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

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BACKGROUND: Few data compare cardiac troponin T (cTnT) and cardiac troponin I (cTnI) in a general population. We sought to 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 with 99th centiles for cTnT (men, 15.5 ng/L; women, 9.0 ng/L) and cTnI (men, 34.2 ng/L; women, 15.6 ng/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, body mass index, and systolic blood pressure ($P < 0.0001$ for all vs cTnT). cTnT was more strongly associated with diabetes ($P < 0.0001$ vs 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. The 99th centiles currently in use are broadly appropriate for men and women up to but not beyond the age of 60 years.

High-sensitivity (hs)[11] assays for the measurement of cardiac troponin T (cTnT) and cardiac 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 for patients with both acute and stable cardiovascular diseases *(1–3)* and may have a role in screening the general population *(1, 4)*.

The IFCC recently updated their guidance on the use of cardiac troponin testing and the criteria used to define an hs-cTn assay *(5)*, which must have adequate precision (<10% CV) at the 99th centile and be able to measure cTn concentrations above the limit of detection in >50% of apparently healthy men and women. They also recommend at least 300 participants in any age- or sex-specific stratum 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

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[11] Nonstandard abbreviations: hs, high sensitivity; cTnT, cardiac troponin T; cTnI, cardiac troponin I; GS:SFHS, Generation Scotland Scottish Family Health Study; SBP, systolic blood pressure; BMI, body mass index; SIMD, Scottish Index of Multiple Deprivation; LoD, limit of detection.

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 hs-cTn assays include the Roche hs-cTnT and the Abbott hs-cTnI assay. As such, often the service provider to local biochemistry laboratories dictates whether cTnT or cTnI is 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 hs 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 to 2010, potential participants were identified at random from those 35 to 65 years of age from the lists of collaborating general medical practices in Scotland, and invited to participate. Participants were also asked to identify ≥1 first-degree relatives 18 years or older who would be able to participate. A total of 21 476 participants between 18 and 98 years of age attended a research clinic in 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/our-resources/scottish-family-health-study). Past medical history, including a diagnosis of diabetes mellitus (type 1 or type 2) and cardiovascular disease (previous 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 °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 ≥35 years of age 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 analyzers, respectively. Both assays were calibrated and quality controlled using the manufacturer's reagents. CVs for cTnI were 6.2% for the low control, 6.0% for intermediate control, and 4.6% for high control. CVs 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 (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 1 decimal place. The limit of detection (LoD) of the cTnT assay is set to 3.0 ng/L by the manufacturer, while we reported anything <1.2 ng/L for cTnI as below the LoD *(16)*. Results below the LoD are reported as half of the LoD (i.e., 1.5 ng/L for cTnT and 0.6 ng/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 and 15.5 ng/L in men *(10)*; cTnI, 15.6 ng/L in women and 34.2 ng/L in men *(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 2000*g* for 5 min before assay.

STATISTICAL ANALYSIS

By clustered family group, the intraclass 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. Therefore, familial clustering was not considered a factor in further analyses. Missing data for classical risk factors [SIMD (most frequently missing) had 1134 missing observations] were imputed by multiple chained imputations over 10 data sets; these were used for all analyses with classical risk factors.

Associations of classical cardiovascular disease risk factors with external sex-specific increased (>99th centile) troponins were illustrated, using categorical variables expressed as frequencies and percentages, and continuous variables as medians (interquartile range) or mean (SD). Differences between these categorized troponin groups were tested using χ^2, rank sum test, or *t*-test, respectively. Associations of continuous classical risk factors and the

