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ORIGINAL ARTICLE
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Association of clinical trial participation after myocardial infarction with socioeconomic status, clinical characteristics, and outcomes

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Aims To investigate whether participants in clinical trials after myocardial infarction (MI) are representable for the post-MI population concerning characteristics, secondary prevention, and prognosis.

Methods and results Cohort study on 31 792 attendants to 1-year revisits after MI throughout Sweden ($n = 2941$ clinical trial participants) between 2008 and 2013 identified in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Individual-level data on socioeconomic status (SES) (disposable income, educational level, and marital status) and outcomes (first recurrent non-fatal MI, coronary heart disease death, fatal or non-fatal stroke until study end 2018) were linked from other national registries. Trial participants were more likely to be men [risk ratio 1.09; 95% confidence interval (CI) 1.07–1.11], and married (1.07; 1.04–1.10), have a highest-quintile income (1.42; 1.36–1.48), and post-secondary education (1.25; 1.18–1.33), while less likely to have a history of MI (0.88; 0.80–0.97), be persistent smokers (0.83; 0.75–0.92) and have left ventricular dysfunction (0.59; 0.44–0.79) compared to non-participants. During a mean 6.7-year follow-up, 5206 outcome events occurred. Risk was lower in trial participants (hazard ratio 0.80; 95% CI 0.72–0.89), also after adjusting for clinical characteristics and post-MI therapies (0.85; 0.77–0.94) and additionally for SES (0.88; 0.79–0.97).

Conclusions Clinical trial participants post-MI are more often male, have higher SES, a more advantageous risk profile, and better prognosis. Additional unmeasured participation bias was implied. Questionable external validity of post-MI trials highlights the importance of complementary studies using real-world data.

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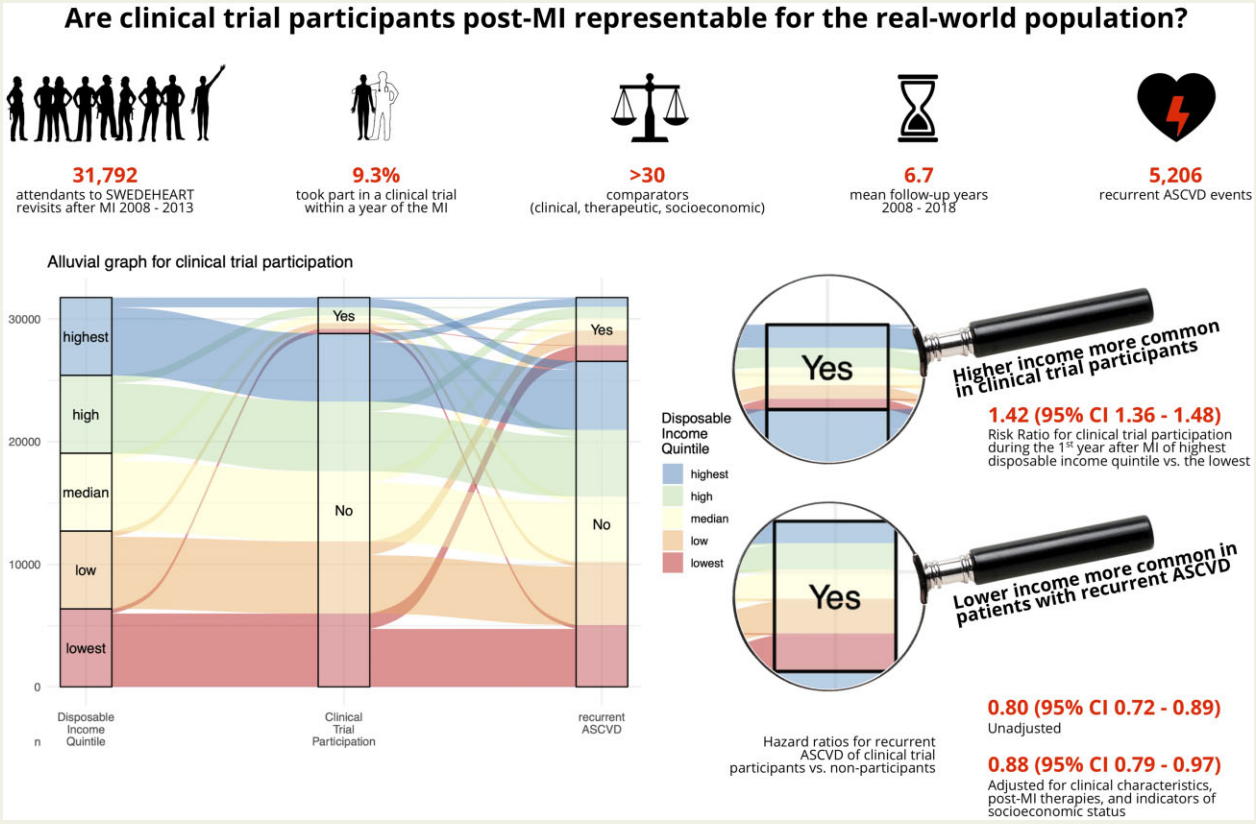
Graphical Abstract



