Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data

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Summary

Background In cardiovascular disease, prevention strategies targeting standard modifiable cardiovascular risk factors (SMuRFs; hypertension, diabetes, hypercholesterolaemia, and smoking) are crucial; however, myocardial infarction in the absence of SMuRFs is not infrequent. The outcomes of individuals without SMuRFs are not well known.

Methods We retrospectively analysed adult patients with first-presentation ST-elevation myocardial infarction (STEMI) using data from the Swedish myocardial infarction registry SWEDEHEART. Clinical characteristics and outcomes of adult patients (age ≥18 years) with and without SMuRFs were examined overall and by sex. Patients with a known history of coronary artery disease were excluded. The primary outcome was all-cause mortality at 30 days after STEMI presentation. Secondary outcomes included cardiovascular mortality, heart failure, and myocardial infarction at 30 days. Endpoints were also examined up to discharge, and to the end of a 12-year follow-up. Multivariable logistic regression models were used to compare in-hospital mortality, and Cox-proportional hazard models and Kaplan-Meier analysis for long-term outcomes.

Findings Between Jan 1, 2005, and May 25, 2018, 9228 (14·9%) of 62 048 patients with STEMI had no SMuRFs reaching diagnostic thresholds. Median age was similar between patients with SMuRFs and patients without SMuRFs (68 years [IQR 59–78]) *vs* 69 years [60–78], p<0·0001). SMuRF-less patients had a similar rate of percutaneous coronary intervention to those with at least one modifiable risk factor, but were significantly less likely to receive statins, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockade (ARB), or β-blockers at discharge. By 30 days after presentation, all-cause mortality was significantly higher in SMuRF-less patients (hazard ratio 1·47 [95% CI 1·37–1·57], p<0·0001). SMuRF-less women had the highest 30-day mortality (381 [17·6%] of 2164), followed by women with SMuRFs (2032 [11·1%] of 18 220), SMuRF-less men (660 [9·3%] of 7064), and men with SMuRFs (2117 [6·1%] of 34 600). The increased risk of 30-day all-cause mortality in SMuRF-less patients remained significant after adjusting for age, sex, left ventricular ejection fraction, creatinine, and blood pressure, but was attenuated on inclusion of pharmacotherapy prescription (ACEI or ARB, β-blocker, or statin) at discharge. Additionally, SMuRF-less patients had a significantly higher rate of in-hospital all-cause mortality than patients with one or more SMuRF (883 [9·6%] *vs* 3411 [6·5%], p<0·0001). Myocardial infarction and heart failure at 30 days were lower in SMuRF-less patients. All-cause mortality remained increased in the SMuRF-less group for more than 8 years in men and up to the 12-year endpoint in women.

Interpretation Individuals who present with STEMI in the absence of SMuRFs have a significantly increased risk of all-cause mortality, compared with those with at least one SMuRF, which was particularly evident in women. The increased early mortality rates are attenuated after adjustment for use of guideline-indicated treatments, highlighting the need for evidence-based pharmacotherapy during the immediate post-infarct period irrespective of perceived low risk.

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Introduction

In coronary artery disease, targeted strategies against the well recognised modifiable risk factors of diabetes, hypercholesterolaemia, hypertension, and smoking (known as the standard modifiable cardiovascular risk factors [SMuRFs])[1,2] have led to major improvements in prevention and treatment. However, a clinically significant proportion of patients present with life-threatening myocardial infarction with no previous symptoms, and none of the SMuRFs at or greater than diagnostic thresholds.[3] We have coined the term SMuRF-less[4] to raise awareness of this pragmatically challenging group and encourage focused research efforts.

SMuRF-less patients are often overlooked in clinical trial publications, which classically report the proportion of patients with each of the known risk factors, but not the proportion with none. In an initial single-centre

Research in context

Evidence before this study

Patients who present with ST-elevation myocardial infarction (STEMI) without modifiable risk factors are not uncommon. The standard for clinical trials is to report the proportion of patients with standard modifiable cardiovascular risk factors (SMuRFs; diabetes, hypertension, hypercholesterolaemia, and smoking). On a review of the international guidelines and their referenced trials, we found an absence of data on the proportion of patients without SMuRFs. Thus, characteristics and outcomes in this group, including adherence and specific response to secondary prevention therapies, are not known. We recently reported an increase in the proportion of SMuRF-less patients with STEMI in the past decade, and in a national cohort, observed an unexpected excess in in-hospital mortality compared with patients with at least one SMuRF. Longer-term outcomes, particularly those driven by progression of atherosclerosis, are not known.

Added value of this study

This study is unprecedented in examining the characteristics and long-term outcomes in patients presenting with STEMI with no apparent SMuRFs, who are commonly assumed to be at low risk of further complications despite having atherosclerosis and life-threatening myocardial infarction with no obvious explanation. Using the comprehensive SWEDEHEART registry, we examined mortality and major adverse cardiovascular events for up to 12 years of follow-up in patients presenting with STEMI without SMuRFs. We present an unexpected finding of significant excess 30-day mortality in SMuRF-less patients, compared with patients with at least one modifiable risk factor, which would appear to compound the already poor outcomes particularly in women. The association of SMuRF-less status with increased early mortality did not appear to be driven by recurrent myocardial infraction or heart failure, and was attenuated after adjustment for use of guideline-indicated treatments targeting angiotensin and β_1-adrenergic neurohormonal pathways. Detailed long-term follow-up of SWEDEHEART data showed that, although progression of atherosclerosis and recurrent myocardial infarction is considerable in patients without SMuRFs, these events are less common than in patients with SMuRFs.

Implications of all the available evidence

Evidence-based pharmacotherapy should be prescribed during the immediate post-infarct period irrespective of perceived low risk. Increased education and awareness are now needed, given that low risk for developing atherosclerosis does not seem to equate to low risk of death or atherosclerotic events after myocardial infarction, and that women without SMuRFs are at the highest risk of mortality in the first 30 days after presentation. SMuRF-less patients should be considered and represented in all clinical trials, and reported alongside the proportion of patients with each individual risk factor. Dedicated meta-analyses of clinical trial data examining the efficacy of secondary prevention pharmacotherapy in SMuRF-less patients would be valuable, and help inform guidelines regarding management of this group. The substantial number of SMuRF-less patients we identified and their high 30-day mortality rate highlights the need to find new biomarkers, to improve early identification and primary prevention of atherosclerosis, where traditional risk algorithms are currently failing.

retrospective study, we showed that the proportion of patients with ST-elevation myocardial infarction (STEMI) who were SMuRF-less increased, from five (10·9%) of 46 patients in 2006, to 26 (27·4%) of 95 patients by 2014.[4] An increase in the proportion of SMuRF-less patients with STEMI was also observed in a large Australian national registry, increasing from 45 (14%) of 337 patients to 132 (23%) of 570 patients between 1999 and 2017.[5] This group had a higher in-hospital mortality rate compared with patients with at least one SMuRF,[5] similar to previous reports in Canadian and US cohorts.[6,7] This unexpected observation requires further appraisal.