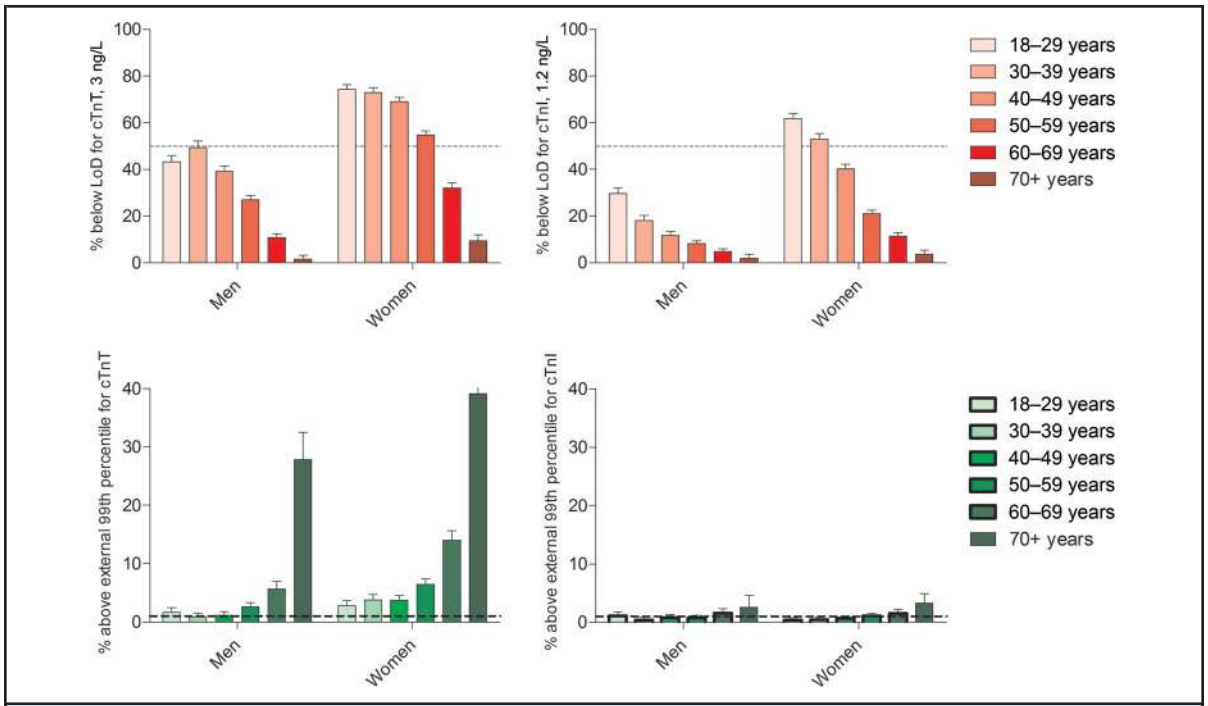

Fig. 1. Age- and sex-stratified percentage of participants with undetectable cTnT (<3 ng/L) and cTnI (<1.2 ng/L) in top panels (red), and percentage of participants above the recommended 99th centile for cTnT and cTnI in lower panels (green).

cardiovascular disease risk score with log-transformed distributions of both troponins were tested using univariable linear regression with robust standard errors and 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 κ 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% CIs (as recommended by Clinical and Laboratory Standards Institute document C28-A3) around the estimates, were determined by bootstrapping 5000 samples in each age- and sex-specific stratum. 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 SDs from the mean, and the second used a rank model to obtain the GS:SFHS 99th 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 99th centile of each troponin (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue11). All statistics were performed using STATA version 14.2.

Results

POPULATION CHARACTERISTICS

Of the 21476 GS:SFHS participants, 19501 participants provided a serum sample and yielded a measurement for both cTn assays (90.8%). The median cTnT in the cohort was 3.3 ng/L (interquartile range, 1.5–6.0), and the median cTnI was 1.9 ng/L (interquartile range, 0.6–3.1). Detectable concentrations of cTnT and cTnI were found in 10395 participants (53.3%) and 14579 (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 the ≤50 to 59 year age-groups had undetectable cTnT, and >50% of women in the ≤30 to 39 year age-groups 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