Keywords Evidence-based medicine • Secondary prevention • Myocardial infarction • Socioeconomic factors

Introduction

Randomized clinical trials produce the highest level of evidence and therefore form the basis for many guidelines. However, an Achilles heel of clinical trials is external validity.[1] If patients included in trials are highly selected, the generalizability of trial results to the entire patient population can be questioned. A small number of studies have previously compared the characteristics of patients enrolled in clinical trials after myocardial infarction (MI) with non-participants and consistently report younger age, predominantly male sex, lower prevalence of cardiovascular risk factors, and lower mortality in trial participants.[2–4] Bias from low respondent-rates is a related concern for external validity in population-based studies.[5] In this type of epidemiological research, study participants not only have fewer comorbidities but also higher socioeconomic status (SES).

No previous study has investigated whether SES affects participation in cardiovascular clinical trials in a nationwide sample of all patients with MI. Nor do we know of any study investigating the implications of participation bias for the long-term risk of recurrent atherosclerotic cardiovascular disease (rASCVD), outcomes frequently used in cardiovascular outcomes trials.[1] We hypothesized that participants in clinical trials after MI, compared to an unselected nationwide sample of non-participants, had a more favourable risk factor profile including SES, received better secondary prevention therapy, and that observed differences in characteristics were explanatory for a lower risk of rASCVD.

Methods

Study design

This observational cohort study was based on prospectively collected individual-level data linked from several national Swedish registries. The study was approved by the Regional Ethical Review Board in Stockholm (DNR 2015/124-31/4 with amendments 2015/1577-32 and 2018/2394-32) and complies with the Declaration of Helsinki. Data linkage was performed by the National Board of Health and Welfare, a government agency, by using the unique personal identification number of all Swedish citizens.[6] Obtaining informed consent in

Table 1 Sociodemographic characteristics of participants and non-participants in clinical trials after myocardial infarction Referent

	Participants	Non-participants	*P*-value[a]	Risk ratio (95% CI)[b]
No. (%) with data	2941 (9.3)	28 851 (90.7)		
Age, years	64.2 (7.8)	63.9 (8.6)	0.091	
Age, categories			<0.001	
<50	156 (5.3)	2169 (7.5)		
50–64	1292 (43.9)	11 926 (41.3)		
65–74	1363 (46.3)	13 172 (45.7)		
≥75 years	130 (4.4)	1584 (5.5)		
Male	2340 (79.6)	21 123 (73.2)	<0.001	1.09 (1.07–1.11)
Follow-up year			<0.001	
2008	432 (14.7)	4408 (15.3)		
2009	497 (16.9)	4242 (14.7)		
2010	494 (16.8)	4118 (14.3)		
2011	501 (17.0)	4833 (16.8)		
2012	553 (18.8)	5295 (18.4)		
2013	464 (15.8)	5955 (20.6)		
Disposable income, quintiles			<0.001	
Lowest	373 (12.7)	5981 (20.8)		referent
Low	470 (16.0)	5881 (20.4)		1.12 (1.06–1.20)
Median	621 (21.1)	5730 (19.9)		1.28 (1.21–1.34)
High	672 (22.9)	5679 (19.7)		1.32 (1–26-1.39)
Highest	802 (27.3)	5545 (19.2)		1.42 (1.36–1.48)
Level of education			<0.001	
≤9 years	856 (29.3)	9826 (34.5)		referent
10–12 years	1352 (46.3)	13 048 (45.9)		1.07 (1.04–1.11)
>12 years	709 (24.3)	5579 (19.6)		1.25 (1.18–1.33)
Marital status			<0.001	
Married	1809 (61.8)	16 553 (57.8)		1.07 (1.04–1.10)
Unmarried	420 (14.3)	4464(15.6)		
Divorced	518 (17.7)	5804 (20.3)		
Widowed	180 (6.1)	1830 (6.4)		

