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Published in:
International Journal of Cardiology

DOI (link to publication from Publisher):
10.2139/ssrn.3948431
10.1016/j.ijcard.2022.06.036

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Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Attar, R., Valentin, J. B., Andell, P., Nielsen, R. E., & Jensen, S. E. (2022). Major adverse cardiovascular events following acute coronary syndrome in patients with bipolar disorder. *International Journal of Cardiology*, *363*, 1-5. https://doi.org/10.2139/ssrn.3948431, https://doi.org/10.1016/j.ijcard.2022.06.036

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International Journal of Cardiology 363 (2022) 1–5

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Major adverse cardiovascular events following acute coronary syndrome in patients with bipolar disorder

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ARTICLE INFO

Keywords:
Bipolar disorder
Acute coronary syndrome
Acute myocardial infarction
Epidemiology

ABSTRACT

Background: Persons with bipolar disorder (BD) have a higher cardiovascular mortality compared to the general population, partially explained by the increased burden of cardiovascular risk factors. Research regarding outcomes following acute coronary syndrome (ACS) in this population remains scarce.
Design: This Danish register-based study included patients diagnosed with BD and ACS in the period between January 1st, 1995, to December 31st, 2013. Study participants were matched 1:2 to patients without BD on sex, date of birth, time of ACS diagnosis and comorbidities. The primary outcome of interest was major adverse cardiovascular events (MACE) a composite of all-cause mortality, reinfarction or stroke. MACE and its individual components were compared between patients with and without BD.
Results: 796 patients with BD were compared to 1592 patients without BD, both groups had a mean age of first ACS of 66.5 years. MACE was 38% increased (HR 1.38 95% CI 1.25–1.54), all-cause mortality was 71% increased (HR 1.71 95% CI 1.52–1.92), stroke was 94% increased (HR 1.94 95% CI 1.56–2.41) and reinfarction rates were 17% lower (HR 0.83 95% CI 0.69–1.00) in the BD population compared to the population without BD. We also found higher prevalences of heart failure (9.1% vs. 6.5%), valve disease (5.3% vs. 3.5%), anemia (8.7% vs. 5.8%), chronic obstructive pulmonary disease (13.4% vs. 9.3%) and stroke (11.8% vs. 7.8%) in the population with BD at baseline, all p-values <0.05.
Conclusion: Bipolar disorder was associated with a higher risk of composite MACE, all-cause mortality, and stroke, after ACS compared to patients without BD.

1. Introduction

Bipolar disorder (BD) is a severe mental illness characterized by episodic swings in mood and behavior that can be manic, depressive or mixed [1]. Persons with bipolar disorder have an increased mortality risk equating to an almost 10-year shorter life span compared to the general population [2,3]. The majority of the excess mortality is either from unnatural causes such as suicide or from natural causes where cardiovascular diseases (CVD) are the largest contributors [2,4,5]. The all-cause mortality as well as cardiovascular mortality is up to two times as high in this population [5,6] partially due to the increased burden of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, smoking, obesity and low physical activity [7–15]. Furthermore, patients with bipolar disorder have lower rates of revascularization [16,17] (percutaneous coronary intervention and coronary artery bypass grafting) following myocardial infarction (MI), which further increases the associated adverse cardiovascular risk [18].

Acute coronary syndrome (ACS) describes a spectrum of clinical presentations caused by decreased blood flow through the coronary arteries. The term ACS includes unstable angina pectoris (UAP), non-ST-

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https://doi.org/10.1016/j.ijcard.2022.06.036
Received 19 October 2021; Received in revised form 19 May 2022; Accepted 10 June 2022
Available online 16 June 2022
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segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) [19]. Research regarding outcomes following ACS in a population with BD remains scarce. The aim of this study is therefore to investigate major adverse cardiovascular events (MACE: defined as mortality, stroke or reinfarction), the individual endpoints of MACE as well as to assess the prevalence of comorbidities in a population with BD.

