ORIGINAL RESEARCH ARTICLE

Sex Differences in Cardiac Troponin Trajectories Over the Life Course

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BACKGROUND: Cardiac troponin concentrations are lower in women than men. We examined whether age- and risk factor-related changes in cardiac troponin over the life course differ by sex and if the trajectory of cardiac troponin was informative in respect of cardiovascular outcomes in women and men in the general population.

METHODS: In the Whitehall II cohort, high-sensitivity cardiac troponin I concentrations were measured on 3 occasions over a 15-year period. Using linear mixed-effects models, the sex-specific trajectories of cardiac troponin were evaluated, and the relationship with conventional cardiovascular risk factors determined. Using multistate joint models, the association between sex-specific trajectories of cardiac troponin and a composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death was evaluated.

RESULTS: In 2142 women and 5151 men (mean, 58±7 and 57±7 years of age, respectively), there were 177 (8.3%) and 520 (10.1%) outcome events, respectively, during a median follow-up of 20.9 (25th to 75th percentile, 15.8–21.3) years. Cardiac troponin concentrations were persistently lower in women than in men (median baseline concentration: 2.4 [25th to 75th percentile, 1.7–3.6] ng/L versus 3.7 [25th to 75th percentile, 2.6–5.8] ng/L, respectively, $P < 0.001$), with women exhibiting a relatively larger increase with advancing age as compared with men ($P_{interaction} < 0.001$). Apart from age, a significant and divergent interaction with sex was found for the association between cardiac troponin and body mass index (BMI) ($P_{interaction} = 0.008$) and diabetes ($P_{interaction} = 0.003$). During follow-up, cardiac troponin concentrations were associated to the outcome in both women and men (adjusted hazard ratio per 2-fold difference [95% CI, 1.34 (1.17–1.52) and 1.30 (1.21–1.40), respectively], $P_{interaction} = 0.752$). The slope of cardiac troponin was significantly associated with the outcome in women, but not in men (adjusted hazard ratio [95% CI, 2.70 (1.01–7.33) and 1.31 (0.62–2.75), respectively], $P_{interaction} = 0.250$).

CONCLUSIONS: Trajectories of cardiac troponin differ between women and men in the general population, with differing associations to conventional risk factors and cardiovascular outcomes. Our findings highlight the importance of a sex-specific approach when serial cardiac troponin testing is applied for cardiovascular risk prediction.

Key Words: age ■ cardiac troponin ■ cardiovascular risk prediction ■ general population ■ sex

S ex differences in preventative cardiovascular medicine are under explored. Recent evidence suggests that the distribution and burden of coronary atherosclerosis is similar in women and men, but that disease onset is delayed by a decade in women.[1] It is important that cardiovascular risk estimation systems recognize this important difference between women and men to ensure approaches to the prevention of cardiovascular disease are equitable.

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Clinical Perspective

What is New?

- We report the sex-specific trajectories of high-sensitivity cardiac troponin I over the life course, and evaluated if the trajectory of cardiac troponin was informative in respect of cardiovascular outcomes in women and men in the general population.
- Cardiac troponin concentrations in women lag around a decade behind men, but women exhibit a steeper trajectory with advancing age.
- Trajectories of cardiac troponin differ between women and men in the general population, with differing associations to conventional risk factors and cardiovascular outcomes.

What Are the Clinical Implications?

- Use of the same cardiac troponin thresholds to guide risk of future cardiovascular events in women and men would not provide equivalent prediction.
- Our findings highlight the importance of a sex-specific approach when serial cardiac troponin testing is applied for cardiovascular risk prediction.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
HR	hazard ratio
ICD	International Classification of Diseases
MI	myocardial infarction

Cardiac troponin is a promising biomarker that may improve cardiovascular risk prediction in the general population.[2–10] With the introduction of high-sensitivity assays, differences in cardiac troponin levels in apparently healthy women and men became evident.[11–13] Although it is now established that cardiac troponin concentrations are lower in women than men in the general population,[11–14] whether changes in cardiac troponin concentration over the life course differ in women and men and how this impacts on cardiovascular risk prediction are unknown. We hypothesize that increases in cardiac troponin with age will be delayed in women compared to men. Insights into sex-specific trajectories and how these are influenced by established cardiovascular risk factors is necessary to guide the use of cardiac troponin in cardiovascular risk estimation systems in women and men.

Using the longitudinal Whitehall II cohort study, we conducted a comprehensive sex-specific analysis of cardiac troponin trajectories over the life course, evaluating their determinants and relationship with cardiovascular outcomes in the general population.

METHODS

Study Population

The Whitehall II study is an ongoing longitudinal observational cohort study of 10 308 British civil servants (6895 men and 3413 women) aged between 35–55 years old when first recruited in 1985.[15] Follow-up has continued over 13 phases, with the most recent assessment completed in 2019. Stored samples were available for cardiac troponin testing from participants assessed on 3 occasions in 1997 to 1999, 2007 to 2009, and 2012 to 2013. We included all participants who had at least 1 measure of cardiac troponin and considered each participant's first cardiac troponin measurement as baseline. The study was approved by the University College London Hospital Committee on the Ethics of Human Research (reference 85/0938), and the study was conducted according to the Declaration of Helsinki.

