Comparison Between High Sensitivity Cardiac Troponin T and Cardiac Troponin I in a Large General Population Cohort

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Running head: cTnT and cTnI general population comparison

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Abbreviations

BMI – Body mass index

cTnI - cardiac troponin I

cTnT - cardiac troponin T

GS:SFHS – Generation Scotland Scottish Family Health Study

SIMD - Scottish Index of Multiple Deprivation

ABSTRACT

Background

Few data compare cardiac troponin T (cTnT) and troponin I (cTnI) in a general population. We sought evaluate the distribution and association between cTnT, cTnI, and cardiovascular risk factors in a large general population cohort.

Methods

High-sensitivity cTnT and cTnI were measured in serum from 19,501 individuals in the Generation Scotland Scottish Family Health Study. Associations with cardiovascular risk factors were compared using age and sex adjusted regression. Observed age- and sex-stratified 99th centiles were compared to 99th centiles for cTnT (men 15.5ng/L, women 9.0ng/L) and cTnI (men 34.2ng/L, women 15.6ng/L) used in clinical practice.

Results

cTnT and cTnI concentrations were detectable in 53.3% and 74.8% of participants respectively and were modestly correlated in unadjusted analyses (R^2=21.3%), and only weakly correlated after adjusting for age and sex (R^2=9.5%). Cardiovascular risk factors were associated with both troponins, but in age and sex adjusted analyses cTnI was more strongly associated with age, male sex, BMI, and SBP (P<0.0001 for all versus cTnT). cTnT was more strongly associated with diabetes (P<0.0001 versus cTnI). The observed 99th centiles were broadly consistent with recommended 99th centiles in younger men and women. After the age of 60 years, observed 99th centiles increased substantially for cTnT, and beyond 70 years of age, the 99th centiles approximately doubled for both troponins.

Conclusions

In the general population, cTnT and cTnI concentrations are weakly correlated and are differentially associated with cardiovascular risk factors. 99th centiles currently in use are broadly appropriate for men and women up to but not beyond the age of 60 years.

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Introduction

High sensitivity (hs) assays for the measurement of cardiac troponin T (cTnT) and troponin I (cTnI) are now used widely for the diagnosis of myocardial infarction. The universal definition of myocardial infarction recommends the 99th centile derived from a normal reference population be used to define myocardial necrosis. However, it is also increasingly apparent that troponin concentrations well below this threshold provide diagnostic and prognostic information in patients with both acute and stable cardiovascular diseases (1–3) and may have a role in screening the general population (1, 4).

The International Federation of Clinical Chemistry and Laboratory Medicine recently updated their guidance on the use of cardiac troponin testing and the criteria used to define a hs-cTn assay (5), which must have adequate precision (<10% coefficient of variation) at the 99th centile and be able to measure cTn concentrations above the limit of detection in more than 50% of apparently healthy men and women. They also recommend at least 300 participants in any age or sex specific strata to define the 99th centile for cardiac biomarkers (6). Several large studies have sought to independently validate the proportion of individuals with detectable cTn concentrations and the appropriateness of the 99th centile for these assays (7–10). However, few studies have measured both cTnI and cTnT in a single large general population cohort (11-12).

Currently, the most frequently used high-sensitivity cardiac troponin assays include the Roche high sensitivity cardiac troponin T and the Abbott high sensitivity cardiac troponin I assay. As such, often the service provider to local biochemistry laboratories dictate whether cTnT or cTnI are measured in individual patients. Whether the performance of these assays, the mechanisms of cTnT and cTnI release into the circulation and subsequent clearance, and their associations with known cardiovascular risk factors are similar is unknown. Using these

clinically available high sensitivity assays, we measured both cTnT and cTnI in the Generation Scotland Scottish Family Health Study (GS:SFHS), a large general population cohort. The aim was to understand the relationship between cTnT and cTnI and how this is influenced by age, sex, and cardiovascular risk factors, and to evaluate how these factors influence the proportion of the population with detectable cTn concentrations and the 99th centile.

Methods

GS:SFHS

The recruitment and design of the study has been reported in detail elsewhere (6). In brief, during 2006-2010 potential participants were identified at random from those aged 35–65 years from the lists of collaborating general medical practices in Scotland, and invited to participate. Participants were also asked to identify one or more first-degree relatives 18 years or older who would be able to participate. A total of 21,476 participants aged between 18 and 98 years attended a research clinic in either Glasgow, Dundee, Perth, Aberdeen or Kilmarnock, Scotland. Participants completed a health questionnaire, and had physical and clinical characteristics (including systolic blood pressure [SBP]and body mass index [BMI]) measured according to a standardized protocol (https://www.ed.ac.uk/generation-scotland/using-resources/scottish-family-health-study). Past medical history, including a diagnosis of diabetes mellitus (type 1 or type 2) and cardiovascular disease (prior myocardial infarction or stroke), was recorded using a self-reported questionnaire. Fasting blood samples were taken, according to a standard operating procedure, and serum samples were separated. Baseline biochemistry measures including total cholesterol, HDL cholesterol, and creatinine were generated at time of collection and additional serum aliquots were stored at -80^{o}C for future biochemical analyses. Scottish Index of Multiple Deprivation (SIMD) scores are

national composite measures of deprivation, and are derived from participant postcodes (13). A composite 10 year cardiovascular risk score was also calculated in participants aged 35y or higher with no prevalent cardiovascular disease, based on the Scottish ASSIGN score used in clinical practice (14, 15)