Summary statistics are presented mean (SD) or *n* (%).
[a]Probability by Student's *t*-test for continuous variables and χ^2-test for categorical variables.
[b]Estimated using univariate Poisson regression models with robust standard errors.

writing from study participants was not feasible as data received by the researchers was pseudonymized. By Swedish law, active consent for inclusion in national quality health registries has been collectively waived. All patients are however informed and have the right to opt-out upon request at any time and have their personal data erased.

Study cohort

Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) is a national quality registry for cardiac care and is described elsewhere.[7,8] All coronary care units in the country report to the registry, with approximately 95% of all MI patients being included, when comparing to the official statistics of national inpatient diagnoses. The cohort for this study was identified from SWEDEHEART's cardiac rehabilitation sub-registry which gathers information on MI survivors, primarily below the age of 75, at routine cardiac rehabilitation visits after 2 months (6–10 weeks) and 1 year (12–14 months). Data collected include risk factor outcomes, lifestyle factors, drug therapies, patient-reported outcome measures, and other relevant information. By 2014, 70/72 (97%) of all cardiac care hospitals throughout Sweden were reporting to SWEDEHEART's cardiac rehabilitation sub-registry with 81% of eligible patients younger than 75 years attending the 1-year visit. Agreement between the registry and health record data is regularly monitored, with a consistency of around 95%.[8,9] All post-MI patients attending the 1-year cardiac rehabilitation visit from 1 January 2008 to 31 December 2013 were eligible for inclusion in the study ($n = 32\,413$) Supplementary material online, *Figure S1* details exclusion criteria rendering the final study sample ($n = 31\,792$).

Exposure and clinical data

The exposure, participation in a clinical trial (no vs. yes—in a lipid treatment trial, or yes—in other clinical trial), was reported to SWEDEHEART at the 2-month and 1-year visits post-MI. All with an affirmative response at either or both visits were defined as trial