The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) captures a large, unbiased population of patients presenting with STEMI,[8] providing an unparalleled opportunity to examine contributing factors and outcomes of SMuRF-less patients with STEMI. Data collection has been ongoing since 1995. In this study, we analysed data from patients with first-presentation STEMI to examine the clinical characteristics of patients without SMuRFs, and compare short-term and long-term outcomes with their counterparts with at least one modifiable risk factor.

For the **SWEDEHEART registry** see https://www.ucr.uu.se/swedeheart/

Methods

Study design and population

Patient data from SWEDEHEART were retrospectively examined overall and by sex. Details of the SWEDEHEART national registry have been published previously.[8,9] Briefly, the registry enrols all patients admitted to cardiac care units in Sweden with myocardial infraction. The registry includes data on patient characteristics, medications, and outcomes and data on acute coronary care, coronary interventions, and secondary prevention. The data quality is monitored by a formal audit process. Long-term outcomes are collected by linkage to mandatory Swedish National Board of Health and Welfare registries, which include the Swedish National Inpatient Register, the Swedish Cause of Death Register (both containing International Classification of Diseases [ICD] codes), and the Swedish Prescribed Drug Register (containing data on all dispensed prescription drugs).[9]

Patients included in the current analysis were age 18 years or older, presented with suspected acute coronary syndrome, and had a hospital diagnosis of STEMI. Patients with a known history of coronary artery disease (percutaneous coronary intervention [PCI], coronary artery bypass graft, or myocardial infarction) were excluded. The regional ethics committee in Stockholm (Sweden) approved the current study in accordance with the Declaration of Helsinki (approval numbers 2012/6013/2, 2018/1957-32, and 2019-04277).

Definition of SMuRFs

The exposure variable was defined as having at least one of the following SMuRFs: current smoker status, hypercholesterolaemia, diabetes, or hypertension. A patient was defined as a current smoker if they had regularly smoked (≥1 cigarette per day) within the past month before the index hospitalisation. Hypercholesterolaemia was defined as having a previous diagnosis of hypercholesterolaemia, previous or ongoing oral LDL cholesterol (LDL-C) lowering treatment, an LDL-C concentration of 3·5 mmol/L or higher, or a total cholesterol concentration of 5·5 mmol/L or higher during the index admission. Diabetes (type 1 and type 2) was defined as having a previous diagnosis of diabetes or previous glucose lowering pharmacotherapy. Hypertension was defined as having a previous diagnosis of hypertension or previous antihypertensive pharmacotherapy, or a new diagnosis of hypertension during the index admission. As both fasting glucose and acute-phase blood pressure are influenced by neurohormonal response to acute myocardial infarction, these were not incorporated in the definitions. Definitions of SMuRFs were based on electronic medical records, (including Anatomical Therapeutic Chemical classifications and ICD codes), hospital findings, and patient self-report on smoking during admission (appendix p 15). SMuRFs were recorded from admission and discharge data.

Outcomes

The primary outcome was all-cause mortality at 30 days after STEMI. Secondary outcomes were: major adverse cardiovascular events (MACE), defined as the composite proportion of patients who died from any cause or had recurrent myocardial infarction, stroke, or heart failure during the index admission or follow-up; cardiovascular mortality (deaths caused by cardiovascular causes [ICD-10 codes I00–I99]); rehospitalisation for heart failure; stroke; coronary revascularisation (PCI and coronary artery bypass grafting); major bleeding; and in-hospital cardiogenic shock. All-cause mortality and secondary outcomes are reported for multiple timepoints: in-hospital, at 30 days and 5 years, and at complete follow-up. The study index date was the admission date and complete follow-up was until a fatal event occurred or May 25, 2018, whichever came first.

The completeness of ascertainment and accuracy of classification of diagnoses in the Swedish national registries and SWEDEHEART are high.[10] Furthermore, data quality and accuracy in SWEDEHEART are monitored yearly.[10]

Statistical analysis

Categorical variables were summarised as frequencies and percentages. Numerical variables were summarised as the mean (SD) or median (IQR) depending on the distribution of data. To investigate differences in the characteristics, in-hospital findings, and management of patients with and without SMuRFs, categorical variables were compared with the χ^2 test and continuous variables

See Online for appendix

	Overall (n=62 048)	SMuRF-less (n=9228)	≥1 SMuRF* (n=52 820)	p value
Admission characteristics				
Age				
n	62 048	9228	52 820	NA
Median (IQR), years	68 (59–78)	69 (60–78)	68 (59–78)	<0·0001
Sex				
Male	41 664 (67·1%)	7064 (76·5%)	34 600 (65·5%)	..
Female	20 384 (32·9%)	2164 (23·5%)	18 220 (34·5%)	<0·0001
SMuRF				
Diabetes	11 251 (18·1%)	..	11 251 (21·3%)	<0·0001
Hypertension	37 193 (59·9%)	..	37 193 (70·4%)	<0·0001
Hypercholesterolaemia	25 583 (41·2%)	..	25 583 (48·4%)	<0·0001
Current smoker	17 193 (27·7%)	..	17 193 (32·6%)	<0·0001
Smoking status†				
Never smoker	23 749 (38·3%)	4964 (53·8%)	18 785 (35·6%)	..
Former smoker	16 831 (27·1%)	3335 (36·1%)	13 496 (25·6%)	..
Current smoker	17 193 (27·7%)	..	17 193 (32·6%)	<0·0001
Body-mass index				
n	51 615	7431	44 184	NA
Median (IQR), kg/m²	26·2 (23·9–29·1)	25·5 (23·5–27·9)	26·3 (24·0–29·3)	<0·0001
Medical history				
Stroke or transient ischaemic attack	4565 (7·4%)	310 (3·6%)	4255 (8·1%)	<0·0001
Peripheral arterial disease	3636 (5·9%)	246 (2·7%)	3390 (6·4%)	<0·0001
Atrial fibrillation	4340 (7·0%)	684 (7·4%)	3656 (6·9%)	0·088
History of bleeding events	2534 (4·1%)	249 (2·7%)	2285 (4·3%)	<0·0001
Hospitalisation for heart failure	2205 (3·6%)	82 (0·9%)	2123 (4·0%)	<0·0001
Cancer	2970 (4·8%)	326 (3·5%)	2644 (5·0%)	<0·0001
Chronic obstructive pulmonary disease	1527 (2·5%)	96 (1·0%)	1431 (2·7%)	<0·0001
Prehospital pharmacotherapy				
Statin	7541 (12·2%)	0	7541 (14·3%)	<0·0001
Aspirin	9183 (14·8%)	477 (5·2%)	8706 (16·5%)	<0·0001
$P2Y_{12}$ inhibitor	1796 (2·9%)	157 (1·7%)	1639 (3·1%)	<0·0001
β-blocker	12 078 (19·5%)	0	12 078 (22·9%)	<0·0001
Angiotensin converting enzyme inhibitor or angiotensin receptor blockade	13 676 (22·0%)	0	13 676 (25·9%)	<0·0001