Clinical Characteristics

For each participant we collected clinical characteristics at baseline and during follow-up. We collected data for the following clinical characteristics: age, sex, ethnic origin (White/other than White), diabetes mellitus, systolic blood pressure, total cholesterol concentration, high-density lipoprotein concentration, low-density lipoprotein concentration, smoking status (never/former/current), BMI, and medication prescriptions (lipid modifying medication/antihypertensive medication/angiotensin-converting enzyme inhibitors inhibitors/antiplatelets/ betablockers). In addition, we collected female-specific data on the menopausal transition (ie, age at which periods had stopped) and the use of female sex-hormone medication (oral contraceptives and hormone replacement therapy).

Cardiac Troponin Measurements

Blood samples for each phase were handled according to a standardized protocol. Fasting venous blood samples were collected, centrifuged, and serum was stored in aliquots at −80 °C until batch analysis was performed. Cardiac troponin I concentrations were measured using the Siemens Atellica IM High Sensitivity Troponin I assay (Siemens Healthineers, Erlangen, Germany). This assay has a limit of blank of 0.5 ng/L, limit of detection of 1.6 ng/L and a limit of quantitation of 2.5 ng/L.[16] The sex-specific 99th percentile upper reference limits are 34 ng/L and 53 ng/L in women and men, respectively. For the analyses, cardiac troponin concentrations below the limit of blank of 0.5 ng/L were assigned a value at the limit of blank.

Clinical Outcomes

Outcomes were collected throughout the study period until March 2019 using the National Health Service Central Registry.[17] Nonfatal events were defined using the Hospital Episode Statistics database records were listed in the primary and secondary position up to March 2019.[18] The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death. Secondary outcomes were nonfatal MI, nonfatal stroke, cardiovascular death, non-cardiovascular death, and all-cause death. Clinical outcomes were defined using the 9th and 10th revision of the

International Classification of Diseases (ICD-9 and ICD-10): cardiovascular death (ICD 9: 340–459 or ICD-10: I00–I99), nonfatal MI (ICD-9: 410 or ICD-10: I21) and nonfatal stroke (ICD-9: 430, 431, 434, 436 or ICD-10 codes: I60, I61, I63, I64), and non-cardiovascular death (all other ICD codes).

Statistical Analysis

Continuous variables are presented as mean, standard deviation, or median, 25th to 75th percentile, as appropriate. Categorical variables are presented as absolute number (%).

We evaluated the temporal pattern of cardiac troponin in women and men over the middle-to-late adulthood life course using linear mixed-effects modeling. The distribution of cardiac troponin was skewed, and to achieve normal distribution we applied $\log_2$ transformation. Age was used as timescale and was entered as fixed effect and random effect in the model. Natural cubic splines in combination with likelihood ratio tests were used to assess non-linear associations. Average cardiac troponin values were estimated over a range of the 0.5th to the 99.5th percentile of age using the final linear mixed-effects model. An interaction term for sex and age was used to estimate the average cardiac troponin trajectories in women and men separately. Univariable and multivariable sex-specific linear mixed-effects models were used to evaluate the association of ethnicity and cardiovascular risk factors determined at baseline and during follow-up, including diabetes status, systolic blood pressure, total cholesterol, high-density lipoprotein, low-density lipoprotein, smoking status, and BMI with repeated measures of cardiac troponin. Repeated measures of the cardiovascular risk factors, assessed at time of cardiac troponin sampling, were entered in the models as fixed effects while repeated cardiac troponin measures were used as outcome. An interaction term for sex and the risk factor of interest was used to estimate associations with cardiac troponin in women and men separately.

Subsequently, we evaluated the sex-specific association of baseline cardiac troponin level and the rate of change during follow-up with the primary outcome. We estimated the sex-specific baseline cardiac troponin level and sex-specific slope parameter for each individual using linear mixed-effects modeling. Based on the results, we classified individuals into the following 4 groups: Group 1 = baseline level < median and change < median; Group 2 = baseline level < median and change ≥ median; Group 3 = baseline level ≥ median and change < median; and Group 4 = baseline level ≥ median and change ≥ median. The estimated median baseline concentration of cardiac troponin was 2.4 ng/L in women and 3.8 ng/L in men, and the median change in cardiac troponin concentration was a 4.4% increase per year in women and a 3.5% increase per year in men. The Kaplan-Meier method was applied to estimate the cumulative incidence of the primary outcome during follow-up, whereas log-rank test was used for between group comparisons. Non-cardiovascular death was considered as competing risk. Additionally, we applied sex-specific multistate joint modeling to evaluate the association between individual cardiac troponin trajectories and cardiovascular events in women and men separately. Joint modeling combines a linear mixed-effects model to describe the trajectory of a predictor with a time-to-event relative risk model to relate the estimated temporal pattern of a predictor with the hazard of the outcome of interest. In the context of repeated measurements, we not only studied the predictive value of cardiac troponin levels, but we also studied the predictive value of the slope of longitudinal trajectory (rate of change). Further details on the joint model application can be found in the Supplemental Material.[19] Regarding the joint model, we adjusted for sex and age in the linear mixed-effects models, whereas unadjusted and adjusted time-to-event models were explored. Adjustment factors included age, diabetes, total cholesterol levels, high-density lipoprotein levels, low-density lipoprotein levels, systolic blood pressure, and smoking status at baseline. Non-cardiovascular death was included in the multistate joint model as a competing risk. The results are presented as hazard ratios (HRs) and 95% confidence intervals per 2-fold difference in cardiac troponin levels and slope (change in cardiac troponin concentration per 5 years).

