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Standard modifiable cardiovascular risk factors and acute coronary syndrome free survival

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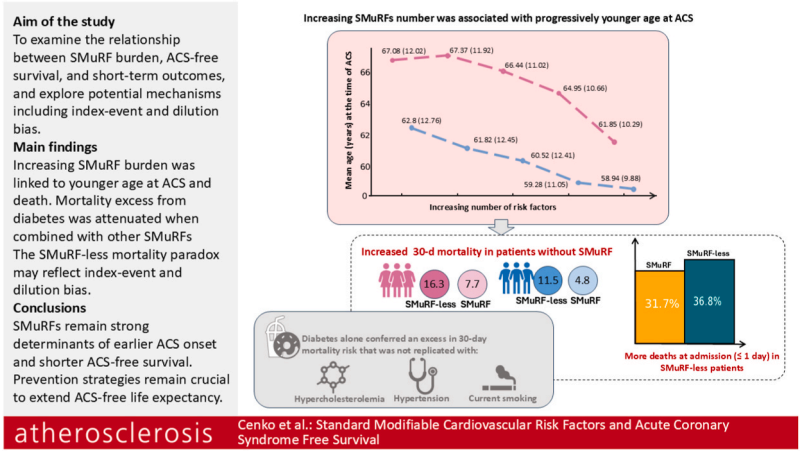
HIGHLIGHTS

- Most patients with first ACS had at least one standard modifiable risk factor (SMuRF).
- Increasing SMuRF burden was linked to younger age at ACS and death.
- Mortality excess from diabetes is attenuated when combined with other SMuRFs.
- SMuRF-less patients showed the highest 30-day mortality after ACS.
- The SMuRF-less mortality paradox may reflect index-event and dilution bias.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: Recent studies suggest that patients without standard modifiable cardiovascular risk factors (SMuRFs), hypertension, hypercholesterolemia, diabetes, or smoking, may experience higher short-term mortality after acute coronary syndrome (ACS) than those with risk factors. This study examined the relationship between SMuRF burden, ACS-free survival, and short-term outcomes, and explored potential mechanisms including index-event and dilution bias.

Methods: We analyzed data from 70,953 Caucasian patients with first-time ACS enrolled between 2005 and 2021 in the ISACS-TC Registry (NCT04008173). Patients with prior coronary heart disease were excluded. Traditional SMuRFs were identified from clinical history. The primary outcome was 30-day all-cause mortality; secondary measures included age at ACS onset and early death from hospital admission (≤1 day). Inverse probability weighting models adjusted for baseline imbalance.

Results: At least one SMuRF was present in 84 % of patients. Increasing SMuRF number was associated with progressively younger age at ACS (women: 67.1 vs 61.9 years; men: 62.8 vs 58.9 years; both $P < 0.001$). Conversely, 30-day mortality showed an inverse pattern, being highest in SMuRF-less patients and lowest among those with multiple SMuRFs (women: 16.3 % vs 7.7 %; men: 11.5 % vs 4.8 %). Diabetes alone conferred excess mortality (RR 1.29 [95 % CI 1.06–1.57] in women; 1.40 [1.16–1.69] in men), whereas isolated smoking, hypertension, or hypercholesterolemia were associated with lower risk. Early deaths at admission (≤1 day) were more frequent in SMuRF-less patients (36.8 % vs 31.7 %), suggesting arrhythmic mechanisms.

Conclusions: SMuRFs remain strong determinants of earlier ACS onset and shorter ACS-free survival. The apparent paradox of higher mortality in SMuRF-less patients likely reflects index-event and dilution bias. Prevention strategies targeting smoking, hypercholesterolemia, and diabetes remain crucial to extend ACS-free life expectancy.

1. Introduction

Recognition of the central role of standard modifiable cardiovascular risk factors (SMuRFs) in the development of coronary artery disease (CAD) has led to major reductions in the risk of cardiovascular events and death from coronary heart disease (CHD). Extensive epidemiological evidence has established current cigarette smoking, diabetes mellitus, hypercholesterolemia, and hypertension as the principal modifiable risk factors for CHD occurrence [1].

Nevertheless, a substantial proportion of patients present with CHD in the absence of any of SMuRFs. Such individuals are estimated to represent up to 30 % of those hospitalized with acute coronary syndromes (ACS) [2]. Earlier studies reported a close association between the number of SMuRFs and adverse outcomes after myocardial infarction [3].More recent investigations have paradoxically found higher mortality among patients without SMuRFs compared with those who have at least one, with women experiencing worse outcomes than men [4–6]. These observations underscore persistent gaps in the understanding of CHD prevention and risk stratification.

Several mechanisms have been advanced to explain this paradox. A frequently overlooked possibility is that previous analyses may have been affected by *index-event bias*, which arises when patients are selected based on the occurrence of ACS without accounting for the age or timing of that first event. Under such circumstances, apparent differences in mortality may not be disease-specific but may instead reflect longer life expectancy free of ACS among those without SMuRFs since age itself is a powerful determinant of CHD mortality. Distinguishing between these interpretations is critical for guiding preventive strategies. If the observed mortality differences are disease-specific, interventions should target presentation and management of ACS, including timely reperfusion and evidence-based pharmacotherapy. Conversely, if they reflect differences in ACS-free life expectancy, prevention efforts should focus on the upstream determinants of cardiovascular health and lifestyle behaviors driving risk-factor development including diet, physical inactivity, and socioeconomic context.

To address these uncertainties, we analyzed data from the International Survey of Acute Coronary Syndromes (ISACS) Archives to assess the prevalence and consistency of the four traditional risk factors across sexes and age groups among patients presenting with first ACS. We further examined the associations between individual and combined risk-factor exposures and both ACS-free survival and mortality from ACS.

