# Smoking cessation and participation in secondary prevention programs after acute myocardial infarction

Thesis

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# Abstract

**Objectives:** The aim of this thesis is to investigate adherence to the secondary prevention measures of smoking cessation, participation in a cardiac rehabilitation program (CRP) and participation in a disease management program (DMP) after acute myocardial infarction (AMI). Additionally, the determining factors for continued smoking and the time point of smoking abstinence should be identified. **Methods:** The data basis originates from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA). Information was collected through computer-assisted telephone interviews and questionnaires completed by study participants and physicians or trained study nurses. **Results:** Six weeks after hospital discharge, smoking cessation was observed in 51.3% of patients who smoked before their AMI. Participation in a CRP within two weeks and in a DMP within two years of discharge from hospital was 58.5% and 24.9%, respectively. The strongest determinants of continued smoking were the absence of hospital complications (OR = 2.70; 95% CI 0.89-8.33), a previous AMI (OR = 2.19; 95% CI 1.10-4.38), no life partner (OR = 1.79; 95% CI 1.05-2.94) and receiving percutaneous coronary intervention or coronary artery bypass grafting (OR = 1.53; 95% CI 0.66-3.54). Most quitters of smoking did so during the hospital stay before the start of the CRP. Smokers were less likely to be enrolled in a DMP compared to non-smokers (RR = 0.67; 95% CI 0.51-0.88). **Conclusion:** The prevalence and determinants of continued smoking six weeks after AMI in Saxony-Anhalt are comparable to other European studies. However, participation in a CRP should not be interpreted as a determinant of smoking cessation, since most individuals had already quit smoking before the CRP began. The association between participation in a CRP and smoking cessation is better explained by the concept of a teachable moment. Since smokers are less likely to participate in a DMP, this measure of secondary prevention is currently not being fully exploited in Saxony-Anhalt.

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# Referat

**Zielsetzung:** Das Ziel dieser Arbeit ist die Untersuchung der Adhärenz nach akutem Herzinfarkt (HI) für die Sekundärpräventionsmaßnahmen Raucherentwöhnung, der Teilnahme an einer Anschlussheilbehandlung (AHB) und der Teilnahme an einem Disease Management Programm (DMP). Zusätzlich sollen Determinanten für das Weiterrauchen und der Zeitpunkt der Rauchabstinenz ermittelt werden. **Methoden:** Die Datenbasis entstammt aus dem Regionalen Herzinfarktregister Sachsen-Anhalts (RHESA). Die Informationen wurden in computergestützten Telefoninterviews und Fragebögen erhoben, die von den Studienteilnehmern und Ärzten oder geschultem Studienpersonal ausgefüllt wurden. **Ergebnisse:** Sechs Wochen nach der Krankenhausentlassung wurde bei 51,3 % der rauchenden HI-Patienten eine Raucherentwöhnung beobachtet. Die Teilnahme an einer AHB und einem DMP lag bei 58,5 % bzw. 24,9 %. Die stärksten Determinanten für anhaltendes Rauchen waren das Ausbleiben von Komplikationen im Krankenhaus (OR = 2,70; 95% CI 0,89-8,33), ein früherer HI (OR = 2,19; 95% CI 1,10-4,38), das Fehlen eines Lebenspartners (OR = 1,79; 95% CI 1,05-2,94) und eine perkutane Koronarintervention oder Koronararterien-Bypass-Operation (OR = 1,53; 95% CI 0,66-3,54). Die meisten Personen, die mit dem Rauchen aufhörten, taten dies bereits während des Krankenhausaufenthaltes vor dem Beginn der AHB. Raucher waren weniger häufig in DMPen eingeschrieben als Nichtraucher (RR = 0,67; 95% CI 0,51-0,88). **Schlussfolgerungen:** Die Prävalenz von und die Determinanten für das Weiterrauchen sechs Wochen nach HI sind vergleichbar mit anderen europäischen Studien. Dennoch sollte die Teilnahme an einer AHB nicht als Determinante für die Raucherentwöhnung interpretiert werden, da die meisten Personen bereits vor Beginn der AHB mit dem Rauchen aufgehört hatten. Der Zusammenhang zwischen der Teilnahme an einer AHB und der Raucherentwöhnung lässt sich besser durch das Konzept des lehrbaren Moments erklären. Da Raucher eher seltener an DMPen teilnehmen, wird das Potenzial dieser Programme in Sachsen-Anhalt aktuell nicht voll ausgeschöpft.

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# List of abbreviations

| | |
|---|---|
| **6MWT** | six-minute walk test |
| **ACE** | Angiotensin-converting enzyme |
| **ACS** | acute coronary syndrome |
| **AHB** | Anschlussheilbehandlung |
| **AMI** | acute myocardial infarction |
| **approx.** | approximately |
| **BMI** | body mass index |
| **CABG** | coronary artery bypass graft |
| **CI** | confidence interval |
| **CVD** | cardiovascular disease |
| **CHD** | coronary heart disease |
| **COPD** | chronic obstructive pulmonary disease |
| **CR** | cardiac rehabilitation |
| **CRF** | cardiorespiratory fitness |
| **CRP** | cardiac rehabilitation program |
| **DMP** | disease management program |
| **e-cigarettes** | electronic cigarettes |
| **e.g.** | exempli gratia (latin) / for example |
| **et al.** | et alii (latin) / and others |
| **HF** | heart failure |
| **HI** | Herzinfarkt |
| **HR** | hazard ratio |
| **i.e.** | id est (latin) / that is |
| **LDL** | low-density lipoprotein |
| **MACE** | major adverse cardiac events |
| **OR** | odds ratio |
| **p** | p-value |

| | |
|---|---|
| **PCI** | percutaneous coronary intervention |
| **P1** | publication 1 |
| **P2** | publication 2 |
| **RHESA** | Regional Myocardial Infarction Registry of Saxony-Anhalt |
| **RR** | relative risk |
| **SMD** | standardized mean difference |
| **$VO_2$ peak** | peak oxygen consumption |
| **vs.** | versus |

# 1 Introduction and objectives

## 1.1 Mortality and morbidity of acute myocardial infarction in Saxony-Anhalt

Even if the age-standardized prevalence of coronary artery disease in Saxony-Anhalt is decreasing slightly, it still represents a major disease and socio-economic burden [1, 2]. For several years now, acute myocardial infarction (AMI) in particular has had one of the highest morbidity (2019: +4%) and mortality (2019: +38%) in Saxony-Anhalt compared to the national average [3]. The excess mortality can also be seen geographically in an east-west gradient in Germany [3]. In 2019, the estimated monetary value of lost productivity from paid and unpaid work due to inpatient hospitalization and rehabilitation was €40,596,791 [2].

## 1.2 Foundation of the Regional Myocardial Infarction Registry of Saxony-Anhalt

Individual factors (e.g. higher prevalence of risk factors and lower socioeconomic level), structural factors (e.g. lower number of first aiders in population and inadequate access to rehabilitation facilities) and procedural factors (e.g. delayed care caused by patients or medical stuff) have all been considered as potential causes of increased mortality [4, 5]. To this day, the extent to which these factors are responsible for the high morbidity and mortality in Saxony-Anhalt is not clearly understood.

Consequently, the population-based Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) was founded in 2013 to improve health monitoring and to gather more valid data on mortality and morbidity with the aim of elucidating the causes of their excess [4]. Three follow-up studies (RHESA-Care 1-3) were conducted in the registry with the focus on symptoms of AMI and their attribution to the heart, patient behavior after symptom onset, as well as cardiac rehabilitation program (CRP) enrollment and

long-term care (Figure 1) [5].

Data collection in RHESA-Care 1 and 2 took place six weeks and two years after hospital discharge, respectively [5]. RHESA-Care 3 was conducted as a cross-sectional study, which was independent of time after hospital discharge [6].