In secondary analyses, we assessed the relationship of cardiac troponin with the cumulative incidence of nonfatal MI, nonfatal stroke, or death from any cause. Using multistate joint models, the relationship between sex-specific trajectories of cardiac troponin and all-cause death and non-cardiovascular death was evaluated. In addition, we explored the effect of menopause on the cardiac troponin trajectory in women using linear mixed-effects models. We anchored the timescale to the menopausal transition (ie, age at which periods stopped) to facilitate the analysis of repeated cardiac troponin in a time interval relative to menopause. For this analysis, we adjusted for the use of female sex-hormones at the time of cardiac troponin sampling. Women who reported that their period stopped as a result of hysterectomy (womb only), chemotherapy, or radiation therapy were excluded from this analysis. To evaluate whether cardiac troponin trajectories in women and men differ in those who have a subsequent MI or stroke, we conducted a sex-specific trajectory analysis where the primary outcome and individual components of the primary outcome were included as interaction terms in the linear mixed-effects models. Finally, we evaluated the sex-specific trajectories by ethnicity (White versus non-White).

Single imputation using mice was applied for the clinical characteristics with missing values using other individual's clinical and outcome data. Statistical analysis was performed in R version 4.2.0 using packages "mice," "nlme," "cmprsk," "survival," and "JMbayes2." Further details on R code for linear mixed-effects models and multistate joint models can be found in the Supplemental Material and the original R code for this study is available upon request.

RESULTS

Clinical Characteristics of Study Population

The total study population comprised 7293 individuals of which 2142 (29.4%) were women and 5151 (70.6%) were men (58±7 and 57±7 years of age at baseline, respectively). At baseline, women had a higher prevalence of diabetes (5.0% versus 4.4%) and were more often current smokers (11.4% versus 8.5%) compared to men (Table 1). Moreover, women were prescribed more antihypertensive medication (19.7% versus 16.6%) but fewer antiplatelet agents (4.9% versus 8.1%) than men.

Table 1.   Baseline Characteristics of Study Population

	Total study population		No primary outcome		Primary outcome	
	Women n=2142	Men n=5151	Women n=1965	Men n=4631	Women n=177	Men n=520
Age (y)	58.1 (7.4)	57.3 (7.0)	57.8 (7.4)	57.0 (7.0)	61.8 (6.5)	60.0 (6.6)
Ethnic origin (% other than White)	298 (13.9)	327 (6.4)	260 (13.2)	272 (5.9)	38 (21.6)	55 (10.6)
Diabetes mellitus (% yes)	108 (5.0)	225 (4.4)	87 (4.4)	189 (4.1)	21 (11.9)	36 (6.9)
Systolic blood pressure (mm Hg)	122.8 (17.9)	124.3 (16.2)	122.0 (17.7)	123.8 (16.0)	131.8 (17.9)	128.7 (17.1)
Total cholesterol (mmol/L)	5.9 (1.1)	5.8 (1.1)	5.9 (1.1)	5.7 (1.1)	6.1 (1.3)	5.9 (1.1)
High-density lipoprotein (mmol/L)	1.7 (0.4)	1.4 (0.4)	1.7 (0.4)	1.4 (0.4)	1.6 (0.4)	1.4 (0.4)
Low-density lipoprotein (mmol/L)	3.7 (1.0)	3.7 (1.0)	3.7 (1.0)	3.7 (1.0)	3.8 (1.2)	3.8 (1.0)
Smoker (%)						
Current smoker	235 (11.4)	430 (8.5)	200 (10.6)	366 (8.1)	35 (20.8)	64 (12.5)
Ex-smoker	706 (34.2)	2,294 (45.4)	658 (34.7)	2,056 (45.2)	48 (28.6)	238 (46.7)
Never-smoker	1,121 (54.4)	2,330 (46.1)	1,036 (54.7)	2,122 (46.7)	85 (50.6)	208 (40.8)
Body mass index (kg/m²)	26.7 (5.2)	26.2 (3.6)	26.7 (5.2)	26.2 (3.6)	27.4 (5.5)	26.8 (4.0)
Cardiovascular disease at baseline (% yes)	140 (6.5)	380 (7.4)	117 (6.0)	284 (6.1)	23 (13.0)	96 (18.5)
Lipid-modifying medication (% yes)	162 (7.6)	454 (8.9)	141 (7.2)	399 (8.7)	21 (12.1)	55 (10.7)
Antihypertensive medication (% yes)	417 (19.7)	850 (16.6)	355 (18.2)	709 (15.4)	62 (35.6)	141 (27.3)
ACE inhibitors (% yes)	160 (7.5)	401 (7.8)	137 (7.0)	340 (7.4)	23 (13.2)	61 (11.8)
Antiplatelets (% yes)	104 (4.9)	414 (8.1)	87 (4.5)	330 (7.2)	17 (9.8)	84 (16.3)
Betablockers (% yes)	139 (6.6)	309 (6.0)	117 (6.0)	255 (5.6)	22 (12.6)	54 (10.5)
Troponin I level at baseline (ng/L)	2.4 (1.7, 3.6)	3.7 (2.6, 5.8)	2.4 (1.7, 3.5)	3.6 (2.5, 5.6)	3.1 (2.2, 5.0)	4.7 (3.0, 9.0)

Continuous variables are presented as mean (SD) or median (25th to 75th percentile), as appropriate. Categorical variables are presented as number (%). Missing values <5% if applicable, except for high-density lipoprotein (9.3%), high-density lipoprotein (10.5%) and body mass index (11.4%). The primary outcome is a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

A total of 1619 (75.6%) and 1090 (50.9%) women and 4199 (81.5%) and 2955 (57.4%) men had a second and third cardiac troponin measurement, respectively. Men were more likely to have detectable concentrations of cardiac troponin compared to women (Figure S1). There were 4847 (94.1%), 4156 (99.0%), and 2941 (99.5%) men, and 1677 (78.3%), 1538 (95.0%), and 1055 (96.8%) women, who had detectable cardiac troponin concentrations at their first, second, and third measurement, respectively. The time between first, second, and third cardiac troponin measurement was similar for women and men (Table S1).