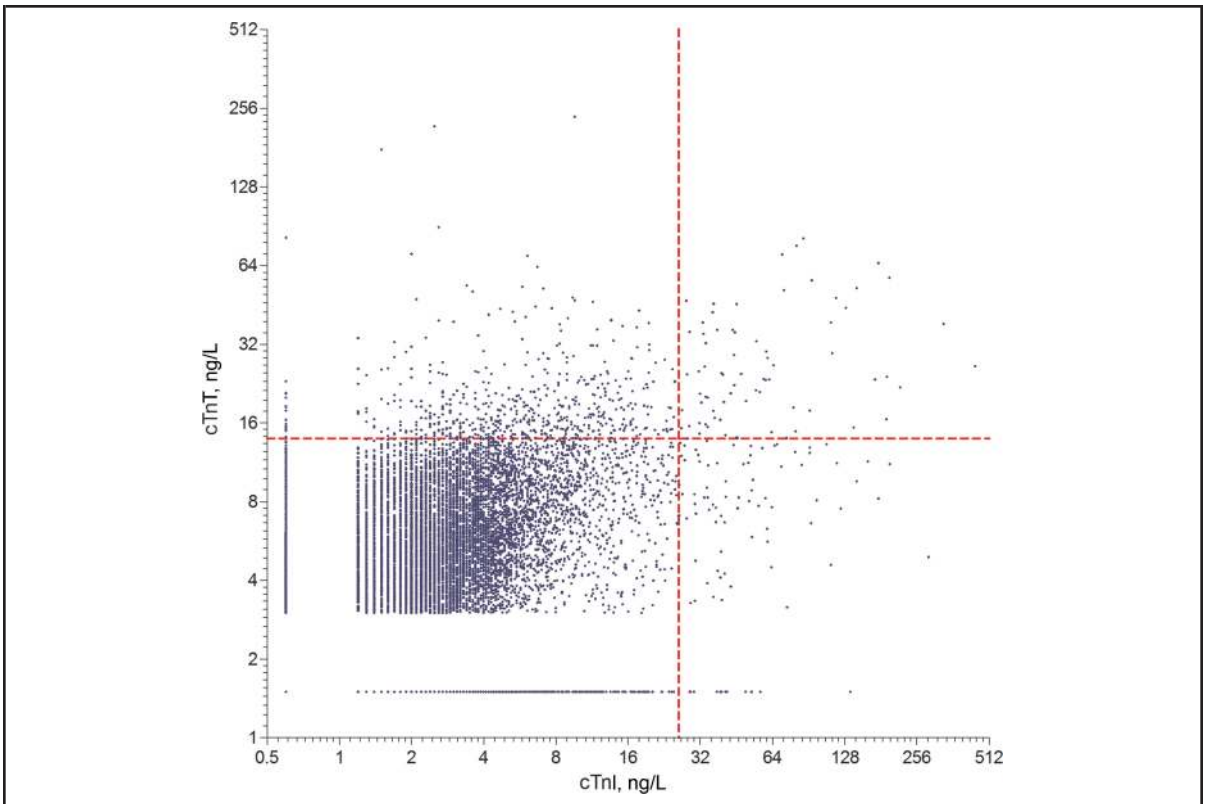

Fig. 2. Illustrative scatter graph of the distributions of cTnT and cTnI, with red dotted line indicating the recommended (non–sex-specific) 99th centile (n = 19 501).
Results below the LoD are reported as half of the LoD (i.e., 1.5 ng/L for cTnT and 0.6 ng/L for cTnI). Axes are on Log2 scale.

β-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% (see Fig. 1 in the online Data Supplement). 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 8855 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 κ = 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% (κ = 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 (15.5 ng/L and 9.0 ng/L, respectively). These participants were older, had a higher BMI, higher SBP, 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 (34.2 ng/L and 15.6 ng/L, respectively). Increased cTnI was associated with older age, higher SBP, 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

Although cardiovascular risk factors were generally associated with both troponin measures, in age- and sex-adjusted analyses, stronger positive associations were

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 <9 ng/L	Women ≥9 ng/L		Men <15.5 ng/L	Men ≥15.5 ng/L		Women <15.6 ng/L	Women ≥15.6 ng/L		Men <34.2 ng/L	Men ≥34.2 ng/L	
	n = 10 478	n = 897	*P* value	n = 7830	n = 296	*P* value	n = 11 260	n = 115	*P* value	n = 8043	n = 83	*P* value
Age, years	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
BMI, kg/m^2	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
SBP, 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 ± SD, 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.

found for cTnI with age, male sex, BMI, and SBP ($P < 0.0001$ for all vs cTnT) (Table 2). cTnT was more strongly positively associated with diabetes, inversely associated with total cholesterol, and positively associated with HDL cholesterol ($P < 0.0001$ vs 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 SIMD. Both troponins were strongly inversely associated with current smoking (Table 2). Sensitivity analysis removing those with cardiovascular disease, diabetes, or taking cholesterol-lowering or blood pressure medications yielded broadly consistent results, although cTnI became more strongly associated with creatinine ($P = 0.001$ vs cTnT) (see Table 1 in the online Data Supplement). A composite 10-year cardiovascular disease risk score calculated in participants without prevalent cardiovascular disease and ≥35 years of age 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 with the recommended 99th centile (Fig. 3).