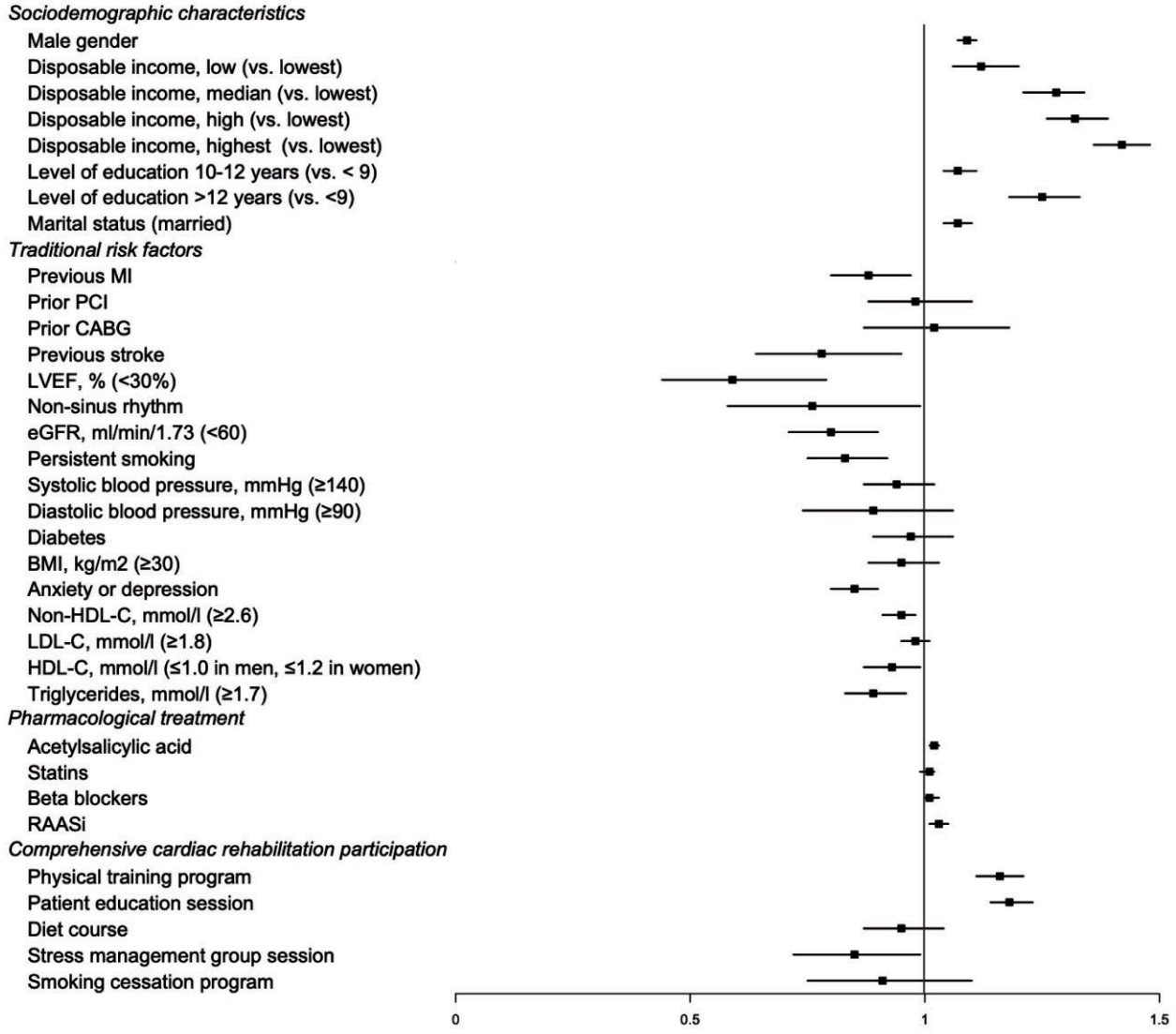


Figure 1 Forest plot depicting univariate associations for traditional cardiovascular risk factors, secondary prevention therapies, and socioeconomic status by trial participation status. Squares and bars represent risk ratios and 95% confidence intervals, respectively. BMI, body mass index; CABG, coronary artery by-pass graft; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RAASi, renin–angiotensin–aldosterone system inhibitor.

participants and those a negative response were defined as non-participants. The definitions and management of SWEDEHEART variables presented in *Tables 1–3* are reported in the Supplementary material online, *Methods*.

Outcomes

The composite endpoint, rASCVD, was defined as the first recurrent event of non-fatal MI, coronary heart disease death, or fatal or non-fatal ischaemic stroke. Data for corresponding ICD-10 codes (I21.0 to 4, I21.9, I22.0 to 1, I22.8 to 9, I46.1, I46.9, and I63.0 to 9) and dates were acquired from the National Inpatient and Cause of Death registries managed by the Swedish National Board of Health and Welfare.[10,11]

Socioeconomic status

Statistics Sweden, a government agency for official Swedish statistics gathers annual labour market, educational, and social sector data.[12] Three indicators were chosen and considered simultaneously to capture the multidimensional construct SES.[13] Mean *disposable income* per household consumption unit was measured in the year preceding the index MI to avoid misclassification from sick leave and categorized into calendar year-

Table 2 Cardiovascular risk factor characteristics of participants and non-participants in clinical trials after myocardial infarction

