

## SUPPLEMENTAL MATERIAL

### **Long-term prognosis of low high-sensitivity cardiac troponin T in the emergency department compared to the general population**

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## **Supplemental information on Swedish registries**

### ***Statistics Sweden***

Statistics Sweden collects data from various reliable sources, including the Swedish Population Register (maintained by the Swedish Tax Agency), which is meticulously updated with information on births, deaths, and migration. Whenever a death occurs in Sweden, a doctor is required to complete both a death certificate and a cause of death certificate. The death certificate must be submitted to the Swedish Tax Agency by the first weekday following the date of death, and subsequently the data is promptly forwarded to Statistics Sweden. The mortality data provided by Statistics Sweden has complete nationwide coverage, and the high accuracy is supported by the fact that the registration of deaths in Sweden is legally mandated and closely integrated with the healthcare system, ensuring that almost all deaths are recorded accurately and promptly.[1] The agency follows rigorous methodological standards in data collection, processing, and dissemination, and updates mortality data regularly, providing annual statistical releases. This timeliness ensures that the data reflects the most current trends and patterns in mortality.

### ***The Swedish National Board of Health and Welfare***

The Swedish National Board of Health and Welfare is a government agency under the Ministry of Health and Social Affairs that maintain health data registries and publish official statistics. Its main functions include developing and supporting the health care and social service sectors through regulations, guidelines, and the dissemination of knowledge to practitioners and policymakers. Some of the key healthcare registers maintained by the Swedish National Board of Health and Welfare, and from which data are used for official statistics include the National Patient Register (NPR), the Prescribed Drug Register, and the Cause of Death Register. The NPR include diagnostic information on diagnoses at discharge

and surgical procedures coded according to the international version of the disease classification (ICD). The diagnosis is registered by the consultant physician in charge of the patient care at the time of discharge from hospital. Thereafter, the diagnostic information is electronically forwarded to the NPR on a yearly basis. The reporting procedure is mandatory for all healthcare providers and is standardized across Sweden. The NPR has virtually complete nationwide coverage of hospital stays since 1987, with estimated underreporting of <1% for inpatient data. For myocardial infarction diagnoses in NPR, the sensitivity is high and the positive predictive value (PPV) has been reported to be 98% to 100%.<sup>[2]</sup> Additionally, the PPV for adjudicated myocardial infarction events according to ICD-codes in the NPR among patients presenting to the ED with chest pain with any elevated hs-cTnT concentration have priorly been reported to be >99%.<sup>[3]</sup>

- 1 Statistics Sweden's website. <https://www.scb.se/en/> (accessed 14 May 2024)
- 2 Ludvigsson JF, Andersson E, Ekblom A, *et al.* External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
- 3 Roos A, Hellgren A, Rafatnia F, *et al.* Investigations, findings, and follow-up in patients with chest pain and elevated high-sensitivity cardiac troponin T levels but no myocardial infarction. *Int J Cardiol*. 2017;232:111–6.

**Supplemental Table 1.** The most common discharge diagnoses at the time of the index visit

	<b>Hs-cTnT concentrations (ng/l)</b>	
	<b>&lt;5 ng/l</b>	<b>5 to 14 ng/l</b>
Number of patients (row-%)	69,090 (62)	42,826 (38)
Discharge directly from the ED, n (%)	60,775 (88)	31,766 (74)
<b>#1, n (%)</b>	Symptoms and/or signs of disease from the circulatory and respiratory organs (ICD: R00-R09) 36,537 (53)	Symptoms and/or signs of disease from the circulatory and respiratory organs (ICD: R00-R09) 19,661 (46)
<b>#2, n (%)</b>	Other symptom diagnoses (ICD: all other R-codes) 4166 (6.0)	Other symptom diagnoses (ICD: all other R-codes) 2385 (5.6)
<b>#3, n (%)</b>	Unspecified pain conditions (ICD: M79) 3905 (5.7)	Unspecified pain conditions (ICD: M79) 1610 (3.8)
<b>#4, n (%)</b>	Medical observation for suspected diseases (ICD: Z03) 1272 (1.8)	Medical observation for suspected diseases (ICD: Z03) 1181 (2.8)
<b>#5, n (%)</b>	Anxiety disorders (ICD: F41) 836 (1.2)	AF or flutter (ICD: I48) 1010 (2.4)
<i>Missing, n (%)</i>	11,940 (17)	7,168 (17)

Abbreviations: AF, atrial fibrillation; AP, angina pectoris; hs-cTnT: high-sensitivity cardiac troponin T.