Sex-Specific Cardiac Troponin Trajectories Over the Life Course

At baseline, median cardiac troponin concentrations were lower in women compared to men (2.4 [25th to 75 th percentile, 1.7–3.6] ng/L versus 3.7 [25th to 75th percentile, 2.6–5.8] ng/L, P<0.001, Table 1). When evaluating the trajectories, both men and women showed an increase in cardiac troponin with advancing age, but concentrations remained lower in women compared to men over the entire middle-to-late adulthood life course (Figure 1A and Figure S2A).

Despite their persistently lower cardiac troponin concentrations, women showed a larger relative increase from 46 years of age onwards (Pinteraction<0.001, Figure 1B and Figure S2B). Women reached equivalent cardiac troponin concentrations approximately a decade after men. For example, a cardiac troponin concentration of 5 ng/L, corresponds with an average age of 73 years and 62 years in women and men, respectively. No difference was observed in the average female-specific cardiac troponin trajectory before or after the menopausal transition (Figure S3). Women and men who experienced the primary outcome during follow-up showed a larger relative increase with advancing age compared to individuals who did not experience the primary outcome (Pinteraction<0.001, Figure S4). The relative increase of cardiac troponin in individuals with the primary outcome compared to those without the primary outcome was similar in women and men (Pinteraction=0.653). We did not find a significant interaction between the individual components of the primary outcome and sex-specific troponin trajectories (Pinteraction MI=0.572; Pinteraction stroke=0.349; Pinteraction CVD death=0.282). A similar pattern in sex-specific trajectories was found in White and non-White individuals (Pinteraction=0.907, Figure S5).
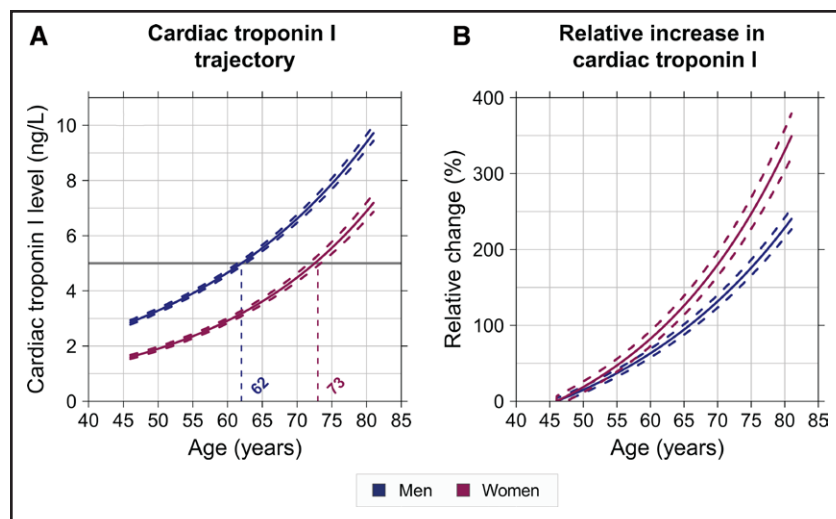
Figure 1. Sex-specific cardiac troponin trajectories.
A, The sex-specific average trajectory of cardiac troponin over the middle to late adulthood life course. **B**, The sex-specific average relative increase in cardiac troponin from 46 years onwards. The solid red line depicts the average trajectory of cardiac troponin in women and the solid blue line depicts the average trajectory of cardiac troponin in men. The dashed lines represent the 95% CIs.

Sex-Specific Longitudinal Relationship Between Risk Factors and Cardiac Troponin

We illustrate the longitudinal relationship between cardiovascular risk factors and cardiac troponin in women and men in Figure 2. In the multivariable model, age, diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein were significantly associated with cardiac troponin in both women and men. Increasing age was more strongly associated with an increase in cardiac troponin concentrations in women than men (*Pinteraction*<0.001, Figure 2B and Table S2). In contrast, BMI was more strongly associated with cardiac troponin in men than women (*Pinteraction*=0.008, Figure 2B and Table S2). Furthermore, diabetes is associated with increased cardiac troponin concentrations in women, while an inverse association was found in men (*Pinteraction*=0.003, Figure 2B and Table S2).

Sex-Specific Association Between the Temporal Pattern of Cardiac Troponin and Primary Outcome

During a median follow-up of 20.9 (25th to 75th percentile, 15.8–21.3) years, the primary outcome occurred in 177 (8.3 %) women and 520 (10.1%) men (Table 1 and Table S3). We evaluated cardiac troponin concentrations at baseline combined with the change over time in relation to the cumulative incidence of the primary outcome. No differences were observed between women and men (Figure 3). Those with the lowest cardiac troponin level at baseline (Group 1 and Group 2) were at lowest risk, and those with the highest cardiac troponin level at baseline (Group 3 and Group 4) were at highest risk (Tables S4 and S5).