Measurement of hs-cTn

hs- cTnT (Roche Diagnostics) and hs- cTnI (ARCHITECT STAT, Abbott Diagnostics) were measured on Cobas e411 and i1000SR analysers respectively. Both assays were calibrated and quality controlled using the manufacturer's reagents. Coefficients of variation for cTnI were 6.2 % for the low control, 6.0% for intermediate control, and 4.6% for high control. Coefficients of variation for cTnT were 5.0% for the low control and 3.4% for the high control. We also participated in the National External Quality Assurance Scheme (NEQAS: https://ukneqas.org.uk/) for these biomarkers during the conduct of study. Some recommendations suggest that troponin results should be reported as whole numbers in an acute clinical setting, partly to reduce the risk of transcription errors. In this study, given the generally low troponin levels in a broadly healthy cohort, and in line with a substantial proportion of published literature, we report results to one decimal place. The limit of detection (LoD) of the cTnT assay is set to 3.0ng/L by the manufacturer, while we reported anything less than 1.2ng/L for cTnI as below the limit of detection (16). Results below the LoD are reported as half of the limit of detection (i.e. 1.5ng/L for cTnT and 0.6ng/L for cTnI) for continuous analyses. The manufacturers report a 99th centile of 14.0 ng/L for cTnT, and 26.2 ng/L for cTnI. In addition there are sex specific 99th centiles defined for both assays (5): cTnT, 9.0 ng/L in women, 15.5 ng/L in men (10); cTnI, women 15.6 ng/L, men 34.2 ng/L (17, 18). A standard operating procedure was developed to facilitate measurement of both

troponin assays in tandem during a single (first) thaw of stored serum aliquots. Stored aliquots were spun at 2000g for 5 minutes before assay.

Statistical analysis

By clustered family group, the intra-class correlation coefficient was 0.18 (95%CI 0.16, 0.19) for cTnT and 0.09 (95%CI 0.07, 0.10) for cTnI, indicating minimal impact of family clustering on these analyses. Familial clustering was therefore not considered a factor in further analyses. Missing data for classical risk factors (1,134 missing observations for SIMD score was most frequently missing, no missing observations for age or sex) were imputed by multiple chained imputations over ten datasets; these were used for all analysis with classical risk factors.

Associations of classical cardiovascular disease risk factors with external sex-specific elevated (>99th centile) troponins were illustrated, using categorical variables expressed as frequencies and percentages, and continuous variables as medians (inter quartile range) or mean (standard deviation). Differences between these categorized troponin groups were tested using chi-squared, rank sum test, or t-test respectively. Associations of continuous classical risk factors and the cardiovascular disease risk score with log-transformed distributions of both troponins were tested using univariable linear regression with robust standard errors, and also using a multivariable (age and sex adjusted) approach for each troponin. Effect estimates were exponentiated to give the percentage effect on geometric mean troponin. The relationship between cTnT and cTnI was illustrated using scatter plots, and linear regression on z-scores from log-transformed troponin concentrations. The weighted Kappa statistic was used to test agreement between cTnT and cTnI by approximate

tertiles (with the lowest tertile for cTnT being results below the LoD, and the lowest tertile for cTnI forced to have approximately the same corresponding proportion of the cohort).

The sex stratified GS:SFHS cTnT and cTnI 99th centiles along with associated bias corrected 90% confidence intervals (as recommended by CLSI document C28-A3) around the estimates were determined by bootstrapping 5000 samples in each age and sex specific strata. The method was repeated in those with no cardiovascular disease. Two sensitivity analyses were conducted; the first removed those with log transformed troponin concentrations >5 standard deviations from the mean, and the second used a rank model to obtain the GS:SFHS 99^{th} centile, and its associated 90% CI from a binomial distribution. We also performed quantile regression using fractional polynomials to model the relationship between age and 99^{th} centile of each troponin (supplement). All statistics were performed using STATA version 14.2.

Results

Population characteristics

Of the 21,476 GS:SFHS participants, 19,501 participants provided a serum sample and yielded a measurement for both cTn assays (90.8%). The median cTnT in the cohort was 3.3ng/L (IQR 1.5, 6.0) and the median cTnI was 1.9ng/L (IQR 0.6, 3.1). Detectable concentrations of cTnT and TnI were found in 10,395 participants (53.3%), and 14,579 (74.8%) respectively. Women and younger individuals were more likely to demonstrate undetectable concentrations of troponin (**Fig 1**). At least 50% of men in each age stratum had detectable cTnT and cTnI. More than 50% of women in ≤50-59 age groups had undetectable cTnT, and more than 50% of women in the ≤30-39 age group had undetectable cTnI (**Fig 1**).