2. Methods

2.1. Study design and population

The study population comprised 70,953 Caucasian patients enrolled in the International Survey of Acute Coronary Syndromes (ISACS) Archives registry network (ClinicalTrials.gov: **NCT04008173**) who presented with a first manifestation of acute coronary syndrome (ACS) between October 2005 and January 2021 (**Supplementary Fig. S1**). Patients with prior coronary heart disease (CHD) or heart failure of unknown origin were excluded. The design and data management procedures of the ISACS Archives have been previously described [7–10].

Local ethics committees at each participating center approved the study. As all data were collected anonymously, institutional review boards waived the requirement for individual informed consent. The study complies with the Declaration of Helsinki. De-identified data were transferred to the Department of Electrical and Computer Engineering, University of California, Los Angeles, for final statistical analyses.

2.2. Outcome measures

The primary outcome was all-cause mortality within 30 days of hospital admission. The 30-day window was chosen to extend follow-up beyond the index hospitalization while minimizing survivor bias. Thirty-day all-cause mortality was assessed through review of hospital records, direct telephone contact with patients or next-of-kin, and confirmation through regional or national mortality registries when available, following the standardized ISACS follow-up protocol. Secondary outcomes included ST-segment elevation myocardial infarction (STEMI), acute heart failure (AHF), and the Shock Index on admission. The diagnosis of AHF was based on clinical symptoms or signs and radiographic evidence of pulmonary congestion and graded using the Killip classification [11]. The Shock Index was defined as the ratio of heart rate

to systolic blood pressure on admission and categorized as < 1.0 (no or mild shock) or ≥ 1.0 (moderate or severe shock) [12]. Coronary artery bypass grafting (CABG) performed as urgent surgery after percutaneous coronary intervention (PCI) was included within the broader category of reperfusion/revascularization procedures.

2.3. Concomitant care and definitions

Medication use at admission and during hospitalization was recorded, including fibrinolysis, antiplatelet agents (aspirin and/or $P2Y_{12}$ inhibitors), heparins (unfractionated heparin or low-molecular-weight heparins), glycoprotein IIb/IIIa inhibitors [GP IIb/IIIa inhibitors], statins, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs] and β-blockers). Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months. Smoking status was self-reported: current smokers were those actively smoking at the time of the index event and during the previous 12 months; former smokers had quit for ≥12 months. Hypertension, hypercholesterolemia, and diabetes were recorded according to documented medical history before admission. A family history of CHD was defined as death from CHD before 55 years in men and 65 years in women among first-degree relatives or grandparents. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2); BMI ≥30 kg/m^2 indicated obesity. Delay to hospital presentation was measured as the time from symptom onset to hospital arrival and categorized as early (<120 min) or delayed (≥120 min) according to American College of Cardiology/American Heart Association (ACC/AHA) guidelines [13].

2.4. Statistical analysis

Patients were categorized according to the type and number of traditional cardiovascular risk factors and stratified by sex. For analyses

Table 1
Baseline characteristics.

	Traditional CHD risk factors N = 59,893	Without traditional CHD risk factors N = 11,060	Standardized difference	*P* value
Age (years), mean ± SD	62.6 ± 11.8	64.4 ± 12.3	−0.1461	<0.0001
Women, n (%)	21,451 (35.8)	4039 (36.5)	−0.0146	0.1578
Coronary heart disease risk factors				
Diabetes, n (%)	15,988 (26.7)	0.0 (0.0)	0.8534	<0.0001
Hypertension, n (%)	44,678 (74.6)	0.0 (0.0)	2.4234	<0.0001
Hypercholesterolemia, n (%)	29,658 (49.5)	0.0 (0.0)	1.4007	<0.0001
Current smokers, n (%)	27,860 (46.5)	0.0 (0.0)	1.3189	<0.0001
Former smokers, n (%)	1068 (1.8)	184 (1.7)	0.0092	0.3692
Family history of CAD, n (%)	19,389 (32.4)	1609 (14.5)	0.4303	<0.0001
BMI ≥30 kg/m^2, n (%)	12,592 (21.0)	1446 (13.1)	0.2126	<0.0001
Clinical history of cardiovascular disorders				
Prior stroke, n (%)	2415 (4.0)	327 (3.0)	0.0586	<0.0001
Peripheral artery disease, n (%)	1526 (2.5)	129 (1.2)	0.1025	<0.0001
Clinical history of comorbidities				
Chronic kidney disease, n (%)	2897 (4.8)	387 (3.5)	0.0670	<0.0001
Clinical presentation				
STEMI, n (%)	3,7512 (62.6)	5917 (53.5)	0.1859	<0.0001
NSTEMI, n (%)	11,952 (20.0)	1581 (14.3)	0.1507	<0.0001
Unstable angina, n (%)	10,429 (17.4)	3562 (32.2)	−0.3477	<0.0001
NSTE-ACS, n (%)	22,381 (37.4)	5143 (46.5)	−0.1859	<0.0001
ST-segment shifts in anterior leads (at ECG), n (%)	12,989 (21.7)	2074 (18.8)	0.0731	<0.0001
Time to admission <12 h, n (%)	44,741 (74.7)	7895 (71.4)	0.0748	<0.0001
Time to admission <2 h, n (%)	13,508 (22.6)	2238 (20.2)	0.0566	<0.0001
HR at admission (bpm), mean ± SD	81.9 ± 19.9	80.4 ± 19.6	0.0803	<0.0001
SBP at admission (mmHg), mean ± SD	139.2 ± 28.2	131.1 ± 29.5	0.2812	<0.0001
Revascularization therapy for STEMI				
Reperfusion therapy (fibrinolysis, PCI or CABG), n (%)	25,731 (43.0)	3648 (33.0)	0.2067	<0.0001
PCI, n (%)	16,456 (27.5)	2311 (20.9)	0.1541	<0.0001
Fibrinolysis, n (%)	11,113 (18.6)	1548 (14.0)	0.1237	<0.0001
Fibrinolysis and PCI, n (%)	1958 (3.3)	233 (2.1)	0.0719	<0.0001
CABG, n (%)	765 (1.3)	134 (1.2)	0.0059	0.5634
Invasive cardiac procedures				
PCI (all ACS), n (%)	22,163 (37.0)	3266 (29.5 %)	0.1591	<0.0001
CABG (all ACS), n (%)	1301 (2.2)	197 (1.8)	0.0281	0.0050
Medications on admission				
Aspirin and/or $P2Y_{12}$ inhibitors, n (%)	56,167 (93.8)	8499 (76.8)	0.4927	<0.0001
Unfractionated heparin, n (%)	33,401 (55.8)	6121 (55.3)	0.0085	0.4096
LMWH, n (%)	27,770 (46.4)	3215 (29.1)	0.3627	<0.0001
Heparins (all), n (%)	52,477 (87.6)	7890 (71.3)	0.4115	<0.0001
GP IIb/IIIa inhibitors, n (%)	4284 (7.2)	754 (6.8)	0.0132	0.2001
Medications during hospitalization				
β-blockers, n (%)	40,714 (68.0)	5268 (47.6)	0.4210	<0.0001
ACE-inhibitors/ARBs, n (%)	43,482 (72.6)	5185 (46.9)	0.5434	<0.0001
Statins, n (%)	47,224 (78.8)	6616 (59.8)	0.4217	<0.0001
Outcomes				
30-day mortality, n (%)	4631 (7.7)	1466 (13.3)	−0.1809	<0.0001
Acute heart failure, n (%)	14,789 (24.7)	2551 (23.1)	0.0382	0.0002
Shock index (moderate to severe), n (%)	2771 (4.6)	786 (7.1)	−0.1057	<0.0001