2. Methods

2.1. Study design and databases

This Danish register-based study includes all patients with an incident diagnosis of ACS in the period between January 1st, 1995 to December 31st, 2013 and a diagnosis of BD between start of register and ACS diagnosis. Study subjects were followed until December 31st, 2014 allowing for a minimum of 1-year follow up for all patients. The data was derived from the National Patient Register (NPR) [20] and Danish Psychiatric Central Research Patient Register (DPCRR) [21] using a unique 10-digit personal identification number assigned to residents of Denmark, which allows for linkage between all databases [22]. The DPCRR was integrated in the NPR in 1995 and data were subsequently also extracted from the NPR. Healthcare in Denmark is tax financed and free for all citizens, furthermore, the hospitals, incl. Psychiatric hospitals, are administered by the Danish regions, and every region are obligated to register all patients in the national patient register. A limitation to the registries used were the lack of data on lifestyle associated risk factors such as smoking, alcohol or substance abuse, physical activity, and body mass index, which consequently could not be adjusted for.

2.2. Study population

All patients in the study had a diagnosis of ACS, which entailed UAP (I20.0), NSTEMI (I21.4), STEMI (I21.0–I21.3) and unspecified AMI (I21.9) defined according to the World Health Organization International Classification of Diseases 10th revision (ICD-10). Patients were stratified according to an additional preceding diagnosis of bipolar disorder (ICD-10 F30 and F31 and ICD-82961, 2963, 2968 and 2969). The ICD 8th version was included since some diagnoses of bipolar disorder preceded the 10th revision; the 9th revision was never introduced in Denmark. Patients with both ACS and bipolar disorder were matched 1:2 to patients without BD on sex, date of birth ($\pm$ 2 years), time of ACS diagnosis ($\pm$ 2 years) and on the exact levels of a risk score, further specified below. Patients without BD had no psychiatric diagnosis in the NPR or DPCR nor a diagnosis of intentional self-harm (ICD-10 F*, X60–X84, Y10–Y34 and ICD-8290–315, E950–E959) in the NPR prior to ACS. All unmatched patients were excluded from subsequent analyses.

2.3. Approvals

The study was authorized and approved by the Danish Protection Agency and the Danish Health Data Authority. According to Danish legislation no ethics approval is required for registry studies.

2.4. Outcomes

The main outcome, MACE, was defined as all-cause mortality, reinfarction (ICD-10 I21.0–I21.4, I21.9) or stroke (hemorrhagic and ischemic ICD-10 I61, I63, I64, I69.3, and I69.4). The secondary outcomes were the individual outcomes of MACE. We also investigated the prevalence of coronary risk factors and comorbidities at baseline.

2.5. Risk score

We used risk score to assess the degree of confounding from comorbidities prior to index. The score is made up of three levels, the first level included patients with 0 comorbidities, the second with 1 or 2 comorbidities and the third level $\geq$ 3 comorbidities. The comorbidities were only counted once and included the following:

- Hyperlipidemia (ICD-10 E78.0–E78.5 and ICD-827900),
- Obesity (ICD-10 E66 and ICD8 27,799),
- Atrial flutter/fibrillation (ICD-10 I48.9 and ICD-842793, 42,794),
- Hypertension (ICD-10 I10.9, I11–I15 and ICD-840009, 4001–4009,
- 401–404, 41,009, 41,109, 41,209, 41,309, 41,409, 43,509, 43,809, 43,700–
- 43,709),
- Heart failure (ICD-10 I50 and ICD-842599, 42,799, 42,899, 42,709,
- 4271),
- Cardiomyopathy (ICD-10 I42, I430–I438 and ICD-87464),
- Sick sinus syndrome (ICD-10 I49.5),
- Mitral and aortic valve disease (ICD-10 I05, I06, I08, I34, I35, and ICD-
- 8394–396),
- Diabetes mellitus (ICD-10 E10–E14 and ICD-8249, 25,000–25,009),
- Anemia (ICD-10 D46, D50–D53, D55–D64 and ICD-8280–285),
- Chronic obstructive pulmonary disease (ICD-10 J42–J44 and ICD8
- 490–492),
- Peripheral artery disease (PAD; ICD-10 I70, I73.9, I74, R02 and ICD-8
- 441–445), and
- Stroke (ICD-10 I61, I63, I64, I69.1, I69.3, I69.4 and ICD-8431, 433, 434).