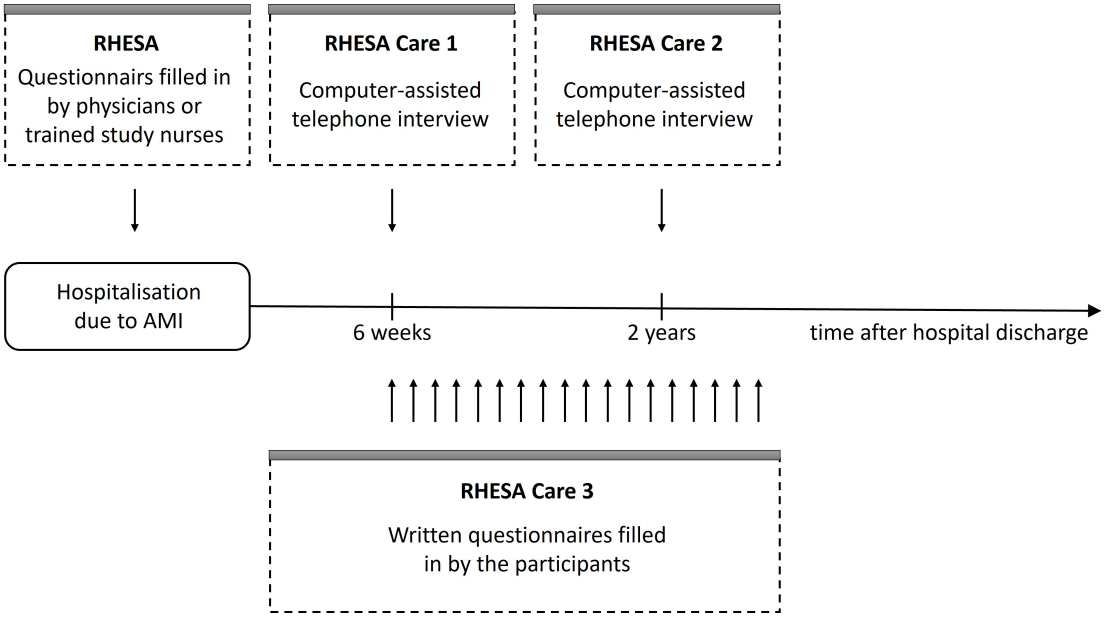


Figure 1: Data collection in the Regional Myocardial Infarction Registry of Saxony-Anhalt and its follow-up studies.

## 1.3 Secondary prevention measures to reduce adverse events from acute myocardial infarction

Even after surviving an AMI, the one-year mortality is still in the range of 10-15% and can be noticeably higher in older patients [7–9]. Data from a large Swedish registry of 97,254 patients, who survived an AMI for more than seven days, showed that 18.3% of these patients experienced either a recurrent AMI, stroke or cardiac death within the first year after the index event [10]. Furthermore, the prognosis can worsen with an increase in the cumulative number of risk factors (e.g. high blood pressure, smoking, diabetes mellitus, obesity and peripheral artery disease) [11].

To prevent further deterioration of health condition, the focus of secondary prevention is on identifying patient's individual risk, referring them to the appropriate health care providers and initiation of treatment to prevent disease progression [12].

### 1.3.1 Clarification of the term secondary prevention

Prevention is defined as any measure that can prevent or delay an impairment of health (illness or injury) and is divided into primary, secondary and tertiary prevention [13].

The aim of *primary prevention* is to maintain health and prevent disease. This can be achieved, for example, by avoiding risk factors or through vaccinations. The key element of *secondary prevention* is the early detection of a disease when it is still asymptomatic, so that its progression can be prevented by timely treatment. This includes, for example, preventive medical check-ups. In contrast, *tertiary prevention* refers to those medical measures that prevent further deterioration or reduce the occurrence of complications after the disease has already become manifest [13].

By definition, measures to prevent a reinfarction would have to be assigned to tertiary prevention, since in such cases, the disease (the myocardial infarction itself) has already happened. In the literature, however, measures after AMI are quite uniformly attributed to secondary prevention. One possible explanation for this may be that there is no real phase of early detection in AMIs [14]. If assigned to tertiary prevention, the secondary prevention phase would be skipped. In the underlying thesis, the term "secondary prevention" is therefore chosen to describe all measures used to avoid a reinfarction and/ or further deterioration in health after an AMI.

### 1.3.2 Smoking cessation

***Benefits and frequency of smoking cessation after acute myocardial infarction***

Quitting smoking always has a positive health effect, regardless of whether the individual has already had an AMI, or not [15–17]. Despite the irreversible damage to the myocardium caused by prolonged ischemia during an AMI [18], it has been shown that smoking cessation after AMI is associated with an approx. 50% reduction in mortality [15, 17, 19]. In a study of 645 smokers who had been hospitalized for acute coronary syndrome (ACS), major adverse cardiac events (MACE) occurred less frequently in the group of individuals who had stopped smoking (HR = 0.61; 95% CI 0.46 – 0.80) [17]. In this context, smoking cessation interventions should begin during hospitalization and continue for a further period after discharge [20]. A systematic review of 25 randomized

and quasi-randomized studies showed that frequency of smoking cessation after discharge was increased by 37% (RR = 1.37; 95% CI 1.27 – 1.48) when intensive counseling interventions were started in the hospital and continued with supportive contacts for at least one month after discharge [21] . Even though weight gain is to be expected after smoking cessation [22], most likely due to increased appetite and decreased energy expenditure [23], the benefits of smoking cessation outweigh the disadvantages of weight gain [24]. A study with 4,254 participants showed that stopping smoking early after ACS reduces the likelihood of having a recurrent AMI by 43% [25].

In general, smoking cessation independently of AMI has not only a positive impact on the health of the smokers themselves, but also on the non-smokers [26, 27]. According to a cross-sectional epidemiological assessment based on global data, it is estimated that 52.3 individuals smoking for 24 years were associated with the death of one non-smoking individual [26]. Researchers were able to show that for each ex-smoker, the average short-term discounted medical costs associated with AMI and stroke would be reduced by $853 per person after seven years (data from 1997) [27].

Despite the numerous benefits of smoking cessation after AMI described above, 40-60% of AMI survivors still do not stop smoking according to the EUROASPIRE IV survey (2012 – 2013) [28]. Within this study, 354 smokers have been registered in the German study center Würzburg, of whom 47% quit smoking in the period between the hospital discharge and the examined interview (on average 1.4 years after the recruiting event) [28]. Considering the enormous individual and societal benefits of quitting smoking after AMI, the question arises as to why only half of smokers quit smoking. However, given the low frequency of annual smoking cessation attempts in the general population (20-50%), a percentage of 50% successful smoking cessation after AMI sounds satisfactory [29, 30]. According to the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report from 2019, 55.1% of cigarette smokers of the non-institutionalized U.S. civilian population had made at least one attempt to quit in the past twelve months [29]. However, in the same period of time only 7.5% of all cigarette smokers succeeded in quitting smoking [29]. Data from a German survey on smoking behavior from 2016-2019 shows that the proportion of smokers who tried to quit smoking in the given year is lower and even declining in the recent years (overall period: 19%; October/November 2016: 33.9%; June/July 2019: 15.8%) [30].

***Determinants of quitting smoking after acute myocardial infarction***

The cognitive response of an individual to the objective experience following a particular event can also be influenced by predisposing factors [31]. Understanding the determinants of persistent smoking could therefore be useful in detecting a vulnerable group of individuals unable to or not willing to stop smoking. Multiple factors have been identified as determinants of persistent smoking after AMI including, sociodemographic characteristics [28, 32–35], smoking behavior [32, 36], risk factors for AMI [32, 37–39] and the extent of medical interventions in the context of AMI [32, 34, 35].

However, these factors can vary regionally and have not yet been investigated for Germany or Saxony-Anhalt. With the introduction of smoke-free legislation in public areas, the opportunities to smoke have decreased [40] and with it, the social acceptance of smoking [41]. The recognition of smoking as an addiction and cause of various cardiovascular disease (CVD), as well as the effects of second-hand smoke, legal restrictions, declining social acceptance and mass media campaigns have all contributed to a decrease in the prevalence of smoking [42]. Smoking cessation programs in CRPs after AMI have been improved, offering a range of effective treatment options, including nicotine replacement therapies, smoking cessation medications, and individual or group counselling sessions, which led to increased success rates in smoking cessation [38, 43].

### 1.3.3 Cardiac rehabilitation programs

***Phases of cardiac rehabilitation***

CRPs are comprehensive medical, physical and lifestyle interventions designed to help individuals recover from cardiovascular diseases. Participation in a CRP is highly recommended to minimize the increased risk of MACE after AMI and to expedite the recovery process [12, 44, 45].

