Clinical outcomes and cardiac rehabilitation in underrepresented groups after percutaneous coronary intervention: an observational study

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Aims	Underrepresentation of migrants, women, and older adults in cardiovascular disease (CVD) trials may contribute to disparate care and survival. Among patients who underwent percutaneous coronary intervention (PCI), we aimed to investigate the associations of (i) underrepresented groups with major adverse cardiac events (MACE), CVD mortality, and non-CVD mortality, (ii) underrepresented groups with cardiac rehabilitation (CR) uptake, and (iii) CR uptake with outcomes.
Methods and results	We included 15 211 consecutive patients from the CARDIOBASE Bern PCI registry (2009–18). In multi-state models comparing transition probabilities of events, sex was not associated with increased risk of any event. For each year increase in age, the increased risk of non-CVD and CVD mortality was 8% [95% confidence interval (CI) 6–9%]. Being migrant was associated with a lower risk of non-CVD mortality [hazard ratio (HR) (95% CI) 0.49 (0.27–0.90)] but not with CVD mortality. In logistic regression analysis, CR uptake was lower among women [odds ratio (95% CI) = 0.72 (0.57–0.86)] and older adults [0.32 (0.27–0.38)], but not among migrants. In cox regression, CR was independently associated with lower all-cause [HR (95% CI) = 0.12 (0.03–0.37)] and CVD mortality [0.1 (0.02–0.7)], but not with MACE [1.08 (0.8–1.4)].
Conclusion	Among underrepresented groups undergoing PCI, age, but not migration status nor sex, contributed to disparities in mortality. Migrant status did not result in lower attendance of CR. Considering the protective associations of CR on CVD mortality independent of age, sex, and migration status, the lower uptake in women and older adults is noteworthy.

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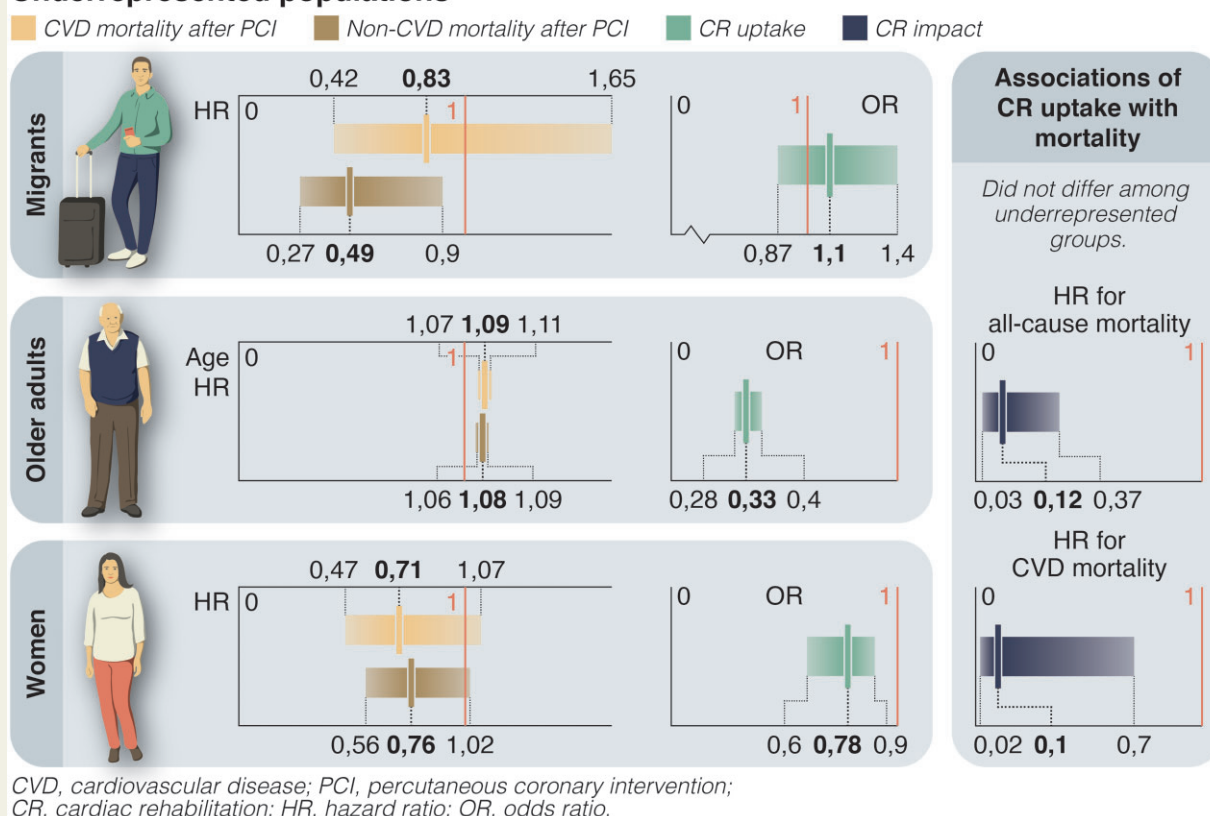†The first two authors contributed equally to the study.

Graphical Abstract

Underrepresented populations

CVD, cardiovascular disease; PCI, percutaneous coronary intervention; CR, cardiac rehabilitation; HR, hazard ratio; OR, odds ratio.

Keywords   Coronary artery disease • Older adults • Migrants • Women • Percutaneous coronary intervention • Cardiac rehabilitation

Introduction

Despite progress in prevention and treatment, coronary artery disease (CAD) remains the leading cause of health loss globally[1] and the most common cause of death related to cardiovascular disease (CVD).[2] Percutaneous coronary intervention (PCI) among patients with acute coronary syndromes (ACS) and secondary prevention strategies improve event-free survival.[3] As PCI techniques and medical therapies have evolved, CVD mortality rates are decreasing mostly in high-income settings.[3] However, persistent disparities in care contribute to the burden of the disease in specific populations.[4]

Migrants, women, and older adults have been underrepresented in cardiovascular clinical trials.[5–9] The implications of underrepresentation in research are far-reaching, as it may raise concerns regarding the validity of guideline recommendations[9] and contribute to disparities in care.[10] Indeed, several observational studies have reported an increased burden of disease and mortality[11,12] and lower uptake of

secondary prevention strategies, such as cardiac rehabilitation (CR) programmes among migrants, women, and older adults with CAD.[13–16]

Despite an ongoing controversy regarding CR survival benefits,[17] CR reduces the risk of cardiovascular hospital admissions and improves the quality of life in patients with CAD.[18] Numerous mechanisms may be responsible for the benefits associated with CR, including antiatherosclerotic, anti-ischaemic, anti-arrhythmic, antithrombotic, and psychologic effects.[19] Therefore, CR is an integral part of clinical practice guidelines for the management of acute (ACS) and chronic coronary syndromes (CCS).[20,21] However, the CR participation rate has remained low over time in both European and non-European countries[22–24] and there is scarce data regarding the associations of migration status, sex, and age with CR outcomes.[25]