Values are mean ± SD or n (%).
ACE, angiotensin converting enzyme; ACS, acute coronary syndromes; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; GP, glycoprotein, HR, heart rate; LMWH, low molecular weight heparins; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

of individual risk factors, exposures were treated as dichotomous variables (presence vs. absence). Baseline characteristics were summarized as numbers (percentages) for categorical variables and mean ± standard deviation (SD) for continuous variables.

Complete data were available for mortality, sex, age, and index event. Missing data for traditional risk factors ranged from 9.8 % to 18.1 % and were addressed using multiple imputation by chained equations (MICE) [14].

To reduce confounding, an inverse probability weighting (IPW) approach based on propensity scores was applied [15]. Covariates included demographic variables, traditional and non-traditional risk factors, prior medical history, and clinical findings at admission. Stabilized weights were used to preserve sample size, with a threshold of 0.01 to limit the influence of extreme values. Balance between groups was confirmed when standardized differences after weighting were <10 % [16].

Odds ratios (ORs) and relative risks (RRs) with corresponding 95 % confidence intervals (CIs) were calculated from logistic regression and IPW models (Supplementary Methods). Trends were assessed using the Pearson correlation coefficient (r). Comparisons between subgroups employed two-sided P values and interaction tests on the logarithmic scale [17]. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Demographic and clinical features of patients with or without SMuRFs are shown in Table 1. Among all patients with ACS, at least one of the four traditional risk factors was present in 84.2 % of women and 84.6 % of men. Except for current smoking, the prevalence of each SMuRF was significantly higher in women than in men. SMuRF-less patients underwent fewer cardiac procedures and were less likely to receive evidence-based medications on admission and during

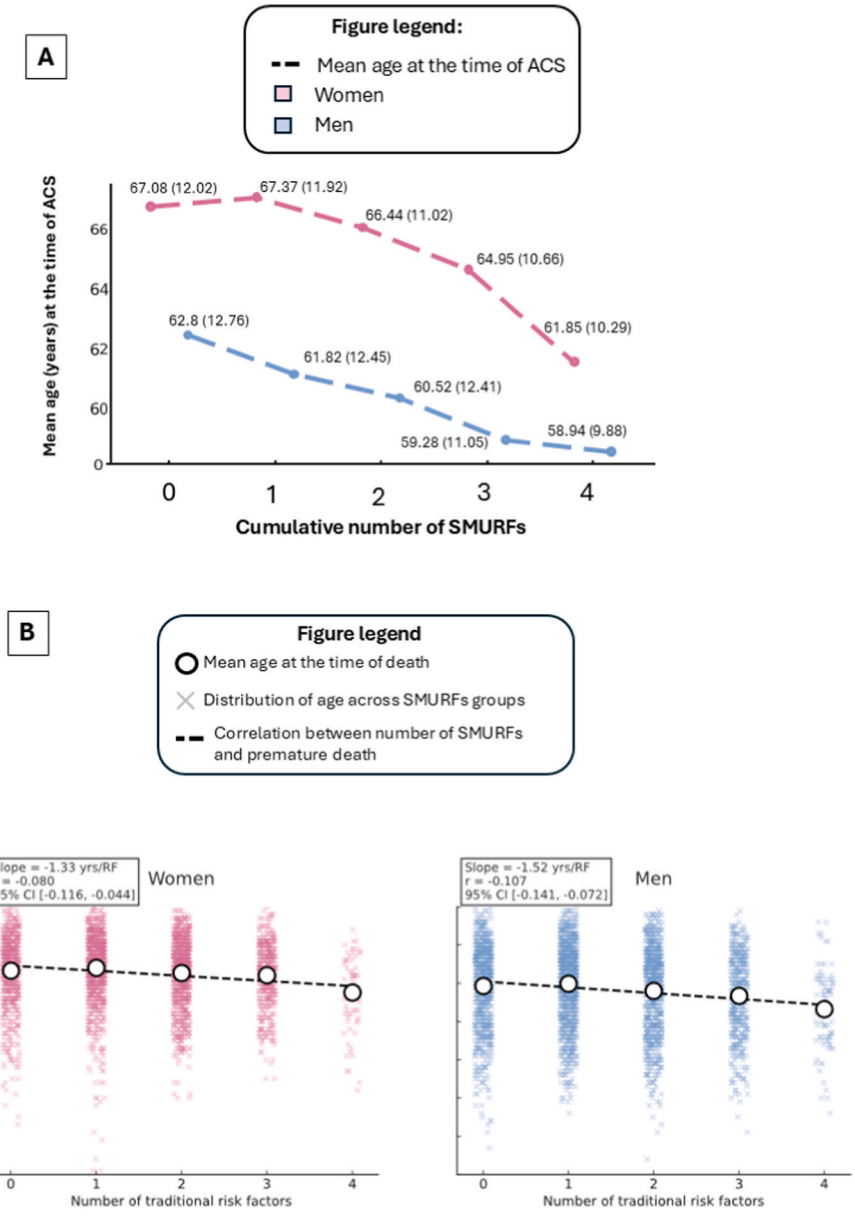

Fig. 1. Panel A, distribution of mean ages at time of presentation from first ACS event, by number of SMURFs; Panel B, distribution of mean ages at time of death from first ACS event, by number of SMURFs