Cardiac rehabilitation (CR) is typically divided into three phases [44]: *Phase one* is initiated during the acute hospitalization period following a cardiac event. It is focused on early mobilization and education on heart-healthy lifestyle modifications [44]. *Phase two* takes place immediately after the hospital stay and is known in Germany as "Anschlussheilbehandlung" or "Anschlussrehabilitation". The aim is to restore the patient's physical capacity as far as possible, taking psycho-social aspects into account, to enable

a successful return to work and social environment. At the same time, secondary prevention aims to prevent the disease from progressing to avert the threat of needing long-term care in chronically ill patients [44]. In this thesis, the term "cardiac rehabilitation" refers exclusively to phase two rehabilitation. *Phase three* is the maintenance program that involves long-term exercise and lifestyle modifications to prevent the recurrence of heart disease. This program aims to maintain the physical, social, and emotional well-being of the patient throughout their lifetime and is typically provided by primary care physicians, possibly in conjunction with rehabilitation physicians and outpatient CR groups (e.g. heart groups) [44].

***Beneficial effects of cardiac rehabilitation***

The main components of CR include exercise training (e.g. resistance and stability training), lifestyle modifications (e.g. smoking cessation, blood pressure control) and psychological interventions (e.g. stress and anxiety reduction) [46]. The main benefits of these interventions are improved physical fitness, reduction in risk factors and the associated reduction in the occurrence of MACE and improved psychological well-being [46]. A large meta-analysis revealed that exercise-based CR reduces the frequency of cardiovascular mortality (by 26%), AMI (by 18%) and all-cause hospitalization (by 23%) compared to usual care at the longest reported follow-up period [47]. However, exercise-based CR has not been associated with lower risk of overall mortality, less frequently performed coronary artery bypass grafts (CABGs) and percutaneous coronary interventions (PCIs) [47].

Improved cardiorespiratory fitness (CRF) is another benefit of participating in CR [48]. It can be measured in rehabilitation settings through cardiopulmonary exercise testing, using for example the peak oxygen consumption ($VO_2$ peak) or by performing the six-minute walk test (6MWT) [49, 50]. A meta-analysis with 229 patients suffering from coronary artery disease has shown that interval training increases the weighted mean $VO_2$ peak by 1.53 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.84-2.23 $ml \cdot kg^{-1} \cdot min^{-1}$; Z = 4.33; p = 0.0001) compared to continuous training [50]. Another meta-analysis that included 102,980 subjects showed that people with low CRF had a 70% higher risk to die ($RR_{adjusted}$ = 1.70; 95% CI 1.51-1.92) and a 40% higher risk of developing coronary heart disease (CHD)/CVD events ($RR_{adjusted}$ = 1.40; 95% CI 1.32-1.48) compared to people with high CRF [48].

Another important benefit of participation in a CRP is improved psychological well-being [46, 51]. This is particularly noteworthy, since approximately 20% of CHD patients may suffer from depression or depressive symptoms [51, 52]. In a study with 522 CR participants after a cardiac event, it was shown that the frequency of depressive symptoms after CR decreased by 63% after CR (from 17% to 6%) [51]. Additional psychological interventions after a cardiac event can also improve anxiety (standardized mean difference (SMD) = -0.24; 95% CI -0.38, -0.09), depression (SMD = -0.27; 95% CI -0.39, -0.15) and stress (SMD = -0.56; 95% CI -0.88, -0.24) as discovered in a meta-analysis of 10,703 individuals [53].

***Determinants of participation in cardiac rehabilitation programs***

According to the EUROASPIRE IV survey, 58.0% of patients in Europe are referred for CR after an AMI and 80.9% of them finally participate [54]. Although smoking cessation is a major goal of CR, the frequency of smoking in the month prior to the recruiting event was higher in the group of individuals not participating in a CRP, as compared to CRP participants (37.0% vs. 30.0%) [54].

Following a socio-ecological health model, factors associated with not participating in CR or dropping out of CR fall into six categories, these are: intrapersonal factors, clinical factors, interpersonal factors, logistical factors, CRP factors and health system factors [55]. In a systematic review of 43 articles, the strongest factors associated with non-participation in CR have been identified as female sex (six studies; OR range = 1.64 – 4.17), low income (four studies; OR range = 1.47 – 5), CABG (five studies; OR range = 0.02 – 0.49), being single (seven studies; OR range = 1.30 – 16.73) and lack of referral to CRP (five studies; OR range = 4.03 – 2514). The strongest factors associated with dropout of CR have been identified as depressive symptoms (four studies; OR range = 1.15 – 2.51), smoking (five studies; OR range = 1.20 – 3.33), high body mass index (BMI) (four studies; OR range = 0.94 – 3.33) and being single (two studies; OR range = 2 – 2.86) [55].

### 1.3.4 Disease management programs

***What does "disease management program" mean?***

The term "disease management program" (DMP) is used very heterogeneously and formulating a globally valid definition is challenging. Nevertheless, most DMPs have the following three features in common: an evidence-based knowledge base, a care system with coordinated care components and continuous quality improvement [56]. Due to the heterogeneity, only German DMPs have been considered in the following section.

In Germany, DMPs were first introduced in 2002 and are structured treatment programs designed to help chronically ill patients cope with their disease [57, 58]. Patients can usually be included in such programs through their health insurance companies and are treated across institutions according to the current state of medical research. These programs are coordinated by general practitioners and are intended to reduce unnecessary complications, the number of hospital stays and the associated health effects, thereby improving and maintaining the quality of life [57, 58]. DMPs are offered in Germany for the following chronic diseases: asthma, chronic obstructive pulmonary disease (COPD), breast cancer, diabetes mellitus type 1 and 2 and CHD [57]. The requirements for the design of DMPs are defined by the Joint Federal Committee [59]. General therapeutic measures include nutritional counselling, smoking cessation, improvement of physical activity, psychotherapy, and the offer of protective vaccinations. Information on comorbidities is provided in the context of CHD and clinical parameters are set as targets (in case of high blood pressure or diabetes mellites). Drug therapy is carried out in accordance with the current guidelines [59].

***Beneficial effects of disease management programs***

Since DMPs are very heterogeneous on a global level and strongly depend on the context, results from evaluations are difficult to compare to each other. In the following, the benefits of CHD-DMPs in Germany will therefore be specifically addressed.

After some criticism in the first few years, DMPs for CHD patients have meanwhile developed into an integral part of care [60]. A study with data from a regional statutory health insurance fund showed that patients (n = 15,360) who participated in a DMP had a lower risk of dying compared to non-participants (HR = 0.757; $p < 0.001$) [61]. It

was also shown that DMP participants induced lower health care expenditure per day compared to non-DMP participants (€58.24 vs. €72.72) and showed increased guideline adherence, as evidenced by an increased proportion of days covered for Angiotensin-converting enzyme (ACE) inhibitors (60.95% vs. 58.92%), anti-platelet agents (74.20% vs. 70.66%), statins (54.18% vs. 52.13%) and beta blockers (61.95% vs. 52.64%) [61]. In addition, better lipid target achievement for secondary prevention could be shown. Data from a prospective registry with 12,154 patients on daily 40 mg Simvastatin treatment showed that more patients from the CHD-DMP group reached the target values for low-density lipoprotein (LDL) cholesterol of < 70 mg/dl compared to the non-DMP group over the entire observation period [i.e. at baseline (8.5% DMP vs. 5.7% no-DMP), at the six-month follow-up (10.3% vs.7.4%) and at the twelve-month follow-up (10.1% vs.7.1%)] [62]. It was also shown that patients in the CHD-DMP group received therapy more frequently with beta blockers (82.9% vs. 61.8%), acetylsalicylic acid (82.0% vs. 60.6%), ACE inhibitors (66.3% vs. 54.2%) and diuretics (41.0% vs. 37.2%) as compared to non-participants [62]. However, since the patients in the CHD-DMP group also had comorbidities more frequently, a causal relationship between participation in DMP and better guideline care cannot be inferred [63].