2.6. Statistical analysis

Fisher's exact and Student's *t*-tests were used to analyze sex and the mean age during ACS diagnosis. Categorical variables are expressed as numbers with percentages and continuous variables as means with standard deviations (sd). Fisher's exact test was used to compare the risk score defined above between the two populations. The primary outcome MACE was analyzed and compared between the populations with and without BD using Cox Proportional Hazard Models and Kaplan-Meier Survival Estimators. The secondary outcomes, all-cause mortality, reinfarction and stroke, were likewise investigated using Cox Proportional Hazard Models. The assumption of proportional hazards was assessed by visual inspection of log-log plots. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Reinfarction was defined as a new diagnosis of ACS following discharge by including a delayed entry variable of 30 days in the statistical analysis. The primary analysis only included patients who survived the hospital stay, and therefore we performed sensitivity analyses on all outcomes including patients who died during the hospital stay. A p-value <0.05 was considered statistically significant. All analyses were performed using STATA version 15 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Patient characteristics

This registry study included 2388 patients: 796 patients with BD and 1592 patients without BD. The mean age of the study population was 66.5 years and 49% were male (Table 1). Patients with BD had a higher prevalence of diagnosed heart failure (9.1% vs. 6.5%), mitral/aortic valve disease (5.3% vs. 3.5%), anemia (8.7% vs. 5.8%), chronic obstructive pulmonary disease (13.4% vs. 9.3%) and stroke (11.8% vs. 7.8%) at baseline. In contrast, lower prevalences of diagnosed hyperlipidemia (4.6% vs. 8.7%) and peripheral artery disease (5.1% vs. 8.9%) were seen in the population with bipolar disorder. All p-values <0.05. In both groups the number of conditions comprising the risk score was distributed such that 34% had zero conditions at baseline, 27% had one

Table 1
Baseline characteristics of the populations with and without bipolar disorder (BD) during index admission for acute coronary syndrome.

	Bipolar	Without BD	P-value
Male n (%)	391 (49.1)	782 (49.1)	1.000
Age mean (sd)	66.6 (11.8)	66.5 (11.8)	0.956
Hyperlipidemia n (%)	37 (4.6)	**139 (8.7)**	**<0.001**
Obesity n (%)	49 (6.1)	93 (5.8)	0.783
Diabetes mellitus n (%)	104 (13.0)	211 (13.2)	0.949
Hypertension n (%)	189 (23.7)	391 (24.5)	0.686
Comorbidities			
Heart failure n (%)	**73 (9.2)**	104 (6.5)	**0.025**
Cardiomyopathy n (%)	7 (0.9)	14 (0.9)	1.000
SSS n (%)	5 (0.6)	10 (0.6)	1.000
Mitral/aortic valve disease n (%)	**42 (5.3)**	56 (3.5)	**0.048**
Atrial fibrillation/flutter n (%)	55 (6.9)	117 (7.3)	0.737
Anemia n (%)	**69 (8.7)**	92 (5.8)	**0.009**
COPD n (%)	**107 (13.4)**	149 (9.3)	**0.003**
PAD	41 (5.1)	**142 (8.9)**	**0.001**
Stroke	**94 (11.8)**	125 (7.8)	**0.002**

Bold value is indicative of statistical significance.
Abbreviations: BD – bipolar disorder, SSS – sick sinus syndrome, COPD – chronic obstructive pulmonary disease, PAD – peripheral artery disease.

condition and 39% had metabolic syndrome.

3.2. Major adverse cardiovascular events

MACE was 38% (HR 1.38, 95% CI 1.25–1.54, $p < 0.001$), all-cause mortality was 71% (HR 1.71, 95% CI 1.52–1.92, $p < 0.001$) and stroke was 94% (HR 1.94, 95% CI 1.56–2.41, $p < 0.001$) higher in patients with BD compared to patients without BD. Reinfarction rates were 17% lower in the population BD compared to patients without BD (HR 0.83, 95% CI 0.69–1.00, $p = 0.049$). (See Fig. 1) (See Table 2).