Improved understanding and identification of disparities in outcomes after PCI and access to CR may inform health stakeholders and policy-makers and help design future interventions to reduce

Figure 1 Flow diagram.
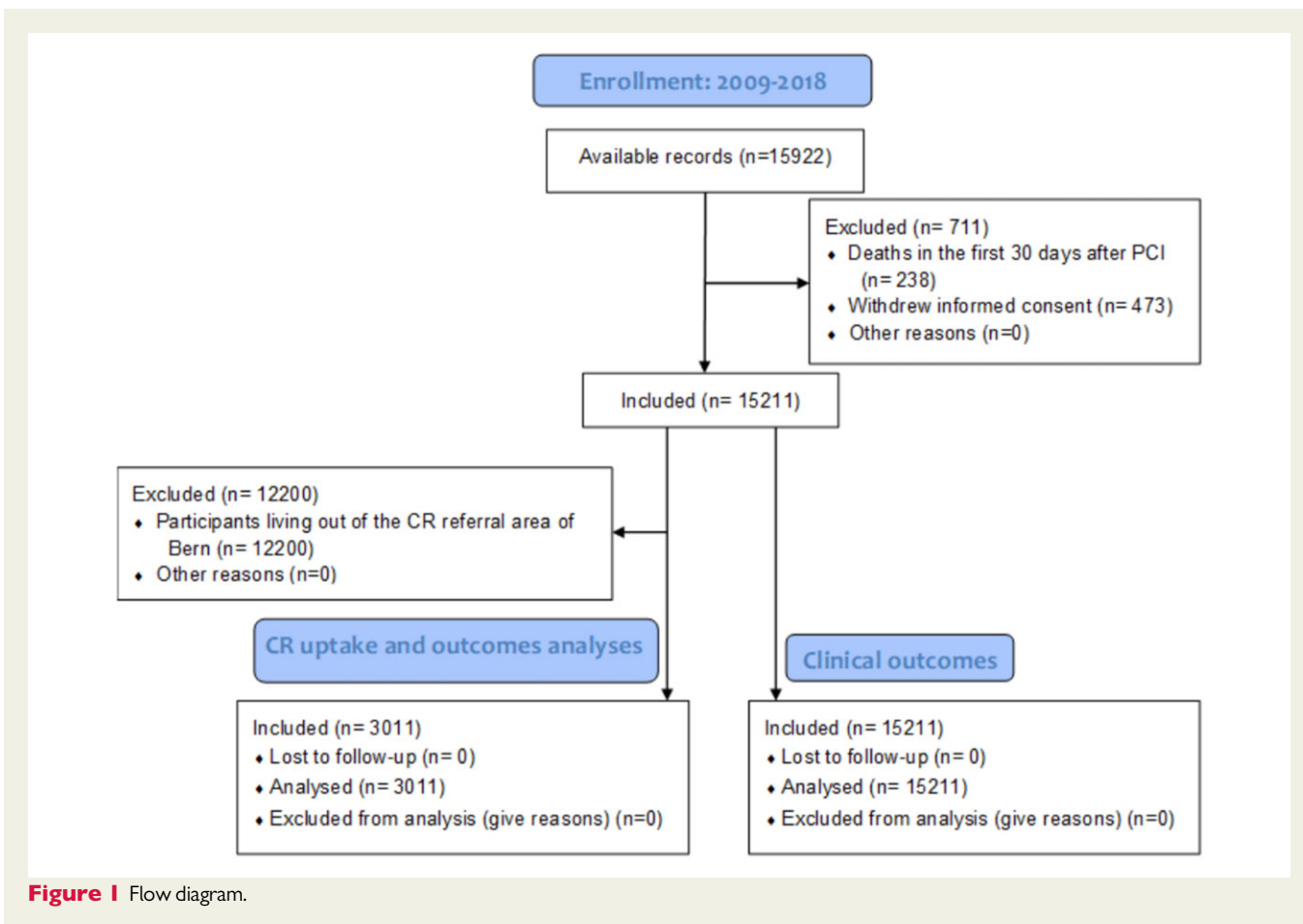
inequities and improve clinical outcomes in patients with CAD in specific settings. Therefore, we aimed to investigate the associations of (i) underrepresented groups with major adverse cardiac events (MACE), CVD mortality, and non-CVD mortality; (ii) underrepresented groups with CR uptake; and (iii) CR uptake with the under (i) specified clinical outcomes, after 1 year of follow-up.

Methods

Study design

For this observational longitudinal study, we included all consecutive patients who underwent PCI at a tertiary care centre between 2009 and 2018 and provided informed consent to participate in CARDIOBASE Bern PCI registry (NCT02241291). *Figure 1* depicts the selection of patients. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[26]

Setting, selection of patients, and data sources

CARDIOBASE registry follows patients prospectively and systematically during 1 year after PCI to assess death, myocardial infarction (MI), stroke, revascularization, and medical treatment. A health questionnaire is sent to all living patients with questions on re-hospitalization and adverse events, followed by telephone contact in case of missing