Using cardiac troponin trajectories, we showed that a 2-fold difference in cardiac troponin levels at any point in time during follow-up was numerically more strongly associated with the primary outcome in women (unadjusted HR, 1.57; 95% CI, 1.29–1.85; *P*<0.001) than in men (unadjusted HR, 1.38; 95% CI, 1.22–1.54; *P*<0.001; *Pinteraction*= 0.235; Table 2). The association persisted, although sex difference disappeared when we included known cardiovascular risk factors at baseline in the model (adjusted HR women, 1.34; 95% CI, 1.17–1.52; *P*<0.001 and adjusted HR men, 1.30; 95% CI, 1.21–1.40; *P*<0.001; *Pinteraction*= 0.752; Table 2). The slope in cardiac troponin was significantly associated with the primary outcome in women (adjusted HR women, 2.70; 95% CI, 1.01–7.33; *P*=0.049), but not in men (adjusted HR men, 1.31; 95% CI, 0.62–2.75; *P*=0.474; *Pinteraction*= 0.250).

Sex-Specific Association Between the Temporal Pattern of Cardiac Troponin and Secondary Outcomes

The cumulative incidence of death from any cause was similar between women and men: 14.0% and 14.1%, respectively (Table S3). In line with our primary analysis, we observed no sex-related difference in the association between the temporal pattern of cardiac troponin and all-cause death (Figure 4). Those with the lowest cardiac troponin level at baseline (Group 1 and Group 2) were at lowest risk, and those with the highest cardiac troponin level at baseline (Group 3 and Group 4) were at highest risk in both women and men. Similar observations were found for nonfatal MI, nonfatal stroke, cardiovascular death, and non-cardiovascular death (Figure S6 through S9).

We observed a 2-fold difference in cardiac troponin levels at any point in time during follow-up in those subsequently dying from any cause for both women (adjusted HR, 1.13; 95% CI, 1.02–1.27; *P*=0.026; Table 2) and men (adjusted HR, 1.19; 95% CI, 1.12–1.27; *P*<0.001; *Pinteraction*=0.441), independent of known
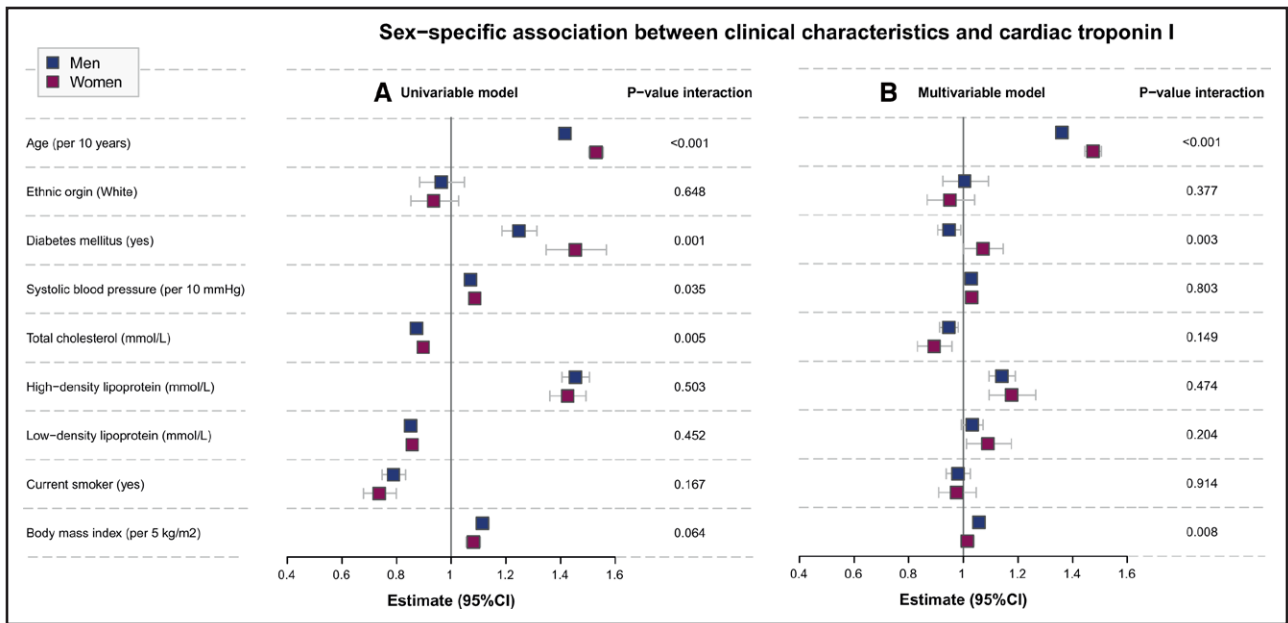
Figure 2. Sex-specific association between clinical characteristics and cardiac troponin.
A, The sex-specific association between repeated measures of clinical characteristics and cardiac troponin in univariable linear mixed-effects analyses. **B**, The sex-specific association between repeated measures of clinical characteristics and cardiac troponin in a multivariable linear mixed-effects analysis. The multivariable model included all of the clinical characteristics evaluated.