**Supplemental Table 2.** Standardized mortality ratios and incidence ratios for myocardial infarction in patients with low or undetectable hs-cTnT concentrations compared to the general population

	Hs-cTnT concentrations (ng/l)	
	<5 ng/l	5 to 14 ng/l
<b>Standardized mortality ratio by sex and age (years)</b>		
Men 18-34	1.35 (95% CI: 1.00-1.79)	2.60 (95% CI: 1.73-3.76)
Women 18-34	1.45 (95% CI: 0.90-2.22)	6.84 (95% CI: 2.22-16.0)
Men 35-44	1.13 (95% CI: 0.84-1.49)	2.55 (95% CI: 1.82-3.47)
Women 35-44	2.08 (95% CI: 1.58-2.70)	8.25 (95% CI: 4.81-13.2)
Men 45-54	0.96 (95% CI: 0.78-1.17)	2.23 (95% CI: 1.88-2.63)
Women 45-54	1.19 (95% CI: 0.98-1.44)	3.62 (95% CI: 2.69-4.76)
Men 55-64	1.04 (95% CI: 0.90-1.20)	1.68 (95% CI: 1.51-1.85)
Women 55-64	0.90 (95% CI: 0.78-1.04)	2.02 (95% CI: 1.72-2.35)
Men 65-74	0.75 (95% CI: 0.64-0.87)	1.14 (95% CI: 1.05-1.22)
Women 65-74	0.76 (95% CI: 0.67-0.86)	1.37 (95% CI: 1.25-1.49)
Men 75-84	0.67 (95% CI: 0.55-0.82)	0.94 (95% CI: 0.87-1.00)
Women 75-84	0.69 (95% CI: 0.60-0.78)	0.95 (95% CI: 0.89 -1.01)
Men 85+	0.46 (95% CI: 0.34-0.62)	0.80 (95% CI: 0.73-0.88)
Women 85+	0.74 (95% CI: 0.64-0.85)	0.82 (95% CI: 0.78-0.86)
<b>Standardized incidence ratio for myocardial infarction by sex and age (years)</b>		
Men 20-34	0.88 (95% CI: 0.11-3.17)	6.18 (95% CI: 1.68-15.8)
Women 20-34	8.63 (95% CI: 2.80-20.1)	n/a*
Men 35-44	2.07 (95% CI: 1.54-2.71)	5.10 (95% CI: 3.74-6.81)
Women 35-44	4.05 (95% CI: 2.69-5.86)	11.4 (95% CI: 4.19-24.9)
Men 45-54	1.49 (95% CI: 1.27-1.73)	2.77 (95% CI: 2.40-3.19)
Women 45-54	1.64 (95% CI: 1.27-2.10)	6.70 (95% CI: 4.83-9.05)
Men 55-64	1.34 (95% CI: 1.18-1.52)	1.78 (95% CI: 1.61-1.97)

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Women 55-64	1.51 (95% CI: 1.27-1.78)	2.41 (95% CI: 1.93-2.99)
Men 65-74	1.24 (95% CI: 1.06-1.44)	1.49 (95% CI: 1.37-1.63)
Women 65-74	1.25 (95% CI: 1.06-1.46)	1.84 (95% CI: 1.62-2.09)
Men 75-84	1.15 (95% CI: 0.88-1.47)	1.20 (95% CI: 1.08-1.34)
Women 75-84	1.32 (95% CI: 1.09-1.58)	1.43 (95% CI: 1.29-1.59)
Men 85+	1.48 (95% CI: 0.86-2.36)	1.02 (95% CI: 0.83-1.26)
Women 85+	1.38 (95% CI: 1.02-1.82)	1.21 (95% CI: 1.06-1.37)

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\*No events observed. Abbreviations: CI: confidence interval; hs-cTnT: high-sensitivity cardiac troponin T.