response. General practitioners and referring cardiologists are contacted if necessary for additional information. External medical records, discharge letters, and coronary angiography documentation are systematically collected and reviewed for patients treated for adverse events at other medical institutions.[27] Baseline clinical and procedural characteristics and all follow-up data are entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) responsible for central data audits and maintenance of the database. A clinical event committee consisting of two cardiologists (or three in case of disagreement) adjudicated all the events based on source documents. We excluded patients who withdrew informed consent (*Figure 1*). Thirty-day mortality is widely used as a surrogate marker of procedural quality and depends largely on the provider's caseload.[28] Therefore, we excluded patients who died within the first 30 days after PCI to avoid immortal bias in the CR uptake analysis, and to account for clinical, instead of procedural-related outcomes in the main analysis. We linked the CARDIOBASE information with the hospital administrative records to obtain the migration status, geographic living area, and participation in CR. We used the geographic living area to select the group of patients for our CR uptake analysis. Because we only had data on CR uptake if CR was completed at our centre, we performed the analysis on CR uptake in the subgroup of patients living in the referral area of our hospital in the city of Bern. We also used the geographic living area to obtain the geocode of the place of residence at the time of PCI and linked our anonymized data to the census-based Swiss National
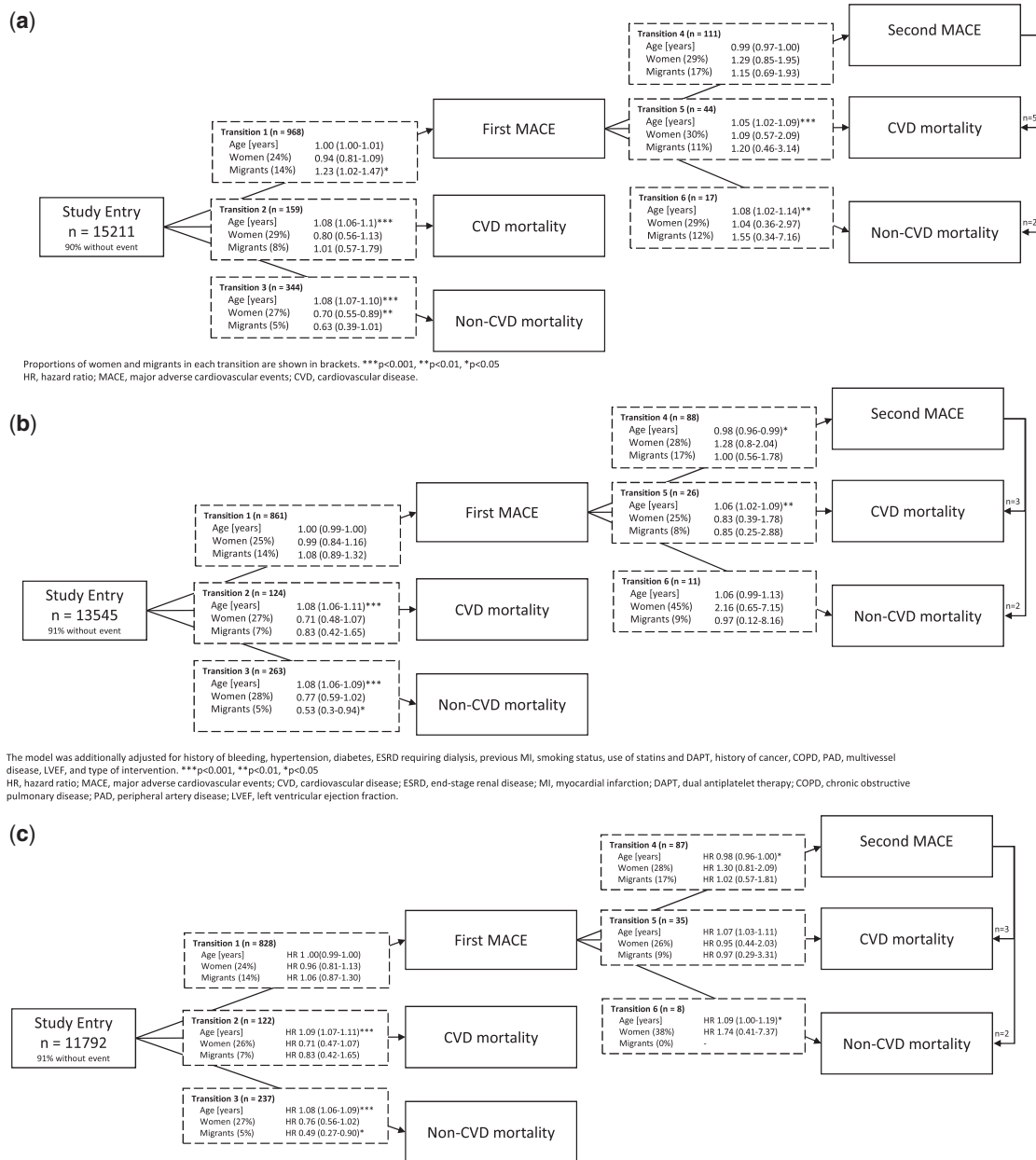
Figure 2 (*A*) Multi-state models with transitional hazard ratios for crude associations of migration status, sex and age with major adverse cardiac events, non cardiovascular mortality, and cardiovascular disease mortality. Proportions of women and migrants in each transition are shown in brackets. ***P* < 0.001, ***P* < 0.01, **P* < 0.05. (*B*) Multi-state models with transitional hazard ratios for adjusted associations of migration status, sex and age with major adverse cardiac events, non cardiovascular mortality, and cardiovascular disease mortality. The model was additionally adjusted for history of bleeding, hypertension, diabetes, end-stage renal disease requiring dialysis, previous myocardial infarction, smoking status, use of statins and dual antiplatelet therapy, history of cancer, chronic obstructive pulmonary disease, peripheral artery disease, multivessel disease, left ventricular ejection fraction, and type of intervention. ***P* < 0.001, ***P* < 0.01, **P* < 0.05. (*C*) Multi-state models with transitional hazard ratios associations of migration status, sex and age with major adverse cardiovascular events, non cardiovascular mortality, and cardiovascular disease mortality, additionally adjusted for socioeconomic position. Proportions of women and migrants in each transition are shown in brackets. The model was adjusted for socioeconomic position in addition to Model B. ***P* < 0.001, ***P* < 0.01, **P* < 0.05. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ESRD, end-stage renal disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events (myocardial infarction, revascularization, or cerebrovascular event); MI, myocardial infarction; PAD, peripheral artery disease; SSEP, Swiss index of socioeconomic position.

Cohort[29] to obtain the Swiss neighbourhood index of socioeconomic position (SSEP).[30]

Statistical analyses

Clinical outcomes after percutaneous coronary intervention for the cohort

We investigated the associations of being a migrant, woman, or older adult, with MACE, CVD, and non-CVD mortality using multi-state models. After 1 year of follow-up, a patient may remain free of events or move to one out of six possible transitions of MACE or death (*Figure 2*). A second MACE, CVD death, and non-CVD death were the final or absorbing states in the model. Model 1 included migrant status, sex, and age as continuous, as independent variables. Model 2 added health-related and intervention-related variables (history of bleeding, hypertension, diabetes, end-stage renal disease (ESRD) requiring dialysis, previous MI, smoking status, use of statins and dual antiplatelet therapy (DAPT), history of cancer, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), multivessel disease, left ventricular ejection fraction (LVEF), and type of intervention. Model 3 added SSEP. In all analyses, we calculated transitional hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs). We used R (Version 3.5.1, R Core Team, 2017) to build the multi-state models.

Cardiac rehabilitation uptake analysis

We investigated the associations of being migrant, woman, or older adult, with CR uptake among patients from the referral area of Bern (Supplementary material online, *Figure S1*) using logistic regression models. A raw model estimated the unadjusted associations and three multivariate logistic regression models estimated the adjusted associations. Model 1 included only information about CR uptake and underrepresented groups (migrant status, sex, and age as continuous) as independent variables. Model 2 added health-related and intervention-related variables (history of bleeding, hypertension, diabetes, ESRD requiring dialysis, previous MI, smoking status, use of statins and DAPT, history of cancer, COPD, PAD, multivessel disease, LVEF, and type of intervention). Model 3 adds SSEP. In all analyses, we reported all proportions and odds ratios (ORs) with the corresponding 95% CI derived from robust standard error calculations.