cardiovascular risk factors. The slope of cardiac troponin was significantly associated with all-cause death in men (adjusted HR, 3.36; 95% CI, 1.65–6.97; *P*=0.001), but not in women (adjusted HR, 1.96; 95% CI, 0.87–4.46; *P*=0.105; *P*interaction=0.333). In contrast, no significant association between the temporal pattern of cardiac
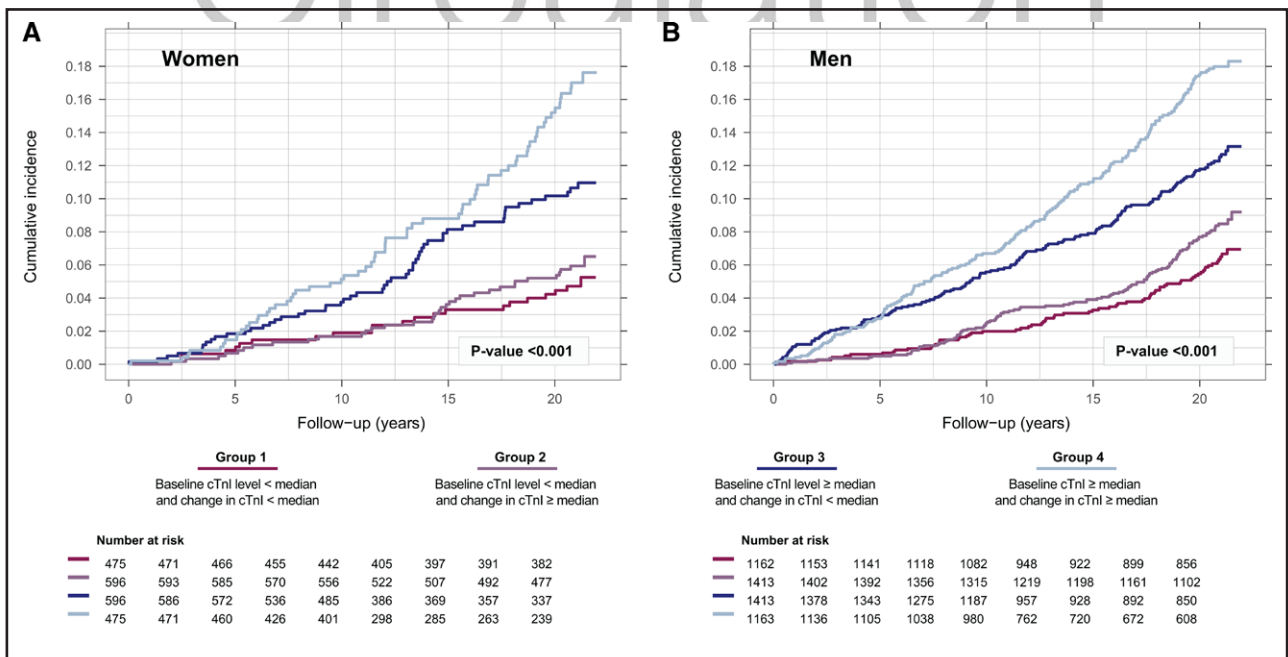
Figure 3. Sex-specific association between cardiac troponin level and change over time and primary outcome.
Group 1 = baseline level < median and change < median; Group 2 = baseline level < median and change ≥ median; Group 3 = baseline level ≥ median and change < median; and Group 4 = baseline level ≥ median and change ≥ median. Log-rank test was used for between group comparisons. The estimated sex-specific median baseline level of cardiac troponin = 2.4 ng/L in women and 3.8 ng/L in men. The estimated sex-specific median change in cardiac troponin level equals a 4.4% increase per year in women and a 3.5% increase per year in men. The primary outcome is a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

troponin and non-cardiovascular death was observed in the adjusted models (Table S6).

DISCUSSION

We conducted a comprehensive sex-specific analysis of the trajectories of cardiac troponin I over the life course in middle-to-late adulthood in the general population. Our study has 3 main findings. First, cardiac troponin concentrations in women lag around a decade behind men, but women exhibit a steeper trajectory with advancing age. Second, apart from age, we observed a significant interaction between sex and diabetes, and sex and BMI on the trajectory of cardiac troponin, suggesting that the impact of these risk factors on the development of subclinical cardiovascular disease may differ between women and men. Finally, the temporal pattern of cardiac troponin was more strongly related to cardiovascular events in women than men, although the association was attenuated after adjustment for cardiovascular risk factors. Our

findings highlight the need for sex-specific approaches when cardiac troponin testing is applied in cardiovascular risk prediction.

In line with previous studies, cardiac troponin concentrations were persistently lower in women than men over the middle-to-late adulthood life course.[11–14] We extend current knowledge by showing that women reach similar cardiac troponin concentrations approximately a decade after men, indicating that the development of coronary artery disease or other heart conditions may be delayed in women. In addition, we observed that women exhibit a greater relative increase in cardiac troponin with advancing age than men. Cardiovascular aging is a complex, multifactorial process, and sex differences arise from intrinsic biological variation as well as sex-specific changes in the myocardium and vasculature that manifest with aging.[20,21] Although our exploratory analysis indicates that type of cardiovascular event does not appear to play a major role in the observed sex differences in troponin trajectories, differences in the prevalence of specific cardiovascular

Table 2. Sex-Specific Association Between Repeated Measurements of Cardiac Troponin I and Clinical Outcome