	Participants	Non-participants	*P*-value[a]	Risk ratio (95% CI)[b]
No. (%) with data	2941 (9.3)	28 851 (90.7)		
Traditional risk factors				
Previous MI	374 (12.8)	4159 (14.5)	0.01	0.88 (0.80–0.97)
Prior PCI	297 (10.1)	2962 (10.3)	0.75	0.98 (0.88–1.10)
Prior CABG	171 (5.8)	1648 (5.7)	0.83	1.02 (0.87–1.18)
Previous stroke	101 (3.5)	1274 (4.5)	0.01	0.78 (0.64–0.95)
LVEF, %			<0.001	
≥50	1607 (64.7)	15 560 (65.0)		
30–50	827 (33.3)	7564 (31.6)		
<30	49 (2.0)	798 (3.3)		0.59 (0.44–0.79)
Non-sinus rhythm	57 (3.2)	732 (4.2)	0.04	0.76 (0.58–0.99)
eGFR, mL/min/1.73	82.8 (18.2)	83.1 (16.6)	0.38	
<60	244 (8.8)	3061 (11.0)		0.80 (0.71–0.90)
Persistent smoking	352 (12.1)	4103 (14.5)	<0.001	0.83 (0.75–0.92)
Systolic blood pressure, mmHg	131.4 (16.2)	131.9 (17.2)	0.10	
≥140	520 (20.3)	5174 (21.5)		0.94 (0.87–1.02)
Diastolic blood pressure, mmHg	77.1 (9.3)	77.0 (10.1)	0.55	
≥90	125 (4.9)	1319 (5.5)		0.89 (0.74–1.06)
Diabetes	483 (16.5)	4877 (16.9)	0.50	0.97 (0.89–1.06)
BMI, kg/m^2	27.7 (4.1)	27.8 (4.5)	0.41	
≥30	560 (25.0)	5424 (26.2)		0.95 (0.88–1.03)
Anxiety or depression	851 (29.2)	9751 (34.4)	<0.001	0.85 (0.80–0-90)
Cholesterol, mmol/L	4.13 (0.90)	4.24 (0.98)	<0.001	
Non-HDL-C, ≥2.6 mmol/L	1284 (59.8)	13 984 (63.2)		0.95 (0.91–0.98)
LDL-C, mmol/L	2.22 (0.76)	2.30 (0.82)	<0.001	
≥1.8	1477 (69.9)	15 387 (71.1)		0.98 (0.95–1.01)
HDL-C, mmol/L	1.27 (0.39)	1.25 (0.37)	0.02	
≤1.0 in men, ≤1.2 in women	746 (34.7)	8263 (37.3)		0.93 (0.87–0.99)
Triglycerides, mmol/L	1.46 (0.89)	1.55 (0.98)	<0.001	
≥1.7	542 (25.4)	6280 (28.5)		0.89 (0.83–0.96)

Summary statistics are presented mean (SD) or *n* (%).
BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Probability by Student's *t*-test for continuous variables and χ^2-test for categorical variables.
[b]Estimated using univariate Poisson regression models with robust standard errors. For non-dichotomous variables, the risk ratio of a selected category was calculated using participants of remaining categories as reference.

specific quintiles to compensate for inflation. *Educational level* was defined as the highest educational attainment during the year of the 1-year visit and categorized as ≤9 years, 10–12 years, and >12 years. *Marital status* was categorized as not married vs. married.

Statistical methods

Patient characteristics were reported as frequencies and percentages for categorical variables, and as means and standard deviations for continuous variables. For the analysis of risk factor profile, secondary prevention therapies, and SES, two-sided Students *t*-test was used for continuous data, chi-square was used for categorical data, and univariate Poisson regression models with robust standard errors were used to estimate risk ratios and 95% confidence intervals (CIs). Thresholds with clinical relevance were chosen for Poisson regression of non-binary outcomes including left ventricular ejection fraction <30%, estimated glomerular filtration rate <60 mL/min/1.73, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, body mass index ≥30 kg/m^2, non-high-density lipoprotein cholesterol (non-HDL-C) ≥2.6 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥1.8 mmol/L, HDL-C ≤1.0 mmol/L among men and ≤1.2 mmol/L among women, triglycerides ≥1.7 mmol/L, highest disposable income quintile (vs. lowest), highest educational level (vs. lowest), and married status (vs. not married). For the analysis of rASCVD, subjects were followed-up from the date of the 1-year visit until first occurrent rASCVD event, censoring, or study end which extended until 31 December 2018. The crude cumulative occurrence of rASCVD by trial participation status was illustrated using Kaplan–Meier curves. Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% CIs in order to assess the association between trial participation and rASCVD. Four models were developed to account for measurable confounding and presumed causal relationships according to clinical experience and literature review. Relationships are illustrated in Supplementary material online, *Figure S2* as a directed

Table 3 Secondary prevention therapies of participants and non-participants in clinical trials at 1-year revisit after myocardial infarction