Clinical outcomes after cardiac rehabilitation uptake

To investigate the associations of CR uptake with MACE, all-cause, and CVD mortality, we implemented three Cox proportional hazard regression models, as above defined. We used time after PCI as the time scale. We verified the proportional hazards assumption by plotting the scaled Schoenfeld residuals. We used log-rank tests to compare the differences in outcomes rates between CR and non-CR participants. In all analyses, we reported HRs with the corresponding 95% CI. We considered *P*-values <0.05 as statistically significant and performed inverse probability weighting (IPW) based on propensity score to balance the CR uptake groups and minimize the impact of bias related to non-random assignment (Supplementary material online, *Methods*). The analyses were performed in Stata (version 16, Corporation, College Station, TX, USA).

Results

Patients and descriptive data

Between 1 January 2009 and 31 October 2018, 15 922 patients with an established diagnosis of CAD were included in CARDIOBASE registry (*Figure 1*). After excluding participants who withdrew

informed consent or died within the first 30 days after PCI, we included 15 211 participants with a mean age (standard deviation) of 67 (12) years. There were 564 deaths during 1-year follow-up. The median time of follow-up (interquartile range) for dead patients was 178 days (77–293). Cardiovascular disease deaths (*n* = 203) accounted for 36% of all deaths. Major adverse cardiac events occurred in 968 patients as a first event, and 111 patients presented a second MACE during 1-year follow-up. All 14 647 remaining patients could be followed-up to 1 year. *Table 1* presents baseline characteristics stratified by migration status, sex, and age group. Migrants, women, and older adults represented 12%, 26%, and 60% of the participants, respectively. Europeans mainly composed our migrant population (Supplementary material online, *Figure S2*). Compared to non-migrants, migrants were more likely to be diabetic (30% vs. 21%) and active smokers (37% vs. 26%). Women were on average 6 years older than men (72 vs. 66) and were more likely to have hypertension (75% vs. 66%). Compared to the group of younger adults, older adults had a higher proportion of women (32% vs. 16%) and patients with hypertension (77% vs. 56%), diabetes (25% vs. 18%), cancer (15% vs. 5%), COPD (8% vs. 4%), PAD (10% vs. 5%), multivessel disease (45% vs. 38%), prior bleeding (5.7% vs. 3%), and hypercholesterolaemia (66% vs. 61%) (*Table 1*).

Analysis of outcomes after percutaneous coronary intervention

At completion of follow-up, 90% of patients remained free of events. We observed 1619 incident outcomes in 1521 patients. The most common first-transition event was MACE (6%), followed by non-CVD mortality (2%), and CVD mortality (1%). After a first MACE, 11% of those patients had a second MACE, 5% died from cardiovascular cause, and 2% died from other causes (*Figure 2A*). Age was associated with a significant risk for non-CVD mortality as a first transition, and CVD mortality in all the transitions, but not with MACE (*Figure 2A*). For each year increase in age, participants had an 8% increased risk of non-CVD and CVD mortality after PCI in the first transition. After a first MACE, the magnitude of the association of age with non-CVD mortality remained consistent (HR = 1.06; 95% CI 1.02–1.09) as for the first transition (*Figure 2A*). After adjustment for health-related factors, migrants had a lower risk of non-CVD mortality as the first event (HR = 0.53; 95% CI 0.3–0.94) (*Figure 2B*). Additional adjustment for SSEP (*Figure 2C*) showed consistent results (HR = 0.48; 95% CI 0.27–0.90). Women were not at higher risk of events in any of the transitions.

The sensitivity analysis for excluded participants who died within the first 30 days after PCI did not reveal any excess of early mortality rates among migrants (HR = 0.7; 95% CI 0.4–1.3) and women (HR = 1.1; 95% CI 0.8–1.5). Similar to the main analysis, older adults had a higher risk of early mortality, compared to patients younger than 65 years (HR = 2.8; 95% CI 1.9–4.4). Therefore, we excluded potential outcome differences in 1-year mortality due to differential mortality that occurred within the first 30 days after PCI.

Cardiac rehabilitation uptake

We included 3011 patients living in the referral area of Bern. Overall, CR uptake was 35%. The lowest CR uptake was 32% in 2009. The highest CR uptake was 38% in 2015. Time trend for uptake was not

Table 1 Baseline characteristics according to underrepresented groups

	Total sample	Age groups <65	Age groups ≥65	P-value for comparison	Sex Male	Sex Female	P-value for comparison	Migration status Non-migrants	Migration status Migrants	P-value for comparison
Sociodemographic factors, n (%)	15 211	6118 (40)	9093 (60)		11 331 (74)	3880 (26)		13 356 (88)	1855 (12)	
Age, years (SD)	67 (12)	55 (7)	75 (7)	—	66 (12)	72 (11)	0.000	68 (11)	61 (12)	0.000
Female sex	3880 (25)	974 (16)	2906 (32)	0.000	—	—	—	3521 (26)	359 (19)	0.000
Migration status	1855 (12)	1149 (19)	706 (8)	0.000	1496 (13)	359 (9)	0.000	—	—	—
SSEP, mean (SD)	54 (11)	53 (11)	54 (11)	0.07	54 (11)	53 (11)	0.11	54 (11)	51 (13)	0.09
Health-related factors, n (%)										
ACS	8375 (55)	3898 (64)	4477 (49)	0.000	6256 (55)	2119 (55)	0.37	7337 (55)	1038 (56)	0.41
Hypertension	10 424 (69)	3407 (56)	7017 (77)	0.000	7509 (66)	2915 (75)	0.000	9200 (69)	1224 (66)	0.02
Diabetes mellitus	3412 (22)	1093 (18)	2319 (25)	0.000	2492 (22)	920 (24)	0.01	2850 (21)	562 (30)	0.000
ESRD requiring dialysis	165 (1.1)	56 (0.9)	109 (1.2)	0.11	114 (1)	51 (1.3)	0.1	140 (1)	25 (1.3)	0.23
History of AMI	2445 (16)	828 (14)	1617 (18)	0.000	2000 (18)	445 (12)	0.000	2089 (16)	356 (19)	0.000
History of cancer	1615 (11)	300 (5)	1315 (15)	0.000	1172 (10)	443 (11)	0.06	1471 (11)	144 (8)	0.000
History of bleeding	694 (4.6)	179 (3)	515 (5.7)	0.000	517 (4.6)	177 (4.6)	0.96	598 (4.5)	96 (5.2)	0.19
History of PAD	1230 (8)	304 (5)	926 (10)	0.000	894 (8)	336 (9)	0.11	1088 (8)	142 (8)	0.49
History of COPD	981 (6.4)	257 (4)	724 (8)	0.000	782 (7)	199 (5)	0.000	873 (6.5)	108 (6)	0.27
Active smoking	4139 (27)	2802 (46)	1337 (15)	0.000	3323 (30)	816 (21)	0.000	3454 (26)	685 (37)	0.000
Former smoking	4585 (30)	1571 (26)	3014 (33)	0.000	3903 (35)	682 (18)	0.000	4054 (31)	531 (29)	0.11
Hypercholesterolaemia	9751 (64)	3741 (61)	6010 (66)	0.04	7291 (65)	2460 (64)	0.58	8497 (64)	1254 (68)	0.03
BMI, kg/m² (SD)	27 (4.6)	28 (5)	27 (5)	0.04	27 (4)	27 (5)	0.13	27 (4.6)	27 (4.5)	0.06
LVEF, % (SD)	53 (13)	54 (11)	54 (11)	0.18	53 (13)	54 (13)	0.16	53 (13)	52 (13)	0.15
Prescription of statins	13 851 (91)	5782 (95)	8069 (89)	0.000	10 454 (92)	3397 (88)	0.000	12 134 (91)	1717 (93)	0.01
Prescription of DAPT	14 481 (95)	5872 (96)	8609 (95)	0.11	10 814 (95)	3667 (95)	0.58	12 698 (95)	1783 (95)	0.13
Intervention-related factors, n (%)										
Multivessel treatment	6391 (42)	2349 (38)	4042 (45)	0.000	4870 (43)	1521 (39)	0.000	5615 (42)	776 (42)	0.88
Balloon angioplasty	1118 (7.3)	434 (7)	684 (7.5)	0.52	859 (7.6)	259 (6.7)	0.19	988 (7)	130 (7)	0.67
Primary stenting	14 079 (92.7)	5676 (93)	8403 (92.5)	0.52	10 477 (92)	3602 (93.3)	0.19	12 355 (93)	1724 (93)	0.67
BMS	746 (4.9)	315 (5)	431 (4.7)	0.52	564 (5)	182 (4.7)	0.19	668 (5)	78 (4.2)	0.67
DES	13 333 (88)	5361 (88)	7972 (88)	0.39	9931 (88)	3420 (88)	0.13	11 687 (88)	1646 (89)	0.25