	Women		Men		
	HR (95% CI)	P value	HR (95% CI)	P value	P value for interaction
Primary outcome					
Crude model*					
Level	1.57 (1.29–1.85)	<0.001	1.38 (1.22–1.54)	<0.001	0.235
Slope	1.74 (0.67–4.75)	0.265	1.17 (0.56–2.55)	0.689	0.528
Adjusted model (age)*					
Level	1.40 (1.23–1.60)	<0.001	1.31 (1.22–1.40)	<0.001	0.352
Slope	2.03 (0.76–5.25)	0.147	1.31 (0.63–2.74)	0.483	0.481
Adjusted model (known CVD risk factors†)*					
Level	1.34 (1.17–1.52)	<0.001	1.30 (1.21–1.40)	<0.001	0.752
Slope	2.70 (1.01–7.33)	0.049	1.31 (0.62–2.75)	0.474	0.250
All-cause death					
Crude model*					
Level	1.36 (1.21–1.52)	<0.001	1.33 (1.24–1.42)	<0.001	0.764
Slope	1.80 (0.84–3.99)	0.139	3.44 (1.76–6.92)	<0.001	0.220
Adjusted model (age)*					
Level	1.15 (1.02–1.29)	0.023	1.19 (1.12–1.27)	<0.001	0.585
Slope	1.91 (0.84–4.38)	0.126	3.66 (1.84–7.47)	<0.001	0.242
Adjusted model (known CVD risk factors†)*					
Level	1.13 (1.02–1.27)	0.026	1.19 (1.12–1.27)	<0.001	0.441
Slope	1.96 (0.87–4.46)	0.105	3.36 (1.65–6.97)	0.001	0.333

CVD indicates cardiovascular disease; and HR, hazard ratio. The primary outcome is a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

*Hazard ratios (HRs) and 95% CIs are given per 2-fold difference in cardiac troponin in level and slope (change in cardiac troponin concentration/5 years). Further details on the multistate joint model application can be found in the Supplemental Material.

† The model adjusted for known cardiovascular risk factors included age, diabetes, total cholesterol, high-density lipoprotein, low-density lipoprotein, systolic blood pressure, and smoking status at baseline, and serial cardiac troponin measurements.
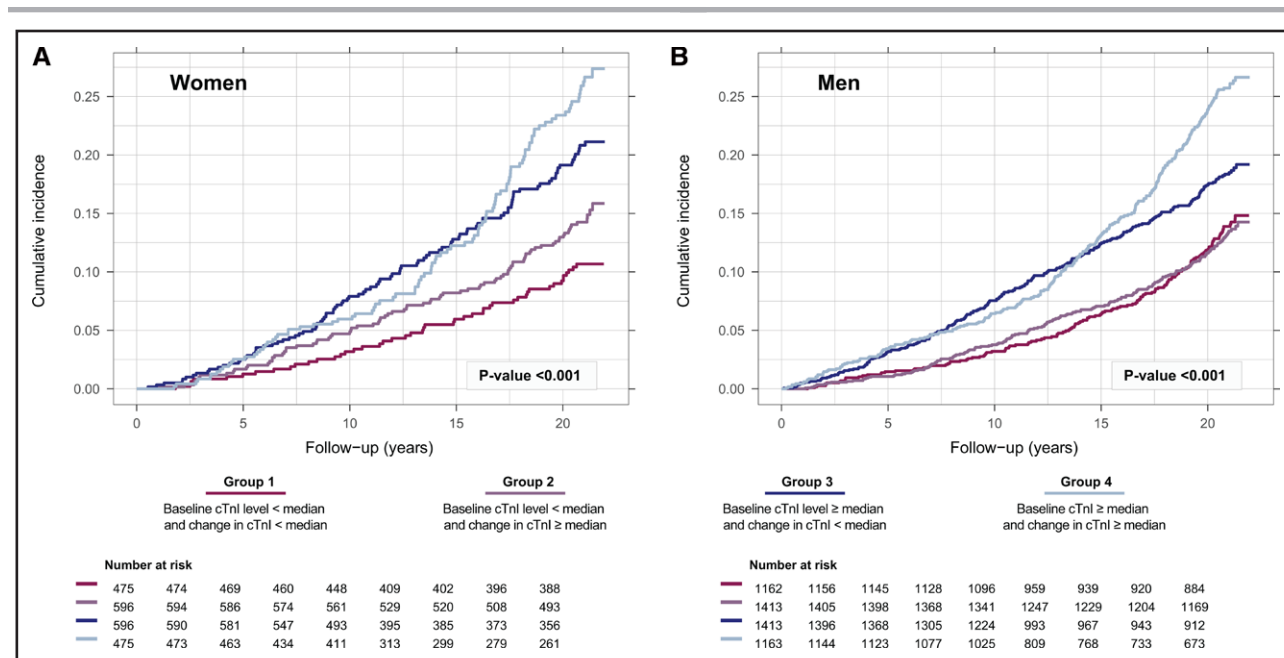
Figure 4. Sex-specific association between cardiac troponin level and change over time and death from any cause.
Group 1 = baseline level < median and change < median; Group 2 = baseline level < median and change ≥ median; Group 3 = baseline level ≥ median and change < median; and Group 4 = baseline level ≥ median and change ≥ median. Log-rank test was used for between group comparisons. The estimated sex-specific median baseline level of cardiac troponin = 2.4 ng/L in women and 3.8 ng/L in men. The estimated sex-specific median change in cardiac troponin level equals a 4.4% increase per year in women and a 3.5% increase per year in men.

conditions, such as hypertension and atherosclerosis, in women and men may have contributed to a divergent distribution of cardiac troponin over time. Furthermore, it has been speculated that sex hormones may play a role in the divergent cardiac troponin concentrations between women and men.[22] Estrogens seem to have a cardioprotective effect in premenopausal women, either directly or indirectly, which diminishes after menopause.[23–25] Moreover, the testosterone to estradiol ratio, rather than the individual sex hormones, has been previously associated with increased risk of cardiovascular events in men.[26] Our explorative analysis suggests no difference in the cardiac troponin trajectory of women pre- and post-menopause, but the role of sex-hormones should be elucidated in further longitudinal studies enrolling women in the decades prior to the menopause.

