Circulation

ORIGINAL RESEARCH ARTICLE

Socioeconomic Disparities and Mediators for Recurrent Atherosclerotic Cardiovascular Disease Events After a First Myocardial Infarction

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BACKGROUND: Low socioeconomic status is associated with worse secondary prevention use and prognosis after myocardial infarction (MI). Actions for health equity improvements warrant identification of risk mediators. Therefore, we assessed mediators of the association between socioeconomic status and first recurrent atherosclerotic cardiovascular disease event (rASCVD) after MI.

METHODS: In this cohort study on 1-year survivors of first-ever MI with Swedish universal health coverage ages 18 to 76 years, individual-level data from SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) and linked national registries was collected from 2006 through 2020. Exposure was socioeconomic status by disposable income quintile (principal proxy), educational level, and marital status. The primary outcome was rASCVD and secondary outcomes were cardiovascular and all-cause mortality. We initially assessed the incremental attenuation of hazard ratios with 95% CIs in sequential multivariable models adding groups of potential mediators (ie, previous risk factors, acute presentation and infarct severity, initial therapies, and secondary prevention). Thereafter, the proportion of excess rASCVD associated with a low income mediated through nonparticipation in cardiac rehabilitation, suboptimal statin management, a cardiometabolic risk profile, persistent smoking, and blood pressure above target after MI were calculated using causal mediation analysis.

RESULTS: Among 68 775 participants (73.8% men), 7064 rASCVD occurred during a mean 5.7-year follow-up. Income, adjusted for age, sex, and calendar year, was associated with rASCVD (hazard ratio, 1.63 [95% CI, 1.51–1.76] in the lowest versus highest income quintile). Risk attenuated most by adjustment for previous risk factors and by adding secondary prevention variables for a final model (hazard ratio, 1.38 [95% CI, 1.26–1.51]) in the lowest versus highest income quintile. The proportions of the excess 15-year rASCVD risk in the lowest income quintile mediated through nonparticipation in cardiac rehabilitation, cardiometabolic risk profile, persistent smoking, and poor blood pressure control were 3.3% (95% CI 2.1–4.8), 3.9% (95% CI, 2.9–5.5), 15.2% (95% 9.1–25.7), and 1.0% (95% CI 0.6–1.5), respectively. Risk mediation through optimal statin management was negligible.

CONCLUSIONS: Nonparticipation in cardiac rehabilitation, a cardiometabolic risk profile, and persistent smoking mediate income-dependent prognosis after MI. In the absence of randomized trials, this causal inference approach may guide decisions to improve health equity.

Key Words: cardiovascular diseases ■ health equity ■ mediation analysis ■ myocardial infarction ■ secondary prevention ■ social determinants of health

Low socioeconomic status (SES) is associated with recurrent atherosclerotic cardiovascular events (rASCVD) after myocardial infarction (MI).[1] Improved prognosis among patients with low SES warrants identification of the underlying mechanisms that can be addressed, but patients with low SES are

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Clinical Perspective

What Is New?

- Risk of a recurrent atherosclerotic event or death was 63% higher in the lowest (versus highest) income quintile among 68 775 first myocardial infarction (MI) survivors with universal health coverage in Sweden.
- A traditional mediation analysis approach suggested that previous risk factors and secondary prevention use were more important mediators of the income-dependent risk for recurrence than socioeconomic disparities regarding clinical presentation, severity, and initial treatment of the incident MI.
- Causal mediation analysis identified lower participation rates in cardiac rehabilitation, persistent smoking, and worse cardiometabolic risk profile after MI among low-income groups as risk mediators.

What Are the Clinical Implications?

- Socioeconomic equity after MI may be improved by implementing methods for increased uptake to cardiac rehabilitation programs including physical training, patient educational sessions, and smoking cessation in low-income groups.
- Considering the universal health coverage of Sweden, socioeconomic health disparities and the reported mediating effects may be greater in countries without universal health coverage.
- Strengthening of efforts against the metabolic syndrome risk profile after MI in low-income groups may be used to improve long-term prognosis in this group.

Nonstandard Abbreviations and Acronyms

AGReMA	A Guideline for Reporting Mediation Analyses
HR	hazard ratio
ICD-10	International Classification of Diseases, 10th revision
MI	myocardial infarction
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
rASCVD	recurrent atherosclerotic cardiovascular disease event
SES	socioeconomic status
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SWEDEHEART	Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies

underrepresented in clinical trials after MI.[2] A disadvantageous cardiovascular risk profile before incident MI, such as metabolic syndrome, has been pointed out as the principal or only explanation.[1,3,4] However, socioeconomic disparities regarding use of guideline-recommended secondary prevention such as statin use and participation in comprehensive cardiac rehabilitation for lifestyle change were recently indicated.[5] Advances in secondary prevention have contributed to the improved prognosis after MI in recent decades.[6] The first year after MI offers a window of opportunity for initiation and consolidation of evidence-based drug therapies and interventions for lifestyle changes.[7,8]

Socioeconomic inequities occurring before, at the time of, and throughout the first year after an incident MI affect the long-term prognosis but the relative importance from each temporal space is unknown. To our knowledge, secondary prevention inequities have not been thoroughly studied as mediators for recurrent events after MI. We therefore hypothesized that secondary prevention inequities are a substantial causal link between low SES and increased risk of rASCVD. This was tested using both a traditional and a more sophisticated methodology for mediation assessment in a large cohort of first-ever MI survivors using nationwide data from multiple linked registries in a country with universal health coverage.

METHODS

Study Design

This cohort study used prospectively collected individual-level data from multiple Swedish national registries. Data linkage and pseudonymization was executed by the National Board of Health and Welfare[9] using the unique personal identification number assigned to all Swedish residents.[10] The study was approved by the Regional Ethical Review Board in Stockholm, conforms to the Declaration of Helsinki, and adheres to the relevant STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and AGReMA (A Guideline for Reporting Mediation Analyses) reporting guidelines.[11,12] Because of the sensitive nature of the data collected for this study, it cannot be made available to a third party by the authors. Requests to access the datasets from researchers with approval from the Swedish Ethical Review Authority and who fulfill the legal and regulatory requirements may be sent to the respective registry holder stated in this article. The authors had full access to the complete data in the study and take responsibility for the integrity of the data and data analysis.