Percentages are based on the population for each column.

ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; BMS, bare metal stents; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; ESRD, end-stage renal disease; LVEF, left ventricular ejection fraction; n, number of participants; PAD, peripheral artery disease; SD, standard deviation; SSEP, Swiss neighbourhood index of socioeconomic position.

Table 2 Cardiac rehabilitation uptake according to underrepresented groups

Total sample (*n* = 3011)	Age groups		Sex		Migration status	
	<65	**≥65**	**Male**	**Female**	**Non-migrants**	**Migrants**
Participation rates,[a] *n* (%) 1058 (35)	652 (53)	406 (23)	874 (38)	184 (25)	829 (33)	229 (45)
Crude ORs	Ref	0.26 (0.2–0.3)	Ref	0.55 (0.4–0.6)	Ref	1.63 (1.3–1.9)
OR (95% CI)[b]	Ref	0.27 (0.2–0.3)	Ref	0.78 (0.6–0.9)	Ref	1.02 (0.8–1.2)
OR (95% CI)[c]	Ref	0.33 (0.27–0.4)	Ref	0.74 (0.6–0.9)	Ref	1.1 (0.9–1.4)
OR (95% CI)[d]	Ref	0.33 (0.28–0.4)	Ref	0.78 (0.6–0.9)	Ref	1.1 (0.87–1.4)

COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; CVD, cardiovascular disease; ESRD, end-stage renal disease; MACE, major adverse cardiac events; MI, myocardial infarction; *n*, number of participants; OR, odds ratios from logistic regression analyses; PVD, peripheral vascular disease; SSEP, Swiss neighbourhood index of socio-economic position.
[a]Participation rates in cardiac rehabilitation only performed in the group of patients living in the metropolitan area of the city of Bern.
[b]Adjusted associations by age, sex, and migration status for uptake in underrepresented groups.
[c]Adjusted model including history of bleeding, hypertension, diabetes, ESRD requiring dialysis, previous MI, smoking status, use of statins and DAPT, history of cancer, COPD, PAD, multivessel disease, LVEF, and type of intervention, in addition to variables included in Model B.
[d]Most adjusted model including and SSEP, in addition to variables included in Model C.

significant (Bonferroni-corrected *P* value = 0.28). The distribution of baseline characteristics according to CR attendance is summarized in Supplementary material online, *Table S1*. Ambulatory CR uptake for migrants, women, and patients older than 65 years was 45%, 25%, and 23%, respectively (Supplementary material online, *Table S1*). Patients' characteristics at baseline significantly differed according to CR uptake. We found the lowest proportions of uptake in patients with diabetes, previous MI, cancer, ESRD requiring dialysis, PAD, and COPD. Compared to patients who did not attend CR, we found a significantly higher prescription of statins (88% vs. 95%) and DAPT (93% vs. 97%) in the group of CR uptake (Supplementary material online, *Table S1*). In the multivariate analysis, we found that age was significantly inverse-associated with CR uptake, and overall rates of CR uptake in women were significantly lower when compared with men. For each year increase in age, participants had 5% lower CR uptake [OR (95% CI) = 0.95 (0.94–0.96)]. For patients older than 65 years, the relative reduction in uptake was 67%, compared to patients younger than 65 years [OR (95% CI) = 0.33 (0.27–0.4)]. Compared to men, women had a 22% relative reduction in CR uptake, independent of age, comorbidities, and socioeconomic status [OR (95% CI) = 0.78 (0.6–0.9)] (*Table 2*). Migration status was initially associated with higher CR uptake, but it was no longer significant after adjustments (*Table 2*).