***Selective enrollment in disease management programs***

Since the aim of DMPs is to improve the care of chronically ill insured persons, these programs should be available to all patients who meet the relevant inclusion criteria [58]. Research within a German cross-sectional study of 7,012 patients recruited by their general practitioners during general health check-ups showed a positive association between DMP participation and male sex ($OR_{adjusted}$ = 2.16; 95% CI 1.57-2.98), higher age (65-74 years vs. 55-64 years: $OR_{adjusted}$ = 1.46; 95% CI 0.93-2.30), higher education (highest vs. lowest: $OR_{adjusted}$ = 1.2; 95% CI 0.77-1.87) and the number of comorbidities (Cumulative Illness Rating Scale-Geriatric per one unit: $OR_{adjusted}$ = 1.52; 95% CI 1.09-2.12) [64]. In another cross-sectional study with 7,070 persons suffering from CHD, it was shown that participation in the DMP was associated with male sex ($OR_{adjusted}$ = 0.70; 95% CI 0.57-0.85), higher age ($\geq$ 81 years vs. $\leq$ 60 years; $OR_{adjusted}$ = 2.12; 95% CI 1.53-2.95), employment/retirement status (old-age pension vs. employed; $OR_{adjusted}$ = 1,54; 95% CI 1.18-2.00) and higher number of comorbidities (Charlson Score: 2 vs. 0; $OR_{adjusted}$ = 1.20;

95% CI 1.02-1.42) [65]. In a study from Canada on 1,803 individuals suffering from CHD or heart failure (HF), the comorbidities were broken down in more detail [66]. From the factors, condition after AMI, condition after stroke, diabetes and smoking, it could be shown that only condition after AMI ($OR_{adjusted}$ = 2.01; 95% CI 1.48-2.74) and smoking ($OR_{adjusted}$ = 0.41 (95% CI 0.22-0.76) were associated with participation in DMPs [66].

## 1.4 Research questions

For the past several decades, mortality from AMI in Saxony-Anhalt was one of the highest compared to other federal states. Several theories have been published about the possible causes of this excess mortality. Evaluation of the population-based data from the RHESA should be able to reveal potential deficits of patient adherence to secondary prevention measures and thus make a further contribution to causal research. Based on the data from the RHESA, this thesis has four aims:

1. The percentage of smoking cessation after an AMI six weeks after discharge from hospital is to be determined in a population with an above-average prevalence of smokers.

2. The timing of smoking cessation is to be identified to shed light on the role of CR.

3. The determinants of continued smoking after AMI are to be identified to characterize a group of patients at higher risk for MACE. This data could be used in future research to develop targeted intervention strategies to better support this vulnerable group during smoking cessation.

4. It is to be determined whether selective enrollment in CRPs or DMPs is related to smoking.

# 2 Discussion

The overarching goal of this thesis is to investigate smoking cessation after AMI and participation in secondary prevention programs such CRPs and/or DMPs in the context of increased mortality from AMI in Saxony-Anhalt.

In the population of the RHESA, one third of patients reported to be active smokers at the time of AMI and half of them stopped smoking afterwards. Eighty-four percent of patients who stopped smoking did so during the hospital stay (before potential CR). The strongest determinants of continued smoking were the absence of hospital complications (OR = 2.70), a previous AMI (OR = 2.19), no life partner (OR = 1.79) and receiving percutaneous coronary intervention or coronary artery bypass grafting (OR = 1.53). No association with continued smoking was found for higher age per five years (OR = 1.00) and male sex compared to female sex (OR = 1.07).

Fifty-nine percent reported having participated in a CRP within two weeks after hospital discharge. The reported participation in a DMP for CHD within the follow-up period of two years was 25%. Patients who were active smokers at the time of their AMI participated less frequently in DMPs (RR = 0.67) compared to non-smokers. This effect of selective enrollment could not be found for smoking and participation in CRPs (RR = 0.95).

Since the results of this work have already been discussed in detail in publications P1 and P2, the following pages provide a broader contextualization of the results with regard to smoking cessation as primary prevention and the role of CRPs and DMPs in secondary prevention.

## 2.1 Smoking habits and primary prevention

The prevalence of current smokers in Germany was 24% in 2020, which was slightly higher than in the entire European Union and the United Kingdom [67]. One reason for this could be the inadequate measures for tobacco control, for which Germany ranks among the lowest in Europe [68]. In 2016, the German Study on Tobacco Use was launched with the aim of examining smoking behavior and attempts to quit in the Ger-

man population [69]. It has been shown that approx. 19% of smokers had at least one quit attempt within the last year of which only about 15% have been successful [70]. In contrast to the low frequency of regular attempts to quit in the general population, data from the RHESA showed that the frequency of successful smoking cessation six weeks after hospital discharge after AMI was 51.3% (P1). This gives a first indication that an AMI can play a special role in smoking cessation. The low success rate in the general population may be due to the fact that evidence-based methods of support are only used in 13.0% of cases [30]. The most common, single, non-evidence-based method to support smoking cessation is the use of electronic cigarettes (e-cigarettes) [30]. It is known that about 80% of those who switch to e-cigarettes in their attempt to quit smoking keep on smoking e-cigarettes for at least one year [71]. Given that smoking e-cigarettes does not show any significant advantage in the development of cardiovascular outcomes such as stroke, AMI and CHD compared to conventional smoking [72], the use of evidence-based methods to support smoking cessation should be promoted.

The most effective measure to reduce the risk of CVD is primary prevention, as by definition, it ensures that AMIs do not occur in the first place [13]. The Framingham study is probably one of the best-known cohort studies in the world and made an important contribution to subsequent health educational campaigns by identifying some of the strongest risk factors [73]. Smoking, diabetes mellitus, arterial hypertension, obesity, increased waist circumference and metabolic syndrome show the highest or the second highest prevalence in Saxony-Anhalt in a nationwide comparison, which is certainly one of the main reasons for the high morbidity and mortality [74]. To reduce the prevalence of smoking, numerous laws have been passed in the last decades in Germany, with a slightly different implementation in the federal states. These include the ban on tobacco advertising on the internet, newspapers and magazines (since 2007 [75]) and the obligation to print shocking images on cigarette boxes (since 2016 [76]). However, in a European comparison the advertising of tobacco products is less restricted and, for example, advertising in adult films is still permitted [68].

## 2.2 Smoking cessation as a secondary prevention measure

If the occurrence of AMI cannot be prevented by measures of primary prevention, measures of secondary prevention are intended to reduce the negative consequences and reinfarctions. As a secondary prevention measure, the reduction of risk factors and the referral for CR after AMI are highly recommended in multiple guidelines from the European Society of Cardiology [20, 45]. Smoking cessation, specifically, is probably one of the most effective secondary prevention measures [20]. In the RHESA, half of patients who were smokers at the time of AMI quit smoking within six weeks after hospital discharge (P1), which is comparable to the European average [28]. However, early identification of those patients who cannot or who do not want to follow the recommendations of health care professionals and do not quit smoking is likely to be important. It has been shown that individuals who continue to smoke regularly show lower adherence to other secondary prevention measures [25, 77]. For example, those who continued to smoke have lower dietary compliance, lower regular exercise adherence [25] and lower probability to initiate and to complete a CRP [77] compared to recent quitters. With the knowledge of factors that determine continued smoking, patients can be identified who need more intensive support, not only in quitting smoking, but also in reducing risk factors in general.

In the RHESA, strongest association for continued smoking was found for patients without a partner, with a recurring AMI, with a low number of newly prescribed drugs and without complications during the hospital stay (P1). According to the recently published meta-analysis by Lovatt et al., the strongest associating factors with smoking cessation is participation in a CRP [78]. However, in our interpretation, the effect of CR on smoking cessation should not be interpreted as causal, since we were able to show that most quitters already stopped smoking during the hospital stay (84%) (P1). It is more likely that the association between participation in a CRP and smoking cessation is due to a common cause – the teachable moment.

### 2.2.1 Acute myocardial infarction as a teachable moment

The concept of "teachable moments" has its roots in the field of educational research and became popular through the book "Human Development and Education" by Robert Havighurst, published in 1952 [79]. He described the teachable moment as a time in life, when learning a particular subject or idea becomes easier. The concept has subsequently been applied to health behavior models as a naturally occurring event resulting in higher motivation for a change in risk behavior [31]. This applies to varying degrees also to clinical visits for acute illnesses, notifications of abnormal test results, disease diagnoses and pregnancies. In the heuristic model proposed by McBride et al., three factors determine whether an event is strong enough to be a teachable moment for smoking cessation, i.e.:

i. the extent to which the event increases perceptions of personal risk and outcome expectations,

ii. the extent to which the event triggers strong affective or emotional reactions,

iii. the extent to which the event redefines the self-concept or the social role [31].