Study Sample and Data Sources

Study participants were people with first-ever MI ages 18 to 76 years attending the routine 1-year revisit (baseline) between January 1, 2006, and December 31, 2020, throughout Sweden and were collected from SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended

Therapies). Hence, the study population after MI was clinically stable. Detailed sample selection is reported in Figure S1. The national registers used in the study are described further in the Expanded Methods in the Supplemental Material.

Exposure

Indicators of SES were selected on the basis of expert recommendation[13,14] and previous studies on the after-MI population.[1,5] Individual-level disposable income (mean per household consumption unit on the basis of household size and composition) was chosen as the primary proxy measure of SES on the basis of a strong association with rASCVD observed in the after-MI setting.[1] Misclassification because of MI-related work absence was counteracted by using the income year preceding the index MI. The income distribution was divided into calendar year–specific quintiles (highest referent) to compensate for inflation and was stratified by sex because of a lower median income in women. In order to study possible aspects of SES that are not captured by income alone, educational levels (attained at baseline) and marital status were studied additionally as exposures.[15] Educational categories corresponding to compulsory, upper secondary, and postsecondary education in Sweden were named ≤9 (referent), 10 to 12, and >12 years for simplicity and marital status was categorized as referent married versus not married (eg, unmarried, divorced, or widowed).

Outcomes

The primary composite outcome (rASCVD) was adopted from the American Heart Association/American College of Cardiology New Pooled Cohort Risk Equations.[16] Defined as the first recurrent nonfatal MI, coronary heart disease death, or fatal or nonfatal ischemic stroke, corresponding ICD-10 (International Classification of Diseases, 10th revision) codes (I21.0 to I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I46.1, I46.9, and I63.0 to I63.9) and dates of events were acquired. Secondary outcomes were cardiovascular death (ICD-10: I00 through I99) and all-cause death. Study participants were followed from the date of the 1-year revisit until first occurrent outcome event, censoring because of death from causes other than rASCVD, migration, or study end on December 31, 2020.

Covariates

A directed acyclic graph was created for selecting and defining covariates (Figure S2).[17] Potential confounders were age, sex, and calendar year of inclusion. Then, 4 groups of potentially mediating covariates were formed by chronologic order of exposure to study participants: risk factor accumulation, MI presentation and severity, initial therapies, and secondary prevention use. Covariates of each group and their definitions and management are reported in the Expanded Methods in the Supplemental Material.

Mediators

For a covariate to be considered a plausible mediator, the following conditions were taken into account: (1) unequal distribution across exposure categories; (2) associated with the outcome; and (3) on the causal pathway between the exposure and the outcome. Aforementioned groups were evaluated in a basic traditional approach of determining quantitatively appreciable mediators.[18,19] For the formal causal mediation analysis, the following secondary prevention activities selected by presumed importance[5] were assessed as mediators: participation in physical training program (yes, no) and patient educational session (yes, no) within cardiac rehabilitation during the first year after MI; and optimal statin management (yes, no), defined as statin intensification during the first year after MI or high-intensity statin at the 1-year revisit. In addition, mediation through the following risk profiles at the 1-year revisit after the index MI was assessed: cardiometabolic risk profile (yes, no), defined by a metabolic syndrome variable according to the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) 2005 definition, created from data collected at the early 2-month follow-up visit after the index MI[20]; persistent smoking (yes, no); and blood pressure above target (yes, no), defined as a systolic blood pressure >140 mm Hg.

Statistical Analyses

Characteristics were reported by disposable income quintile (SES) as frequencies and percentages for categorical variables and as means and SDs for continuous variables. Crude incidence rates were calculated as the number of events per 1000 person-years by disposable income quintiles and Kaplan-Meier survival estimates were used to illustrate crude associations between SES and rASCVD.

Traditional Mediation Approach

Cox proportional hazards models were used to estimate cause-specific hazard ratios (HRs) and 95% CIs of the association between SES and rASCVD. The proportional hazards assumption was tested using Schoenfeld residuals. Five models were considered on the basis of a directed acyclic graph (Figure S2).[17] The base model included disposable income as proxy for SES and potential confounders age, sex, and calendar year. For each of the 4 sequential models, risk attenuation attributable to an added group of covariates was interpreted as indicative of mediation assuming a rare outcome.[18,19] The second model was further adjusted for covariates categorized as previous risk factor accumulation. In a third model, covariates categorized as MI presentation and severity were added. The fourth model also included covariates categorized as initial therapies and the final model added covariates categorized as secondary prevention use. Restricted cubic splines with 4 knots were used to adjust for age in the models. Competing events of death not attributable to rASCVD were treated as censoring events. A competing risk analysis, such as the Fine and Gray model,[21] estimates the subdistribution HR and would capture any potential effect of SES on the competing event (death from other causes) in addition to any potential effect of SES on rASCVD. In the current study, this was not appropriate, so we estimated cause-specific HRs.

Causal Mediation Analyses

To estimate the effect of low income on rASCVD mediated through a selected potential mediator, a causal mediation analysis on time-to-event data was performed to allow for mathematically consistent interpretation of causal mediation.[22–24] Exposure, mediators (or hypothetical interventions on mediators), and outcomes were separated and sequential in time. The total association between the highest and lowest income quintile on rASCVD was separated into total natural direct effects and pure natural indirect effects, as specified by VanderWeele

in 2014.[24] The mediation was adapted into a survival setting by dividing 1 — the survival function into total natural direct effects and pure natural indirect effects over follow-up time. Details are provided in the Expanded Methods in the Supplemental Material. A Cox proportional hazards model adjusted for age, sex, and calendar year was used for the primary outcome and combined with a logistic regression model estimating the association between the exposure and each selected mediator, which also was adjusted for confounding age, sex, and calendar year. Thus, estimates of pure natural indirect effects (ie, proportion mediated through a potential mediator) between the highest and lowest income quintile on rASCVD were calculated for nonparticipation in physical training program and patient educational sessions within cardiac rehabilitation, suboptimal statin management, the selected cardiometabolic risk profile after MI (the metabolic syndrome), persistent smoking, and blood pressure above target. Intervals around the estimates were calculated as 95% bootstrap intervals (referred to as 95% CI) on the basis of 1000 resamplings.

