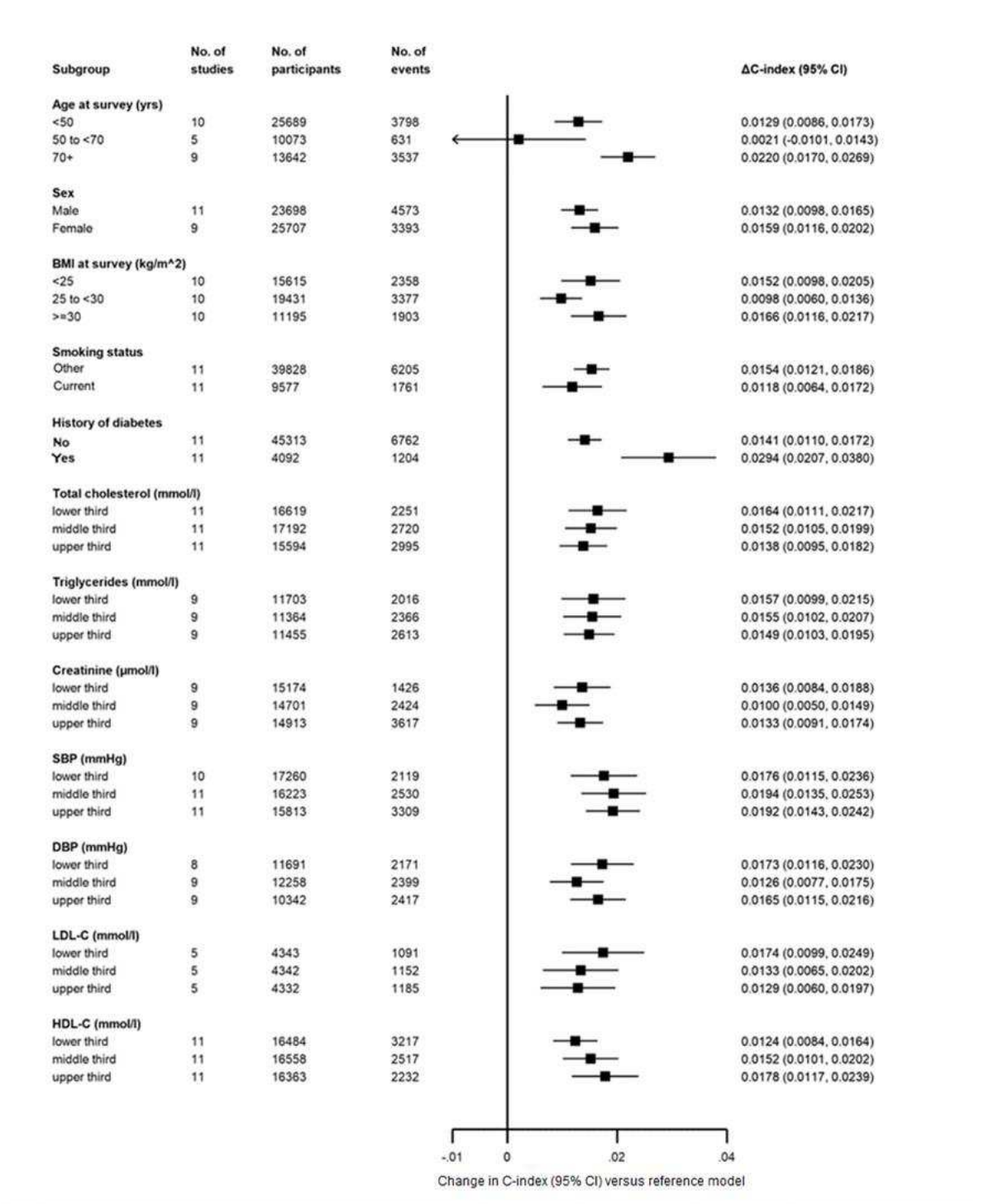
Adding HDL-C and total cholesterol together shows the similar increase in C-index than adding HDL-C and non-HDL-C together. CRP NT-proBNP, cardiac troponin, and eGFR were added to models assuming linear associations.

Supplementary Figure 17: Improvement in risk discrimination for first-onset CVD after addition of cardiac troponin T or cardiac troponin I compared with other circulating biomarkers assuming non-linearity in the association.