	Participants	Non-participants	*P*-value[a]	Risk ratio (95% CI)[b]
No. (%) with data	2941 (9.3)	28 851 (90.7)		
Pharmacological treatment				
Acetylsalicylic acid	2749 (94.5)	26 162 (92.5)	<0.001	1.02 (1.01–1.03)
Statins	2658 (92.2)	25 926 (91.7)	0.34	1.01 (0.99–1.02)
Beta blockers	2551 (87.8)	24 489 (86.6)	0.09	1.01 (1.00–1.03)
RAAS inhibitors	2362 (81.1)	22 228 (78.5)	0.001	1.03 (1.01–1.05)
Calcium antagonists	593 (20.4)	5404 (19.1)	0.09	
Diuretics	474 (16.3)	5707 (20.2)	<0.001	
Nitrates	202 (7.0)	2566 (9.1)	<0.001	
Oral anticoagulants	140 (4.8)	1809 (6.4)	0.003	
Non-statin LLT	163 (5.9)	1438 (5.1)	0.08	
Comprehensive cardiac rehabilitation participation				
Physical training programme	1372 (47.0)	11 481 (40.5)	<0.001	1.16 (1.11–1.21)
Patient education session	1643 (56.4)	13 498 (47.6)	<0.001	1.18 (1.14–1.23)
Diet course	443 (15.2)	4528 (16.0)	0.27	0.95 (0.87–1.04)
Stress management group session	153 (5.3)	1756 (6.2)	0.04	0.85 (0.72–0.99)
Smoking cessation programme	111	1126	0.35	0.91 (0.75–1.10)

Summary statistics are presented mean (SD) or *n* (%).
LLT, lipid lowering therapy; RAAS, renin–angiotensin–aldosterone system.
[a]Probability by χ^2-test.
[b]Estimated using univariate Poisson regression models with robust standard errors.

acyclic graph.[14] Model I was adjusted for age, sex, and calendar year. Model II was further adjusted for traditional risk factors including previous MI, previous stroke, prior coronary artery bypass grafting, left ventricular ejection fraction, heart rhythm, smoking status, diabetes (with oral and insulin treatment), systolic blood pressure, estimated glomerular filtration rate, body mass index, symptoms of anxiety or depression, total cholesterol, LDL-C, HDL-C, and triglycerides. Model III was further adjusted for use of secondary prevention therapies including evidence-based drugs (acetylsalicylic acid, statins, beta blockers, and renin–angiotensin–aldosterone system inhibitors) and participation in cardiac rehabilitation programmes (physical training, patient education, dietary advice, smoking cessation, and stress management group sessions). Model IV was further adjusted for SES (disposable income, educational level, and marital status). Restricted cubic splines with four knots were used to adjust for age in the models. Missing values are reported in Supplementary material online, *Table S1* and were included in the models as a separate category. The proportional hazards assumption was assessed by means of scaled Schoenfeld's residuals. No evidence of departure from this assumption was observed. Data management and statistical analyses were performed using Stata version 15 (StataCorp, College Station, TX, USA).

Results

Out of the final study sample, 2941 subjects had participated in a clinical trial while 28 851 were classified as non-participants. The proportion of men participating in a trial was greater than in non-participants whereas mean age was similar in the two groups (*Table 1*). Approximately 5% were older than the registry's optional upper age limit of 75 years in both groups. Regarding SES, trial participants were more likely to be married, have higher disposable income and higher level of education. Associations were strong between all three indicators of high SES and clinical trial participation (*Figure 1*).

Regarding risk factor profile (*Table 2*), left ventricular dysfunction, kidney disease, persistent smoking, symptoms of anxiety and depression, history of stroke, prior MI, and non-sinus rhythm at the 1-year visit were all less common in trial participants, whereas no difference was observed for diabetes or mean values of blood pressure or body mass index. There was no difference between groups regarding LDL-C, while trial participants were more likely of having levels of triglycerides, HDL-C, and non-HDL-C at target. Overall, a more advantageous risk factor profile was associated with participation in clinical trials (*Figure 1*).

Regarding secondary prevention therapies (*Table 3*), trial participants were more likely to use acetylsalicylic acid and renin–angiotensin–aldosterone system inhibitors and were more likely to have participated in the physical training and patient education programmes during the first year post-MI, whereas non-participants were more likely to take diuretics, nitrates, and oral anticoagulants. Use of most evidence-based therapies were associated with trial participation (*Figure 1*).