(Table 1 continues on next page)

	Overall (n=62 048)	SMuRF-less (n=9228)	≥1 SMuRF* (n=52 820)	p value
(Continued from previous page)				
Laboratory variables				
Creatinine				
n	59 480	8657	50 823	NA
Median (IQR), µmol/L	80 (68–96)	81 (70–95)	80 (68–96)	0·0001
Total cholesterol				
n	48 179	6286	41 893	NA
Median (IQR), mmol/L	5·0 (4·2–5·8)	4·5 (4·0–4·9)	5·1 (4·3–5·9)	<0·0001
Triglycerides				
n	44 834	5971	38 863	NA
Median (IQR), mmol/L	1·3 (1·0–1·8)	1·1 (0·8–1·5)	1·3 (1·0–1·9)	<0·0001
HDL cholesterol				
n	46 720	6142	40 578	NA
Median (IQR), mmol/L	1·2 (1·0–1·4)	1·2 (1·0–1·4)‡	1·2 (1·0–1·4)‡	<0·0001
LDL cholesterol				
n	45 539	6035	39 504	NA
Median (IQR), mmol/L	3·1 (2·4–3·8)	2·7 (2·3–3·1)	3·2 (2·5–3·9)	<0·0001
Glycated haemoglobin A_{1c}				
n	8865	1117	7748	NA
Median (IQR), mmol/mol	39·0 (36·0–44·0)	37·0 (34·0–40·0)	40·0 (36·0–46·0)	<0·0001
Glucose				
n	53 527	7612	45 915	NA
Median (IQR), mmol/L	7·3 (6·2–9·3)	7·0 (6·1–8·5)	7·4 (6·2–9·4)	<0·0001
C-reactive protein				
n	54 154	7797	46 357	NA
Median (IQR), mg/L	5·0 (2·5–12·0)	5·0 (2·0–14·0)	5·0 (2·6–12·0)	0·37

SMuRF=standard modifiable cardiovascular risk factor. NA=not applicable. *23 690 (44·9%) patients with one SMuRF, 20 728 (39·2%) patients with two SMuRFs, 7437 (14·1%) patients with three SMuRFs, and 965 (1·8%) patients with four SMuRFs. †Data missing on 4275 patients; assumed to be non-smokers. ‡Higher in the SMuRF-less group; numbers only equal after rounding.

Table 1: **Baseline clinical and demographic characteristics of patients with and without SMuRFs**

with Mann-Whitney non-parametric tests. Multivariable logistic regression analyses were done to adjust for potential confounders and to estimate the adjusted odds ratio and 95% CIs for the binary outcome of in-hospital all-cause mortality. We assessed the associations between the exposure variable and study outcomes using Cox proportional hazards regression models, with calculation of hazard ratios (HRs) and 95% CIs, presented in tables or with forest plots, in the total population and by sex. Due to differential distribution between the groups, variables included in adjusted multivariable logistic regression and Cox proportional hazards models were age (per 10-year increase), sex, left ventricular ejection fraction (LVEF) less than 40%, pre-admission cardiac arrest, cardiac troponins exceeding the diagnostic thresholds at first laboratory sampling, ongoing (pre-admission) aspirin therapy, heart rate (per 10 beats per min increase), systolic blood pressure (per 10 mm Hg increase), and serum or plasma creatinine (per 10 µmol/L increase). We did additional Cox regression models including interaction terms for sex and LVEF lower than 40%. As a post-hoc analysis, HRs were assessed in a dataset with multiple imputation of missing covariates, LVEF being the most commonly missing. The contribution of SCAD to mortality was also considered in a post-hoc analysis of subgroups according to spontaneous coronary artery dissection (SCAD) status.

Kaplan-Meier survival probability estimates were calculated from the date of admission up to 30 days (all-cause mortality) and up to the total available follow-up at 12 years (all-cause mortality and cardiovascular mortality), stratified according to sex and LVEF less than 40%, and assessed with the log-rank test. Censoring was done in patients who had a non-fatal outcome at the time of a given outcome (appendix p 1). Censoring was also done at the end of data capture and after 5 years from the index event to ensure proportionality across outcomes. To adjust for different distributions of covariates across the SMuRF-less and SMuRF groups, we did a post-hoc comparison of standardised survival curves on the basis of a flexible survival model (appendix pp 2–3). We also did a series of post-hoc mediation analyses to examine the degree to which specific variables might contribute to outcomes in SMuRF-less patients presenting with STEMI (appendix p 1).[11] Full methods for our secondary analyses are described in the appendix (pp 1–3). For the variables used for SMuRF categorisation, missing data were generally minimal (<2% patients) and the risk factor assumed to be absent. Due to a higher proportion of missing data on smoking status, we also did a sensitivity analysis to obtain HRs for all-cause mortality when smoking status was imputed with the assumption that the data were missing at random.

All analyses were done with SAS software (version 9.4) and R software (version 3.5.0). A two-sided p value of less than 0·05 was considered to indicate statistical significance.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2005, and May 25, 2018, 74 679 adult patients with STEMI were registered in SWEDEHEART and 62 048 were eligible for inclusion in our study. Our population included 20 384 (32·9%) women and 41 664 (67·1%) men, with a median follow-up of 4·9 years (IQR 1·8–8·5). These patients comprised the population after excluding individuals with a history of coronary artery disease. Of the 62 048 patients, 9228 (14·9%) had no documented SMuRFs (ie, were SMuRF-less) before or during hospitalisation (appendix p 15). A higher proportion of male patients were SMuRF-less compared with female patients (7064 [17·0%] of 41 664 *vs* 2164 [10·6%] of 20 384, p<0·001). The number of

SMuRF-less patients did not increase during the study period (appendix p 16). Smoking status was unknown and assumed to be non-smoker in 4275 (6·9%) of the 62 048 patients.