**Supplemental Table 3.** Annual mortality and myocardial infarctions rates in the general population during the follow-up

	Year										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>Mortality by sex and age (years)</b> (deaths per 10,000 persons)											
Men 18-34	4.7	4.5	4.7	4.8	4.8	4.9	4.5	4.7	4.5	4.2	4.5
Women 18-34	2.6	2.6	2.4	2.5	2.4	2.5	2.5	2.5	2.6	2.3	2.2
Men 35-44	9.3	9.6	9.3	9.4	9.2	9.5	9.9	10.1	9.5	8.9	8.0
Women 35-44	5.6	5.8	6.3	6.0	5.6	5.0	5.5	5.2	5.2	5.9	5.8
Men 45-54	26	25	24	24	23	23	22	21	21	19	20
Women 45-54	16	16	17	16	16	14	14	15	14	13	13
Men 55-64	73	70	68	67	64	64	62	60	59	56	60
Women 55-64	48	45	44	44	43	43	42	40	40	38	36
Men 65-74	176	174	169	167	165	167	167	162	167	161	172
Women 65-74	114	110	113	112	110	111	112	114	115	107	112
Men 75-84	579	556	550	521	504	497	484	466	460	429	473
Women 75-84	387	378	382	373	349	355	344	343	329	310	336
Men 85+	1746	1733	1804	1733	1689	1737	1691	1737	1695	1609	1825
Women 85+	1457	1461	1516	1462	1431	1450	1457	1472	1456	1371	1516
<b>Myocardial infarction by sex and age (years)</b> (events per 10,000 persons)											
Men 20-34	0.4	0.6	0.3	0.3	0.4	0.3	0.5	0.3	0.4	0.5	0.2
Women 20-34	0.1	0.2	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1
Men 35-44	5.9	5.6	5.6	4.8	5.6	5.9	5.0	5.6	4.9	4.7	4.5
Women 35-44	1.6	1.6	1.7	1.4	1.3	1.3	1.4	1.4	1.4	1.5	1.3
Men 45-54	31	30	29	26	26	26	24	24	23	22	21
Women 45-54	9.5	9.1	8.8	7.2	7.7	6.4	6.7	6.9	6.0	5.5	4.6
Men 55-64	72	73	73	66	66	63	64	61	59	58	52
Women 55-64	22	22	22	20	20	20	19	18	17	17	16
Men 65-74	129	127	125	113	113	108	105	102	97	96	84



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Women 65-74	52	52	53	45	47	45	40	42	41	37	34
Men 75-84	234	224	211	196	189	173	172	163	151	152	127
Women 75-84	130	121	121	113	103	101	95	88	79	77	70
Men 85+	365	363	357	316	287	287	267	260	229	217	186
Women 85+	239	238	236	213	199	181	170	160	149	144	119

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Data extracted from Statistics Sweden and the Swedish Board of Health and Welfare.

**Supplemental Table 4.** Risks with low hs-cTnT concentrations and no initial myocardial infarction compared with the general population in patients with and without unstable angina pectoris

	<b>Hs-cTnT concentrations (ng/l)</b>	
	<b>&lt;5 ng/l</b>	<b>5 to 14 ng/l</b>
<b>All-cause mortality</b>		
<u>Patients with UAP</u>		
Number of patients, n (row-%)	170 (19)	709 (81)
Number of deaths, n (%)	10 (5.9)	71 (10)
<b>Standardized mortality rate ratios</b> (SMRs), (95% CI)	0.68 (0.33-1.25)	0.74 (0.57-0.93)
<u>Patients without UAP</u>		
Number of patients, n (row-%)	68,920 (62)	42,117 (38)
Number of deaths, n (%)	1759 (2.6)	5463 (13)
<b>Standardized mortality rate ratios</b> (SMRs), (95% CI)	0.83 (0.79-0.87)	1.03 (1.00-1.05)
<b>Myocardial infarction</b>		
<u>Patients with UAP</u>		
Number of patients who survived the index visit	170	709
Number of MIs, n (%)	26 (15)	98 (14)
<b>Standardized incidence rate ratio</b> (SIR), (95% CI)	3.67 (2.40-5.38)	2.56 (2.08-3.12)
<u>Patients without UAP</u>		
Number of patients who survived the index visit	68,916	42,082
Number of MIs, n (%)	1255 (1.8)	2482 (5.9)
<b>Standardized incidence rate ratio</b> (SIR), (95% CI)	1.37 (1.30-1.45)	1.54 (1.48-1.60)

Abbreviations: CI: confidence interval; hs-cTnT: high-sensitivity cardiac troponin T, UAP: unstable angina pectoris. SMR and SIRs were standardized by patient age, sex, and calendar year.