Missing data are reported in Table S1. For variables with higher percentages of missing values (eg, body mass index, admission ECG ST-segment deviation, maximum troponin level, and left ventricular ejection fraction), missing values were included in the models as a separate category. Sensitivity analyses, including complete case analysis, longitudinal stability of disposable income using a 5-year average of income as a proxy for SES, and assessment of robustness of causal mediation analysis findings, are described in the Expanded Methods. Data management and statistical analyses were performed using Stata versions 15 and 16 (StataCorp) and R version 4.0.2 (R Foundation for Statistical Computing) for causal mediation analysis.

RESULTS

In the final study sample (n=68 775), 73.8% (n=50 762) were men and mean (SD) age was 63.3 (8.7) years. The 3 indictors of SES were concordant, with clear associations between higher disposable income, higher educational level, and marriage. Table 1 reports patient characteristics collected throughout the course of MI care until the 1-year revisit by disposable income quintiles. Participants with lower income were more likely to have a history of diabetes, obesity, and current smoking, but similar frequencies were observed for the remaining traditional comorbid cardiovascular risk factors. At admission for the index MI, low income was associated with higher rates of atypical presenting symptoms, more severe myocardial injury, and coronary disease, but the proportion with ST-segment–elevation MI was equal across income quintiles. Despite more severe MIs, participants with lower income were less often subject to acute angiographic interventions and less frequently prescribed dual antiplatelet therapy at discharge from the index MI. Associations between disposable income and secondary prevention use in a subpopulation of this cohort from 2005 through 2013 was recently described and analyzed in detail.[5] Secondary prevention use overall favored higher SES, in particular with regard to programs within comprehensive cardiac rehabilitation and various aspects of lipid management.

Association Between SES and rASCVD

During a mean follow-up of 5.7 years, rASCVD occurred in 7064 (10.3%) study participants at a stable annual 1.8% risk. Recurrence rates per 1000 person-years (95% CIs) are reported in Table 2 and were higher in the lowest (23.6; 95% CI, 22.5–24.7) versus highest (14.2; 95% CI, 13.4–15.0) income quintile, in study participants with ≤9 years (20.0; 95% CI, 19.3–20.9) versus >12 years (14.7; 95% CI, 13.9–15.5) of education, and in participants who were not married (19.7; 95% CI, 19.0–20.4) versus married (16.8; 95% CI, 16.2–17.3). Kaplan-Meier estimates of the rASCVD-free proportion in relation to income quintiles are presented in Figure 1.

Traditional Mediation Approach

The association between disposable income quintiles and rASCVD according to the 5 Cox regression models are presented as forest plots and HRs with 95% CIs in Figure 2. The proportional hazards assumption was not violated (P=0.297). There was a strong and graded association between income and rASCVD in the model adjusted for age, sex, and calendar year (HR, 1.63 [95% CI, 1.51–1.76] in the lowest versus highest income quintile). In the model that additionally adjusted for previous risk factors, the strength of the association was attenuated, which indicated possible risk mediation (HR, 1.47 [95% CI, 1.36–1.60] in the lowest versus highest income quintile). Subsequent adjustment for MI presentation and severity affected the association with rASCVD (HR, 1.43 [95% CI, 1.32–1.55]); adding initial therapies did not. However, by adding secondary prevention activities, the association between disposable income and rASCVD was further attenuated (HR, 1.38 [95% CI, 1.26–1.51] in the lowest versus highest income quintile).

Causal Mediation Analyses

Total excess risk of rASCVD for the lowest versus highest income quintile and the total natural direct effects and pure natural indirect effects of this risk due to selected plausible mediators are reported in Figure S3. The mediating proportions by follow-up time are reported in Figure 3 and Table S2. The proportion of excess risk associated with the lowest versus highest income quintile mediated through nonparticipation in physical training programs and patient educational sessions within cardiac rehabilitation increased by time and was 3.3% (95% CI, 2.1–4.8) and 3.2% (95% CI, 2.0–4.6), respectively, at the 15-year follow-up. For example, if we were able to make physical training program participation rates equal, the proportion

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Table 1. Participant Characteristics, by Quintiles of Disposable Income*