ACS, acute coronary syndrome, SMURF, standard modifiable risk factor.

hospitalization than those with at least one risk factor.

3.2. Prevalence of SMuRFs and age at hospital presentation

An inverse relationship was observed between the number of SMuRFs and age at the time of the ACS event (Fig. 1a and Supplementary Table 1). The presence of all four risk factors reduced the age at presentation by nearly half a decade compared with the absence of any risk factor, both in women (from 67.1 ± 12.0 to 61.9 ± 10.3 years; r = −0.089, 95 % CI −0.101 to −0.077; P < 0.001) and men (from 62.8 ± 12.8 to 58.9 ± 9.9 years; r = −0.096, 95 % CI −0.106 to −0.087; P < 0.001).

3.3. Prevalence of SMuRFs and age of death

A clear relationship emerged between the number of risk factors and age at death (Fig. 1b and Supplementary Table 2). The mean age at death declined progressively with increasing number of risk factors, from 73.3 ± 9.8 to 67.6 ± 10.6 years in women (r = −0.080, 95 % CI -0.116–0.044; P < 0.001) and from 69.3 ± 11.2 to 63.2 ± 10.8 years in men (r = −0.107, 95 % CI -0.141–0.072; P < 0.001).

3.4. Relationship between SMuRFs and premature ACS and death from ACS

To further explore these associations, we examined predictors of premature ACS, defined as ACS occurring before the mean age of presentation among SMuRF-less patients (<67 years in women and <63 years in men). In multivariable logistic regression models (Fig. 2), current smoking was the strongest predictor of premature ACS (OR 4.14; 95 % CI 3.89–4.40 in women; 2.94; 95 % CI 2.82–3.06 in men). Hypercholesterolemia was also associated with premature ACS (OR 1.37; 95 % CI 1.30–1.46 in women; 1.47; 95 % CI 1.41–1.54 in men). Among SMuRFs, diabetes showed the strongest association with death from premature ACS (OR 1.38; 95 % CI 1.15–1.65 in women; 1.41; 95 % CI 1.21–1.65 in men). The adverse impact of current smoking on mortality was greater in women than in men (OR 1.35; 95 % CI 1.12–1.62 vs 0.99; 95 % CI 0.86–1.13). Hypertension showed an inverse association with premature ACS.

3.5. Timing of death

Among fatal ACS cases (n = 6097), at least one traditional risk factor was present in 77.6 % of women and 74.5 % of men. As shown in Fig. 3, 31.7 % of deaths among patients with any traditional risk factor

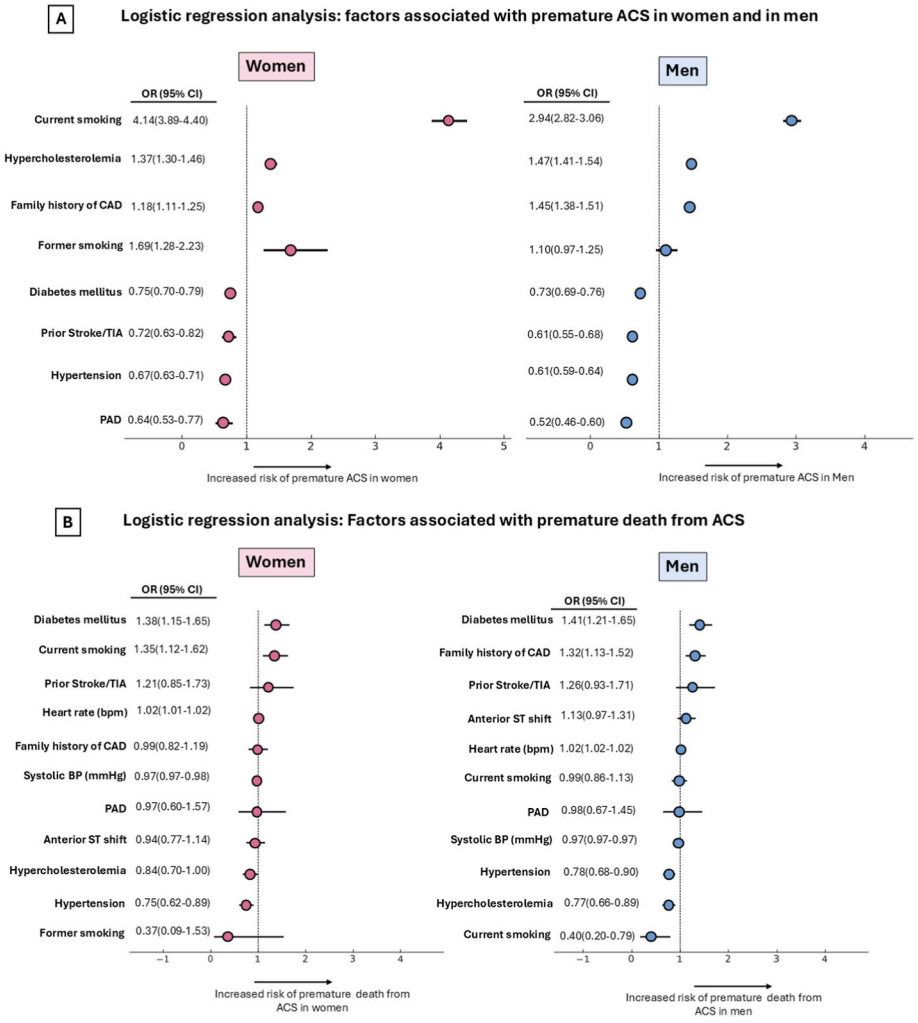

Fig. 2. Logistic regression analyses; Panel A factors associated with premature ACS in women and in men; Panel B Factors associated with premature death from ACS

Error bars indicate standard deviations.

ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; PAD, peripheral artery disease.

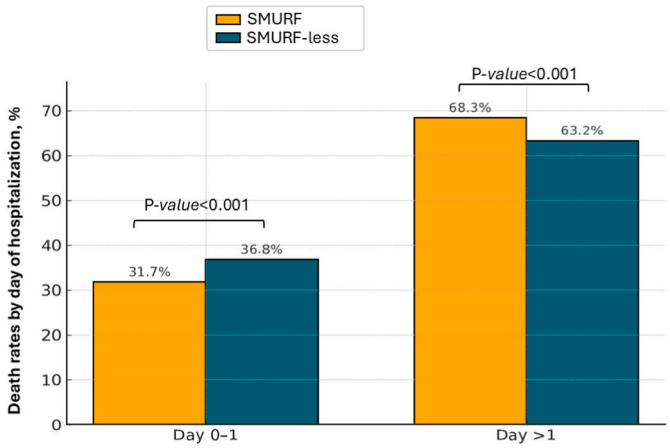

Fig. 3. Distribution of death rates across days of hospitalization, stratified by presence or absence of SMURFs
SMURF, standard modifiable risk factor.

occurred on day 0 or day 1 (the day of presentation or the following day), compared with 36.8 % among those without risk factors (P < 0.001). After the first day, mortality rates were similar or slightly lower in patients with no traditional risk factors.

3.6. *Adjusted mortality for patients with at least one SMuRF*

To account for potential confounding by disease severity and coexisting factors, we applied inverse probability weighting models (Table 2). Patients with at least one SMuRF had significantly lower 30-day mortality than those without (8.1 % vs 11.4 %; RR 0.68, 95 % CI 0.64–0.73). Conversely, they showed higher rates of STEMI (62.8 % vs 53.3 %; RR 1.48, 95 % CI 1.42–1.54) and AHF on admission (25.1 % vs 20.9 %; RR 1.27, 95 % CI 1.21–1.33). Shock Index ≥1.0 did not differ significantly (4.9 % vs 5.3 %; RR 0.92, 95 % CI 0.84–1.01). Sensitivity analyses confirmed similar adjusted estimates for the primary and secondary outcomes even under conditions of comparable in-hospital management (**Supplementary Results,** Tables S3–S8).

3.7. *Individual risk factors and outcomes*

To examine potential selection bias inherent in defining exposure as "one or more SMuRFs," we conducted a more granular analysis isolating the contribution of each individual SMuRF to outcomes (Table 3). Patients with diabetes were more likely to present with acute heart failure (AHF) and had higher 30-day mortality compared with SMuRF-less patients. The relative risks (RRs) for mortality were 1.29 in women (95 % CI 1.06–1.57) and 1.40 in men (95 % CI 1.16–1.69). In contrast, patients with isolated smoking, hypertension, or hypercholesterolemia exhibited significantly lower mortality than SMuRF-less individuals. Among these, RRs ranged from 0.53 (95 % CI 0.42–0.67) in women who smoked to 0.46 (95 % CI 0.37–0.59) in men with hypercholesterolemia (Fig. 4, Tables S 9 to S 12). Only patients with hypertension showed higher rates of AHF in both women and men.

3.8. *Attenuation of risk and dilution bias among patients with multiple SMuRFs*

To investigate whether dilution bias contributed to the apparent paradox observed in patients with one or more SMuRFs, we redefined exposure by creating more homogeneous subgroups—specifically, patients with diabetes in combination with a single additional SMuRF (Fig. 5). The excess 30-day mortality associated with diabetes alone was attenuated when diabetes coexisted with other SMuRFs. The relative risks (RRs) for 30-day mortality in patients with diabetes who also

Table 2
Inverse probability weighting: clinical factors and outcomes stratified by traditional coronary heart disease risk factor status.

Characteristics	Traditional CHD risk factors (N = 59,893)	Without Traditional CHD risk factors (N = 11,060)	Standardized difference	*P* value
Age (years), mean ± SD	62.9 ± 11.8	62.6 ± 12.7	0.0218	0.1711
Coroanry heart disease risk factors				
Family history of CAD, %	29.6	29.6	−0.0005	1.0000
Former smokers, %	1.8	1.9	−0.0115	0.7908
BMI ≥30 kg/m^2, %	19.8	20.0	−0.0062	0.7595
Clinical history of cardiovascular disorders				
Peripheral artery disease, %	2.3	2.1	0.0126	0.6178
Prior stroke, %	3.9	4.0	−0.0069	0.8261
Clinical presentation on admission				
ST-segment shifts in anterior leads (at ECG), n (%)	21.2	21.4	−0.0044	0.7626
SBP at admission (mmHg), mean ± SD	137.9 ± 28.4	138.4 ± 29.9	−0.0167	0.0712
HR at admission (bpm), mean ± SD	81.7 ± 19.9	81.8 ± 20.2	−0.0041	0.2796
Outcomes				
30-day mortality, %	8.1	11.4	−0.1125	<0.0001
Risk Ratio (95 % CI)	0.68 (0.64–0.73)		−0.1125	<0.0001
Acute heart failure, %	25.1	20.9	0.0995	<0.0001
Risk Ratio (95 % CI)	1.27 (1.21–1.33)		0.0995	<0.0001
Shock index (moderate to severe), %	4.9	5.3	−0.0173	0.0988
Risk Ratio (95 % CI)	0.92 (0.84–1.01)		−0.0173	0.0908
STEMI, %	62.8	53.3	0.1937	<0.0001
Risk Ratio (95 % CI)	1.48 (1.42–1.54)		0.1937	<0.0001