The likelihood of a positive change in behavior increases with the degree to which all three areas are influenced, either alone or in combination with timely interventions [31]. Considering this model and the identified determining factors for continuing smoking (P1), it is conceivable that a life partner may not only assist in the practical implementation of smoking cessation but also may trigger an emotional response (ii), if patients become aware of their responsibility (iii) towards their relatives. In a clinical context, the occurrence of complications in the hospital and a high number of newly prescribed drugs could increase the perceived risk severity. This can lead to a higher likelihood of quitting smoking to avoid further adverse events (i). Interventions such as PCI and/or CABG have been shown to have a slight association with continuous smoking (P1). However, the estimated effect has a broad confidence interval, since less than 5% of individuals had neither a PCI nor a CABG. Other studies showed that performing CABG was associated with quitting smoking, whereas this effect was not found for PCI [32, 34, 38]. This may be due to the fact that performing a CABG is more invasive and is therefore perceived as more dramatic (i). However, since these studies are older and revascularization management has improved in recent decades [80, 81], the effect of conducting a PCI or a CABG

on smoking cessation may have decreased. The occurrence of a recurrent myocardial infarction in smokers who did not quit smoking after the previous AMI showed an association with continued smoking (P1). In the teachable moment theory, an association with quitting smoking would have been more plausible. We expected greater awareness of the importance of smoking as a risk factor in individuals who have already suffered an AMI and thus have greater interest in behavior change. One explanation could be that these smokers already found it difficult to quit after the previous AMI, or that these smokers generally refuse to quit. If individuals identify themselves as "heart patients", they would assume that mitigation of risk factors would be expected (iii). One possible reason why recurrent AMIs were more likely to be associated with continued smoking could be, that in these patients the addiction to smoking is stronger. Unfortunately, this theory remains only a conjecture, since we did not consider the degree of addiction in our study.

According to McBride et al., the likelihood of the desired behavior change can be increased when a proximally timed intervention occurs that increases the factors of the above-mentioned heuristic model [31]. Therefore, the strengthening of these factors should be given greater emphasis in smoking cessation programs. One of these interventions is probably the smoke-free policy in the hospitals, which can be extended through inpatient CRPs.

### 2.2.2 Participation of smokers in cardiac rehabilitation programs and disease management programs

A further secondary prevention measure that is associated with a reduction in the incidence of cardiovascular mortality, reinfarction and hospitalization is the participation in a CRP [47]. In the RHESA, the participation in a CRP was associated with a reduction of 44% for MACE (composite endpoint of reinfarction, stroke, death, PCI and CABG) (P2). This is comparable to the results of a meta-analysis by Ji et al., in that participation in a CRP reduced the risk of MACE by 51% in 8,180 individuals suffering from an ACS [82]. In view of the compelling benefits, it is sobering that only 58.5% of the RHESA population participated in a CRP after AMI, leaving this form of secondary prevention widely underused (P2). Nevertheless, participation in the RHESA is higher than participation in the EUROASPIRE IV survey, in which a participation of 46.9% was determined

at 78 study centers from 24 European countries [54]. With this generally low proportion of participation, the question arises as to which individuals participate in CRPs. In the RHESA sample, the risk factors smoking (RR = 0.95), diabetes mellitus (RR = 0.98) and hypertension (RR = 0.98) were not associated with participation in a CRP (P2). This is different to the results of a meta-analysis by Resurrección et al., which indicate that the risk factors smoking (OR = 1.69), diabetes mellitus (OR = 1.82) and hypertension (OR = 1.72) are associated with non-participation [55]. Since the reduction of these risk factors is a stated goal of CRPs [45], one might assume that the potential of CRPs in the RHESA population is somewhat better exploited than in the underlying population of the before mentioned meta-analysis.

However, there are some difficulties in quantifying the actual effect of participating in a CRP on smoking cessation. The main reason for this is that most of the results come from cohort studies that determine smoking exposure at the time of the index event (e.g. AMI or ACS) or at hospital admission and not before the start of the CRP [78]. An exception is the study of Völler et al. in that the smoking status was assessed from patient history directly before the start of the CRP [83]. Out of the 2,441 patients who took part in rehabilitation, nicotine abuse was reduced from 39% to 5% of the participants [83]. However, the validity of the reported smoking status before the CR should be critically questioned since rehabilitation usually begins within two weeks after hospital discharge and patients probably do not describe themselves as non-smokers because they had quit smoking within these two weeks. This assumption is supported by the fact that in the RHESA, the prevalence of smokers in the group of patients participating in a CRP at the time of the AMI (P2) is similar to the prevalence of smokers in the above-mentioned study by Völler et al. (36% vs 39%) [83]. It is possible that the role of the CR is not so much to initiate smoking cessation but rather to support the implementation of the previously made decision of smokers to abstain.

With regard to the recommended smoking cessation, it is known that the number of relapses increases with increasing time after AMI [32, 84] and remains relatively constant after one year at the latest [85]. Consequently, long-term interventions such as DMPs may have the potential to promote long-term abstinence. A direct comparison with the KORA Myocardial Infarction Registry of Augsburg shows that the participation in CHD-DMP is slightly lower in the RHESA population (27% [86] vs. 25% (P2)). A possible reason may

be the remuneration of the treating physicians, which is regulated individually in the federal states and the statutory health insurances. In Saxony-Anhalt in particular, services are remunerated only once for patients who are enrolled in more than one DMP and are cared for by the same coordinating physician [87]. If a patient is already enrolled in a DMP (e.g. for diabetes mellitus), an additional enrollment in CHD-DMP is rather unlikely. In addition, in the RHESA population, the prevalence of smoking among CHD-DMP participants is lower compared to non-CHD-DMP participants – a circumstance that was not found in the KORA study (RR = 0.67 (P2) vs. OR = 0.95 [86]). The causes for the effect of selective enrollment of smokers into CHD-DMPs in the RHESA population remains unclear and it lowers the expectations for these programs. The actual effect of DMPs on smoking cessation is described inconsistently in the literature [88]. Gapp et al. concluded that among 2,330 AMI patients in the KORA study, DMP participants were more likely to seek medical advice about smoking (OR = 3.77) and finally smoked less frequently (OR = 0.78) compared to non-DMP participants [86]. However, since this was a cross-sectional study, no causal interpretation of the effect on smoking cessation is permitted. The lack of randomized trials is also a frequently criticized issue in studying the benefits of DMPs [89, 90]. Even though a positive association has been postulated in numerous studies for participation in DMPs for type two diabetes on mortality, frequency of angina pectoris and frequency of stroke [91], a selection bias cannot be ruled out. Since it could be shown that the guideline care also improved over time in non-DMP participants, a so-called spillover effect may be present and estimated effects may be diluted [92]. Health care stakeholders will, therefore, continue to face the challenge of estimating the effectiveness of DMPs in the future.

## 2.3 Strengths and limitations

The strength of this thesis is that the data used to investigate smoking cessation and participation in CRPs and DMPs come from a population-based register and not from a hospital-based register. In studies that obtain their data from hospital-based registers, there is a risk that treated patients are not representative of the study region under examination, but only of the patients who live in the vicinity of the hospital. As a result, the effects may be biased by selection. Additionally, information on the patients and their care in hospital

was collected via different data sources, i.e. a hospital survey questionnaire (completed by trained physicians or study nurses), computer-assisted telephone interviews and written patient questionnaires within the follow-up. This allowed us to examine the determinants of continuous smoking across a wide range of variables. Another major benefit is that we assessed the timing of smoking cessation. As a result, the participation in CRPs was not regarded as a determining factor, since the chronological sequence does not permit it.

However, our study has some limitations. The data collection via computer-assisted telephone interviews and written questionnaires had the disadvantage of being self-assessed by the patients and not through clinical examinations (e.g. smoking status). This could theoretically lead to both biased and less precise effect estimates. In addition, we were not able to estimate the actual effect of CR participation on smoking cessation with our study design, although we were able to prove that the measured association should not be interpreted causally. Whether participation in a CRP supports former smokers in their abstinence and whether there is a possibility of intervention to strengthen the teachable moment remains the task of future research.

## 2.4 Conclusion

This thesis provides an up-to-date overview of the adherence of patients to secondary prevention measures after AMI in Saxony-Anhalt such as smoking cessation and participation in CRPs and/or DMPs. Most patients who stop smoking after an AMI do so during the hospital stay and the frequency of smoking cessation is comparable to other European countries. Determining factors for continued smoking in the population of the RHESA could be identified and can be plausibly explained with the theory of teachable moments. For this vulnerable group of persistent smokers, the task of future research could be to develop targeted smoking cessation programs and thus further improve health after an AMI.

Participation of smokers in DMPs is lower in the population of the RHESA than in previous studies on the German population. Future research should therefore explore the reasons for the selective enrollment in DMPs and support the development of measures to motivate people with risk factors to participate in these programs.