Clinical outcomes after cardiac rehabilitation uptake

The event rates in the group of patients living in the CR referral area of Bern were as follows: all-cause mortality was 3.1% (*n* = 96), CVD mortality was 1.3% (*n* = 39), and MACE was 11.2% (*n* = 336). Among age, sex, and migrations status, only age was associated with all-cause and CVD mortality (Supplementary material online, *Table S2*). After multiple adjustment for CR uptake, baseline health-related, and intervention-related factors, participants older than 65 years had a 3.1-fold risk of all-cause mortality [HR (95% CI) = 3.1 (1.4–6)], and 5.3-fold risk of CVD mortality [HR (95% CI) = 5.3 (1.2–23)],

compared to participants younger than 65 years (Supplementary material online, *Table S2*). Results remained similar after additional adjusting for SSEP (Supplementary material online, *Table S2*). The rates for MACE did not differ among categories of migration status, age, and sex. We observed an independent association of CR uptake with all-cause (HR [95% CI] = 0.12 [0.04–0.4]) and CVD mortality [HR (95% CI) = 0.12 (0.02–0.9)], but not with MACE [HR (95% CI) = 1.1 (0.86–1.5)] (Supplementary material online, *Table S3* and *Figure S3*). After propensity score inverse weighting, we obtained balanced distributions of weights, which ranged between 1.02 and 3.1 in the group of no-uptake, and 1.4 and 17 in the group of uptake. The final IPW sample size was 5953 weighted participants in equally balanced groups of 2953 (no-uptake) and 3000 (uptake). We obtained consistent estimation of CR uptake associations with all-cause [HR (95% CI) = 0.26 (0.1–0.62)], CVD mortality [HR (95% CI) = 0.06 (0.08–0.44)], and MACE [HR (95% CI) = 1.06 (0.82–1.4)] from generalized estimating equations based on the IPW from the propensity score (Supplementary material online, *Table S3*).

Discussion

Overall, we found that CVD and non-CVD mortality after PCI were strongly associated with age, while taking into account all other considered factors. Migrants had a lower risk of non-CVD mortality after PCI, while women and older adults, but not migrants, were less likely to attend ambulatory CR. In all groups of age, gender, and migration status, CR was independently associated with lower rates of all-cause and CVD mortality, even after adjusting for health and intervention-related factors, socioeconomic status, and controlling for confounding by indication.

As expected, increasing age resulted in higher incidence of CVD mortality and all-cause mortality, independent of health-related factors and SSEP. Furthermore, we observed a consistent magnitude of the effect of age across all the transitions to mortality, independent of the cause of death or MACE as a previous transition. Increasing age

also resulted in decreased CR uptake. One may argue that older patients are more frail, and present the typical decline in exercise capacity as part of the ageing process, preventing them from attending CR as suggested by some evidence.[31,32] However, a recent study evaluating uptake and adherence to CR programmes in older adults from eight European countries found that perceived lack of usefulness was the main reason for refusing CR participation.[33] Nevertheless, CR has been reported to offset the same risks that prevent vulnerable patients from attending CR, as it improves physical function and facilitates independence in older adults.[34] Moreover, we used health-related factors to adjust for CR uptake and CR associations with our outcomes of interest. Despite the higher mortality among the older participants, age did not attenuate the protective associations of CR in our setting, highlighting the need to intensify efforts in recruiting and facilitating access to CR for older patients. As supported by recent evidence, home-based mobile programmes are a safe and effective alternative to improve fitness and increase physical activity in older patients who declined hospital-based CR.[35,36]

Despite the lower CR uptake among women, we observed a trend towards a lower risk of CVD and non-CVD mortality in women after PCI. Although an excess of mortality after PCI has been repeatedly reported for women, especially in early PCI cohorts,[11] global temporal analyses have shown a progressive decline in mortality for both sexes, and a reduction in the gender gap of mortality after PCI.[37] Our study extends this previous work, as we did not observe any difference in early or late mortality in women after PCI. Secular trends of improvement in PCI techniques and patient selection may explain at least in part our findings. The different baseline risk profiles between sexes may explain the lack of significance after multiple adjustments. While women were older and had a higher prevalence of hypertension, men were more likely to be smokers and have a history of MI. Unmeasured factors related to lifestyle habits, such as physical activity, sleep, alcohol consumption, and diet, might also explain the higher survival we found in women before the multivariate analyses.

We did not analyse the possible explanations for the low overall rates of CR uptake in women in this study. However, a meta-analysis that evaluated barriers to CR in women found that transportation, home obligations, lack of insurance, and financial concerns limit the participation of women in CR.[38] Given the independent protective associations of CR with mortality after PCI, our findings regarding disadvantaged access to comprehensive CR in women are a call to action to improve CR uptake in this group. To address such barriers related to transportation and time constraints, tailored home-based CR programmes may play a role in helping to provide more options to women.[39]

Current evidence supports the lower non-CVD mortality among migrants observed in our setting. A meta-analysis from all global regions found that migrants had a 30% relative reduction in all-cause standardized mortality ratios when compared with the general population from host countries.[40] However, the estimates for CVD mortality were highly heterogeneous ($I^2 = 99.62\%$), and the individual studies did not compare equally treated populations as we did. Some evidence[41,42] supports the healthy migrant hypothesis—immigrants to high-income settings tend to be healthier than the native population—as a possible *ad hoc* explanation of unexpected immigrant health advantages. Instead, we found a

worse clinical profile among migrants compared to Swiss patients. In this study, the proportions of diabetes, ESRD requiring dialysis, previous MI, active smoking, and hypercholesterolaemia were higher in migrants than in non-migrants. Salmon bias hypothesis is another possible explanation for the observed mortality advantage of migrants.[41] Salmon bias states that ill migrants tend to return to their countries of origin, while healthy migrants stay in the host country. In this study, there were no losses to follow-up supporting salmon bias theory. We add to the current knowledge because without healthy migrant effect and salmon bias, we still found a survival advantage, which cannot be fully explained by the two most accepted hypotheses. Despite the lack of significance after multivariate analysis, we also found an initial trend towards higher CR uptake among the migrant population. The higher CR uptake of migrants in the uncorrected model was age-driven, and became non-significant after multiple adjustment.

Our results contrast with other reports from the literature, as previous studies evaluating underrepresented populations have reported disparities in CR uptake with lower uptake among racial and ethnic groups.[15,25] For instance, a recent study of German rehabilitation care found that foreign nationals attend rehabilitation services less often than German nationals do, even after adjusting for multiple factors, such as age and socioeconomic status.[43] In addition, compared to German nationals, migrants were less satisfied with the rehabilitation programmes and completed them with a lower subjective perception of success.[44] However, a recent scoping review found inconsistent results in the utilization of medical rehabilitation services by persons of working age with a migrant background in comparison with non-migrants.[45] These inconsistencies may be due to differences in the type of rehabilitation, country-specific social inequalities, and structural characteristics of the migrant population. Therefore, our results should be interpreted according to the structure of our migrant population and the Bern circumstances, where patients from European countries represented more than 80% of the migrant population. Also particular for our setting, where the migrant population rose to more than 25% during the 20th century,[46] the following conditions may have played a role in the participation of migrants in the CR programme. First, the healthcare system upholds the principles of universality and equality through means, such as compulsory health insurance.[47] Second, all the insurance companies reimburse the CR programme. Third, in 2002, Switzerland launched the Immigration and Health initiative to bridge gaps for migrants in the healthcare system,[46] reinforced by the creation of the Swiss Hospitals for Equity Network.