Values are mean ± SD, percentages, or risk ratio (95 % CI).
BMI, body mass index; CAD, coronary artery disease; ECG, electrocardiogram; HR, heart rate; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

smoked were 1.39 (95 % CI 0.92–2.09) for women and 0.89 (95 % CI 0.68–1.17) for men. For those with concomitant hypercholesterolemia, RRs were 0.91 (95 % CI 0.66–1.25) in women and 0.75 (95 % CI 0.53–1.06) in men, while in those with hypertension, RRs were 1.14 (95 % CI 0.99–1.32) in women and 1.12 (95 % CI 0.96–1.31) in men (Fig. 5; Tables S12–S15). Presentation with AHF also differed across subgroups: it was most common in women with hypertension or hypercholesterolemia, and in men with hypertension.

4. Discussion

Our study indicates that the vast majority of patients presenting with ACS as first manifestation of CHD have traditional risk factor exposure, consistent with the results of previous studies [3,18–21]. For fatal ACS, prior exposure to at least one traditional CHD risk factor ranged from 74 % to 77 %. Differences in SMuRF burden translated into marked variations in ACS-free survival and subsequent mortality: patients with all four SMuRFs died, on average, about five years earlier than SMuRF-less individuals. In contrast, retrospective analyses of 30-day mortality

Table 3
Inverse probability weighting: Women versus men. Clinical factors and outcomes stratified by presence of one single SMURF versus absence of risk factors.

	Women			*Men*		
Outcomes	One SMURF	SMuRF-less	*P* value	One SMURF	SMuRF-less	*P* value
Diabetes mellitus						
30-day mortality, %	20.7	16.8		15.9	11.9	
Risk Ratio (95 % CI)	1.29 (1.06–1.57)		0.01	1.40 (1.16–1.69)		0.001
Acute Heart Failure, %	40.4	27.7		30.5	21.3	
Risk Ratio (95 % CI)	1.77 (1.50–2.08)		<0.0001	1.62 (1.40–1.89)		<0.0001
Current smoking						
30-day mortality, %	8.4	14.8		7.1	10.2	
Risk Ratio (95 % CI)	0.53 (0.42–0.67)		<0.0001	0.68 (0.59–0.77)		<0.0001
Acute Heart Failure, %	21.8	25.1		19.3	18.8	
Risk Ratio (95 % CI)	0.83 (0.71–0.98)		0.0273	1.03 (0.94–1.13)		0.50
Hypertension						
30-day mortality, %	13.6	15.5		8.6	11.0	
Risk Ratio (95 % CI)	0.86 (0.76–0.97)		0.01	0.77 (0.68–0.86)		<0.0001
Acute Heart Failure, %	31.2	27.0		23.8	20.8	
Risk Ratio (95 % CI)	1.23 (1.12–1.35)		<0.0001	1.19 (1.09–1.29)		<0.0001
Hypercholesterolemia						
30-day mortality, %	10.5	16.0		5.6	11.4	
Risk Ratio (95 % CI)	0.62 (0.48–0.79)		<0.0001	0.46 (0.37–0.59)		<0.0001
Acute Heart Failure, %	27.5	26.6		17.8	20.5	
Risk Ratio (95 % CI)	1.04 (0.88–1.24)		0.62	0.84 (0.73–0.97)		0.02

Values are mean ± SD, percentages, or risk ratio (95 % CI).
SMURF, standard modifiable risk factor.

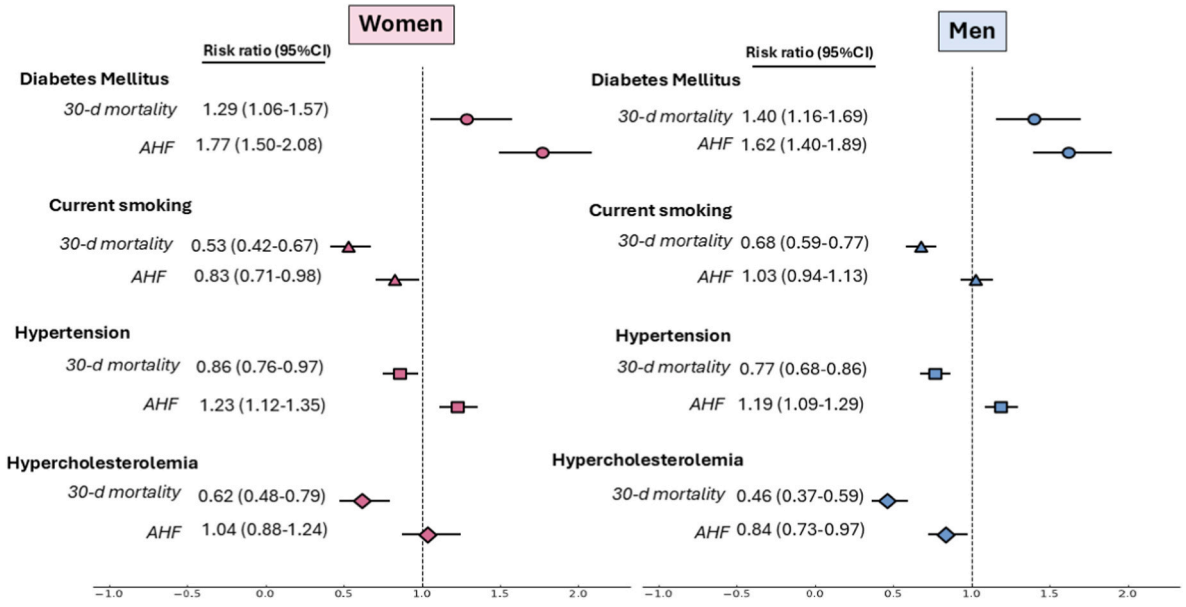

Fig. 4. Inverse Probability Wieghting: Effect of isolated SMURFs on outcomes, by sex
AHF, Acute heart failure; CI, confidence interval.

revealed a paradoxical pattern. Patients without SMuRFs experienced higher early mortality after ACS than those with one or more SMuRFs. However, deaths among SMuRF-less patients occurred later in life, consistent with their longer ACS-free survival prior to the event. Together, these observations raise important clinical and methodological considerations.