**Supplemental Table 5.** Causes of death in patients with low or undetectable hs-cTnT concentrations

	Hs-cTnT concentrations (ng/l)	
	<5 ng/l	5 to 14 ng/l
<b>All-cause mortality</b>		
Number of deaths, n (row-%)	1769 (24)	5,534 (76)
<b>Cardiovascular causes of death</b>		
Number of cardiovascular deaths, n (% of total)	333 (19)	1606 (29)
Ischemic heart disease, n (%)	150 (8.5)	621 (11)
Heart failure, n (%)	39 (2.2)	223 (4.0)
Arrhythmias, n (%)	21 (1.2)	146 (2.6)
Valvular heart disease, n (%)	12 (0.7)	61 (1.1)
Aortic aneurysm/dissection, n (%)	11 (0.6)	79 (1.4)
Ischemic stroke, n (%)	20 (1.1)	143 (2.6)
Hemorrhagic stroke, n (%)	31 (1.8)	73 (1.3)
Other arterial disease, n (%)	5 (0.3)	50 (0.9)
Other cardiovascular causes, n (%)	44 (2.5)	210 (3.8)
<b>Non-cardiovascular causes of death</b>		
Number of non-cardiovascular deaths, n (% of total)	1436 (81)	3928 (71)
Cancer disease, n (%)	717 (41)	1729 (31)
Gastrointestinal disease, n (%)	69 (3.9)	200 (3.6)
Endocrinological disease, n (%)	22 (1.2)	88 (1.6)
Non-cerebrovascular neurological disorders, n (%)	89 (5.0)	303 (5.5)
Hematological disease, n (%)	6 (0.3)	10 (0.2)
Lung disease, n (%)	97 (5.0)	303 (5.5)
Infectious disease, n (%)	21 (1.2)	133 (2.4)
Psychiatric disorders, n (%)	47 (2.7)	300 (5.4)
Urogenital disease, n (%)	6 (0.3)	34 (0.6)
Other non-cardiovascular causes, n (%)	362 (20)	768 (14)

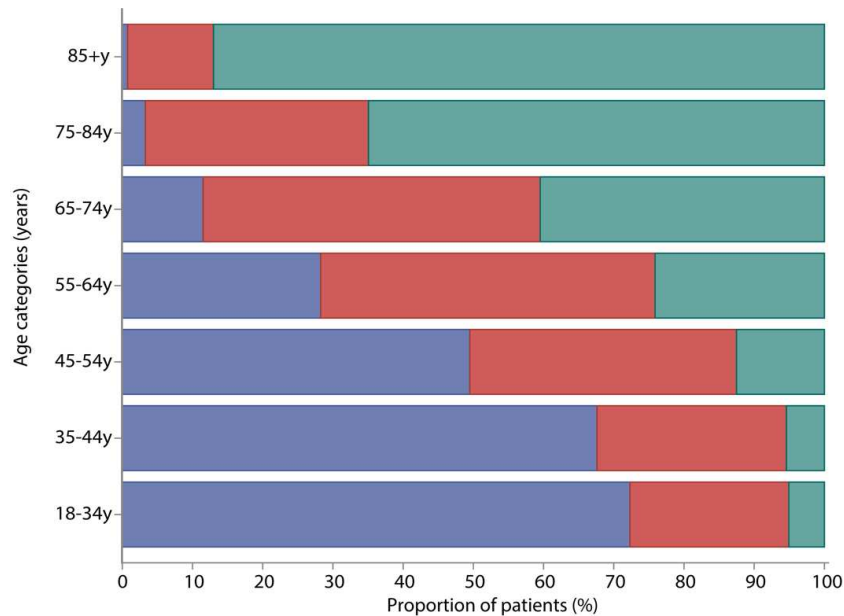
Abbreviations: hs-cTnT: high-sensitivity cardiac troponin T.