Table 2
Main outcomes of MACE and the individual outcomes comparing the populations with and without bipolar disorder (BD).

	Population	Events n (%)	HR (95% CI)	P-value
MACE	Bipolar	582 (73.0)	1.38 (1.25–1.54)	<0.001
	Without BD	951 (59.7)		
All-cause mortality	Bipolar	482 (60.5)	1.71 (1.52–1.92)	<0.001
	Without BD	677 (42.5)		
Stroke	Bipolar	147 (18.4)	1.94 (1.56–2.41)	<0.001
	Without BD	182 (11.4)		
Reinfarction	Bipolar	160 (20.1)	0.83 (0.69–1.00)	0.049
	Without BD	416 (26.1)		

Abbreviations: BD – bipolar disorder, MACE – major adverse cardiovascular events, HR (95% CI) – hazard ratios and 95% confidence intervals,

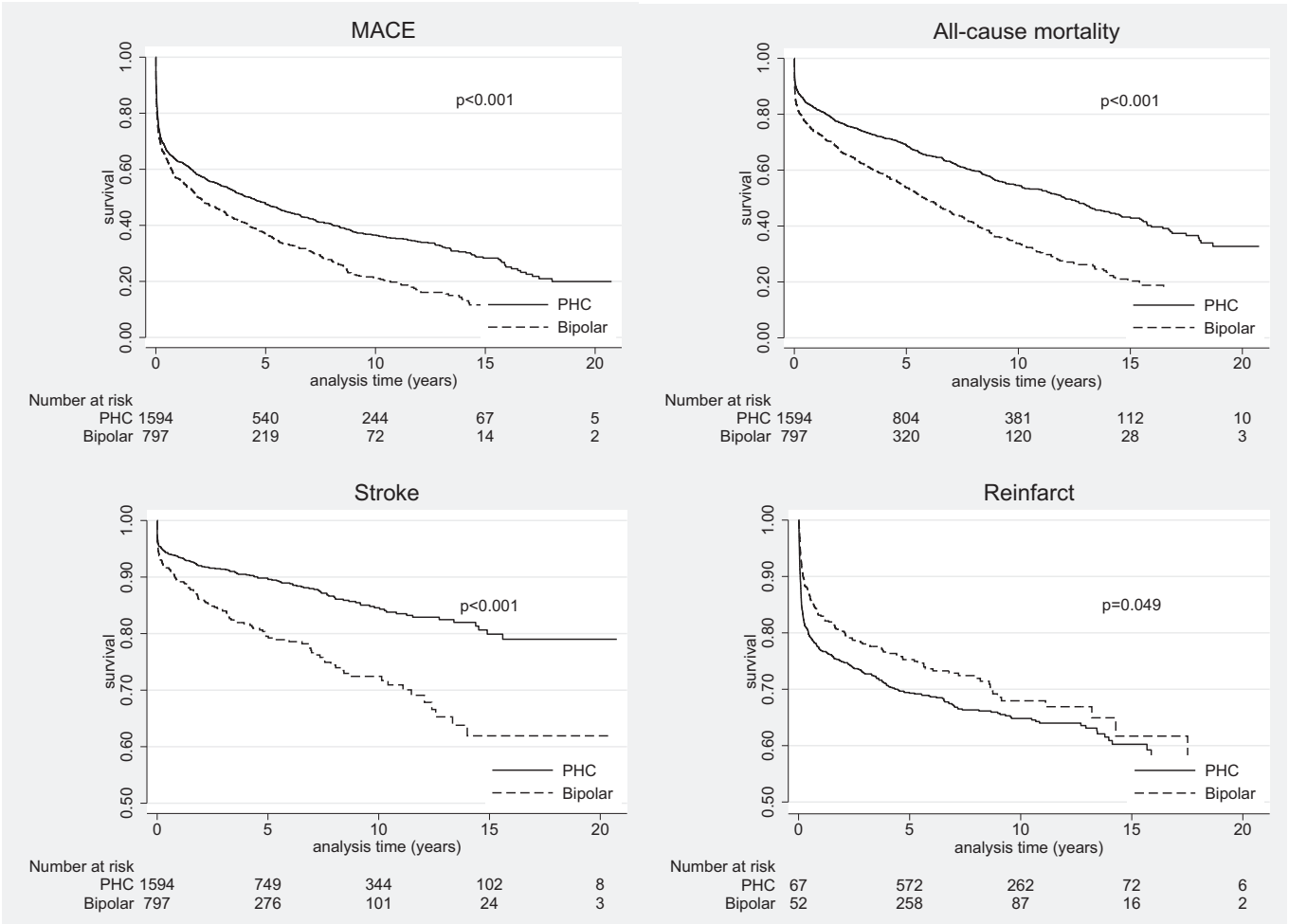

Fig. 1. Kaplan-Meier curves showing the estimates of (A) MACE, (B) all-cause mortality, (C) stroke and (D) reinfarction in the populations with and without bipolar disorder.
Figure footnote: Abbreviations: MACE – major adverse cardiac events, PHC – psychiatric healthy control population i.e without bipolar disorder.

3.3. Sensitivity analyses

Sensitivity analyses only including hospital survivors increased the HR of stroke to 2.08 (95% CI 1.65–2.60) from the primary analysis HR of 1.94, whereas the remaining outcomes were unaffected by sensitivity analyses.

4. Discussion

In this nationwide Danish register-based study, patients with BD had an almost 40% higher risk of MACE, a 70% higher risk of all-cause mortality and an almost doubled risk of stroke compared to patients without BD following ACS. They also had higher prevalences of various comorbidities at baseline compared to patients without BD.

4.1. Mortality

Patients with BD had an increased all-cause mortality, this is in accordance with previous research [2,4–6]. The Danish registry for causes of death are not regularly validated and may invalidate the analyses, hence our outcome is not stratified by cause. In a Swedish study [2] the authors found 38% of the total mortality to be due to CVD, 44% due to other natural causes and 18% due to suicide. These numbers are not homogenous throughout literature as some studies suggest suicide to make up a larger part of the mortality [4,5] and others argue that death from natural causes in BD is comparable to the general population [4]. In regards to mortality following ACS, the 70% higher mortality in this study corroborates with another study that found the 1-year mortality after MI to be 63% higher in patients with BD compared to a population without severe mental illness [23]. Current research investigating BD on clinical outcomes following ACS is sparse. However, in