Because atherosclerosis typically develops later in women than in men, a high SMuRF burden in women would be expected to shift ACS to older ages, as in men with comparable burden. Our findings support this interpretation. The presence of all four SMuRFs reduced the age at hospital presentation and death by nearly half a decade. ACS-free survival declined from approximately 63 to 59 years in men and from 67 to 62 years in women. In essence, patients with SMuRFs carry a survival disadvantage relative to SMuRF-less peers.

Individual SMuRFs showed distinct quantitative relationships with premature ACS, defined as events occurring before the mean age of presentation among SMuRF-less patients (<67 years in women and <63 years in men). Current smoking exerted the greatest influence, increasing the odds of premature ACS more than fourfold (OR 4.14). Hypercholesterolemia was likewise associated with earlier onset (OR 1.37), indicating that lipid abnormalities accelerate the clinical expression of coronary disease. In contrast, diabetes was not related to the occurrence of premature ACS but showed the strongest association with mortality once premature ACS had occurred, underscoring its role

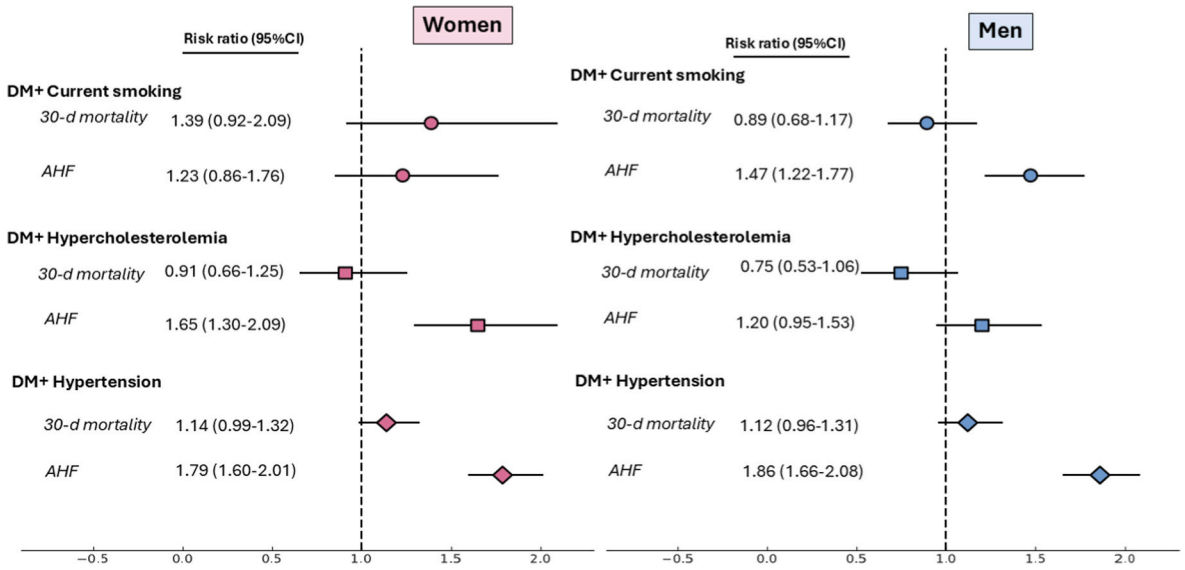

Fig. 5. Inverse Probability Wieghting: dilution of diabetes effect on outcomes when combining it with one further risk factor, by sex
AHF, Acute heart failure; DM, diabetes mellitus; CI, confidence interval.

in post-event vulnerability. Hypertension was not significantly associated with either the timing or fatality of ACS.

These findings should not be interpreted to imply that hypertension lacks overall cardiovascular impact. Our analyses were confined to first ACS events and therefore capture only one manifestation of cardiovascular disease. Treatment prioritization must consider the broader spectrum of initial CVD presentations across SMuRFs [22]. Hypertension remains a major determinant of heart failure and stroke [23,24], and is particularly common among younger stroke patients [25]. Diabetes, in turn, is associated with a wide range of incident cardiovascular diseases, with heart failure and peripheral arterial disease representing frequent first clinical manifestations [26], and with out-of-hospital cardiac arrest and sudden cardiac death also contributing importantly to premature mortality [27]. These associations suggest that diabetes may account for a substantial share of post-ACS survival variance and could partly explain the higher pre-hospital mortality and resulting index-event bias observed in retrospective analyses.

Recent attention has focused on SMuRF-less ACS, as several reports have shown higher all-cause mortality compared with patients possessing one or more SMuRFs. A related claim is that mortality is higher in women than in men within this subgroup [28]. Our results confirm a strong inverse association between SMuRF count and 30-day mortality, even after adjustment for age, BMI, family history of CAD, and other cardiovascular comorbidities. However, earlier data supporting a sex-specific excess risk appear to have been over-interpreted [4]. In our study, adjusted relative risks for all-cause mortality in patients with vs without SMuRFs were similar in men and women. Thus, sex-based outcome differences exist in ACS, but do not vary according to SMuRF status [29,30].

The mechanisms underlying the excess mortality observed in SMuRF-less ACS remain uncertain. In our cohort, this association persisted even though patients with one or more SMuRFs presented more frequently with ST-segment elevation and higher Killip class, both markers of greater clinical severity. Thus, SMuRF-less status is unlikely to represent patients who were simply too ill to provide an adequate medical history. Nor can the finding be attributed to undertreatment, since subgroup analyses restricted to patients receiving equitable, evidence-based in-hospital care yielded estimates comparable to those observed in the overall matched population.