Relationship between cTnT and cTnI

A scatter graph illustrates a modest relationship between cTnT and cTnI (**Fig 2**). Using linear regression, the beta-coefficient for z-scores of log cTnI and log cTnT was 0.46 (95%CI 0.45, 0.47) and the R^2 was 21.3% (online **Supplemental Fig s1**). After adjusting for age and sex, the R^2 between cTnT and cTnI was 9.5%. After excluding those with undetectable levels of either troponin and adjusting for age and sex, the R^2 between cTnT and cTnI was 12.8% in the remaining 8,855 individuals.

Comparing the distribution of tertiles for cTnT and cTnI, the expected agreement based on chance alone was 55.7%, but actual agreement was 70.8% (weighted kappa=0.34). Using the non-sex specific recommended 99th centile to categorize low and high cTn values, the expected agreement was 96.2%, and the observed agreement was 96.9% (kappa=0.19).

Associations of troponin above the recommended 99th centiles with cardiovascular risk factors

There were 296 male participants (3.6%) and 897 female participants (7.9%) with a cTnT result above the recommended 99th centile (15.5ng/L and 9.0ng/L, respectively). These participants were older, had a higher BMI, higher systolic blood pressure, higher serum creatinine, more frequently had a history of cardiovascular disease or diabetes, and more often used blood pressure or cholesterol medications in both sexes (**Table 1**). They also had lower total cholesterol concentrations among men only, had higher HDL-cholesterol concentrations among women only, and were less frequently current smokers in both sexes (**Table 1**).

For cTnI, 83 male participants (1.0%) and 115 female participants (1.0%) were above the recommended 99th centile (34.2ng/L and 15.6ng/L, respectively). Increased cTnI was associated with older age, higher systolic blood pressure, history of cardiovascular disease, and use of blood pressure or cholesterol medications in both sexes (**Table 1**). There was also an inverse association with current smoking in both sexes. However, high cTnI was not associated with BMI, total cholesterol or HDL-cholesterol in either sex (**Table 1**).

Continuous associations of troponins with cardiovascular risk factors

While cardiovascular risk factors were generally associated with both troponin measures, in age and sex adjusted analyses, stronger positive associations were found for cTnI with age, male sex, BMI, and SBP (P<0.0001 for all versus cTnT) (**Table 2**). cTnT was more strongly positively associated with diabetes, was inversely associated with total cholesterol, and positively associated with HDL-cholesterol (P<0.0001 versus cTnI) (**Table 2**). Both troponins had similar positive associations with prevalent cardiovascular disease, use of blood pressure lowering and cholesterol lowering medications and creatinine, and had no association with the Scottish Index of Multiple Deprivation. Both troponins were strongly inversely associated with current smoking (**Table 2**). Sensitivity analysis removing those with cardiovascular disease, diabetes, taking cholesterol lowering or blood pressure medications yielded broadly consistent results, although cTnI became more strongly associated with creatinine (P=0.001 versus cTnT) (online **Supplemental Table s1**). A composite 10 year cardiovascular disease risk score calculated in participants without prevalent cardiovascular disease ≥35 years yielded similar positive associations with both cTnT and cTnI (p=0.34 comparing association with cTnT and cTnI) (**Table 2**).

GS:SFHS 99th centiles stratified by age and sex

The 99th centiles stratified by age and sex were determined in the GS:SFHS and compared to the recommended 99th centile (**Fig 3**).

The observed 99th centile for cTnT was 21.4ng/L for men under 30 years, 15.4ng/L at 30-39 years, 16.3ng/L at 40-49 years, 20.4ng/L at 50-59 years, 25.2ng/L at 60-69 years, and 47.1ng/L at 70 years and over (**Fig 3**, online **Supplemental Table s2**). As such, the observed 99th centile was approximately double the recommended 99th centile in men aged 60-69, and triple in men aged 70 years and over. Among men aged 60-69 and 70 years and over, 5.7% (95%CI 4.6, 7.0%) and 27.9% (95%CI 23.6, 32.5%) respectively had a cTnT value above the 99th centile used in clinical practice (**Fig 1**).

The corresponding age-group specific observed 99th centiles for women were 10.7ng/L, 11.2ng/L, 12.4ng/L, 13.7ng/L, 18.9ng/L, and 38.6 ng/L. As such, the observed 99th centile was also approximately double the recommended 99th centile in women aged 60-69, and triple in women aged over 70 years (**Fig 3**, online **Supplemental Table s2**). Among women aged 60-69 and 70 years and over, 10.1% (95%CI 8.8, 11.5%) and 39.1% (95%CI 35.3, 43.0%) respectively had a cTnT value above the recommended 99th centile (**Fig 1**).