The observed 99th centile for cTnT was 21.4 ng/L for men <30 years of age, 15.4 ng/L at 30 to 39 years of age, 16.3 ng/L at 40 to 49 years of age, 20.4 ng/L at 50 to 59 years of age, 25.2 ng/L at 60 to 69 years of age, and 47.1 ng/L at ≥70 years of age (Fig. 3; see also Table 2 in the online Data Supplement). As such, the observed 99th centile was approximately double the recommended 99th centile in men 60 to 69 years of age and triple in men ≥70 years of age. Among men 60 to 69 and ≥70 years of age, 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 10.7 ng/L, 11.2 ng/L, 12.4 ng/L, 13.7 ng/L, 18.9 ng/L, and 38.6 ng/L. As such, the observed 99th centile was also approximately double the recommended 99th centile in women 60 to 69 years of age and triple in women ≥70 years of age (Fig. 3; see Table 2 in the online Data Supplement). Among women 60 to 69 and ≥70 years of age, 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 34.4 ng/L for men <30 years, 22.9 ng/L at 30 to 39 years of age, 30.4 ng/L at 40 to 49 years of age, 27.0 ng/L at 50 to 59 years of age, 42.9 ng/L at 60 to 69 years of age, and 86.2 ng/L in those ≥70 years of age (Fig. 3; see also Table 2 in the online Data Supplement). As such, the observed 99th centile was approximately double the recommended 99th centile in men ≥70 years of age. Among men 60 to 69 and ≥70 years of age, 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 9.3 ng/L, 8.7 ng/L, 12.5 ng/L, 16.9 ng/L, 17.4 ng/L, and 39.2 ng/L. As such, the observed 99th centile was also approximately double the recommended 99th centile in women >70 years of age (Fig. 3; see also Table 2 in the online Data Supplement). Among women 60 to 69 and ≥70 years of age, 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; see Table 2 in the online Data Supplement). For both cTnT and cTnI, excluding participants with outlying troponin values had little impact on estimates (see Table 3 in the online Data Supplement). Further, using a rank model had little impact on the estimated 99th centiles (see Table 4 in the online Data Supplement). Using a continuous model confirmed, and more finely modeled, the effect of older age on 99th centiles of both troponins (see Fig. 2 in the online Data Supplement).

Discussion

We report several important findings that are relevant to clinical practice and the potential future use of troponin in cardiovascular disease 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 most younger women. Second, there was a surprisingly weak association between cTnT and cTnI, particularly after considering both are higher in older people and men. This expands on previous work suggesting the 99th centiles are not biologically equivalent for the 2 troponins. Third, we observed important differences in the associations of cardiovascular disease risk factors with cTnT and cTnI, 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 overdiagnosis 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

Table 2. Univariable and age- and sex-adjusted association of cardiovascular disease risk factors with cTnT and cTnI (n = 19 501).[a]

	Univariable model		Age- and sex-adjusted model		
	cTnT	cTnI	cTnT	cTnI	*P* value comparing association with cTnT vs cTnI
Age (per 5 years)[b]	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[b]	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
BMI (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
SBP (per 5 mmHg)	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 10 mg/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 5 mg/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 0.1 mg/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)[c]	2.8% (2.6, 2.9)	2.7% (2.6, 2.9)	–	–	–

[a] A positive percentage indicates a relative increase in troponin for a corresponding increase in the risk factor, whereas a negative percentage indicates an inverse association.
[b] Age effect adjusted for sex, and sex effect adjusted for age.
[c] Composite cardiovascular disease risk score calculated in people without cardiovascular disease ≥35 years of age (n = 14 257).