Prior comparisons of mortality in "≥1 SMuRF" vs "SMuRF-less" groups often assume symmetric contributions of SMuRFs to acute outcomes. Formal contrasts of individual SMuRF effects on mortality are scarce. To address this gap, we evaluated the independent impact of each SMuRF on short-term mortality after ACS. We observed a strong and consistent association between diabetes, when present as the sole SMuRF, and increased short-term mortality, in line with previous research [31,32]. In contrast, patients with isolated smoking, hypertension, or hypercholesterolemia exhibited significantly lower mortality compared with SMuRF-less individuals. Although the reasons why these risk factors are paradoxically associated with better ACS outcomes were not within the scope of our study, our data offer support for some hypotheses while casting doubt on others.

There may be statistical issues at play. A central concern is index-event bias, which occurs when analyses are conditioned on the occurrence of ACS. The risks of both ACS and ACS mortality rise with age and with SMuRF burden. Conditioning on having ACS can, therefore, induce spurious dependencies among risk factors. SMuRF-less patients, who tend to develop ACS later in life after a longer ACS-free interval may require less cumulative exposure to risk factors to experience an event. Thus, their higher early post-ACS mortality early can partly reflect older age at index rather than disease-specific lethality.

A second, complementary mechanism is dilution bias. When exposures co-occur and share overlapping pathways or trigger earlier detection and treatment, the marginal effect of a single SMuRF can appear attenuated. In our analyses, diabetes alone carried excess 30-day mortality, but this excess was attenuated or absent when diabetes coexisted with smoking, hypercholesterolemia, or hypertension. This pattern is consistent with dilution bias: the coexistence of other SMuRFs may (a) lead to earlier preventive therapy (e.g., statins, antihypertensives, antiplatelets), (b) reflect shared causal pathways that obscure the independent effect of a single factor, or (c) redistribute risk across other initial CVD manifestations such as heart failure or stroke. On this background, dilution bias should be viewed as a plausible explanatory framework rather than a demonstrated causal mechanism.

Other explanations deserve mention. SMuRF-less patients could harbor non-traditional factors (prediabetes, physical inactivity, psychosocial stress, family history). Yet in our cohort, obesity, family history, and former smoking were less common in SMuRF-less patients. Given the strong positive associations between prediabetes/physical inactivity and obesity [33], these factors are unlikely to explain the excess mortality. Psychosocial factors often operate as barriers to adherence in populations with SMuRFs [34,35], but appear insufficient to account for the higher early mortality seen in SMuRF-less ACS.

Most notably, the timing of death differed between groups. Early

deaths (within day 0–1) accounted for 36.8 % of total 30-day mortality in SMuRF-less patients, compared with 31.7 % among those with ≥1 SMuRF. Beyond the first day, outcomes were similar or slightly better in SMuRF-less individuals. This pattern, higher early mortality without greater clinical severity at presentation (Killip class), points to malignant ventricular arrhythmias as a likely determinant of death. Many patients with post-ACS arrhythmias do not survive to admission or die shortly thereafter [36]. This underscores the need for public-health strategies to identify arrhythmic risk markers with added predictive value for ACS mortality.

5. Limitations

This observational analysis is subject to residual confounding, though IPW minimized imbalances. We lacked a non-ACS control; however, prior work shows high SMuRF exposure even among individuals without clinical CHD(18). SMuRF ascertainment by general practitioners may introduce misclassification bias as true SMuRF prevalence is likely higher, as ~30 % of patients with hypertension, hypercholesterolemia, or diabetes are unaware of their condition [37,38]. Data on pre-event medications were incomplete and therefore excluded from analysis; prior therapy could have attenuated the apparent predictive power of SMuRFs for ACS occurrence. Restricting to first ACS reduces potential bias from secondary prevention. We lacked direct biochemical measures of glycemia. This limitation, common to many large registry analyses, may have led to underestimation or misclassification of diabetes prevalence and attenuated its observed association with outcomes. Discharge medications were not included in adjustment models because the primary endpoint was 30-day mortality, and discharge therapies are prescribed only to patients who survive the acute hospitalization. Adjusting for treatments received after survival introduces immortal time bias, which could distort comparisons between SMuRF-less patients and those with SMuRFs. For this reason, only medications administered at hospital admission were considered in multivariable and weighting analyses. Finally, adjudicated cause-of-death information was not systematically collected, precluding reliable cause-specific mortality analyses. To address this gap, we examined timing of death, STEMI rates, Killip class, acute heart failure, and shock index as physiologic correlates of early post-ACS mortality, but these remain proxy measures. Because the cohort consisted primarily of European White patients, generalizability of absolute lifetime risk estimates to other racial/ethnic groups remains uncertain.

5.1. Future directions

Future research should aim to clarify the mechanisms underlying the excess early mortality observed in SMuRF-less ACS. Prospective studies incorporating continuous rhythm monitoring, biomarkers of electrical instability, advanced imaging, and genomic or metabolic profiling are needed to determine whether malignant ventricular arrhythmias or other non-ischemic pathways contribute to heightened early risk.

5.2. Conclusions

These findings have practical implications for prevention and public health. Despite perceptions that modern cardiovascular care neutralizes risk, SMuRFs remain powerful precursors of ACS and are associated with substantially shorter ACS-free survival. Reducing hypercholesterolemia and smoking, along with effective diabetes management offers the greatest opportunity to extend ACS-free life and lower ACS mortality. At the same time, SMuRF-less status should not be read as reassuring in ACS. Elevated early mortality suggests an arrhythmic vulnerability that warrants improved pre-hospital detection and early in-hospital protection. Awareness of shorter survival with SMuRFs may help motivate lifestyle change and adherence to preventive therapy in both women and men.

Authors contributions

RB and EC designed and wrote the first draft of the study. JY carried out the statistical analyses. All authors contributed to further drafts and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RB is the guarantor.

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Declaration of competing interest

The authors have none to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120616.

Data availability

To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study. The source codes for this manuscript are uploaded on GitHub.

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