The observed 99th centile for cTnI was 34.4ng/L for men under 30 years, 22.9ng/L at 30-39 years, 30.4ng/L at 40-49 years, 27.0ng/L at 50-59 years, 42.9ng/L at 60-69 years, and 86.2ng/L in those 70 years and over (**Fig 3**, online **Supplemental Table s2**). As such, the observed 99th centile was approximately double the recommended 99th centile in men aged 70 years and over. Among men aged 60-69 years and 70 years and over 1.6% (95%CI 1.0, 2.3%)

and 2.6% (95%CI 1.3, 4.6%) respectively had a cTnI value above the recommended 99th centile (**Fig 1**).

The corresponding observed age-group specific 99th centiles in women were 9.3ng/L, 8.7ng/L, 12.5ng/L, 16.9ng/L, 17.4ng/L, and 39.2ng/L. As such, the observed 99th centile was also approximately double the recommended 99th centile in women over 70 years (**Fig 3**, online **Supplemental Table s2**). Among women aged 60-69 years and 70 years and over, 1.6% (95%CI 1.1, 2.2%) and 3.3% (95%CI 2.1, 5.0%) respectively had a cTnI value above the recommended 99th centile (**Fig 1**).

Excluding those with cardiovascular disease had limited impact on the 99th centile for men or women for either assay (**Fig 3,** online **Supplemental Table s2**). For both cTnT and cTnI, excluding participants with outlying troponin values had little impact on estimates (online **Supplemental Table s3**). Further, using a rank model had little impact on the estimated 99th centiles (online **Supplemental Table s4**). Using a continuous model confirmed, and more finely modelled, the effect of older age on 99th centiles of both troponins (online **Supplemental Figure s2**).

Discussion

We report several important findings that are relevant to clinical practice, and the potential future use of troponin in CVD risk prediction. First, just over half of participants had detectable concentrations of cTnT whereas three quarters had detectable concentrations of cTnI. Troponin was undetectable in the majority of younger women. Second, there was a surprisingly weak association between cTnT and cTnI, particularly after taking into account the fact that both are higher in older people and in men. This expands on previous work

suggesting the 99th centiles are not biologically equivalent for the two troponins. Third, we observed important differences in the associations of cardiovascular disease risk factors with cTnT and cTnI respectively, although they had similar associations with a composite cardiovascular disease risk score overall. Therefore, these assays may be capturing distinct predictive information in the general population. Finally, the 99th centiles recommended for use in clinical practice, particularly for cTnT, may not be appropriate in older persons. This could lead to over-diagnosis of myocardial infarction and more referrals for further clinical investigation if troponin is used as a screening tool in the general population. These findings may inform the selection of cTnT or cTnI tests for both diagnosis and cardiovascular risk screening.

Since the cardiac troponin heterotrimer exists as a complex in the same cardiomyocytes (19), the modest inter-relationship of cTnT and cTnI, and their distinct associations with risk factors for myocardial damage, may be viewed as somewhat surprising. Previous reports demonstrate that they have distinct release kinetics in the acute setting; cTnI peaks earlier following MI (20). In addition, following intense aerobic exercise, both cTnT and cTnI increase, although it appears cTnI may continue to rise at least 5 hours after exercise, whereas cTnT plateaus earlier (21). There is therefore evidence that kinetics of release of troponins into the blood stream may explain at least part of the differences between cTnT and cTnI in our study. Although a recent study level meta-analysis suggested similar associations of cTnT and cTnI with CVD risk (*P* for interaction=0.027 suggesting that cTnT may be more strongly associated with risk) (4), our work comparing the two markers within individuals suggests that differences between studies might bias this comparison. Further work is required to investigate the distinct causal determinants of increased circulating troponins in the general

312 population as well as to identify the comparative (and combined) clinical utility of cTnT and
313 cTnI in cardiovascular disease risk prediction in the general adult population.
314
315 The slight increase in cTnT and cTnI in young (age 18-29) men compared to men in their 30s
316 and 40s is also potentially surprising. However, troponins are influenced by left ventricular
317 mass, which is likely to be higher in young men (22, 23). The inverse association of both
318 cTnT and cTnI with current smoking that we report is consistent with data from the HUNT
319 study, which reported that cTnI was inversely associated with smoking after adjustment for
320 multiple potential confounding variables. (24) Data from the ARIC study raise a more
321 complex picture for cTnT, reporting a weak inverse association between cTnT and current
322 smoking, but a positive association with the number of pack-years. (25) Our data also show
323 an inverse association of cTnT, but not cTnI, with total cholesterol. Similar data for cTnT has
324 been previously reported in the older men from the British Regional Heart Study, although a
325 positive association was observed in younger participants from the MIDSPAN family study
326 (26). The positive association of cTnI with total cholesterol appears more consistent; indeed,
327 it has been demonstrated in a randomized controlled trial that statin treatment rapidly causes
328 decline in cTnI (1).
329
330 Our results also highlight that although the recommended 99th centiles for cTnT and cTnI
331 (16) fit generally well with GS:SFHS results for those aged <60 years, such cut-offs are much
332 higher beyond the age of 60 years for cTnT, and beyond the age of 70 for cTnI. For instance,
333 fully a third of men over the age of 70 had a cTnT above the predefined 99th centile of
334 15.5ng/L. In elderly people, increased troponin concentrations may reflect subclinical
335 myocardial injury (27). If troponin is to be utilized for population level cardiovascular disease
336 risk screening, this means older patients will be more frequently identified with increased

troponins on screening, and will be more likely to be referred for further cardiovascular testing such as echocardiography or coronary angiography. This may be entirely appropriate as raised troponin in this group may well reflect undiagnosed structural or coronary heart disease (28). Clinicians therefore need to be aware of the effect of age on troponin reference concentrations, and further evaluation of the 99th centile, or biological equivalents, in older patients with chest pain would be welcome. Use of serial testing of troponin may be helpful to demonstrate myocardial injury is chronic in an individual.