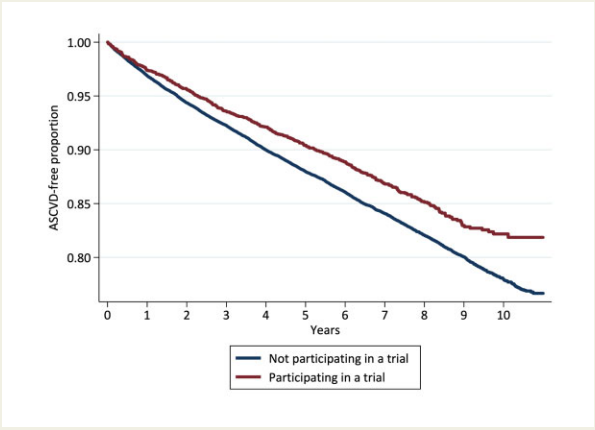


Figure 2 Kaplan–Meier estimate depicting the rASCVD-free proportion by participation in a clinical trial after MI. rASCVD, first recurrent event of atherosclerotic cardiovascular disease.

Association between participation and rASCVD

During a mean follow-up of 6.7 years (total 211 951 person-years), rASCVD occurred in 16.4% ($n = 5206$) of the study population. The event rate was lower in trial participants, 20.0 (95% CI 18.2–22.1) vs. 25.1 (95% CI 24.4–25.8) per 1000 person-years in non-participants. *Figure 2* illustrates crude risk for rASCVD in relation to participation in a clinical trial. The 5- and 10-year absolute differences in rASCVD-free proportion between groups were 2.4% and 4.2%, respectively. The unadjusted HR for rASCVD in trial participants compared to non-participants was 0.80, 95% CI 0.72–0.89 and was independent of age, gender, and calendar year. Risk reduction associated with trial participation in sequential models was attenuated by adjusting for traditional cardiovascular risk factors (HR 0.85, 95% CI 0.76–0.94) but not from adding secondary prevention therapies (HR 0.85, 95% CI 0.77–0.94). In a final model however, adding SES attenuated the association further (HR 0.88, 95% CI 0.79–0.97).

Discussion

A novel finding in this large nationwide real-world sample was that clinical trial participants after MI constitute a highly selected group. Compared to non-participants, they were more often male and married, had a higher income and level of education, a more favourable cardiovascular risk profile, and received secondary prevention therapy more consistent with guideline recommendations. We also report better long-term prognosis for outcomes relevant in cardiovascular trial participants. Although the better prognosis was partially explained by cardiovascular risk profile and SES, the association was independent of the observed dissimilarities which indicates additional unmeasured participation bias. Overall, our data questions to what extent findings from clinical trials post-MI can be applied to the overall post-MI population. Regardless hierarchical evidence by study design, well-designed observational studies on real-world registry data are vital for evidence-based medicine, in particular for improving evidence-based medicine in groups that are under-represented in clinical trials.

We observed no age difference associated with trial participation in contrast to previous related studies. This may be because of similar age restrictions of the registry and trial samples. We did however observe a strong sex difference with a lower proportion of women among participants. Although female representation has improved in clinical trials on some types of cardiovascular disease, women remain underrepresented in trials on lipid lowering therapies,[4] and trials on coronary disease in general.[15,16] Here, we confirm these findings which is concerning.[17] A further underrepresentation of women in trials, compared to registry data, will hamper the study of possible heterogeneity of treatment effects by sex due to low power in the female subgroup.[18] In the current study, gender misrepresentation did not affect risk of rASCVD but other important aspects of trials such as sex specific drug safety issues were not evaluated.

In the current study, SES was higher in trial participants than in non-participants which partially explained their lower risk of rASCVD. SES has repeatedly been associated with abundance of cardiovascular risk factors, a lower quality of care[19] and patient adherence[20], incident[21] and recurrent cardiovascular disease.[22] Our observation, that clinical trial participants have higher SES, is a novel addition to the many roles of SES in cardiovascular disease and research. Similar to the findings of our study, income level was a strong indicator of SES associated with participation in cancer treatment trials in a nationwide US survey.[23] Major reasons for non-participation in these trials were that the question of taking part had not been brought up for discussion in patient–physician interaction or that it was discussed but the patient was ultimately not offered to take part. Low SES was associated with both explanations. We further report that educational level was an important indicator of SES in the context of trial participation. Post-MI patients with lower education may incline towards non-participation in trials because of required health literacy and cognitive abilities to assimilate comprehensive fine printed documentation related to trial enrolment and conduct.[24] In a recent meta-analysis, patient adherence to therapies was strongly associated with health literacy. Interventions for improving health literacy were reported to be efficient and also to improve adherence, particularly in samples with low SES.[25] It is unclear how findings of treatment effects in higher SES groups translate to effects in lower SES groups that may have lower adherence to therapies in addition to other possible differences. In addition, our findings should be put in the context of data from genetic epidemiology that supports a causal link between education and incident coronary heart disease.[21]