In summary, secondary prevention measures can be well studied with the extensive data from the RHESA. However, there are questions, such as the effect of participating in a CRP on smoking cessation and continued abstinence, which cannot be answered conclusively. To determine the reasons for the different mortality rates among the federal states of Germany, the regional myocardial infarction registries should be more closely networked to ensure pooled analyses.

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# 4 Theses

(1) Approximately 50% of smokers do stop smoking after an acute myocardial infarction.

(2) 84% of quitters begin abstinence during the hospital stay.

(3) Strongest determinants for continued smoking were the absence of hospital complications (OR = 2.70; 95% CI 0.89-8.33), a previous AMI (OR = 2.19; 95% CI 1.10-4.38), no life partner (OR = 1.79; 95% CI 1.05-2.94) and receiving percutaneous coronary intervention or coronary artery bypass grafting (OR = 1.53; 95% CI 0.66-3.54).

(4) The identified determinants support the theory of acute myocardial infarction as a teachable moment in which the probability of behavioral changes are increased through increased risk perception (hospital complications) and emotional reactions (responsibility for life partners).

(5) 58.5% of patients with acute myocardial infarction participate in a cardiac rehabilitation program within six weeks after hospital discharge.

(6) Selective enrollment of smokers in cardiac rehabilitation programs is not present in the population of the Regional Myocardial Infarction Registry of Saxony-Anhalt (RR = 0.95; 95% CI 0.85-1.06).

(7) 24.9% of patients with acute myocardial infarction participate in a disease management program for coronary heart disease within two years after hospital discharge.

(8) Smokers are less frequently enrolled in disease management programs compared to non-smokers (RR = 0.67; 95% CI 0.51-0.88).

# Publications

## List of included publications

(P1) **Höpner** J, Junge U, Schmidt-Pokrzywniak A, Fischer C, and Mikolajczyk R. Determinants of persistent smoking after acute myocardial infarction: an observational study. BMC Cardiovascular Disorders 1 2020;20:384

(P2) Fischer C, **Höpner** J, Hartwig S, Noutsias M, and Mikolajczyk R. Participation in disease management programs and major adverse cardiac events in patients after acute myocardial infarction: a longitudinal study based on registry data. BMC Cardiovascular Disorders 1 2021;21:18

# Publication 1

**Title:**

Determinants of persistent smoking after acute myocardial infarction: an observational study

**Personal contribution:**

Developing of research question, literature search, conduction of subject interviews (RHESA-Care 2), development of questionnaire (RHESA-Care 3), writing amendment for Ethics Committee, data cleaning, conception of analysis, conduction of analysis, presentation of results, writing manuscript, revision of manuscript

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RESEARCH ARTICLE Open Access

# Determinants of persistent smoking after acute myocardial infarction: an observational study

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## Abstract

**Background:** Smoking cessation is one of the most effective secondary prevention measures after acute myocardial infarction (AMI). However, around 50% of smokers do not quit smoking after AMI. The aim of the present study is to estimate the proportion of patients quitting smoking and to identify determinants of persistent smoking after AMI in a region with increased cardiovascular mortality. We also assessed the time of smoking cessation after AMI.

**Methods:** We used follow-up data of patients registered with the Regional Myocardial Infarction Registry in Saxony-Anhalt (RHESA) in Germany. We assessed smoking status and determinants of persistent smoking six weeks after discharge from hospital after AMI. Information on smoking, sociodemographic characteristics, risk factors for AMI, experienced symptoms of AMI, and clinical care were gathered in a computer-assisted telephone interview and questionnaires filled out by study subjects and physicians or study nurses.

**Results:** Out of 372 smokers at the time of AMI, 191 (51.3%) reported that they quit smoking within six weeks after discharge from hospital after AMI. Strongest determinant of persistent smoking was a previous AMI before the current one (OR = 2.19, 95%CI 1.10–4.38) and strongest determinants of smoking cessation were experiencing complications in the hospital (0.37, 95%CI 0.12–1.12) and having a life partner (0.56, 95%CI 0.34–0.95). Most individuals who stopped smoking did so during the initial stay in the hospital, before the cardiac rehabilitation (CR).

**Conclusions:** Persistent smoking after AMI and its determinants were similar in our region to previous studies. CR cannot be viewed as determinant of smoking cessation – more likely the same teachable moment induces behavioural change with regard to smoking and participation in CR.


**Keywords:** Smoking, Secondary prevention, Myocardial infarction, Predictors, Teachable moment, RHESA

## Background

For many years, Saxony-Anhalt has been one of the federal states in Germany with the highest incidence and mortality of acute myocardial infarction (AMI) [1]. In 2013, the age-standardized incidence of AMI (349 / 100, 000 persons) was 28.3% above the national average. In order to identify reasons for the high incidence and mortality, the Regional Myocardial Infarction Registry (RHESA) was established in 2013 [2]. One potential explanation for the high incidence is the highest or second highest prevalence of common risk factors for AMI in Saxony-Anhalt among the German federal states (i.e. smoking, diabetes mellitus, arterial hypertension, obesity, increased waist circumference and the metabolic syndrome) [3]. However, it still remains unclear whether there is additional contribution of insufficient secondary prevention in Saxony-Anhalt including behavioral

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change, resulting in elevated rates of repeated infarctions with poor prognosis.

One of the most effective secondary prevention measures after AMI is smoking cessation [4]. A meta-analysis of twelve studies with a follow-up from two to ten years after AMI reported a 0.54 (95% CI 0.46–0.62) times reduced overall mortality for quitters compared to those who continued smoking [5]. However, according to the multi-centre study EUROASPIRE IV survey, 40–60% of AMI survivors in Europe do not stop smoking after AMI [6]. In Würzburg, the German study centre of that study, the quit rate was 47%.

One suggested mechanism to explain smoking cessation after AMI is that of a teachable moment - a naturally occurring event resulting in higher motivation for a change in risk behaviour [7]. Additionally, support provided at the right time can increase the possibility of a strong teachable moment encouraging smoking cessation [7, 8]. This support is available to patients during rehabilitation where, for example, the duration of the smoke-free policy that started in the hospital is prolonged, or pharmacological or psychological assistance is offered [9–11]. Predictors of persistent smoking after AMI have been identified in previous studies. These are sociodemographic characteristics [6, 12–15], smoking behaviour [11, 12], risk factors for AMI [12, 15], and the extent of medical interventions in the context of AMI [12, 14, 15]. Nevertheless, these factors can have different importance in various regions.

In the current analysis, we aimed to estimate the proportion of patients successful in quitting smoking after AMI in Saxony-Anhalt and to identify factors that determine persistent smoking after AMI in our region. We also address the question, when patients after AMI quit smoking in our population.

## Methods

### Study design and setting

RHESA-CARE 1 and 3 (RC1, RC3) are follow-up studies of patients who agreed to participate in the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) [2, 16]. The inclusion criteria for RHESA were age of 25 or more and being an inhabitant of the city of Halle (Saale) or the rural area of Altmark in Saxony-Anhalt (Germany) and being diagnosed with AMI in the hospital. While in RHESA we used multiple sources of information on mortality and morbidity of AMI in the population, in the follow-up studies only patients who provided informed consent during their stay in a hospital were included. In RC1, we contacted all AMI survivors who were registered with RHESA between April 2014 and January 2018 and agreed to participate in an active follow-up. The contact was six weeks after their hospital discharge. Since RHESA continued to recruit patients beyond the end of the RC1 study, we conducted an additional follow-up to include patients registered after January 2018, but included all patients registered with RHESA between June 2013 and January 2019. This follow up was conducted between February and May 2019 for all patients independently from discharge date after AMI including some participants of RC1. RC3 used a substantially shortened RC1 questionnaire with some additional questions for example regarding time of smoking cessation. Only those participants that reported in RC1 (or RC3 if RC1 information was not available) that they have been smokers at the time of AMI are part of this analysis.

### Variables

All variables of interest were gathered either through computer-assisted telephone interview (CATI) (RC1), written questionnaires (RC3) or by questionnaires answered by physicians or study nurses in the hospital (as part of RHESA). Quality and data comparability were ensured by using standardized and validated instruments that have been used in similar studies [17–19].