Strengths of this study include the ability to directly compare cTnT and cTnI in the general population as well as the large size, and wide age range, which allows stratified analysis of the 99th centiles with sufficient power in most strata according to guidelines (6). Both troponins were measured using assays comparable to most clinical biochemistry departments. Weaknesses include the family structure of GS:SFHS , although we demonstrate this had little impact on data in terms of clustering within families. A large proportion of participants had undetectable troponin. This is suboptimal for continuous statistical analyses, but is an important feature in describing the utility of the measurements in the general population. Analyses are cross-sectional and thus we can only comment on the general trends of associations with risk factors with troponin concentrations without causal inferences. The 99th centiles for cTnT and cTnI are not biological equivalents (29,30); they are observational cutoffs taken from distinct populations. Direct comparison of the differences between the troponins based only on the cutoffs may therefore be misleading, although continuous models support our analyses as well.

In conclusion, in a large cohort study from a general population, cTnT and cTnI concentrations are differentially associated with cardiovascular risk factors and are weakly

correlated with each other. Existing sex specific 99th centiles are broadly appropriate for both men and women up to the age of 60 years. Beyond the age of 70, the 99th centile is approximately 3-fold higher for cTnT in both men and women and 2-fold higher for cTnI in women.

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Figure Legends

Figure 1

Age and sex stratified percentage of participants with undetectable cTnT (<3ng/L) and cTnI (<1.2ng/L) in upper panels (red), and percentage of participants above the recommended 99th centile for cTnT and cTnI in lower panels (green).

Figure 2

Illustrative scatter graph of the distributions of cTnT and cTnI, with red dotted line indicating the recommended (non-sex specific) 99th centile (n=19,501). Results below the LoD are reported as half of the limit of detection (i.e. 1.5ng/L for cTnT and 0.6ng/L for cTnI). Axes are on Log2 scale.

Figure 3

Age and sex stratified predicted troponin 99th centiles within GS:SFHS (with 90% CI), with sensitivity analysis excluding those with cardiovascular disease. Black dotted line indicates the non-sex specific recommended 99th centile, red dotted line indicates the recommended 99th centile for women only, blue dotted line the 99th centile for men only.

Table 1 Population characteristics among men, stratified by status above or below the recommended sex specific 99th centile of cTnT and cTnI

	hs-cTnT						hs-cTnI					
	Women <9ng/L	Women ≥9ng/L	*P*-value	Men <15.5ng/L	Men ≥15.5ng/L	*P*-value	Women <15.6ng/L	Women ≥15.6ng/L	*P*-value	Men <34.2ng/L	Men ≥34.2ng/L	*P*-value
	n=10478	n=897		n=7830	n=296		n=11260	n=115		n=8043	n=83	
Age	46.2±14.2	59.4±15.8	0.0001	46.3±14.8	61.8±17.2	<0.0001	47.1±14.8	56.9±15.8	0.0001	46.8±15.2	51.1±17.7	0.0098
Body mass index (kg/M2)	26.4±5.6	27.3±5.7	<0.0001	26.8±4.5	28.2±5.1	<0.0001	26.5±5.6	26.5±5.8	0.955	26.9±4.5	27.4±5	0.2692
Systolic blood pressure (mmHg)	127.2±17.8	137.4±21.4	<0.0001	135.9±15.7	142.0±20.5	<0.0001	127.9±18.2	138.4±23.4	<0.0001	136.0±15.9	141.8±17.8	0.0064
Total cholesterol (mg/dl)	200±42	201±44	0.6167	194±41	177±40	<0.0001	200±42	200±45	0.969	194±41	187±42	0.132
HDL-cholesterol (mg/dl)	61±16	63±18	0.0004	50±13	50±15	0.762	61±16	62±15	0.6536	50±13	48±13	0.0907
SIMD score	12 (7,24)	12 (7,25)	0.3336	11 [7, 21]	11 [6,19]	0.445	12 (7,24)	12 (8,25)	0.586	11 [7, 21]	11 [7, 21]	0.930
Creatinine (mg/dl)	0.73±0.12	0.79±0.30	<0.0001	0.91±0.15	1.06±0.36	<0.0001	0.74±14	0.78±19	0.0004	0.92±0.16	0.92±0.16	0.854
Current smoker	1843 (17.6%)	119 (13.3%)	0.0010	1617 (20.7%)	29 (9.8%)	<0.0001	1955 (17.4%)	7 (6.0%)	0.0015	1639 (20.4%)	7 (8.4%)	0.0071
Baseline heart disease or stroke	287 (2.7%)	82 (9.1%)	<0.0001	444 (5.7%)	64 (21.6%)	<0.0001	355 (3.2%)	14 (12.2%)	<0.0001	495 (6.2%)	13 (15.7%)	0.0004