Characteristic	Disposable income quintile				
	Lowest	Low	Median	High	Highest
No. (%) with data	13 768	13 753	13 756	13 753	13 745
Sociodemographic characteristics					
Educational level, y					
≤9	5221 (39.3)	4791 (35.5)	3892 (28.7)	3399 (24.9)	2289 (16.8)
10–12	6124 (46.0)	6727 (49.8)	6920 (51.0)	6769 (49.6)	5580 (43.1)
≥12	1967 (14.8)	1979 (14.7)	2763 (20.4)	3476 (25.5)	5787 (42.4)
Married	5547 (40.6)	7193 (52.6)	8274 (60.5)	8626 (63.0)	9497 (69.3)
Year of annual follow-up					
2006	370 (2.7)	383 (2.8)	384 (2.8)	375 (2.7)	385 (2.8)
2007	615 (4.5)	590 (4.3)	589 (4.3)	585 (4.3)	583 (4.2)
2008	760 (5.5)	799 (5.8)	797 (5.8)	805 (5.9)	794 (5.8)
2009	770 (5.6)	746 (5.4)	753 (5.5)	757 (5.5)	754 (5.5)
2010	754 (5.5)	729 (5.3)	737 (5.4)	721 (5.2)	727 (5.3)
2011	828 (6.0)	843 (6.1)	841 (6.1)	846 (6.2)	874 (6.4)
2012	922 (6.7)	941 (6.8)	940 (6.8)	950 (6.9)	909 (6.6)
2013	1040 (7.6)	1012 (7.4)	994 (7.2)	989 (7.2)	1002 (7.3)
2014	976 (7.1)	1009 (7.3)	1012 (7.4)	1016 (7.4)	993 (7.2)
2015	1061 (7.7)	1057 (7.7)	1049 (7.6)	1075 (7.8)	1089 (7.9)
2016	1129 (8.2)	1109 (8.1)	1113 (8.1)	1093 (8.0)	1107 (8.1)
2017	1104 (8.0)	1088 (8.0)	1100 (8.0)	1103 (8.0)	1093 (8.0)
2018	1147 (8.3)	1151 (8.3)	1144 (8.3)	1133 (8.2)	1141 (8.3)
2019	1134 (8.2)	1147 (8.4)	1156 (8.4)	1153 (8.4)	1147 (8.3)
2020	1158 (8.4)	1149 (8.3)	1147 (8.3)	1152 (8.4)	1147 (8.3)
Sex					
Female	3609 (26.2)	3601 (26.2)	3605 (26.2)	3601 (26.2)	3597 (26.2)
Male	10 159 (73.8)	10 152 (73.8)	10 151 (73.8)	10 152 (73.8)	10 148 (73.8)
Age, yrs	62.4±10.1	64.8±9.5	63.3±8.6	62.6±7.6	63.3±8.7
Previous risk factor accumulation					
Smoking					
Never	3943 (29.4)	4565 (33.9)	4958 (36.8)	5034 (37.3)	5876 (43.8)
Former	3824 (28.5)	4664 (34.6)	4537 (33.7)	4618 (34.2)	4666 (34.8)
Current	5656 (42.1)	4239 (31.5)	3961 (29.4)	3841 (28.5)	2870 (21.4)
BMI, kg/m²					
≤18.5 (underweight)	104 (0.8)	99 (0.8)	82 (0.6)	66 (0.5)	57 (0.4)
18.5–24.9	3302 (26.1)	3417 (26.9)	3390 (26.6)	3327 (26.1)	3870 (30.1)
25–29.9 (overweight)	5399 (42.6)	5686 (44.7)	5796 (45.4)	5980 (46.8)	6150 (47.8)
>30 (obese)	3861 (30.5)	3526 (27.7)	3491 (27.4)	3401 (26.6)	2780 (21.6)
Hypertension	5423 (39.6)	5899 (43.1)	5620 (41.0)	5396 (39.4)	5379 (39.3)
Diabetes	2568 (18.7)	2160 (15.7)	1927 (14.0)	1666 (12.1)	1423 (10.4)
Hyperlipidemia	2111 (15.4)	2212 (16.1)	2102 (15.3)	1883 (13.7)	1882 (13.8)
eGFR, mL/min per 1.73 m²					
≥90	6193 (46.2)	5140 (38.4)	5747 (42.9)	6005 (44.8)	5482 (41.2)
60–89	5806 (43.3)	6771 (50.6)	6474 (48.3)	6419 (47.9)	6903 (51.8)
30–59	1245 (9.3)	1345 (10.0)	1069 (8.0)	884 (6.6)	872 (6.5)
<30	150 (1.1)	129 (1.0)	113 (0.8)	89 (0.7)	62 (0.5)
History of congestive heart failure	182 (1.3)	157 (1.2)	102 (0.8)	90 (0.7)	93 (0.7)

(*Continued*)

Table 1. Continued

Characteristic	Disposable income quintile				
	Lowest	Low	Median	High	Highest
MI presentation and severity					
Main complaint chest pain	12 477 (90.9)	12 448 (90.9)	12 575 (91.9)	12 636 (92.3)	12 635 (92.4)
Admission ECG ST-segment elevation	6130 (47.3)	5945 (45.9)	5983 (46.3)	5991 (48.7)	5789 (45.1)
Admission ECG nonsinus rhythm	700 (5.1)	810 (5.9)	620 (4.5)	579 (4.2)	579 (4.2)
Angiographic findings					
MINOCA	913 (6.9)	951 (7.2)	1045 (7.9)	993 (7.5)	1051 (7.9)
1-vessel	6258 (47.4)	6309 (48.0)	6628 (50.0)	6759 (50.9)	6742 (50.5)
2-vessel	3379 (25.6)	3377 (25.7)	3291 (24.8)	3280 (24.7)	3293 (24.7)
3-vessel or left main	2643 (20.0)	2518 (19.1)	2287 (17.3)	2255 (17.0)	2258 (16.9)
Troponin maximum, quintiles					
Lowest	1997 (16.0)	2057 (16.6)	2047 (16.5)	2036 (16.3)	2160 (17.4)
Low	2249 (18.0)	2359 (19.0)	2333 (18.8)	2415 (19.4)	2318 (18.7)
Median	2456 (19.7)	2523 (20.3)	2567 (20.6)	2414 (19.4)	2413 (19.5)
High	2684 (21.5)	2657 (21.4)	2596 (20.9)	2645 (21.2)	2720 (21.9)
Highest	3094 (24.8)	2828 (22.8)	2893 (23.3)	2943 (23.6)	2786 (22.5)
LVEF, %					
≥50	7874 (65.0)	7962 (66.2)	8198 (68.2)	8302 (68.5)	8700 (70.5)
40–49	2567 (21.2)	2483 (20.6)	2401 (20.0)	2410 (19.9)	2433 (19.7)
<40	1679 (13.9)	1584 (13.2)	1423 (11.8)	1413 (11.7)	1209 (9.8)
Initial therapies					
Dual antiplatelet treatment at discharge	11 990 (87.1)	12 018 (87.5)	12 098 (88.0)	12 220 (88.9)	12 203 (88.8)
Angiography performed	13 193 (95.8)	13 155 (95.7)	13 251 (96.3)	13 287 (96.6)	13 344 (97.1)
PCI if angiographic pathology	10 599 (77.0)	10 605 (77.1)	10 647 (77.4)	10 815 (78.6)	10 788 (78.5)
Planned procedure, referral at discharge	1154 (9.8)	1094 (9.2)	1069 (9.0)	1105 (9.4)	1081 (9.2)
Secondary prevention use, target achievements, and risk profile during the first year after MI					
Cardiac rehabilitation participation					
Physical training program†	5144 (37.7)	6093 (44.6)	6878 (50.3)	7313 (53.5)	7974 (58.4)
Patient educational session†	5112 (37.5)	6571 (48.1)	7389 (54.0)	7860 (57.6)	8098 (59.3)
Stress management group sessions‡	583 (4.3)	645 (4.7)	801 (5.9)	834 (6.1)	924 (6.8)
Among patients reporting depression or anxiety (n=22 652)	317 (6.0)	311 (6.7)	379 (8.4)	383 (9.0)	410 (10.4)