**Supplemental Table 6.** Risk of a composite endpoint of major adverse cardiovascular events and all-cause mortality in patients with low hs-cTnT concentrations

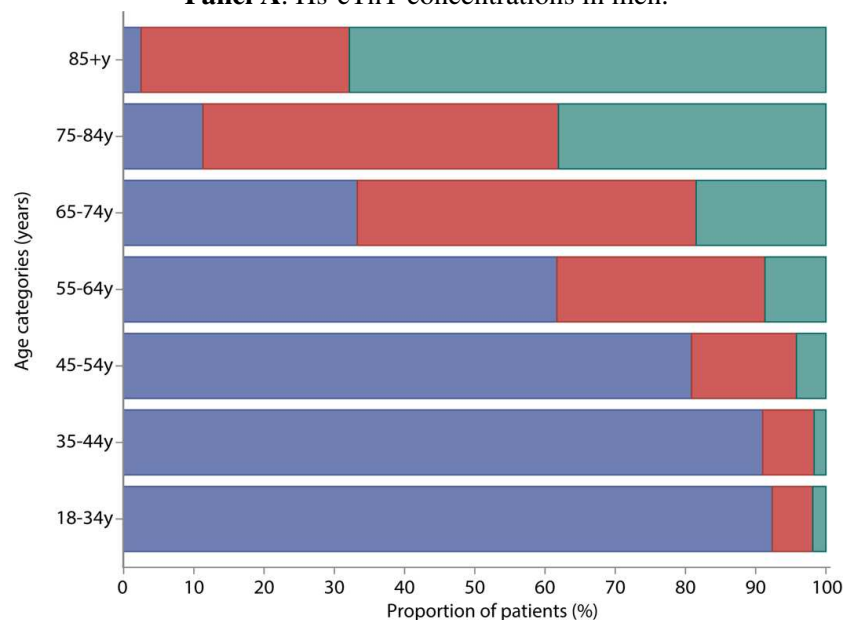
	Hs-cTnT concentrations (ng/l)	
	<5 ng/l	5 to 14 ng/l
<b>Combined endpoint of all-cause mortality and MACE<sup>b</sup></b>		
Number of patients who survived the index visit	69,086	42,791
Number of events, n (%)	3579 (5.2)	9356 (22)
Events per 10,000 person-years, (95% CI)	80.2 (77.6-82.9)	385 (377-393)
1-year crude cumulative event risk, (95% CI)	0.90% (0.83-0.97)	5.10% (4.90-5.31)
5-year crude cumulative event risk, (95% CI)	3.55% (3.41-3.69)	17.1% (16.7-17.4)
Unadjusted HR, (95% CI)	Ref. (1.0)	4.87 (4.69-5.06)
Age- and sex-adjusted HR, (95% CI)	Ref. (1.0)	1.76 (1.68 -1.184)
<b>Multivariable adjusted HR<sup>a</sup>, (95% CI)</b>	Ref. (1.0)	1.61 (1.54-1.68)

Abbreviations: CI: confidence interval; MACE: major adverse cardiovascular event. <sup>a</sup>Multivariable adjustment was made for the following time-dependent variables: age, sex, eGFR, prior myocardial infarction, heart failure, prior chronic obstructive pulmonary disease, atrial fibrillation, diabetes, and treatment with aspirin, P2Y12-inhibitors (clopidogrel, prasugrel, dipyridol, and ticagrelor), oral anticoagulants (Warfarin and DOAC), beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins. <sup>b</sup>Includes myocardial infarction, heart failure hospitalization, stroke, or cardiovascular death.

**Supplemental Figure 1.** High-sensitivity cardiac troponin T concentration proportions in patients categorized by age and sex. *Abbreviations:* Hs-cTnT: high-sensitivity cardiac troponin T.