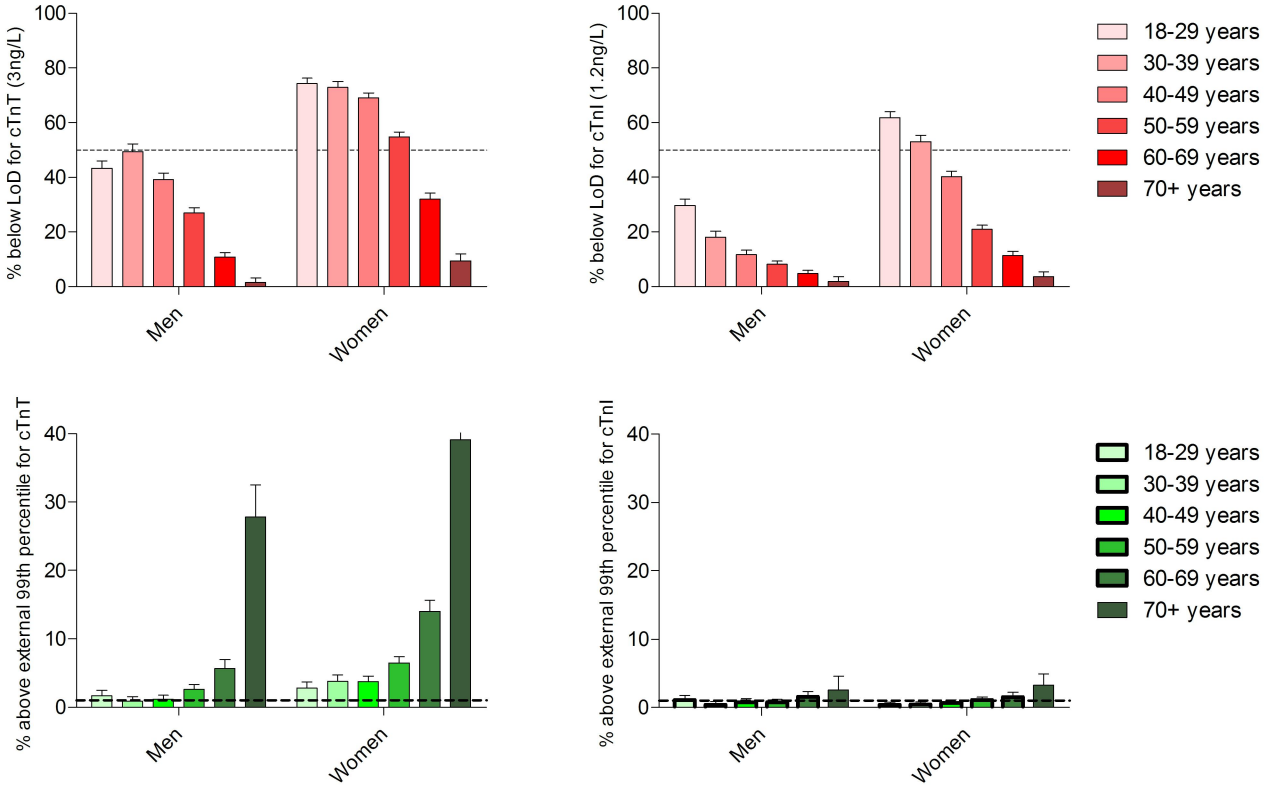
Baseline diabetes	196 (1.9%)	60 (6.7%)	<0.0001		258 (3.3%)	48 (16.2%)	<0.0001		249 (2.2%)	7 (6.1%)	0.0053		302 (3.8%)	4 (4.8%)	0.6123
Baseline use of cholesterol lowering medications	488 (4.7%)	116 (12.9%)	<0.0001		609 (7.8%)	69 (23.3%)	<0.0001		591 (5.2%)	13 (11.3%)	0.004		661 (8.2%)	17 (20.5%)	<0.0001
Baseline use of blood pressure lowering medications	680 (6.5%)	152 (16.9%)	<0.0001		664 (8.5%)	78 (26.4%)	<0.0001		815 (7.2%)	17 (14.8%)	0.002		726 (9%)	16 (19.3%)	0.0013