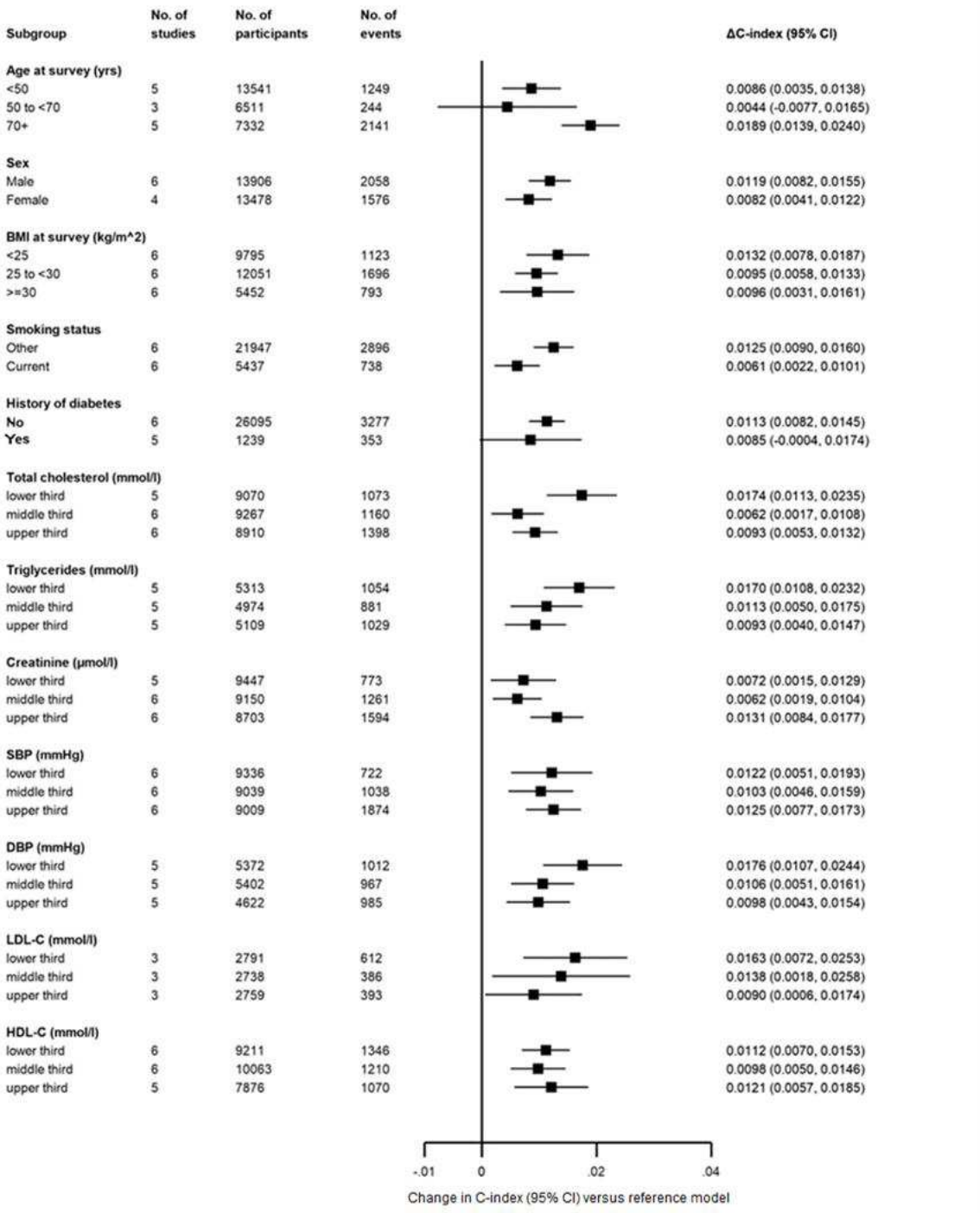
CRP NT-proBNP, cardiac troponin, and eGFR were added to models using quadratic terms (biomarker+biomarker2).

Supplementary Figure 18: Improvement in risk discrimination by subgroups for first-onset CVD by addition of information about cardiac troponin T to the conventional risk factor model



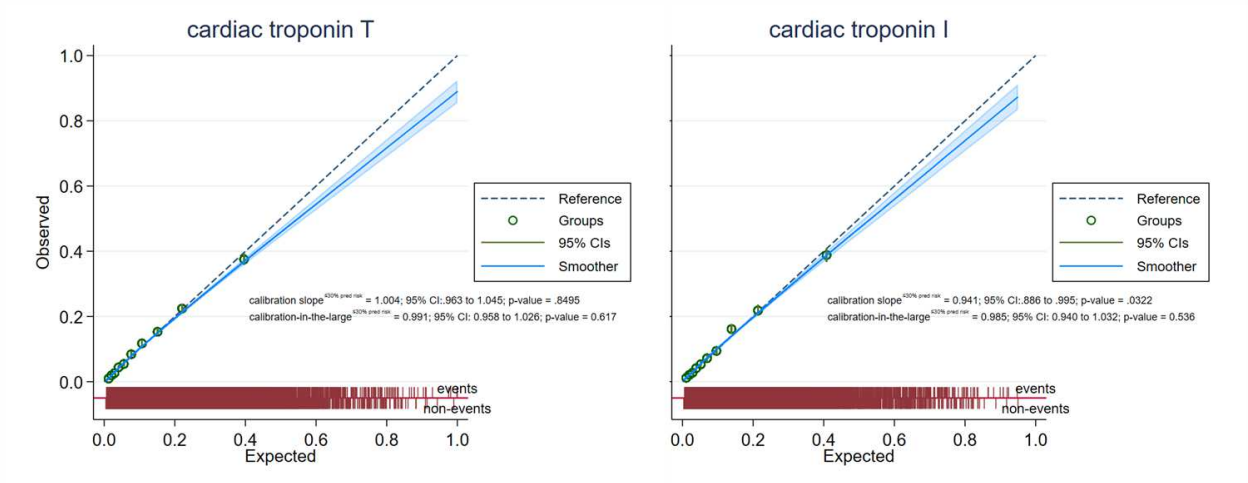
Cardiac troponin T was (natural) log-transformed. Δ C-index indicates the change in C-index with reference to the conventional risk factor model which included information about age, smoking status, systolic blood pressure, history of diabetes, HDL-C, and concentration of total cholesterol, where appropriate.

Supplementary Figure 19: Improvement in risk discrimination by subgroups for first-onset CVD by addition of information about cardiac troponin I to the conventional risk factor model.



Cardiac troponin I was (natural) log-transformed. Δ C-index indicates the change in C-index with reference to the conventional risk factor model which included information about age, smoking status, systolic blood pressure, history of diabetes, HDL-C, and concentration of total cholesterol, where appropriate.

Supplementary Figure 20: Observed versus predicted risk for cohorts measuring cardiac troponin T and cardiac troponin I.



The outcome is first-onset CVD within 10 years. Calibration plots were produced after cross-validation to adjust for overfitting of the model. The ideal intercept was calculated using the methods described in a recent publication.[32]

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