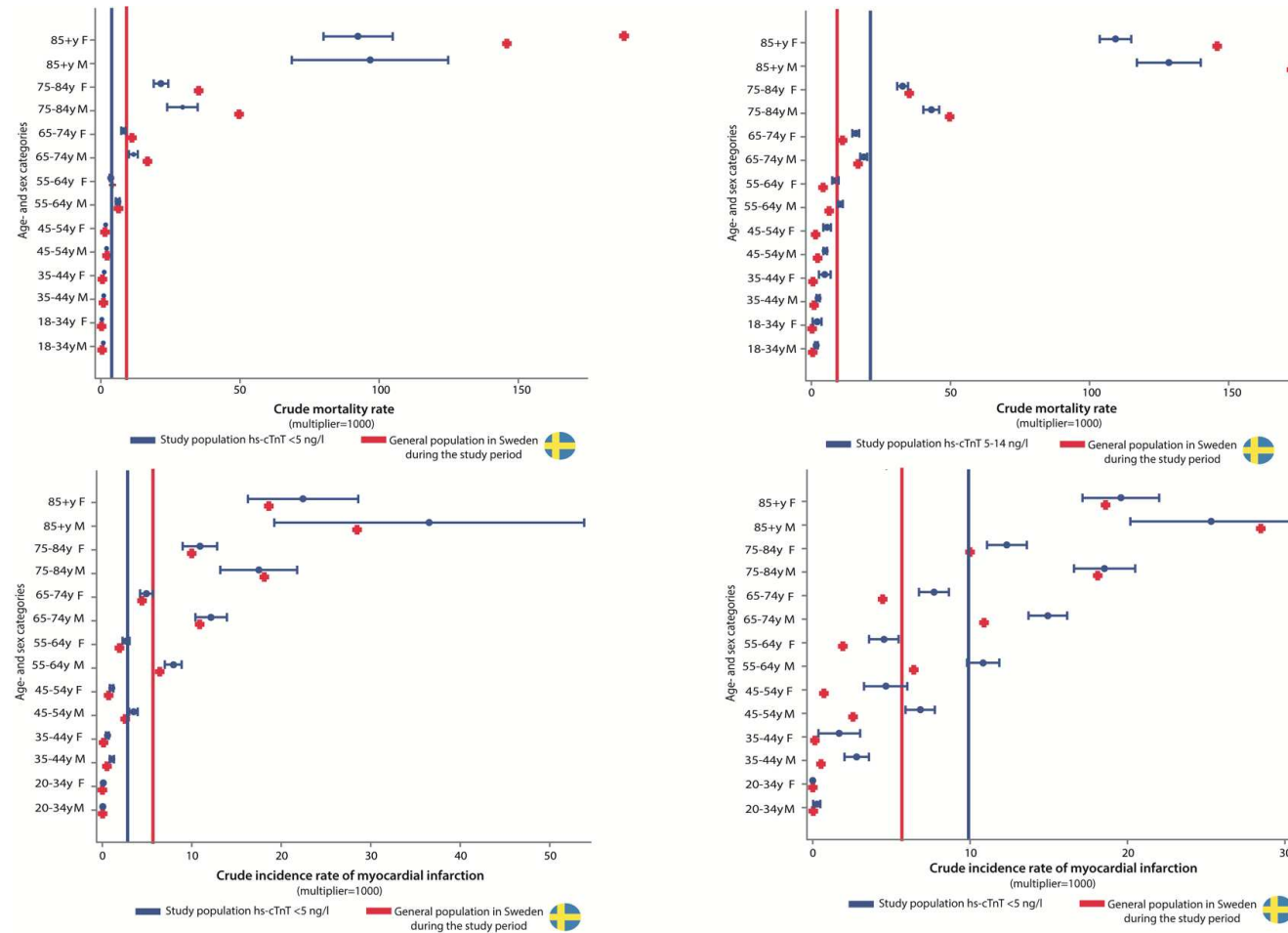
**Panel A.** Hs-cTnT concentrations in men.



**Panel B.** Hs-cTnT concentrations in women.

**Supplemental Figure 2.** Mortality rates and incidence rates of myocardial infarction. *Abbreviations:* hs-cTnT: high-sensitivity cardiac troponin