contrast to the present results, a study from the U.S. [18] investigating outcomes following MI in patients with severe mental illness, interestingly found that patients with bipolar disorder had slightly lower rates of mortality, stroke and cardiac complications following MI compared to a non-severe mental illness population. Our investigation is not completely comparable with the U.S. study, as the two studies differs on comparisons group, setting and follow-up time. However, the most notable difference is the fact that the results of the U.S study is adjusted for socioeconomic status (represented by region of hospital and income). Socio economic status may well be a confounder of BD on MACE, but it may also be a mediator, making it difficult to disentangle socioeconomic status from psychiatric disease when investigating the total effect of BD. In addition, the U.S. study was conducted in hospital, where patients are routinely monitored, advocating that the lack of symptom awareness is a key mediator for the effect of BD on MACE following ACS. The authors of the U.S. study did however conclude lower rates of revascularization in patients with BD which is in consensus with other research findings [16,17].

4.2. Reinfarction and stroke

The lower risk of reinfarction seen in our study population with BD is a unique finding, since it is to our understanding the first time it has been investigated. Nevertheless, researchers have examined the association between BD and MI, and one study [24] investigating the long-term risk of MI found an increased risk of the composite of fatal, non-fatal MI or stroke (HR 1.54, 95% CI 1.02–2.33), however, this HR was unadjusted for cardiovascular risk factors and subsequent adjustment rendered the results no longer statistically significant. Similarly, a systematic review [25] comprising >13 million participants, found no increased risk for MI in a population with BD, however, this study was limited by significant heterogeneity amongst the studies included. The same review concluded an increased relative risk for stroke (RR 1.74, 95% CI 1.29–2.35), which is slightly lower than the risk presented in our study of almost doubled risk of stroke in the population with BD. With the increased cardiovascular risk and mortality in mind, and the lower risk of reinfarction found in this study, one may contemplate whether these patients arrived at the hospital in due course to receive a diagnosis of reinfarction, or in fact died prematurely to establishing the cause of death as reinfarction.