(*Continued*)

Table 1. Continued

Characteristic	Disposable income quintile				
	Lowest	Low	Median	High	Highest
Smoking cessation program‡	986 (7.6)	856 (6.6)	824 (6.3)	785 (6.0)	593 (4.6)
Among smokers at index MI (n=20 360)	870 (15.6)	724 (17.2)	668 (17.0)	646 (17.0)	447 (15.7)
Persistent smoking at baseline†	2670 (47.2)	1786 (42.1)	1509 (38.1)	1219 (31.7)	831 (29.0)
Metabolic syndrome after MI†	4458 (42.0)	4217 (38.3)	4134 (37.1)	4024 (36.2)	3489 (31.2)
Lipid management					
Lipid profile monitoring at any revisit	12 669 (92.0)	12 725 (92.5)	12 788 (93.0)	12 763 (92.8)	12 857 (93.5)
Statin therapy intensification§‖	4077 (29.6)	3996 (29.1)	4054 (29.5)	4064 (29.5)	3990 (29.0)
Statins at baseline	12 242 (91.4)	12 443 (92.2)	12 526 (92.7)	12 580 (93.1)	12 572 (93.1)
High-intensity statins§#	5914 (43.0)	5893 (42.8)	6131 (44.6)	6180 (44.9)	6236 (45.4)
Systolic blood pressure <140 mm Hg†	9428 (68.5)	9364 (68.1)	9655 (70.2)	9594 (69.8)	9920 (72.2)
Screening for depression or anxiety	11 986 (87.1)	12 376 (90.0)	12 462 (90.6)	12 398 (90.1)	12 408 (90.3)
Depression or anxiety reported at 2-month visit	5278 (44.3)	4643 (37.7)	4537 (36.6)	4239 (34.3)	3959 (32.0)
Acetylsalicylic acid at baseline	12 160 (90.7)	12 222 (90.5)	12 378 (91.5)	12 521 (92.6)	12 452 (92.2)
β-blockers at baseline	11 271 (84.1)	11 340 (84.0)	11 226 (83.0)	11 225 (83.1)	10 881 (80.5)
β-blockers if LVEF <40% (n=7308)	1494 (92.1)	1442 (93.0)	1303 (93.1)	1289 (92.7)	1093 (91.8)
RAAS inhibition at baseline	10 413 (77.9)	10 717 (79.5)	10 682 (79.1)	10 693 (79.3)	10 567 (78.4)
RAAS inhibition if LVEF <40%, diabetes, or hypertension (n=34 787)	6063 (86.3)	6296 (88.0)	6029 (88.1)	5888 (88.9)	5712 (89.5)

Values are n (%) or mean±SD. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system.

*Disposable income by household consumption unit was stratified by sex and calendar year.

†Pearson χ^2 for homogeneity across income quintiles probability <0.0001.

‡Low rates of participation in part explained by programs not being available at all cardiac care centers.

§Data on prescription claims derived from the National Prescribed Drug Register.

‖Pearson χ^2 for homogeneity across income quintiles probability 0.72.

#Pearson χ^2 for homogeneity across income quintiles probability <0.001.

of excess rASCVD in the lowest versus highest income quintile would drop by 3.3%. Equivalent mediation through blood pressure above target was 1.0% (95% CI, 0.7–1.5) and was negligible through suboptimal statin management (0.24%; 95% CI, 0.12–0.37). The proportion of excess rASCVD in the lowest income quintile 15 years after the baseline visit mediated through after-MI metabolic syndrome and persistent smoking was 3.9% (95% CI, 2.9–5.5) and 15.2% (95% CI, 9.1–25.7), respectively.

Sensitivity Analyses

Table S3 reports risk estimates for rASCVD using a base model that included SES indicators disposable income, educational level, and marital status. Risk associated with disposable income and not being married was attenuated but remained strong, whereas the association with educational level was much weaker. The association between disposable income and rASCVD was somewhat stronger when the exposure was on the basis of the average of a 5-year period compared with the year before incident MI, whereas attenuation by sequential models were similar (Table S4). Risk estimates in complete case analysis were similar to the primary analysis (Table S5). When other income groups were compared (Figure S4, Table S6, and Table S7), the effect mediated through nonparticipation in physical training or patient educational sessions was similar, and remained low through suboptimal statin management, whereas the proportion mediated through cardiometabolic risk profile differed between compared income groups. The effect mediated by suboptimal statin management and through nonparticipation in physical training program within cardiac rehabilitation were similar in the subgroup with metabolic syndrome (n=20 322) compared with the full cohort (Figure S5 and Table S8), but was higher compared with the subgroup without metabolic syndrome.

Secondary Outcomes

During mean 6.1-year follow-ups, there were 7608 (11.1%) and 2679 (3.9%) events of all-cause and cardiovascular deaths, respectively (Figures S6 and S7). The risk gradients were steeper for all-cause and cardiovascular death (model adjusted for age, sex, and calendar year; HR, 1.99 [95% CI, 1.84–2.15] and HR, 2.30 [95% CI, 2.01–2.63] in the lowest versus highest income quintile, respectively) than for rASCVD (Table S9). Associated risks were attenuated by adjustment for previous risk factor accumulation, acute presentation, and secondary prevention activities, but not affected by initial therapies.