In this study, the cardiovascular risk profile of trial participants was healthier than in non-participants which conforms with previous research on participation in cardiovascular trials.[2] This finding may be somewhat surprising, considering that a risk augmentation is often intended by the selection criteria for outcomes trials post-MI.[26] We also report that adjustment for cardiovascular risk profile attenuated, but only to a small extent, the lower risk associated with participation for rASCVD during long-term follow-up.

We report a better utilization of secondary prevention therapies in clinical trial participants vs. non-participants. For instance, trial participants were more likely to use acetylsalicylic acid and to participate in physical training programme within cardiac rehabilitation, both evidence-based therapies for morbidity and mortality benefits post-MI.[27,28] Potential underlying reasons include the relatively closer monitoring and interaction with health care providers of trial

participants and that better patient involvement and education may exert a positive effect on patient compliance. Second, the hospitals engaged in post-MI trials have been associated with providing care more adherent to guidelines and better long-term patient outcomes in the USA.[29] With this in mind, the declining trend of hospital participation in post-MI trials observed over the past few years is alarming.[29] A third reason for poorer secondary prevention therapy in non-participants may be related to SES.[19]

Finally, the fully adjusted multivariable model provided a bias-minimized estimate of the direct effect of trial participation on rASCVD that remained significant.[14] This indicates additional unmeasured and unexplained parts of the selection process to clinical trials post-MI that may be related to investigators preference for special characteristics or mechanisms related to more frequent interaction with healthcare providers, such as better coping strategies and self-efficacy. Besides the implications for external validity of clinical trials post-MI, the better prognosis observed in participants may provide an explanation for overestimated event rates in the design of many clinical trials and this finding may be used to improve power-calculations in future studies.

Main strengths of this study were the large cohort size and access to registries with nationwide coverage providing individual-level data on multiple cardiovascular risk factors, therapies, indicators of SES, and outcomes often used in cardiovascular trials during extensive follow-up time.[8,10,12] By inclusion criteria all study participants had similar access to emergent healthcare, therapies, and follow-up. The study population was highly representative of the Swedish post-MI population based on size and the nationwide inclusion. Generalization to other countries must however be made cautiously. Main weaknesses were that, unlike well-designed randomized trials, residual confounding exist in all observational studies. Furthermore, we did not have data stratified by reporting centre, on whether a non-participant had been considered for a trial, nor on the proportion that had been offered but declined participation in a trial. This may have implications for how to improve the situation and minimize participation bias in the future. Also, there is participation bias in registry-based observational studies too. It is likely the upper age limit of revisit registrations in SWEDEHEART underestimated possible age differences between our study groups. Analogous, the observed difference in cardiovascular risk profile may have been underestimated as post-MI patients not taking part in cardiac rehabilitation (approximately 20% of Swedish post-MI patients) more often had a history of hypertension, diabetes, heart failure, and multiple cardiovascular events compared with registry-participants.[9]

In conclusion, patients taking part in clinical trials after MI are poor representatives of the overall post-MI population. The participation bias of post-MI trials extends beyond differences in cardiovascular risk profile, guideline-directed therapies, and SES. External validity should be carefully considered in the interpretation of post-MI trials, with particular concern regarding risk profile and SES. Novel registry-based randomized clinical trials are more cost-efficient than their conventional counterpart and may allow for minimally selective inclusion of more representable post-MI participants,[30] as well as increase the proportion of recommendations that are supported by trial evidence in major guidelines.[31] Unmeasured constituents of trial participation bias remain to be identified in future research.

Lead author biography

Dr Joel Ohm is an emergency and intermediary care internist at the Karolinska University Hospital in Stockholm, Sweden. He recently obtained a PhD at Karolinska Institutet on socioeconomic status and risk assessment in secondary prevention after myocardial infarction.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Consent

Active informed consent from study participants was not feasible. Data accessed by the researchers was pseudonymized and the study involved no infringement of personal integrity.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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