Baseline demographics, distribution of SMuRFs, and pre-admission medications are presented in table 1. Median age was similar between patients with SMuRFs and patients without SMuRFs (68 years [IQR 59–78]) *vs* 69 years [60–78], p<0·0001). In patients with SMuRFs (n=52 820), the most common SMuRF was hypertension (37 193 [70·4%] patients), followed by hypercholesterolaemia (25 583 [48·4%]), current smoking (17 193 [32·6%]), and diabetes (11 251 [21·3%]). SMuRF-less patients were less likely to have a history of heart failure, stroke or transient ischaemic attack, peripheral arterial disease, malignancy, chronic obstructive pulmonary disease, peripheral arterial disease, or bleeding events. SMuRF-less patients had significantly lower LDL-C and triglycerides, and significantly higher HDL cholesterol (HDL-C) at admission, than patients with SMuRFs. Obesity was not an obvious explanation for STEMI presentations in the absence of SMuRFs, with the median body-mass index (BMI) in the SMuRF-less group being 25 kg/m² (IQR 23–28) and significantly lower than the median BMI in patients with SMuRFs (26 kg/m² [24–29], p<0·0001). Glycated haemoglobin A_{1c}, when measured, was significantly lower in the SMuRF-less group and within normal limits (normal: 31–46 mmol/mol).

At presentation of STEMI, SMuRF-less patients had significantly lower systolic blood pressure and heart rate than patients with SMuRFs (table 2). SMuRF-less patients also had a significantly higher likelihood of presenting with cardiac arrest than patients with SMuRFs. We observed no difference in the rate of primary PCI or thrombolysis between the two groups. The time from symptom onset to the start of primary PCI was significantly shorter (by 12 min) in SMuRF-less patients. Despite this more rapid triage, the SMuRF-less group had a significantly higher concentrations of troponins, and significantly lower LVEF. Multivessel coronary artery disease was significantly less common in SMuRF-less patients. Patients without SMuRFs more commonly had a left anterior descending culprit than patients with risk factors, and the difference in culprit lesion territory was significant between the groups. In addition to variables in table 2, data on SCAD were available from the year 2015 onwards. Although the proportion of SCAD was significantly higher in the SMuRF-less group, overall numbers were low, with SCAD underlying STEMI presentations in 16 (1·7%) of 932 SMuRF-less patients and 38 (0·8%) of 4898 patients with SMuRFs (p=0·0060) during the study period.

Among patients with known medications at discharge, those without SMuRFs were significantly less likely to be receiving a statin at discharge (7597 [85·0%] of 8942 patients *vs* 45 876 [88·5%] of 51 812 patients, p<0·0001; table 2). Additionally, despite higher peak troponin, and worse left ventricular function, SMuRF-less group received less prescriptions for angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockade (ARB; 6261 [75·2%] of 8324 patients *vs* 40 444 [82·0%] of 49 343 patients, p<0·0001) and β-blocker (7382 [88·7%] of 8324 patients *vs* 44 914 [91·0%] of 49 333 patients, p<0·0001) than patients with SMuRFs (table 2). The disparity in administration of secondary prevention was greatest for SMuRF-less women (appendix p 6), with only 1261 (69·0%) of 1872 receiving ACEI or ARB and 1557 (85·2%) of 1827 receiving

	Overall (n=62 048)	SMuRF-less (n=9228)	≥1 SMuRF (n=52 820)	p value
Presentation characteristics				
Systolic blood pressure				
n	59 602	8842	50 760	NA
Median (IQR), mm Hg	140 (120–160)	140 (120–158)	140 (121–160)	<0·0001
Diastolic blood pressure				
n	56 840	8431	48 409	NA
Median (IQR), mm Hg	83 (70–95)	80 (70–95)	84 (70–96)	<0·0001
Heart rate				
n	59 866	8895	50 971	NA
Median (IQR), beats per min	76 (64–90)	75 (62–90)	76 (64–90)	0·0013
Cardiac arrest at presentation	4031 (6·5%)	753 (8·2%)	3278 (6·2%)	<0·0001
Left ventricular function grade (European Society of Cardiology guidelines[12])*				
Normal (≥50%)	24 322/50 987 (47·7%)	3311/7445 (44·5%)	21 011/43 542 (48·3%)	..
Slightly lower than normal (40–49%)	13 587/50 987 (26·6%)	1997/7445 (26·8%)	11 590/43 542 (26·6%)	..
Moderately lower than normal (30–39%)	8831/50 987 (17·3%)	1401/7445 (18·8%)	7430/43 542 (17·1%)	..
Severely lower than normal (<30%)	3582/50 987 (7·0%)	626/7445 (8·4%)	2956/43 542 (6·8%)	..
Unknown	665/50 987 (1·3%)	110/7445 (1·5%)	555/43 542 (1·3%)	<0·0001
Culprit lesion territory				
Intermediate	433 (0·7%)	70 (0·8%)	363 (0·7%)	..
Left anterior descending artery	23 569 (38·0%)	3834 (41·5%)	19 735 (37·4%)	..
Left circumflex artery	6897 (11·1%)	937 (10·2%)	5960 (11·3%)	..
Left main coronary artery	620 (1·0%)	122 (1·3%)	498 (0·9%)	..
Right coronary artery	19 626 (31·6%)	2620 (28·4%)	17 006 (32·2%)	..
Unknown	10 865 (17·5%)	1641 (17·8%)	9224 (17·5%)	<0·0001
Multivessel coronary artery disease	23 748/55 454 (42·8%)	3108/8206 (37·9%)	20 640/47 248 (43·7%)	<0·0001
Troponin T				
n	13 542	2034	11 508	NA
Median (IQR), µg/L	2·8 (0·9–7·5)	3·0 (1·0–7·4)	2·7 (0·9–7·5)	0·18
Troponin T (high-sensitivity)				
n	24 302	3749	20 553	NA
Median (IQR), ng/L	2230 (730–5299)	2474 (821–5680)	2170 (718–5235)	<0·0001
Troponin I				
n	17 207	2244	14 963	NA
Median (IQR), ng/mL	22·1 (5·2–50·0)	24·8 (6·0–50·0)	22·0 (5·0–50·0)	0·0094