DISCUSSION

In this large and contemporary real-world cohort of first-ever MI survivors followed for up to 15 years from the routine 1-year revisit, we observed a strong association

Table 2. Crude rASCVD Recurrence Rates, by SES Indicator

Socioeconomic status indicator	rASCVD events/ person-years	Recurrence rates per 1000 person-years (95% CI)
Disposable income (quintiles by year and sex)		
Lowest	1762/74 797	23.6 (22.5–24.7)
Low	1523/76 031	20.0 (19.1–21.1)
Median	1366/78 567	17.4 (16.5–18.3)
High	1264/79 857	15.8 (15.0–16.7)
Highest	1149/80 905	14.2 (13.4–15.0)
Educational level, yrs		
≤9	2380/118 739	20.0 (19.3–20.9)
10–12	3215/179 523	17.9 (17.3–18.5)
>12	1264/86 256	14.7 (13.9–15.5)
Marital status		
Not married	3165/161 009	19.7 (19.0–20.4)
Married	3835/228 693	16.8 (16.2–17.3)

rASCVD indicates first recurrent atherosclerotic cardiovascular disease event; and SES, socioeconomic status.

between disposable income and rASCVD. This association was mediated by a cardiovascular risk factor profile but also by use of secondary prevention during the first year after the MI. Using a causal inference approach, mediating effects were observed for the metabolic syndrome after MI, participation in physical training programs and patient educational sessions within cardiac rehabilitation, and persistent smoking. The identification of risk mediators for recurrence within secondary prevention is a novel finding and may help reduce health disparities in this setting. This study offers perspective from other studies on SES and rASCVD because the socioeconomic disparities reported here were estimated in a country with universal health care and may be greater in countries without.

In this study, nonparticipation in cardiac rehabilitation programs was identified as a mediator for the effect of a lower income on the risk of recurrent events. Cardiac rehabilitation on the basis of physical training is evidence-based[25] and promoting physical activity may be a means to reduce cardiovascular health disparities.[26] Although no mortality benefit has been shown for patient educational sessions within cardiac rehabilitation, it improves health-related quality of life and may reduce risk of fatal and nonfatal cardiovascular events.[27] Smoking cessation is pivotal for the secondary prevention of rASCVD and means to increase participation in cardiac rehabilitation among low-SES groups may reduce the proportion continuing to smoke.[28] Means to improve cardiac rehabilitation uptake are warranted in general and especially in people with lower SES.[29] In a recent randomized trial, providing financial incentives to patients with low SES after MI improved cardiac rehabilitation participation and completion and reduced the number of emergency department visits and rehospitalizations.[30] Furthermore, decentralization of cardiac rehabilitation centers to socioeconomically deprived areas, as well as home-based cardiac rehabilitation, may reduce the cost of transportation and improve equity.[31] Cardiac rehabilitation uptake improvements may reduce SES inequalities, is cost-effective, and there are tools available for policymakers for estimating population health gains and societal cost by participation.[32] Contrary to our expectations, differences in lipid management during the first year merely mediated excess rASCVD in lower-income groups during follow-up. Lowering levels of low-density lipoprotein cholesterol with statins is a cornerstone of

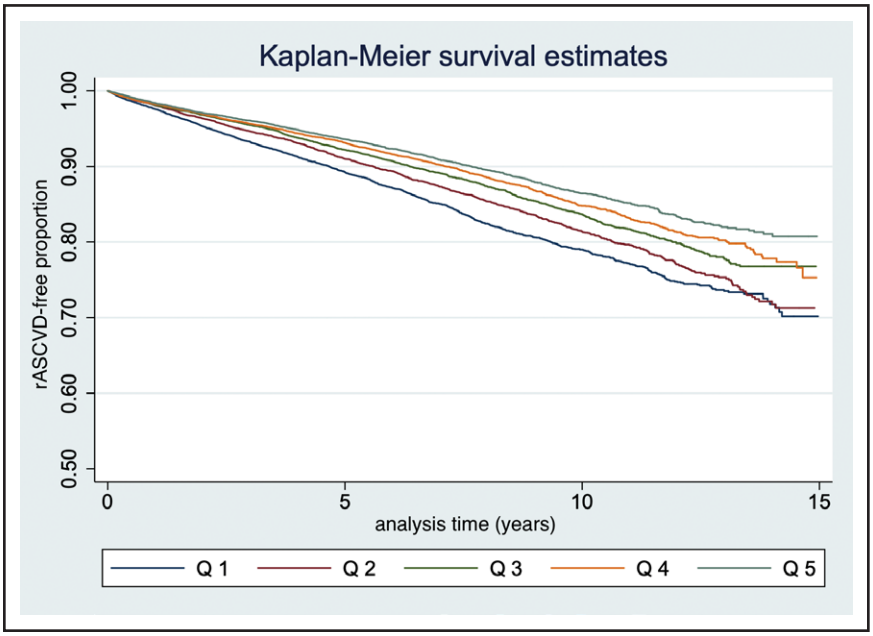

Figure 1. Kaplan-Meier curves of rASCVD-free proportion by disposable income quintile.
Q indicates disposable income quintile; and rASCVD, first recurrent atherosclerotic cardiovascular disease event.