Despite the specificity of our clinical setting, our results indicate the need to evaluate if inclusive policies at the country and health system levels may help overcome health disadvantages and exclusions in migrants. By comparing how rates of CR uptake among migrants and nationals change over time, future studies should evaluate the impact of health policies addressing health inequities in the migrant population across different countries and different migrant origins.

Limitations and strengths

Due to its observational design, this study is limited by the fact that we did not investigate other potential unmeasured

confounders that may affect both CR uptake and clinical benefit, such as baseline physical activity levels, nutritional status, disability, and frailty. However,[48] in PCI patients, frailty as a clinical syndrome with progressive decrease in physical function, is associated with the same health-related factors that we used for adjustment, including previous MI, diabetes, hypertension, age, sex, and ESRD.[49]

Another limitation of this study is that, in practice, stationary CR programmes are also used for CR eligible patients who have difficulty accessing CR ambulatory programmes. Patients who are disabled, frail, or have limited cognitive function may decide to perform CR in stationary centres. Since our hospital does not offer such a programme and we do not have data on how many of our PCI patients took up stationary CR at other centres, we may have underestimated CR uptake rate in the older patients. However, in our cohort of PCI patients, ambulatory CR is the intervention of choice, whereas stationary CR is preferred after coronary artery by-pass grafting, valve surgery, and percutaneous aortic valve replacement. Therefore, we do not expect an important proportion of stationary CR among our participants.

Strengths include the prospective study design and a large number of participants with extensive and detailed information on covariates and outcomes. The large sample size allowed us to adjust for multiple confounders, which provided consistent findings. Despite the limitations of observational designs, our real-life setting, the all-comers design, and the fact that we controlled for immortal bias and confounding by indication make this study more representative of the general population and current practice patterns than randomized trials with strict selection criteria. Finally, this study is based on standardized adjudication of clinically meaningful outcomes.

Conclusion

In this study, among underrepresented groups undergoing PCI, age, but not migration status nor female sex contributed to disparities in mortality. Migrant status did not result in lower attendance of a structured CR programme. Considering the protective associations of CR with CVD mortality irrespective of age, sex, and migration status, the lower uptake in women and older adults is noteworthy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author only with the permission of CARDIOBASE.

References

1. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**:1151–1210.
2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Ärnlöv J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Bärnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castañeda-Orjuela CA, Castillo-Rivas J, Catalá-López F, Choi J-Y, Christensen H, Cirillo M, Cooper L Jr, Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang Y-H, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin M-J, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;**70**:1–25.
3. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, Mussolino ME, Hsu LL, Addou E, Engelgau MM, Gordon D. Decline in cardiovascular mortality: possible causes and implications. *Circ Res* 2017;**120**:366–380.

4. Corrà U, Piepoli MF. Secondary prevention: where we are. *Eur J Prev Cardiol* 2017;**24**:14–21.

5. Ceron C, Vilcant V, Verma G, Zeltser R, Makaryus A. Minority representation in cardiovascular clinical trials. *J Am Coll Cardiol* 2019;**73**:3045–3045.

6. Khan SU, Khan MZ, Raghu Subramanian C, Riaz H, Khan MU, Lone AN, Khan MS, Benson E-M, Alkhouli M, Blaha MJ, Blumenthal RS, Gulati M, Michos ED. Participation of women and older participants in randomized clinical trials of lipid-lowering therapies: a systematic review. *JAMA Network Open* 2020;**3**: e205202.

7. Khan MS, Shahid I, Siddiqi TJ, Khan SU, Warraich HJ, Greene SJ, Butler J, Michos ED. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc* 2020;**9**:e015594.

8. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 2020;**141**: 540–548.

9. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. *JAMA Intern Med* 2014;**174**:1868–1870.

10. Youmans QR, Hastings-Spaine L, Princewill O, Shobayo T, Okwuosa IS. Disparities in cardiovascular care: past, present, and solutions. *Cleveland Clin J Med* 2019;**86**:621–632.

11. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: a systematic review. *Circulation* 2014;**130**:757–767.

12. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA Intern Med* 2014;**174**:1822–1830.

13. Li S, Fonarow GC, Mukamal K, Xu H, Matsouaka RA, Devore AD, Bhatt DL. Sex and racial disparities in cardiac rehabilitation referral at hospital discharge and gaps in long-term mortality. *J Am Heart Assoc* 2018;**7**:e008088.

14. Scott LA, Ben-Or K, Allen JK. Why are women missing from outpatient cardiac rehabilitation programs? A review of multilevel factors affecting referral, enrollment, and completion. *J Womens Health (Larchmt)* 2002;**11**:773–791.

15. Castellanos LR, Viramontes O, Bains NK, Zepeda IA. Disparities in cardiac rehabilitation among individuals from racial and ethnic groups and rural communities—a systematic review. *J Racial Ethn Health Disparities* 2019;**6**:1.

16. Chauhan U, Baker D, Lester H, Edwards R. Exploring uptake of cardiac rehabilitation in a minority ethnic population in England: a qualitative study. *Eur J Cardiovasc Nurs* 2010;**9**:68–74.

17. Powell R, McGregor G, Ennis S, Kimani PK, Underwood M. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. *BMJ Open* 2018;**8**:e019656.

18. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016;**1**:CD001800.

19. Franklin BA, Lavie CJ, Squires RW, Milani RV. Exercise-based cardiac rehabilitation and improvements in cardiorespiratory fitness: implications regarding patient benefit. *Mayo Clin Proc* 2013;**88**:431–437.

20. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.

21. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

22. Kotseva K, De Bacquer D, Jennings C, Gyberg V, De Backer G, Rydénz L, Amouyel P, Bruthans J, Cifkova R, Deckers JW, De Sutter J, Fraz Z, Graham I, Keber I, Lehto S, Moore D, Pajak A, Wood D; EUROASPIRE Investigators. Time trends in lifestyle, risk factor control, and use of evidence-based medications in patients with coronary heart disease in Europe: results from 3 EUROASPIRE Surveys, 1999–2013. *Global Heart* 2017;**12**:315–322.e3.

23. Peters AE, Keeley EC. Trends and predictors of participation in cardiac rehabilitation following acute myocardial infarction: data from the behavioral risk factor surveillance system. *J Am Heart Assoc* 2017;**7**:e007664.

24. Hermann M, Witassek F, Erne P, Radovanovic D, Rickli H. Referral for cardiac rehabilitation after acute myocardial infarction: insights from nationwide AMIS Plus registry 2005-2017. *Int J Cardiol* 2018;**261**:1–5.

25. Findlay B, Oh P, Grace SL. Cardiac rehabilitation outcomes by ethnocultural background: results from the Canadian Cardiac Rehab Registry. *J Cardiopulm Rehabil Prev* 2017;**37**:334–340.

26. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–1457.