4.3. Comorbidities

In this study patients with BD had an increased prevalence of heart failure, mitral/aortic valve disease, anemia, chronic obstructive lung disease and stroke at baseline. A study from the U.S [26] investigating cardiovascular risk factors concluded patients with bipolar disorder to be under-evaluated for these. The same study also found that over 50% of the patients included in the study met the criteria for MetS. The reported prevalence of MetS is varying, a study from the U.S [12] reported 30% of the population with BD to meet the criteria of MetS and another Spanish study [13] concluded the overall prevalence of MetS to be 22.4%, corresponding to a 58% higher prevalence when compared to the general population. The varying prevalence rates of MetS in the literature can amongst other reasons be ascribed to the dissimilarities in lifestyles between countries and/or the different criterions used to define MetS. This is exemplified in a Belgian study [27] investigating the prevalence of MetS in sixty patients, who reported three different prevalence rates of 16.7%, 18.3% and 30.0% in the same population, depending on the criteria used, which renders it difficult to establish a unanimous prevalence based on current literature.

4.4. Risk factors

Patients with BD have a higher risk of MetS, a syndrome entailing amongst other risk factors, hyperlipidemia. It was therefore surprising to find lower rates of hyperlipidemia in the BD in our study, despite the many reported high prevalences of MetS and the evident association between antipsychotic medication and weight gain [28]. One study reported that patients appear to be normal weight prior to being diagnosed with bipolar disorder (at the age of 18), suggesting the disorder and subsequent treatment as accountable variables for the increased weight [29]. Moreover, no increased prevalence of diabetes nor hypertension were seen in our study population with BD, despite an increase being the common notion in the literature [7,8,30–32]. The increased prevalence of chronic obstructive lung disease in our study is corroborated by previous research [7] as well as by the acknowledged increased smoking rates in mental illness populations, with no exception for those with BD [33]. Persons with BD have worse exercise and eating habits, and less often report that their health care provider discuss these matters with them [34]. There is also evidence of substance [35] and alcohol abuse [7,35] which is related with lengthier episodes of depression and mania respectively [36]. The negative health effect of these psychiatric variables are many, nonetheless, in terms of rehabilitation, research has shown that depression and anxiousness are associated with noncompliance in exercise independent of physical status [37], which points to the cruciality of ensuring proper treatment of both mental and physical illness following ACS in order to succeed with cardiac rehabilitation.

4.5. Limitations

The primary limitation is the unavailability of data on important confounders such as smoking, exercise and dietary information as well as symptom awareness. Secondly, we do not have data on previous and in-hospital medication to understand how these patients were treated. Thirdly, using registries encompasses a risk of selection bias where some patient groups might not be included and hence the results can be biased and thereby misrepresenting the reality of care. Finally, registries also carry the risk of misclassification of ICD-codes upon admittance and discharge resulting in misrepresentation of the reality. Moreover, the estimated prevalence of bipolar disease in Europe is approximately 1%

[38], however, this prevalence is not consistent with the much lower yearly incidence of bipolar disease found in DPCRR and NPR [39]. Thus, patients with bipolar disease in Denmark is likely underrepresented by the patients in the current study, leaving some probability, that the control group entails a small portion of patients with bipolar disease, although the disease burden of these patients may be milder than the clinically ill patients identified in the registries. Hence, the effects found in this study may only be compatible with severe cases of bipolar disease.

5. Conclusion

The study population with bipolar disorder had an 70% percent increased all-cause mortality risk, a doubled risk of stroke and a 40% higher risk of major adverse cardiovascular events (MACE: a composite of all-cause mortality, reinfarction and stroke) following acute coronary syndrome when compared to the general population.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors report no conflict of interest.

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