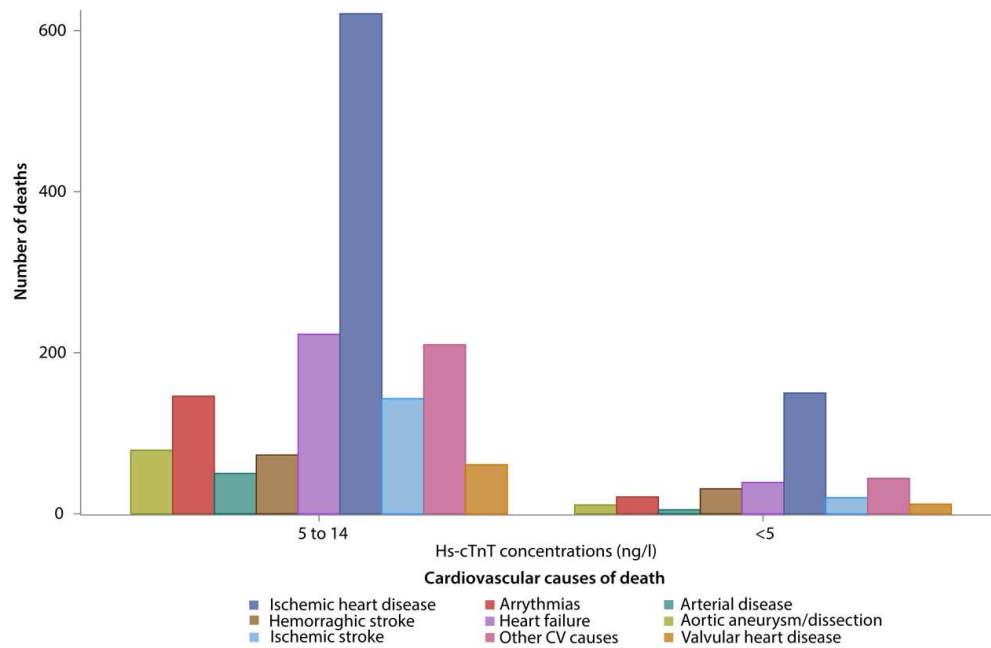
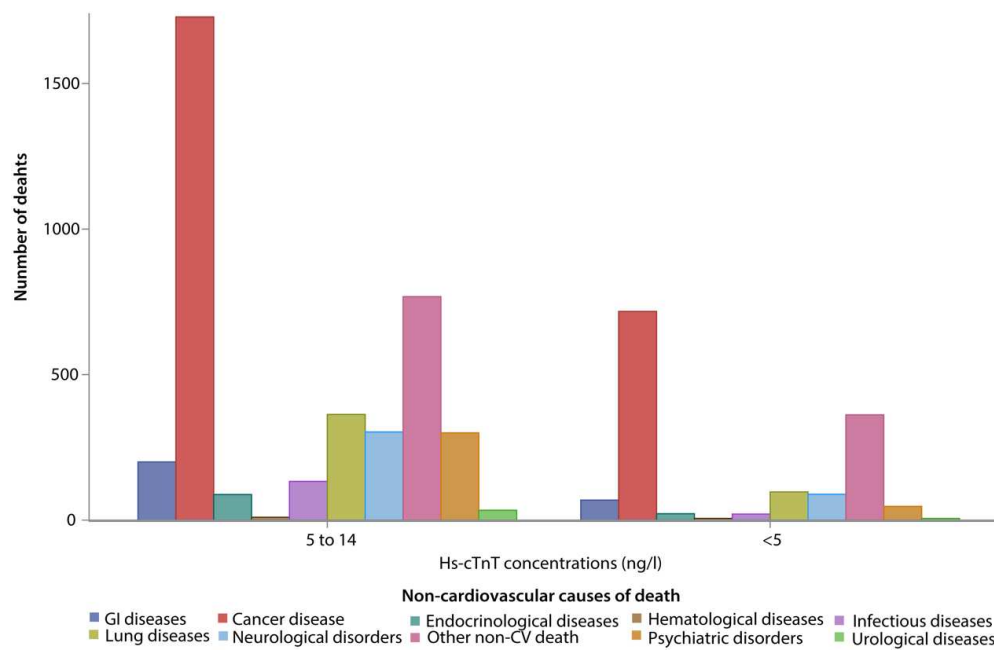
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**Panel A** (upper left) and **Panel B** (upper right): Crude mortality rates. **Panel C** (lower left) and **Panel D** (lower right): Crude incidence of myocardial infarction.

**Supplemental Figure 3.** Cardiovascular and non-cardiovascular causes of death.

*Abbreviations:* Hs-cTnT: high-sensitivity cardiac troponin T; CV: cardiovascular; GI: gastrointestinal.

**Panel A.** Cardiovascular causes of death.**Panel B.** Non-cardiovascular causes of death.



**Supplemental Figure 4.** Risk of first major adverse cardiovascular events as separate outcomes. *Abbreviations:* CI: confidence interval; HR: hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; pyr, person-years.