(Table 2 continues on next page)

	Overall (n=62 048)	SMuRF-less (n=9228)	≥1 SMuRF (n=52 820)	p value
(Continued from previous page)				
In-hospital management				
Thrombolysis	4823 (7·8%)	701 (7·6%)	4122 (7·8%)	0·49
Primary PCI	44 299 (71·4%)	6625 (71·8%)	37 674 (71·3%)	0·36
Coronary artery bypass grafting	1002 (1·6%)	186 (2·0%)	816 (1·5%)	0·0009
Symptom onset to heart intensive care or emergency room admission				
n	58 403	8645	49 758	NA
Median (IQR), h	3·1 (1·8–6·5)	3·0 (1·8–6·3)	3·1 (1·8–6·5)	0·0004
Symptom onset to angiography start				
n	46 479	6928	39 551	NA
Median (IQR), h	3·5 (2·2–7·0)	3·3 (2·1–6·7)	3·5 (2·2–7·0)	0·0046
Reperfusion therapy time (PCI)*				
<90 min	32 137/48 304 (66·5%)	4734/7213 (65·6%)	27 403/41 091 (66·7%)	..
≥90 min	16 167/48 304 (33·5%)	2479/7213 (34·4%)	13 688/41 091 (33·3%)	0·079
In-hospital complications				
All-cause death, myocardial infarction, heart failure, or stroke†	18 058 (29·1%)	2790 (30·2%)	15 268 (28·9%)	0·0095
All-cause death	4294 (6·9%)	883 (9·6%)	3411 (6·5%)	<0·0001
Myocardial infarction	2146 (3·5%)	336 (3·6%)	1810 (3·4%)	0·30
Stroke	771 (1·2%)	102 (1·1%)	669 (1·3%)	0·20
Heart failure*	14 796/59 416 (24·9%)	2161/8794 (24·6%)	12 635/50 622 (25·0%)	0·44
Major bleeding	1331 (2·1%)	188 (2·0%)	1143 (2·2%)	0·44
Cardiogenic shock	2734 (4·4%)	578 (6·3%)	2156 (4·1%)	<0·0001
Length of stay, days, median (IQR)	4·0 (3·0–6·0)	4·0 (3·0–6·0)	4·0 (3·0–6·0)	0·18
Discharge medications*‡				
Statin	53 473/60 754 (88·0%)	7597/8942 (85·0%)	45 876/51 812 (88·5%)	<0·0001
Aspirin	54 781/57 662 (95·0%)	7926/8326 (95·2%)	46 855/49 336 (95·0%)	0·38
$P2Y_{12}$ inhibitor	52 517/57 754 (90·9%)	7553/8345 (90·5%)	44 964/49 409 (91·0%)	0·15
β-blocker	52 296/57 657 (90·7%)	7382/8324 (88·7%)	44 914/49 333 (91·0%)	<0·0001
Angiotensin converting enzyme inhibitor or angiotensin receptor blockade	46 705/57 667 (81·0%)	6261/8324 (75·2%)	40 444/49 343 (82·0%)	<0·0001

SMuRF=standard modifiable cardiovascular risk factor. NA=not applicable. PCI=percutaneous coronary intervention. *Denominators represent available data. †Collectively defined as major adverse cardiovascular events; patients with more than one MACE component were counted once. ‡Unless death occurred before discharge.

Table 2: **Presentation characteristics and in-hospital findings and management**

β-blocker compared with their counterparts with at least one SMuRF (12 905 [78·4%] of 16 469 and 14 793 [89·9%] of 16 464, respectively). SMuRF-less patients had significantly higher unadjusted rates of in-hospital death (883 [9·6%] patients *vs* 3411 [6·5%] patients, p<0·0001), cardiogenic shock (578 [6·3%] *vs* 2156 [4·1%], p<0·0001), and combined MACE (2790 [30·2%] *vs* 15 268 [28·9%], p=0·0095) than patients with SMuRFs (table 2). In-hospital outcomes adjusted for sex, LVEF lower than 40%, prehospital cardiac arrest, heart rate and creatinine, and systolic blood pressure analysed by multivariable logistic regression are summarised in the appendix (p 7). In this model, SMuRF-less status, female sex, LVEF lower than 40%, pre-admission cardiac arrest, older age, lower systolic blood pressure, higher heart rate, and higher creatinine were significantly associated with mortality (appendix p 7).

At 30 days after STEMI presentation, SMuRF-less patients had significantly higher all-cause mortality than patients with one or more SMuRF (1041 [11·3%] of 9228 *vs* 4149 [7·9%] of 52 820; HR 1·47 [95% CI 1·37–1·57], p<0·0001; figure 1). This difference appeared to be caused by cardiovascular mortality. The rates of recurrent myocardial infarction and stroke were similar between the groups, and the rates of revascularisation and rehospitalisation for heart failure were lower in the SMuRF-less group than in patients with SMuRFs (figure 1). Cumulative event curves for all-cause mortality are presented by SMuRF status and according to sex (figure 2). The curves separated from the initial day of STEMI presentation. The unadjusted HRs for all-cause mortality were similar for SMuRF-less men (HR 1·56 [95% CI 1·43–1·70], p<0·0001) and women (HR 1·63 [1·46–1·82], p<0·0001; p value for interaction=0·48). However, mortality in women was almost double that in men in the SMuRF-less and SMuRF groups, reported in 381 (17·6%) of 2164 SMuRF-less women and 2032 (11·2%) of 18 220 women with SMuRFs at 30 days (*vs* 660 [9·3%] of 7064 SMuRF-less men and 2117 [6·1%] of 34 600 men with SMuRFs). The association between absence of SMuRFs and increased mortality remained in the adjusted model (HR 1·24 [1·10–1·39], p=0·0003]; appendix pp 8, 17). In our sensitivity analysis that imputed missing data for those with missing smoking status (with the assumption that this was missing at random), the excess mortality in SMuRF-less patients was attenuated, but remained significant. Adjusted HRs were similar between the main model and the post-hoc analysis with imputed missing covariate data (appendix p 10). Post-hoc adjusted standardised survival curves are presented in the appendix (p 18), accounting for covariates differentially distributed between the groups. When stratified by LVEF, unadjusted all-cause mortality remained significantly higher in the absence of SMuRFs in patients with low systolic function (LVEF <40%; HR 1·54 [95% CI 1·29–1·84, p<0·0001), and patients with preserved systolic function (LVEF ≥40%; HR 1·24 [1·10–1·40], p=0·0005; p value for interaction=0·051). However, total deaths were higher in patients with low systolic function (appendix p 19).