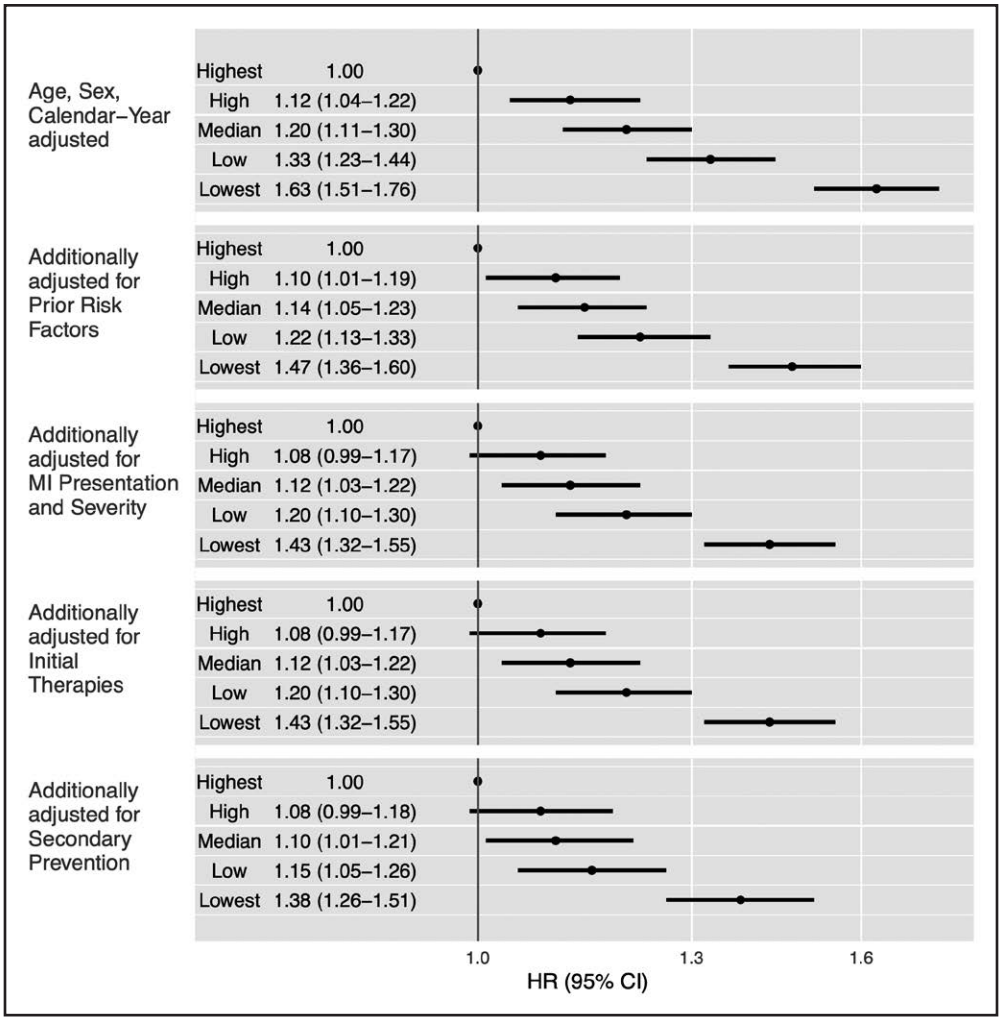

Figure 2. Forest plots depicting the association between disposable income quintile and rASCVD by analysis model.
All multivariable Cox regression models included the covariates disposable income, age, sex, and calendar year. Previous risk factors indicates smoking, body mass index, hypertension, diabetes, estimated glomerular filtration rate, congestive heart failure, and hyperlipidemia. Myocardial infarction (MI) presentation and severity indicates main complaint, admission ECG ST-segment deviation and rhythm, angiographic findings, troponin max level, and left ventricular ejection fraction. Initial therapies indicates dual antiplatelet therapy initiation, percutaneous coronary intervention if angiographic indication, and referral for planned procedure. Secondary prevention indicates participation in cardiac rehabilitation programs (eg, physical training, patient education, smoking cessation, stress management group sessions), lipid management (eg, lipid profile monitoring, statin therapy intensification, statins/high intensity at baseline), screening for depression and anxiety, and use of acetylsalicylic acid, β-blockers, or renin-angiotensin-aldosterone system inhibitors at baseline. HR indicates hazard ratio; and rASCVD, first recurrent atherosclerotic cardiovascular event.

secondary prevention with a solid evidence base,[33,34] and lower income is associated with suboptimal lipid management during the first year after MI, according to a previous study.[5] Partial explanations may include that rates of statin use in the Swedish population after MI are high overall and that the association between rASCVD and lipid-lowering treatment intensity on the basis of reaching low-density lipoprotein cholesterol target levels within this population is weak.[35]

We also report that persisting cardiometabolic risk profile after MI was attenuating the risk of low SES on rASCVD. This is consistent with studies on potential risk mediators in the primary prevention setting.[36–38] Overall, the literature addresses risk mediation in the association between SES and recurrent cardiovascular disease more sparingly.[3,4,39] In the current study, SES correlated strongly with a cardiometabolic risk profile and the metabolic syndrome after MI was mediating rASCVD in low SES. In a 2007 study with similarities to ours,[3] a traditional mediation approach included measures of both acute MI care and secondary prevention activities in assessment of the association between SES and 1-year mortality. However, the sample size was small, a large proportion (19%) of their cohort were analyzed with imputed values for the exposure (income), and more sophisticated methods for assessing mediation were not used. The time at risk is another important consideration for the comparison between the current and other studies.[4,39] Severe hemodynamic instability