27. Ueki Y, Karagiannis A, Zanchin C, Zanchin T, Stortecky S, Koskinas KC, Siontis GCM, Praz F, Otsuka T, Hunziker L, Heg D, Moschovitis A, Seiler C, Billinger M, Pilgrim T, Valgimigli M, Windecker S, Räber L. Validation of high-risk features for stent-related ischemic events as endorsed by the 2017 DAPT guidelines. *JACC Cardiovasc Interv* 2019;**12**:820–830.

28. Khatana SAM, Fiorilli PN, Nathan AS, Kolansky DM, Mitra N, Groeneveld PW, Giri J. Association between 30-day mortality after percutaneous coronary intervention and education and certification variables for New York State Interventional Cardiologists. *Circ Cardiovasc Interv* 2018;**11**:e006094.

29. Spoerri A, Zwahlen M, Egger M, Bopp M. The Swiss National Cohort: a unique database for national and international researchers. *Int J Public Health* 2010;**55**:239–242.

30. Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M; Swiss National Cohort and Swiss Household Panel. A Swiss neighbourhood index of socioeconomic position: development and association with mortality. *J Epidemiol Commun Health* 2012;**66**:1129–1136.

31. Flint K, Kennedy K, Arnold SV, Dodson JA, Cresci S, Alexander KP. Slow gait speed and cardiac rehabilitation participation in older adults after acute myocardial infarction. *J Am Heart Assoc* 2018;**7**:e008296.

32. Grace SL, Gravely-Witte S, Brual J, Monette G, Suskin N, Higginson L, Alter DA, Stewart DE. Contribution of patient and physician factors to cardiac rehabilitation enrollment: a prospective multilevel study. European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise. *Physiology* 2008;**15**:548–556.

33. González-Salvado V, Peña-Gil C, Lado-Baleato Ó, Cadarso-Suárez C, Prada-Ramallal G, Prescott E, Wilhelm M, Eser P, Iliou MC, Zeymer U, Ardissino D, Bruins W, van der Velde AE, Van't Hof AWJ, de Kluiver EP, Kolkman EK, Prins L, González Juanatey JR. Offering, participation and adherence to cardiac rehabilitation programmes in the elderly: a European comparison based on the EU-CaRE multicentre observational study. *Eur J Prev Cardiol* 2021;**28**:558–568.

34. Schopfer DW, Forman DE. Cardiac rehabilitation in older adults. *Can J Cardiol* 2016;**32**:1088–1096.

35. Prescott E, Meindersma EP, van der Velde AE, Gonzalez-Juanatey JR, Iliou MC, Ardissino D, Zoccai GB, Zeymer U, Prins LF, Van't Hof AW, Wilhelm M, de Kluiver EP. A EUropean study on effectiveness and sustainability of current Cardiac Rehabilitation programmes in the Elderly: design of the EU-CaRE randomised controlled trial. *Eur J Prev Cardiol* 2016;**23**:27–40.

36. Snoek JA, Prescott EI, van der Velde AE, Eijsvogels TMH, Mikkelsen N, Prins LF, Bruins W, Meindersma E, González-Juanatey JR, Peña-Gil C, González-Salvado V, Moatemri F, Iliou M-C, Marcin T, Eser P, Wilhelm M, Van't Hof AWJ, de Kluiver EP. Effectiveness of home-based mobile guided cardiac rehabilitation as alternative strategy for nonparticipation in clinic-based cardiac rehabilitation among elderly patients in Europe: a randomized clinical trial. *JAMA Cardiol* 2021;**6**:463–468.

37. Raphael CE, Singh M, Bell M, Crusan D, Lennon RJ, Lerman A, Prasad A, Rihal CS, Gersh BJ, Gulati R. Sex differences in long-term cause-specific mortality after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2018;**11**:e006062.

38. Supervía M, Medina-Inojosa JR, Yeung C, Lopez-Jimenez F, Squires RW, Pérez-Terzic CM, Brewer LC, Leth SE, Thomas RJ. Cardiac Rehabilitation for Women: A Systematic Review of Barriers and Solutions. *Mayo Clinic Proceedings* 2017; **92**:565–577.

39. Mamataz T, Ghisi GLM, Pakosh M, Grace SL. Nature, availability, and utilization of women-focused cardiac rehabilitation: a systematic review. *BMC Cardiovasc Disord* 2021;**21**:459.

40. Aldridge RW, Nellums LB, Bartlett S, Barr AL, Patel P, Burns R, Hargreaves S, Miranda JJ, Tollman S, Friedland JS, Abubakar I. Global patterns of mortality in international migrants: a systematic review and meta-analysis. *Lancet* 2018;**392**:2553–2566.

41. Lu Y, Qin L. Healthy migrant and salmon bias hypotheses: a study of health and internal migration in China. *Soc Sci Med* 2014;**102**:41–48.

42. Singh GK, Hiatt RA. Trends and disparities in socioeconomic and behavioural characteristics, life expectancy, and cause-specific mortality of native-born and foreign-born populations in the United States, 1979-2003. *Int J Epidemiol* 2006; **35**:903–919.

43. Brzoska P, Razum O. Utilization of medical rehabilitation prior to disability retirement: Comparison of German and non-German nationals with a special focus on ethnic German resettlers. *Z Gerontol Geriatr* 2019;**52**:70–77.

44. Brzoska P, Sauzet O, Yilmaz-Aslan Y, Widera T, Razum O. Self-rated treatment outcomes in medical rehabilitation among German and non-German nationals residing in Germany: an exploratory cross-sectional study. *BMC Health Serv Res* 2016;**16**:105.

45. Dyck M, Breckenkamp J, Wicherski J, Schröder CC, Du Prel JB, Razum O. Utilisation of medical rehabilitation services by persons of working age with a migrant background, in comparison to non-migrants: a scoping review. *Public Health Rev* 2020;**41**:17.

46. Swiss Confederation (2008) Migration and Public Health. Summary to the Federal Strategy Phase II (2008-2013). Federal Office of Public Health. https://www.bag.admin.ch/dam/bag/en/dokumente/nat-gesundheitsstrategien/nat-programm-migration-und-gesundheit/dok-2019/migrazione-e-salute-2008-2013.pdf.download.pdf/migration-and-health-2008-2013.pdf

47. De Pietro C, Camenzind P, Sturny I, Crivelli L, Edwards-Garavoglia S, Spranger A, Wittenbecher F, Quentin W. Switzerland: health system review. *Health Syst Transit* 2015;**17**:1–288; xix.

48. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol Ser A* 2004;**59**:255–263.

49. Gharacholou SM, Roger VL, Lennon RJ, Rihal CS, Sloan JA, Spertus JA, Singh M. Comparison of frail patients versus nonfrail patients ≥65 years of age undergoing percutaneous coronary intervention. *Am J Cardiol* 2012;**109**:1569–1575.