ACEI or ARB, β-blockade, and statin prescription at discharge were significantly lower in the SMuRF-less group than in patients with SMuRFs (table 2). To examine whether low use of evidence-based pharmacological therapies among SMuRF-less patients could partially explain their higher short-term mortality rates, post-hoc

mediation analyses were done. In analyses adjusted for discharge therapy, prescription of each pharmacotherapy was associated with expected lower mortality at 30 days, without accounting for SMuRF status (appendix p 8). We then studied the effect of including each pharmacotherapy in the adjusted analysis, accounting for SMuRF-less status. In patients alive at discharge, the inclusion of each pharmacotherapy resulted in a loss (ACEI or ARB and statin) or attenuation (β-blocker) of the significant association of SMuRF-less status with 30-day mortality (appendix p 8), consistent with a partial contribution to the mortality association.

Given that the proportion of SCAD was higher in SMuRF-less individuals, we considered the possible contribution of SCAD to mortality in a post-hoc analysis. However, overall 30-day mortality in female patients with SCAD was lower (two [6·5%] of 31 patients) than in female patients without SCAD (241 [14·1%] of 1710, p=0·22). Numbers in men were too low for meaningful analysis.

Unadjusted cardiovascular mortality remained higher in the SMuRF-less group for up to 12 years in men and women (figure 3). Regarding all-cause mortality in patients with and without SMuRFs, survival curves crossed after around 9 years in men, but difference in survival persisted up to the 12-year endpoint in women (figure 3). The events that contributed to higher all-cause and cardiovascular deaths in SMuRF-less patients occurred in the first 30 days. SMuRF-less patients who survived up to 30 days were observed to have lower all-cause and cardiovascular mortality throughout the 12-year follow-up than their counterparts with at least one modifiable risk factor (appendix pp 14, 20). The rates of recurrent myocardial infarction, rehospitalisation for heart failure, major bleeding, and coronary revascularisation were lower in the SMuRF-less group up to 5 years before adjustment (appendix pp 9, 21) and after (appendix p 11).

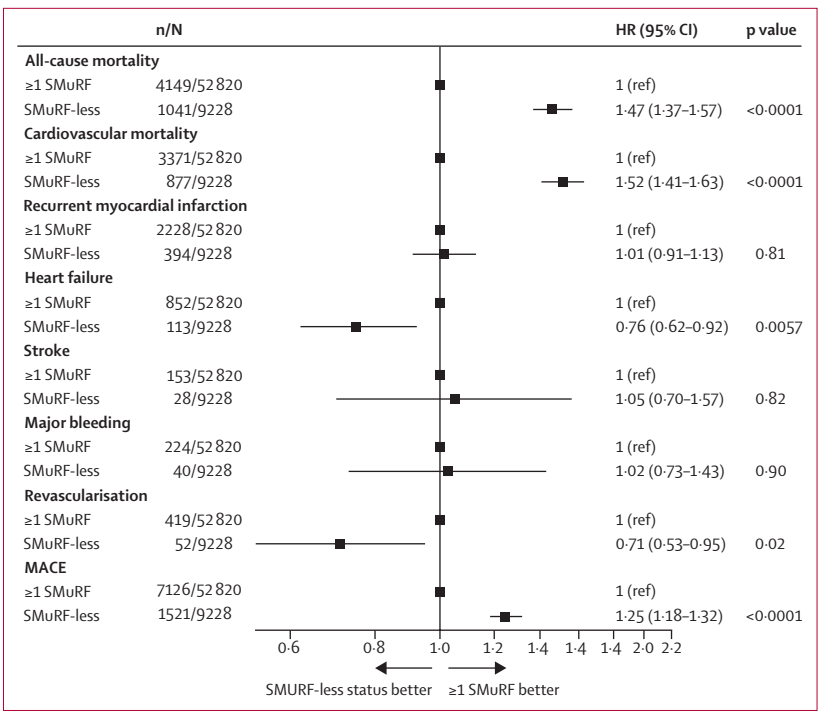

Figure 1: **HRs for primary and secondary outcomes between patients with and without SMuRFs at 30 days**
Point estimates and 95% CIs are presented from unadjusted analyses; results of adjusted analyses are provided in the appendix (p 17). HR=hazard ratio. SMuRF=standard modifiable cardiovascular risk factor. MACE=major adverse cardiovascular events.

Discussion

This study of extensive multicentre data highlights the importance of an often overlooked subgroup of patients, who despite having no traditional risk factors, present with STEMI. We used data from one of the largest and most comprehensive registries on heart disease and myocardial infarction globally, with more than 60 000 individuals included in our analysis. We observed that, for SMuRF-less patients, particularly women, in-hospital and 30-day mortality were in substantial excess, versus the mortality rates in individuals perceived to be at be high risk of STEMI on the basis of traditional risk factors for atherosclerosis.

The proportion of SMuRF-less patients with STEMI identified throughout the study period was lower than expected and did not increase over time, in contrast to our previously reported cohorts.[4,5] This might reflect differences in risk factor identification or burden, primary prevention programmes, and genetic predisposition between the present study cohort and Australian and Canadian cohorts.[4,6,10] However, our subgroup still represents a large number of people presenting with life-threatening STEMI who did not benefit from primary prevention strategies.

The SMuRF-less group was likely to include people with missed risk factors; multiple subthreshold risk factors; and heightened host susceptibility to the drivers of atherosclerosis. The number of individuals whose risk factors had been missed was probably less than in previous studies due to inclusion of detailed clinical phenotype, additional biochemistry, and in-hospital diagnoses, when available. Furthermore, we were also able to study less typical risk factors. The lower BMI, lower triglyceride concentrations, and higher HDL-C concentrations in the SMuRF-less group versus patients with SMuRFs suggest that these factors are not driving the atherosclerosis. C-reactive protein concentrations were similar between the groups, and rates of malignancy and chronic obstructive pulmonary disease were lower in SMuRF-less patients. We considered alternative causes of STEMI, including SCAD when data were available. Although the proportion of STEMI attributable to SCAD was significantly higher in SMuRF-less individuals, SCAD was only evident in 1·7% of this group, and was associated with lower mortality than STEMI attributable to standard atherosclerotic risk factors in women.