Apart from age, we identified that the longitudinal relationship between cardiac troponin and diabetes and BMI was modified by sex. A strong association between diabetes and cardiac troponin was observed in women, while an inverse association was observed in men. These findings align with the accumulating evidence suggesting that diabetes confers a higher cardiovascular risk in women than it does in men, independent of other risk factors.[27,28] The diabetes-related increased risk of cardiovascular disease in women as compared to men is likely to be multifactorial.[29] This may be due to the combination of a more rapid progression in cardiovascular and metabolic risk factor profile, delayed diagnosis and less intensive treatment of diabetes, more involvement

of inflammatory factors, higher susceptibility to oxidative stress, and genetic or hormonal factors.[29] The sex-related difference in the association between BMI and cardiac troponin may be attributed to different traits of adipose tissue. Namely, adipose tissue in women typically represents subcutaneous adipose tissue, whereas in men it represents visceral/abdominal adipose tissue.[30] Subcutaneous adipose tissue exerts protective effects, whereas visceral/abdominal adipose tissue induces harmful metabolic alterations and increases the risk of cardiovascular disease.[30]

Previous studies have demonstrated that serial cardiac troponin testing is a promising tool for cardiovascular risk estimation,[8–10] but whether a sex-specific approach should be considered when serial testing is applied has not yet been elucidated. The sex-specific association between cardiac troponin measured at a single timepoint and future cardiovascular risk is well established.[6,31–38] We found in our study that the temporal pattern of cardiac troponin was independently associated with future cardiovascular events. In line with previous studies that evaluated cardiac troponin at a single time point, we show no relationship between the temporal pattern of cardiac troponin and non-cardiovascular deaths which is an important consideration when using cardiac troponin for risk prediction. We previously demonstrated that a sex-specific approach is required for risk prediction when using a single cardiac troponin measurement, but also that the interaction with sex is mostly explained by the prevalence of cardiovascular risk factors and prior

disease.[34] Similarly, the level of cardiac troponin was more strongly related to cardiovascular events in women than men in the current study, and this divergence by sex disappeared after adjustment for known cardiovascular risk factors. Our study suggests that the rate of change of cardiac troponin may be more informative in women than in men as we only observed a significant relationship between rate of change in cardiac troponin and the primary outcome in women. The findings of the current study highlight the importance of a sex-specific approach when using high-sensitivity cardiac troponin testing for risk stratification and targeting preventative treatments of cardiovascular disease. Use of the same thresholds to guide risk of future cardiovascular events in women and men would not provide equivalent prediction and such thresholds would be challenging to apply in older populations or diabetic individuals. Ideally, cardiac troponin would be used as a continuous, longitudinal measure in a dynamic cardiovascular risk prediction tool that incorporates sex, age, and other clinical features, thereby eliminating the problem of under- or overestimation for other important subgroups apart from sex. Such a dynamic risk prediction tool could provide a more individualized approach for both women and men to improve outcomes and provide additional public health benefits. A dynamic measure of risk could encourage patients to remain on therapy or guide clinicians to escalate therapy where risk remains elevated. Further work is needed to evaluate whether including serial measures of lifestyle factors (eg, diet and physical activity), traditional cardiovascular risk factors (eg, blood pressure and cholesterol), and other biomarkers (eg, N-terminal pro-B-type natriuretic peptide and creatinine) incorporated in an interactive and dynamic clinical tool could improve cardiovascular risk prediction in both women and men.

Our study has several strengths. First, our study is the first that conducted a sex-specific analysis of cardiac troponin trajectories in a general population setting. So far, studies on the sex-specific associations of cardiac troponin in the general population have traditionally performed cross-sectional measurements only[13] or have left a short time interval between just 2 repeated measurements.[8,39] Second, the Whitehall II study includes extensive phenotyping of almost the entire cohort, which allowed us to evaluate the sex-specific association between repeated measures of clinical characteristics and cardiac troponin. Third, complete follow-up for over 20 years ensured we had sufficient cardiovascular events to evaluate prediction of the cardiac troponin trajectory in men and women separately.

Some limitations of our study need to be acknowledged. First, men were overrepresented in the Whitehall II study. Second, the Whitehall II study comprises a mostly White population and generalizing our findings to other ethnic groups should be done with caution. Although we conducted a separate analysis in White and non-White individuals and found a similar pattern, further research is required to evaluate the impact of different ethnicities on troponin trajectories in women and men over the life course. Third, we relied on Hospital Episode Statistics to identify outcome events, and whilst this will result in some misclassification this is likely to be similar in women and men. Finally, we have only evaluated 1 cardiac troponin assay which precludes extrapolation of our findings to other cardiac troponin I assays.

In conclusion, trajectories of cardiac troponin differ between women and men in the general population, with differing associations to conventional risk factors and cardiovascular outcomes. Our findings highlight the importance of a sex-specific risk approach when serial cardiac troponin testing is applied to cardiovascular risk prediction.

ARTICLE INFORMATION

Disclosures

Dr Shah has received honoraria from Abbott Diagnostics. Dr Mills has acted as a consultant for Abbott Diagnostics, Siemens Healthineers, Roche, and LumiraDx. The other authors have no conflicts of interest.

Supplemental Material

Tables S1–S6

Figures S1–S9

The principle of joint modelling

R code and educational material of linear mixed-effects models and multistate joint models

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