Smoking status at the time of AMI was self-reported in both, RC1 and RC3. In RC1 individuals were also asked about smoking status at the date of interview (six weeks after hospital discharge). In RC3, we asked if and when the individuals had stopped smoking and if and when they started smoking again. Thus, we were able to determine the smoking status six weeks after discharge from hospital also for those who participated only in RC3. Individuals that reported that they quit smoking within six weeks after discharge from hospital were considered as quitters. When continuation of daily or occasional smoking was reported six weeks after discharge from hospital, individuals were considered as persistent smokers. Based on a literature search, we identified four categories of potential determinants of smoking cessation: sociodemographic characteristics, risk factors for AMI, experienced symptoms of AMI, and clinical care.

For the first category of possible determinants of smoking cessation, we gathered information on age, sex, net income per household (metric variable assessed in steps of 500 €), education (according to the international standard classification of education (ISCED-97) with 3 levels (low, mid, high)), and having life partner. In the second category of potential determinants, we asked the participants for a confirmed diagnosis of arterial hypertension and diabetes mellitus and previous AMI. Participants were further asked if they had any intention to quit smoking before the AMI occurred. The third category of potential determinants included the presence of fear of death during the AMI as a binary variable. Information on the fourth category of potential determinants was gathered through hospital questionnaire answered

by physicians or study nurses. The questionnaire contained information on the type of AMI (STEMI vs. NSTEMI) interventions after AMI (percutaneous coronary intervention (PCI)) or coronary artery bypass graft (CABG) vs. no intervention), complications in the hospital (i.e. shock, intubation, reanimation, severe bleeding, stroke or re-intervention, the number of newly prescribed drugs after hospital and the duration of hospitalisation (in days). We used the number of newly prescribed drugs as an auxiliary information for the perceived severity of heart disease. We assumed that this perceived severity can possibly strengthen the teachable moment associated with AMI and therefore increase the probability of smoking cessation.

In addition, we assessed the information on participation in cardiac rehabilitation (CR) within 2 weeks after hospital discharge in RC1 and in RC3, if it was not available in RC1. Using RC3 as a preferred source of information showed only minor differences in sensitivity analysis (data not shown).

### Statistical analysis

For sample characteristics, continuous variables were expressed as mean ± standard deviation for normally distributed data or as median and interquartile range for non-normally distributed data. Categorical variables were reported as frequencies and percentages (%).

Under the assumption of missing at random (MAR), we used multiple imputation to compensate incompleteness of information on age, sex, education, comorbidities (arterial hypertension, diabetes mellitus), fear of death during AMI, STEMI vs. non-STEMI status, intervention in the context of AMI, number of newly prescribed drugs, and duration of hospitalisation after AMI. Seventy complete data sets were generated according to the rounded-up percentage of incomplete cases. Fully conditional specification method was used in order to impute categorical variables and in order to not rely on normal distribution of continuous variables. The imputed models contained above-named variables, as well as information on region (Halle or Altmark) and on transfer between hospitals in order to conduct interventions after AMI (yes/ no). We used univariable logistic regression on the original dataset to obtain unadjusted effects of determinants on continuing smoking. We performed multivariable logistic regression on the imputed datasets and applied Rubin's rule to combine their results [20]. Considering the high number of variables and to avoid overadjustment, we subdivided the covariates into 3 levels. Level 1 included information on the sociodemographic variables, level 2 information on the history of risk factors, and level 3 information on the symptoms of AMI and clinical care after AMI. Determinants where adjusted for all the variables in the same level and the previous level(s). All calculations were performed in SAS software version 9.4 (The SAS Institute, Cary, NC, USA).

## Results

### Sample characteristics

One thousand one hundred fourteen persons were enrolled in our study, of whom 288 only participated in RC1, 313 only in RC3, and 513 in both, RC1 and RC3 (Fig. 1). Three hundred seventy-two individuals reported being smokers at the time of AMI and about half of them (51.3%) reported having stopped smoking within six weeks after hospital discharge. Differences between persistent smokers and those who stopped smoking existed for sociodemographic characteristics, risk factors for AMI, and clinical care after AMI but not for the experienced AMI symptoms (Table 1). Respondents of RC3 had on average slightly higher mean age at the time of AMI (0.83 years), had more often male sex (71.8% vs. 69.7%), and more often were from the urban region city of Halle (58.0% vs. 56.2%) compared to respondents of RC1.

### Determinants of smoking cessation

We identified having a previous AMI compared to no previous AMI (OR = 2.19, 95%CI 1.10–4.38) and receiving PCI or CABG compared to no intervention (OR = 1.53, 95%CI 0.66–3.54) as the strongest determinants of persistent smoking, and having a life partner compared to no life partner (OR = 0.56, 95%CI 0.34–0.95) and experiencing complications in the hospital compared to no complications (OR = 0.37, 95%CI 0.12–1.12) as the strongest determinants of smoking cessation (Table 2). Effects of age, sex, having STEMI and the duration of hospitalisation were close to the null effect.

### Time of smoking cessation

Among those who stopped smoking within six weeks after hospital discharge, most stopped smoking already during hospital stay (Table 3). Among those who attended CR, some stopped smoking before CR. Overall, smoking cessation was more common and restarting smoking less common among those who attended CR in comparison to those who did not, but the attendance to CR cannot be considered as the cause of smoking cessation, as it occurred mostly before CR.

## Discussion

In our study population, about 50% of smoking AMI patients stopped smoking within six weeks after discharge from hospital after AMI. The strongest determinants of smoking cessation were having a life partner and having experienced complications in the hospital. Persistent smoking was most strongly determined by having

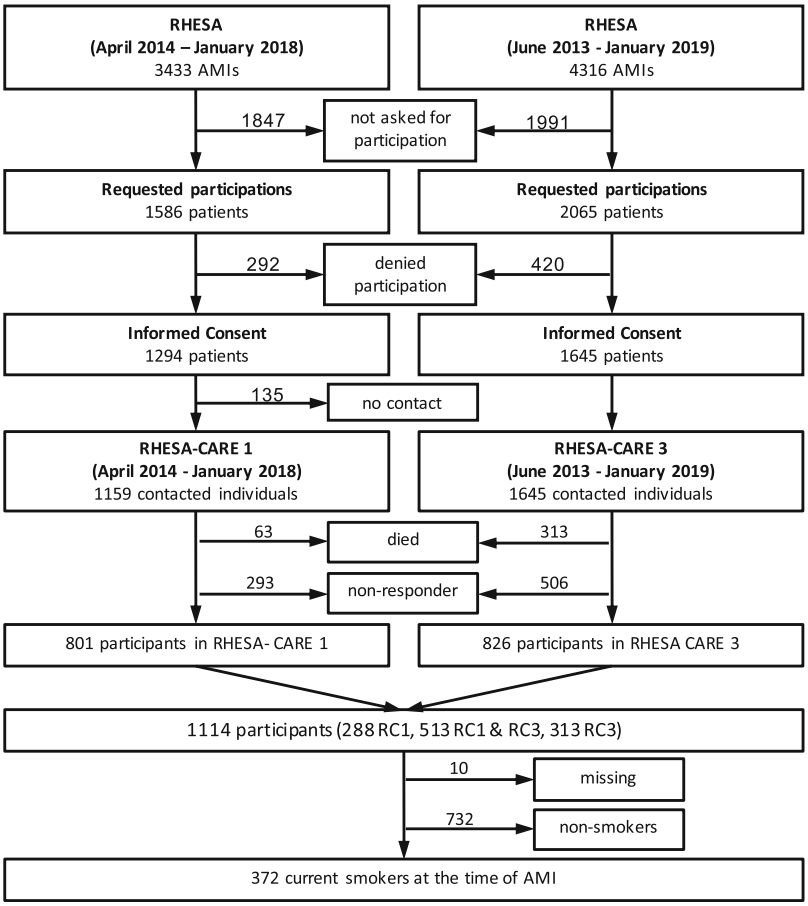


**Fig. 1** "Flow diagram of study population"

previous myocardial infarction and by receiving PCI or CABG. More than 80% of those who stopped smoking after AMI did so before hospital discharge and thus also before CR.

### Implications and comparison to previous studies

The proportion of quitters in our study population corresponded to the average quit rate of European patients with coronary heart disease [6]. The proportion of quitters in our study population was even slightly higher than the proportion reported for Germany in the above study (51% vs 47%). Thus, it does not appear that this factor could explain the morbidity/mortality excess in our region in Germany.