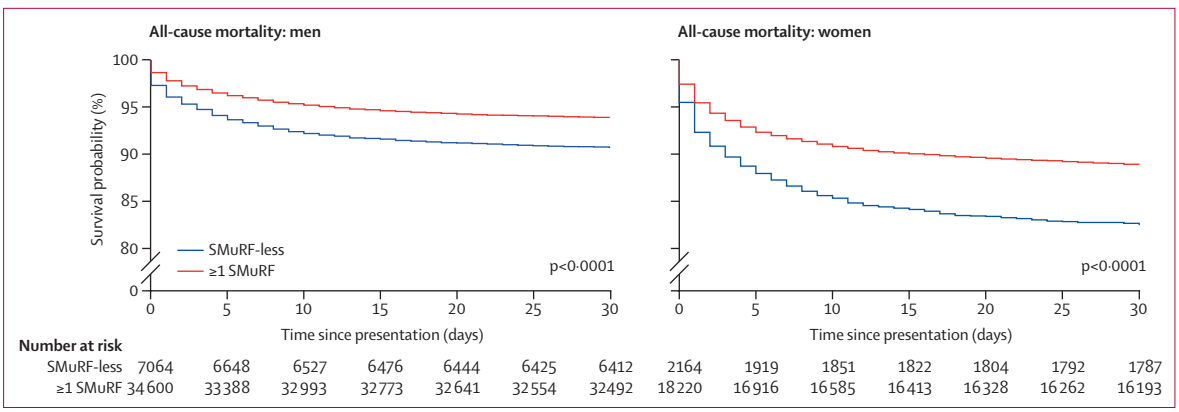

Figure 2: **Kaplan-Meier survival curves for all-cause mortality up to 30 days**
SMuRF=standard modifiable cardiovascular risk factor.

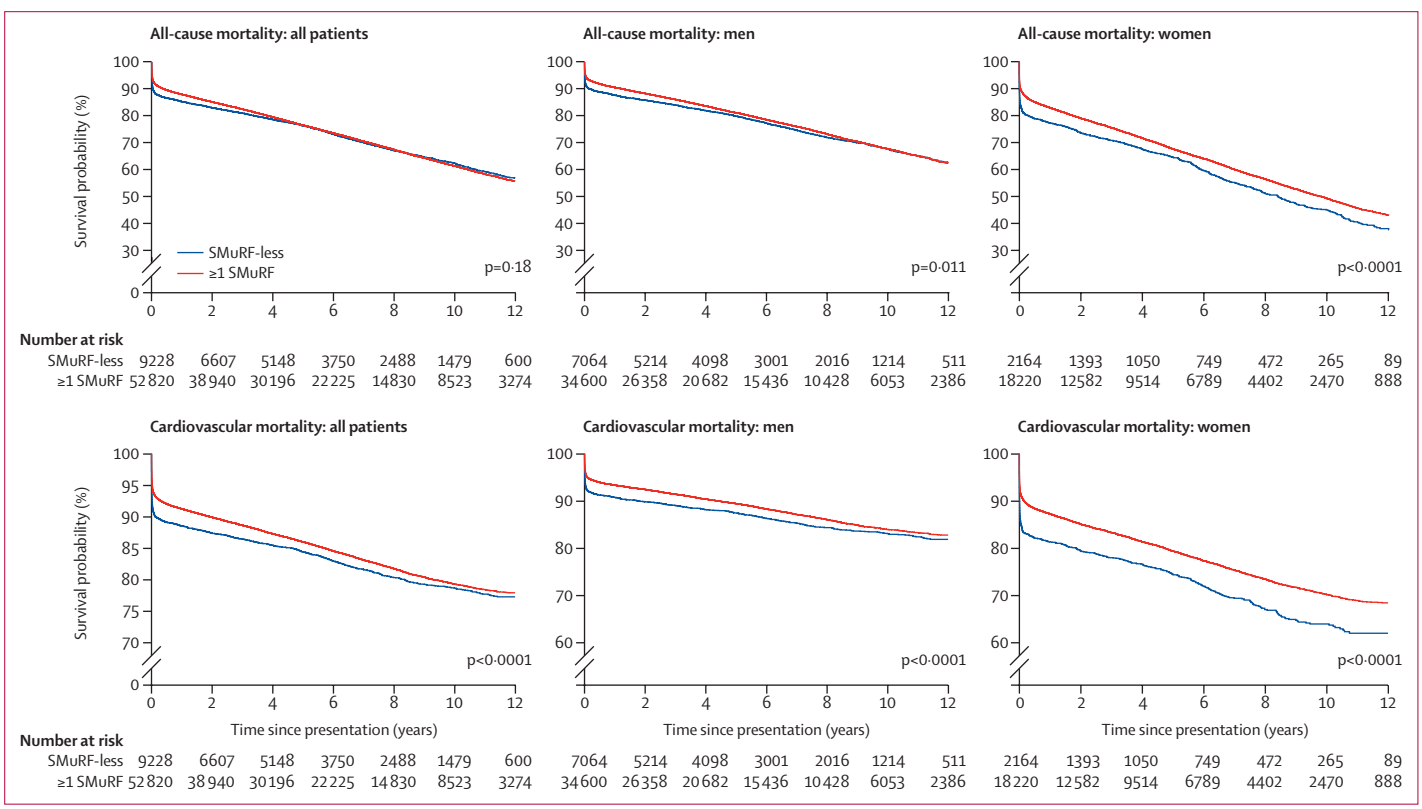

Figure 3: **Kaplan-Meier survival curves for all-cause mortality and cardiovascular mortality up to 12 years**
SMuRF=standard modifiable cardiovascular risk factor.

The association of SMuRF-less status with increased mortality, particularly in women, is a key finding, compounding the reported excess mortality in women after STEMI,[13,14] with mortality in SMuRF-less women approaching 18% at 30 days. We considered potential factors contributing to this increased mortality. Although the SMuRF-less group had slightly higher troponin concentrations and worse left ventricular systolic function, adjusting for these factors did not have an effect on the observed difference in mortality between patients with and without SMuRFs. We examined whether perceived low risk in STEMI cases might have slowed patient presentation times, or influenced emergency triage times, but this bias did not appear to be present, with SMuRF-less patients receiving similar rates and more rapid primary PCI than patients with at least one SMuRF. However, lower prescriptions of evidence-based medical therapy at discharge were observed in SMuRF-less patients, particularly in women, and mediation analysis suggested this suboptimal secondary prevention contributed to the

increase in mortality. Evidence-based medical therapy was more closely aligned with guideline recommendations in men, but remained significantly lower in SMuRF-less men than in those with at least one modifiable risk factor. The use of evidence-based medication in patients with risk factors was consistent with studies in recent years.[5,15]

The increased mortality, without increased rates of myocardial infarction or heart failure in the SMuRF-less group, indicates the likelihood of arrhythmia as a contributor. The mediation analyses support the hypothesis that suboptimal prescription rates of ACEI or ARB and β-blocker contributed to the increased mortality. This finding is consistent with previous studies showing the beneficial effect of ACEI on 30-day mortality after STEMI, with most of the benefit observed in the first week.[16] Early β-blocker therapy has also been shown to reduce mortality.[17,18] These findings reaffirm the importance of commencing evidence-based pharmacotherapy including in the early post-STEMI phase to prevent cardiovascular death, irrespective of risk factor status.