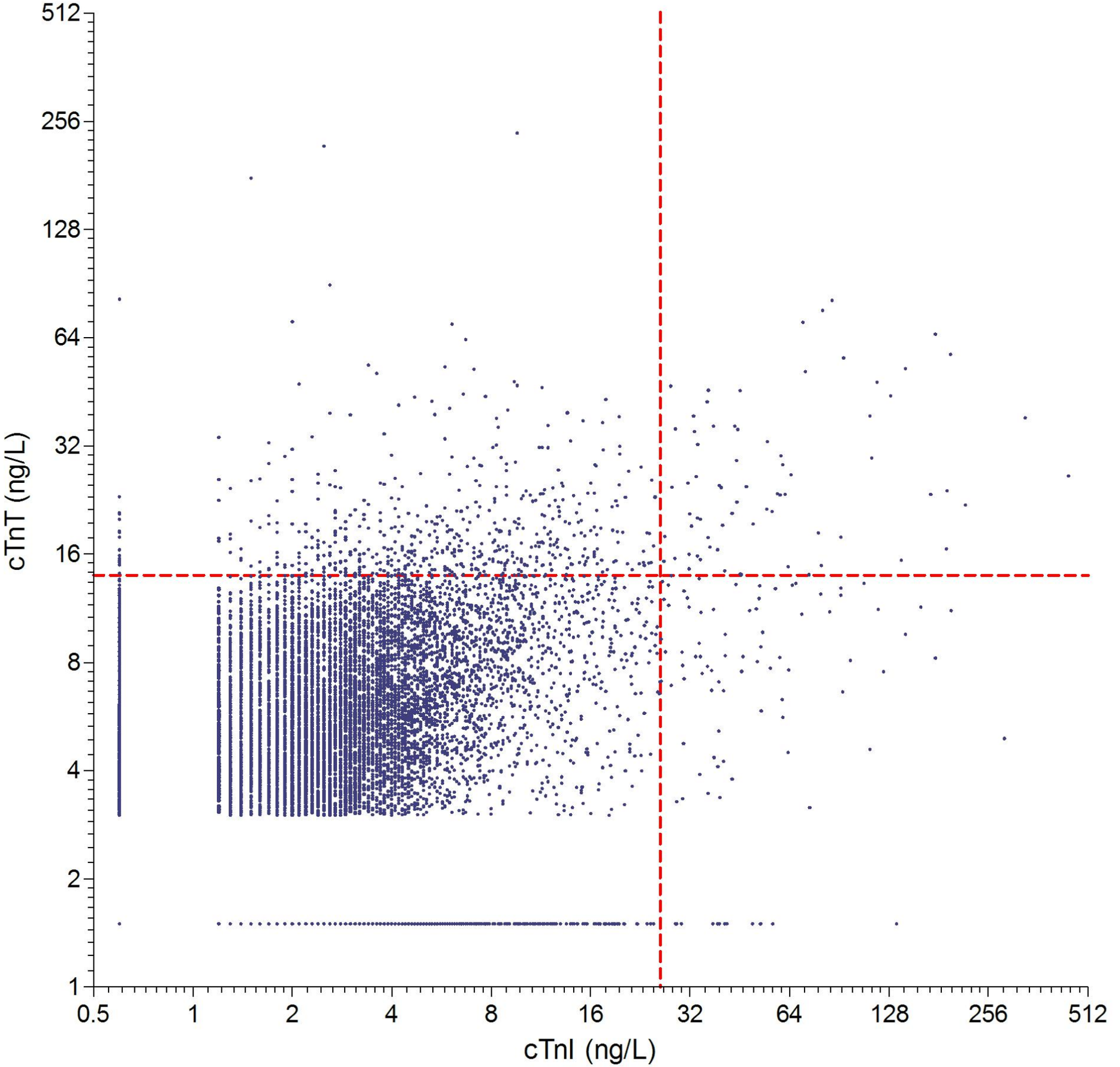
Data are mean ±standard deviation, median [interquartile range], or n (%). To convert total cholesterol and HDL cholesterol to mmol/l multiply by 0.02586. To convert creatinine to μmol/L multiply by 88.4

Table 2 Univariable and age and sex adjusted association of cardiovascular disease risk factors with cTnT and cTnI (n=19,501). A positive percentage indicates a relative increase in troponin for a corresponding increase in the risk factor, while a negative percentage indicates an inverse association.