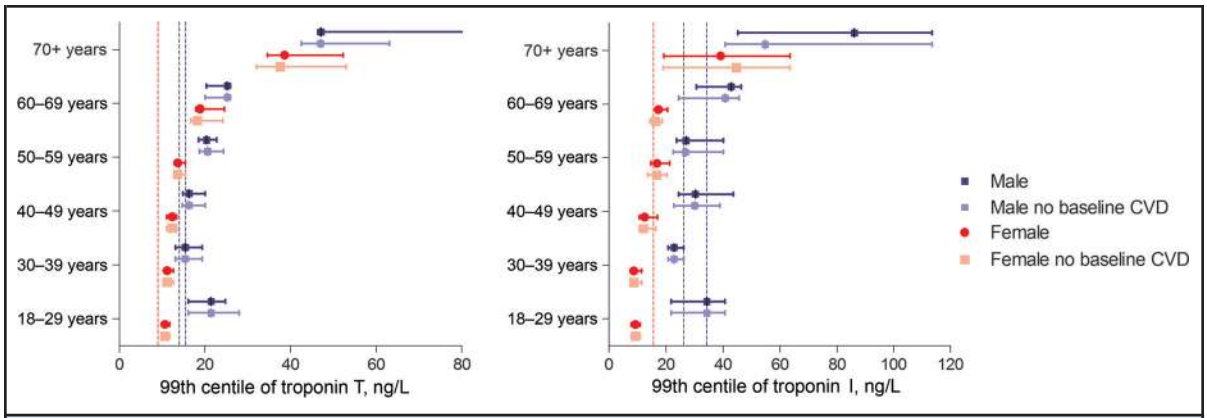

Fig. 3. Age- and sex-stratified predicted troponin 99th centiles within GS:SFHS (with 90% CI), with sensitivity analysis excluding those with cardiovascular disease.

The black dotted line indicates the non–sex-specific recommended 99th centile; the red dotted line indicates the recommended 99th centile for women only; and the blue dotted line indicates the 99th centile for men only.

cTnT or cTnI tests for both diagnosis and cardiovascular risk screening.

Because the cardiac troponin heterotrimer exists as a complex in the same cardiomyocytes *(19)*, the modest interrelationship of cTnT and cTnI, as well as 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 after myocardial infarction *(20)*. In addition, after intense aerobic exercise, both cTnT and cTnI increase, although it appears cTnI may continue to rise at least 5 h after exercise, whereas cTnT plateaus earlier *(21)*. Therefore, there is evidence that kinetics of release of troponins into the bloodstream 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 cardiovascular disease risk (P for interaction = 0.027, suggesting that cTnT may be more strongly associated with risk) *(4)*, our work comparing the 2 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 population, as well as to identify the comparative (and combined) clinical utility of cTnT and cTnI in cardiovascular disease risk prediction in the general adult population.

The slight increase in cTnT and cTnI in young (ages 18–29 years) men compared with men in their 30s and 40s is also potentially surprising. However, troponins are influenced by left ventricular mass, which is likely to be higher in young men *(22, 23)*. The inverse association of both cTnT and cTnI with current smoking that we report is consistent with data from the HUNT study, which reported that cTnI was inversely associated with smoking after adjustment for multiple potential confounding variables *(24)*. Data from the ARIC study raise a more complex picture for cTnT, reporting a weak inverse association between cTnT and current smoking but a positive association with the number of pack-years *(25)*. Our data also show an inverse association of cTnT, but not cTnI, with total cholesterol. Similar data for cTnT have been previously reported in the older men from the British Regional Heart Study, although a positive association was observed in younger participants from the MIDSPAN family study *(26)*. The positive association of cTnI with total cholesterol appears more consistent; indeed, it has been demonstrated in a randomized controlled trial that statin treatment causes rapid decline in cTnI *(1)*.

Our results also highlight that although the recommended 99th centiles for cTnT and cTnI *(16)* fit generally well with GS:SFHS results for those <60 years of age, such cutoffs are much higher beyond the age of 60 years for cTnT and beyond the age of 70 years for cTnI. For instance, fully one-third of men over the age of 70 years had a cTnT above the predefined 99th centile of 15.5 ng/L. In elderly people, increased troponin concentrations may reflect subclinical myocardial injury *(27)*. If troponin is to be used for population-level cardiovascular disease 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)*. There-

fore, clinicians 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; thus, we can comment only 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. Therefore, direct comparison of the differences between the troponins based only on the cutoffs may 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 years, 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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