For the first time, detailed long-term survival outcomes of SMuRF-less patients with STEMI have been assessed. Although unadjusted all-cause mortality remained higher in the SMuRF-less group for more than 8 years in men and throughout the 12-year follow-up in women, the separation of cumulative mortality event curves occurred early and appeared to gradually reduce after 30 days in men. The early separation of the survival curves in both sexes are consistent with the early mortality mechanism being arrhythmia, known to be most frequent in the early phase after STEMI.[19] In contrast, we observed similar or improved outcomes for other components of 30-day MACE in SMuRF-less patients compared with their counterparts, including myocardial infarction, stroke, and rehospitalisation for heart failure. Indeed, SMuRF-less individuals who survived up to 30 days had improved survival for the entirety of follow-up (appendix p 20).

This study has several strengths including the large number of patients, the long follow-up, the comprehensive data due to data linkage between registries, and the universally used public health-care system in Sweden. However, the study also has limitations. The data are observational and although we adjusted for known confounders, there may have been additional confounders. SMuRFs were defined as categorical based on clinical diagnosis and accepted cutoff values; however, some are continuous and a gradient of risk is probable.[20] The number of patients with missed SMuRFs was minimised by the detailed phenotype data and discharge diagnosis of the study cohort, and the linkage of several parallel data sources, including the mandatory national Swedish registries. Previously published studies of these registries have shown high completeness of ascertainment and accuracy of classification of diagnoses.[10] Ex-smoking status was not considered, and the dataset for smoking status was less complete than for the other SMuRFs. Although a number of less typical risk factors were able to be examined (eg, triglycerides, HDL-C, and malignancy), less common risk contributors such as lipoprotein(a), clonal haematopoiesis of indeterminate potential, and polygenic risk scores were not available. Furthermore, no information on family history of premature coronary artery disease, socioeconomic factors, or psychosocial risk factors were available. Additionally, information on possible differences in access to or use of health-care was unavailable. We did not account for potential time-dependent effects as we felt it unlikely that they would impact our primary outcome assessed at 30 days. However, in our longer-term follow-up analyses, time-dependent effects could introduce uncertainty in the findings. Among patients identified to have at least one SMuRF, some will have had risk factors just reaching the prevention thresholds. We were not able to account for the possibility that appropriate targeting of these risk factors and optimisation of overall cardiometabolic health might attenuate the overall risk of death in this group. Additionally, data were missing on some covariates, most frequently for LVEF. To limit the potential bias of missing data, the analyses were done in imputed datasets, with essentially the same results.

The findings that we present counter a general sense of complacency that has arisen that coronary artery disease is a solved problem, and that it is predominantly self-induced when individuals are unable to adequately manage their modifiable risk factors. This potentially damaging idea that partially stems from the misinterpretation of population-level data such as the INTERHEART study, which showed that nine modifiable risk factors accounted for more than 90% of population attributable risk for myocardial infarction.[21] Such a study has been crucial for estimating the societal effect of risk factors and the potential value of health policies targeting these. However, population attributable risk is not expected to sum to 100% and should not be used to argue against the importance of unravelling new mechanisms and markers of disease.[22] Indeed, data in this study highlight that, at an individual level, a patient presenting with life-threatening atherosclerosis without adequate explanation is not uncommon, and these patients are at high risk of cardiovascular disease and death and require equitable evidence-based treatment at an early stage. Additionally, the data indicate an unmet need for new biomarkers to identify individuals at risk of atherosclerotic events many years before they present with their first myocardial infarction, which would provide an opportunity to effectively target patient lifestyle and prescribe pharmacotherapies.[23,24]

In conclusion, the proportion of STEMI presentations occurring in the absence of identified standard risk factors was not insubstantial. These patients, particularly SMuRF-less women, have a higher risk of mortality compared with patients with STEMI who have at least one standard risk factor. These findings counter the common assumption that lower traditional risk for

atherosclerosis equates to lower risk after myocardial infarction, and highlight the need for evidence-based pharmacotherapy during the immediate post-infarct period irrespective of baseline risk factors or sex.

Contributors

GAF conceived and initiated the study, drafted the manuscript, and led the editing of the manuscript. STV contributed to study conception, data analyses and interpretation, and drafted the manuscript with GAF. NH did the statistical analysis and drafted components of the Results section. JS, JA, CA, VD, and ML assisted in data analyses and interpretation, and edited the manuscript. EH coordinated the study (in particular access to data), oversaw data analyses, and edited the manuscript. All authors had access to all the data. NH, STV, GAF, and EH accessed and verified the data. All authors approved the manuscript and are responsible for the decision to submit for publication.

Declaration of interests

GAF reports personal consulting fees from CSL and Janssen, and grants from Abbott Diagnostics, outside the submitted work. GAF also has a patent "biomarkers and oxidative stress" (USA Patent and Trademark Office; May 2, 2017; US9638699B2) issued to Northern Sydney Local Health District. JA reports grants from AstraZeneca, and personal fees from AstraZeneca, Bayer, Pfizer, Bristol Myers Squibb, and Boehringer Ingelheim, outside the submitted work. JS reports ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Eli Lilly, Boehringer, Bayer, and AstraZeneca, outside the submitted work. EH reports grants and personal fees from Amgen and Sanofi, and personal fees from Bayer and NovoNordisk, outside the submitted work. CA is supported by a New South Wales Health Early-Mid Career Fellowship and a Medical Research Future Fund Priority investigator grant from the Australian National Health and Medical Research Council. All other authors declare no competing interests.

Data sharing

SWEDEHEART does not allow individual data sharing to third parties. Access to aggregated data might be granted following review by the SWEDEHEART steering committee. Such requests can be submitted to the SWEDEHEART steering committee (contact details online) for consideration.

For **contact details** see https://www.ucr.uu.se/swedeheart/kontakt/support

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