	Univariable model			Age and sex adjusted model		
	cTnT	cTnI		cTnT	cTnI	*P*-value comparing association with cTnT vs. cTnI
Age (per 5 years) [a]	9.5% (9.2, 9.9)	11.3% (10.9, 11.7)		9.6% (9.3, 10.0)	11.4% (11.1, 11.8)	<0.0001
Male sex [a]	44.0% (41.8, 46.2)	53.1% (50.7, 55.5)		44.7% (42.7, 46.8)	54.0% (51.7, 56.2)	<0.0001
Body mass index (per kg/m^2)	1.5% (1.2, 1.7)	2.8% (2.6, 3.1)		0.3% (0.0, 0.5)	1.4% (1.2, 1.7)	<0.0001
Systolic blood pressure (per 5mmHg)	5.7% (5.4, 6.1)	8.6% (8.3, 9.0)		1.1% (0.8, 1.5)	3.7% (3.3, 4.0)	<0.0001
Total cholesterol (per 10mg/dl)	-1.0% (-1.4, -0.7)	1.0% (0.7, 1.4)		-1.7% (-2.0, -1.5)	0.5% (0.2, 0.8)	<0.0001
HDL-cholesterol (per 5mg/dl)	-1.0% (-1.4, -0.6)	-2.1% (-2.6, -1.7)		0.4% (0.0, 0.8)	-0.3% (-0.7, 0.2)	0.003
SIMD score (per 10 units)	-2.4% (-3.2, -1.7)	-2.0% (-2.9, -1.2)		-0.4% (-1.2, 0.3)	0.4% (-0.4, 1.1)	0.0486
Creatinine (per 0.1mg/dl)	9.4% (8.3, 10.5)	10.9% (9.5, 12.4)		2.7% (1.8, 3.6)	3.3% (2.5, 4.1)	0.239
Current smoker	-17.1% (-19.8, -14.3)	-19.8% (-22.8, -16.8)		-10.6% (-13.2, -8.0)	-12.0% (-14.8, -9.5)	0.3331
Baseline heart disease or stroke	59.5% (53.7, 65.2)	66.3% (60.0, 72.7)		22.6% (17.6, 27.6)	22.2% (16.3, 28.0)	0.8883
Baseline diabetes	59.4% (52.1, 66.7)	34.5% (26.6, 42.5)		32.7% (26.4, 39.0)	2.1% (-4.9, 9.1)	<0.0001
Baseline use of cholesterol lowering medications	57.2% (52.6, 61.8)	61.1% (56.5, 65.7)		22.4% (18.1, 26.7)	19.2% (14.8, 23.6)	0.2178
Baseline use of blood pressure lowering medications	55.3% (51.1, 59.4)	65.3% (61.2, 69.3)		25.2% (21.3, 29.0)	29.4% (25.4, 33.3)	0.0766
Cardiovascular disease risk score (per 1% increase in 10 year risk) [b]	2.8% (2.6, 2.9)	2.7% (2.6, 2.9)		-	-	-

[a] Age effect adjusted for sex, and sex effect adjusted for age [b] Composite cardiovascular disease risk score calculated in people without cardiovascular disease aged ≥35 years (n=14,257).


% below LoD for cTnT (3ng/L)
100
80
60
40
20
0
Men
Women
% below LoD for cTnI (1.2ng/L)
18-29 years
30-39 years
40-49 years
50-59 years
60-69 years
70+ years
% above external 99th percentile for cTnT
40
30
20
10
% above external 99th percentile for cTnI


512
256
128
64
32
16
8
4
2
1
cTnT (ng/L)
0.5
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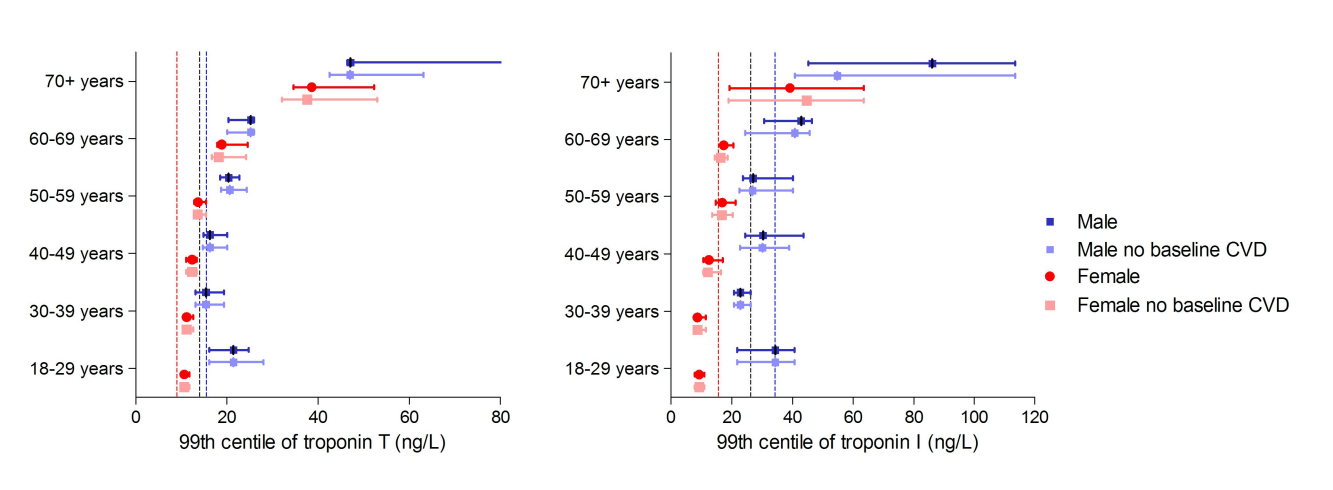
cTnI (ng/L)


70+ years
60-69 years
50-59 years
40-49 years
30-39 years
18-29 years
0
20
40
60
80
99th centile of troponin T (ng/L)
70+ years
60-69 years
50-59 years
40-49 years
30-39 years
18-29 years
0
20
40
60
80
100
120
99th centile of troponin I (ng/L)
Male
Male no baseline CVD
Female
Female no baseline CVD