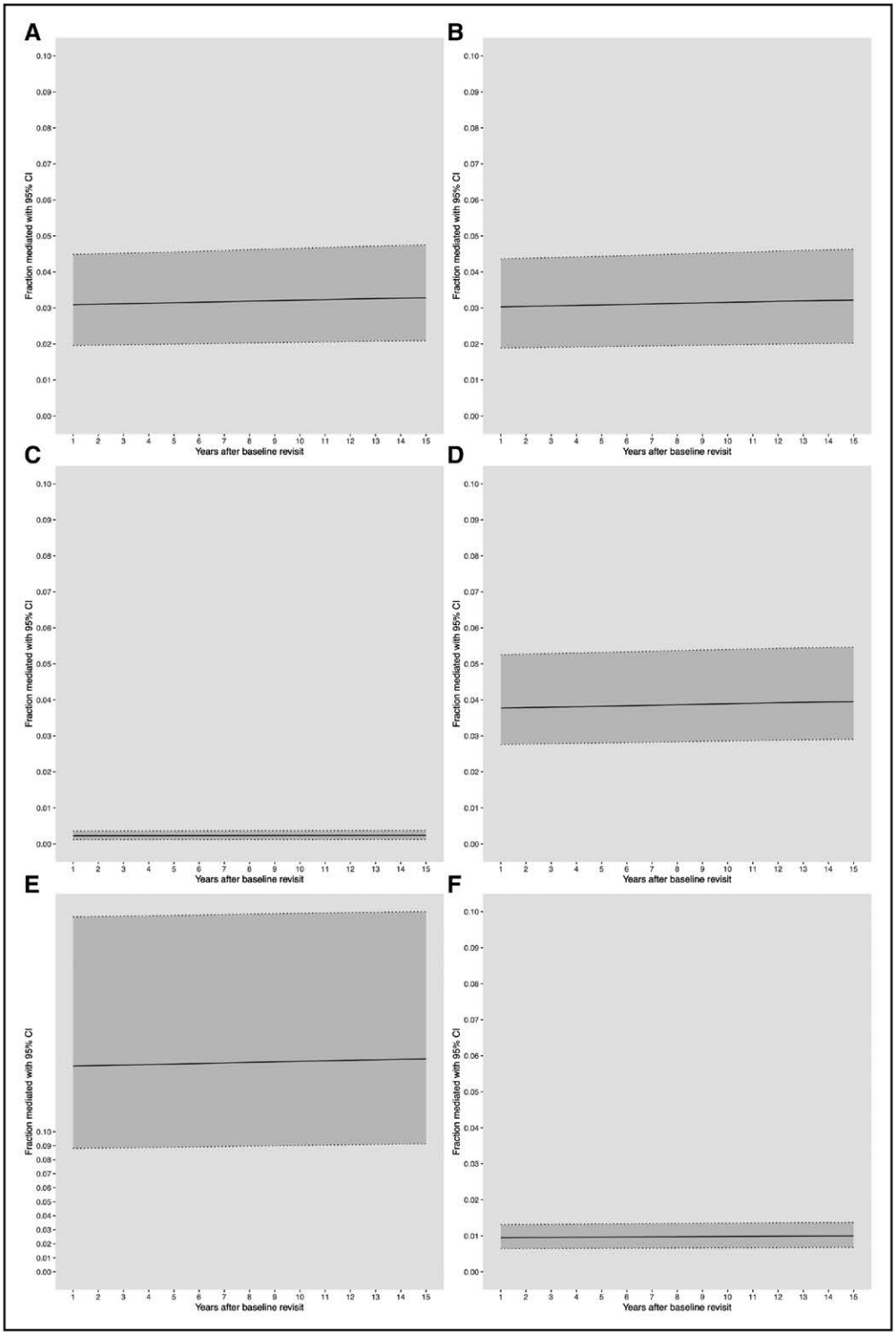

Figure 3. Proportion of the total excess probability of rASCVD because of income in the lowest quintile mediated through plausible mediator.

A, Mediating proportion through nonparticipation in physical training programs within cardiac rehabilitation. **B**, Mediating proportion through nonparticipation in patient educational sessions within cardiac rehabilitation. **C**, Mediating proportion through suboptimal statin therapy management. **D**, Mediating proportion through cardiometabolic risk profile after myocardial infarction (the metabolic syndrome). **E**, Mediating proportion through persistent smoking. **F**, Mediating proportion through blood pressure above target. Mediating proportions were the excess probability of first recurrent atherosclerotic cardiovascular disease event (rASCVD) associated with an income in the lowest quintile (TOT) attributed to the estimated pure natural indirect effect for a potential mediator. TOT was the complement of the survival function on the basis of a model adjusted for age, sex, and calendar year and the plausible mediator was assessed in a logistic model. CI bootstrap intervals on the basis of 1000 resamplings.

because of cardiogenic shock, stent thrombosis, or malignant arrhythmias adds to mortality in the early phase after MI, whereas the current study evaluated risk in the stable phase beyond the 1-year revisit.[40] A strong, unexplained association was observed in the final multivariable Cox regression model of the traditional mediation approach. The mediating effects observed with the causal inference approach were small relative to the total effect of SES on rASCVD. Other plausible mediators, unavailable in this study, may include socioeconomic determinants of health that are established early in the life course of an individual,[41] dietary factors, and long-term compliance.

Strengths and Limitations

Main strengths of this study were cohort size and the comprehensiveness, completeness, and validity of Swedish national registries.[42,43] The follow-up for rASCVD is uniquely long and also contributed to precise estimates. Nationwide inclusion and a recent study period make results representable for 1-year survivors of a first-ever MI in Sweden and comparable populations and health care systems. Two methodologic approaches of mediation analysis were used in this study, each with strengths complementary to weaknesses of the other. Differences in results were not conflicting and provide a thorough assessment of mediation in the study setting. Limitations include the risk of residual confounding and hence violation of the sequential ignorability assumption, inherent from the observational design despite measures taken to minimize confounding bias. The cumulative number of covariates and effect decomposition are limitations of the traditional basic approach to mediation analysis. The 4 assumptions on nonconfounding for the causal mediation approach are strong. To test our results for robustness to possible violations, we performed sensitivity analyses in accordance with the guideline for reporting mediation analyses (AGReMA).[12] The causal inference method used few covariates and allowed for effect decomposition but may introduce exposure-induced mediator–outcome confounding through influence from multiple mediators of interest, although this was not obvious in performed sensitivity analyses. Data on regional differences in SES and secondary prevention were unavailable. Lack of a summary measure on SES, such as a census-level deprivation index, may hamper comparison with studies that include one. However, the use of individual-level SES is a major strength because area-level SES underestimates the association with health outcomes.[44] The disposable income measure used was a stable proxy for SES. A smoking cessation program was not available at all cardiac care centers, which may explain low rates of participation. Despite the wealth of clinical data collected and analyzed until the 1-year revisit, we were unable to control for persistence with lifestyle habits and therapies beyond the baseline revisit.

Conclusions

Socioeconomic disparities in cardiometabolic risk profile and secondary prevention use mediate higher long-term risk of rASCVD in people with low SES after MI. Our data specifically identified nonparticipation in a physical training program and patient educational sessions within cardiac rehabilitation, the metabolic syndrome after MI, and persistent smoking as mediators. Improved health equity after MI needs future research on efficient methods for clinicians and policymakers to improve cardiac rehabilitation uptake and completion in low-SES groups. The mediating proportions were overall small. Other causal mechanisms for worse prognosis in lower SES remain to be disclosed.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

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