Factors that were associated with smoking cessation were found in the category of sociodemographic characteristics, risk factors for AMI, and clinical care, but not in symptoms of AMI. We found no association between age at hospitalisation due to AMI and smoking cessation. Most of the previous studies showed similar results [13–15], although some studies showed a positive association between higher age and smoking cessation [6, 12]. Furthermore, we saw no association between sex and smoking cessation. While one other study showed a similar finding [14], some other studies showed a protective effect [6, 13, 15] and one other a harmful effect [12] of male sex on continuous smoking in comparison to female sex. There can be various explanations of these findings – including different smoking behaviors of the respective populations and the different survey periods. A higher net household income had a positive effect on smoking cessation which is concordant to other studies [12, 21]. The German Health Interview and Examination Survey for Adults (DEGS1) from 2013 showed that higher socio economic status is not only associated with lower prevalence of smoking, but also with higher cessation independently of AMI [22]. Having a life partner was associated more often with smoking cessation

**Table 1** Sample characteristics of persistent smokers and quitters

| | persistent smokers (***N*** = 181) | quitters (***N*** = 191) | missing (%) |
|---|---|---|---|
| **Sociodemographic characteristics** | | | |
| Mean age[R] in years (SD) | 56.7 (10.2) | 56.8 (8.9) | 0.5 |
| Male sex[R], n (%) | 125 (69.8) | 140 (73.3) | 0.5 |
| Net income[1,3] per household, n (%) | | | |
| 0–1000 € | 49 (28.2) | 24 (13.3) | 4.8 |
| 1001–3000 € | 113 (64.9) | 118 (65.6) | |
| > 3000 € | 12 (6.9) | 38 (21.1) | |
| Education[1] | | | |
| Low education | 11 (8.5) | 8 (5.7) | 27.4 |
| Intermediate education | 90 (69.8) | 89 (63.1) | |
| High education | 28 (21.7) | 44 (31.2) | |
| Life partner[1,3], n (%) | 99 (54.7) | 145 (75.9) | 0 |
| **Risk factors for AMI** | | | |
| Arterial hypertension[R], n (%) | 143 (80.8) | 139 (74.3) | 2.2 |
| Diabetes mellitus[R], n (%) | 45 (25.4) | 37 (20.0) | 2.7 |
| Previous AMI[1,3], n (%) | 31 (17.1) | 15 (7.9) | 0 |
| Intension to quit smoking[3] n (%) | 32 (28.8) | 53 (37.1) | 31.7 |
| **Experienced symptoms of AMI** | | | |
| Fear of death[1], n (%) | 27 (21.8) | 34 (25.4) | 30.7 |
| **Clinical care** | | | |
| STEMI[R], n (%) | 95 (53.1) | 103 (53.9) | 0.5 |
| Intervention (PCI)[R], n (%) | 163 (97.0) | 169 (96.6) | 7.8 |
| Intervention (CABG)[R], n (%) | 2 (1.2) | 8 (4.6) | 8.3 |
| Complications[R], n (%) | 6 (3.4) | 15 (7.9) | 0.8 |
| Mean number of new drugs[1] (SD) | 4.2 (2.2) | 5.3 (2.0) | 27.2 |
| Median hospitalisation duration[R] (Q1-Q3) | 6 (4–7) | 6 (5–8) | 21.2 |
| Attending cardiac rehabilitation[1,3], n (%) | 71 (39.4) | 111 (58.4) | 0.5 |

[R] Information from questionnaire distributed in the hospitals (RHESA)
[1] Information from computer assisted telephone interviews (RHESA-CARE 1)
[3] Information from written questionnaires (RHESA-CARE 3)

compared to not having a life partner, which has also been shown in previous studies [12, 14, 15]. We hypothesise that people having a life partner feel not only responsible for themselves, they might feel a responsibility for their partner as well. This may increase the emotional component of the teachable moment and could lead to a higher cessation rate. Additionally, those people may experience additional support in the process of quitting and staying away from cigarette smoking. Individuals diagnosed with arterial hypertension had a higher risk to continue smoking. This effect was also found elsewhere [12]. We found a strong association between having a history of AMI and continuous smoking. People that are not able to stop smoking after their first myocardial infarction are less likely to stop smoking after their next cardiac events. A comparison with other studies is not feasible because those either excluded subjects with previous myocardial infarctions in the first place, or they only provided descriptive data about cessation rates [12, 15]. In our study, we found that subjects who suffered complications in the hospital had the highest chance of quitting smoking. Since only a few people in the hospital suffered complications, the confidence interval is very wide. A longer stay in hospital and a higher number of newly prescribed drugs after AMI were only slightly associated with smoking cessation. The number of new drugs was used as a proxy for the perceived severity of heart disease. We can imagine that taking new drugs every day will give patients a lasting feeling of illness. In contrast to other studies [12, 14], we found a positive association between being subject of a PCI or CABG on the one side and continuing smoking

**Table 2** Determinants of persistent smoking from logistic regression models

| | $OR_{raw}$ | $OR_{Adjusted}$ |
|---|---|---|
| ***Sociodemographic characteristics*** | | |
| Age (per 5 years) | 0.99 | 1.00 (0.98–1.02) |
| Sex (male vs. female) | 0.84 | 1.07 (0.65–1.75) |
| Income (per 500 €) | 0.76 | 0.82 (0.72–0.94) |
| Education (mid vs. low) | 0.74 | 0.83 (0.32–2.18) |
| Education (high vs. low) | 0.46 | 0.76 (0.26–2.19) |
| Life partner (yes vs. no) | 0.38 | 0.56 (0.34–0.95) |
| ***Risk factors for AMI*** | | |
| Hypertension (yes vs. no) | 1.45 | 1.44 (0.84–2.49) |
| Diabetes mellitus (yes vs. no) | 1.36 | 1.11 (0.64–1.94) |
| Previous AMI (yes vs. no) | 2.42 | 2.19 (1.10–4.38) |
| Intension to quit smoking (yes vs. no) | 0.69 | 0.83 (0.48–1.43) |
| ***Symptoms*** | | |
| Fear of death (yes vs. no) | 0.82 | 0.86 (0.45–1.65) |
| ***Clinical Care*** | | |
| STEMI (yes vs. no) | 0.97 | 1.07 (0.66–1.73) |
| Intervention (yes vs. no) | 1.14 | 1.53 (0.66–3.54) |
| Complication (yes vs. no) | 0.40 | 0.37 (0.12–1.12) |
| New prescribed drugs (per 1 drug) | 0.79 | 0.86 (0.75–0.98) |
| Hospitalisation duration (per 3 days) | 0.79 | 0.95 (0.87–1.02) |

on the other. However, more than 90% of the subjects in our study got a PCI, and thus the non-intervention group was very small. Nevertheless, many of the cited publications looking for predictors of smoking cessation have been published over 20 years ago. It could be interpreted as a signal suggesting that today's hospital interventions and the stay itself are no longer considered as life-threatening as it was years before.

Several previous studies assessed CR as potential determinant of smoking cessation [11, 13, 23, 24]. We could show in our study, that those who participated in CR not only were more likely to quit smoking, they mostly quit already before attending CR. This may suggest that those who attend CR are more strongly motivated to modify their risk behavior even before attending CR compared to those who do not attend CR. Those who attend CR are also more likely not to restart smoking – but we cannot say if this is also due to selection, or possibly because of additional support during CR.

### Strength and limitations

The strength of our study is the use of data from a population-based registry of AMI with a systematic follow up – in contrast to studies based on hospital samples only. Furthermore, we were able to assess a very broad set of determinants of smoking cessation after AMI.

At the same time, our study has some limitations. Information on smoking and several of the variables assessed as determinants was self-reported and thus subject to reporting bias. The recall bias could be increased by the fact that for some participants the AMI was several years ago. We had relatively limited information on smoking behavior before AMI. Furthermore, we were not able to shed light on whether CR contributes to smoking cessation – we could only show that it would be incorrect to attribute smoking cessation to CR. Although the sample size is relatively small, we could answer the posed questions. In regression analyses, the sample fulfilled the rule of thumb with at least 10 events per variable [25].

## Conclusion

In our cohort of AMI patients from a population-based registry in a region with a comparably high cardiovascular morbidity and mortality, 51.3% stopped smoking within six weeks after discharge from hospital, similarly to other European and German data. Also, the determinants of smoking cessation were similar to previous studies, therefore an explanation of elevated mortality has to be searched in other areas. While CR was considered determinant of smoking cessation in previous studies, it appears that among those who attend CR, most stop smoking already before starting CR.

**Table 3** Time of smoking cessation

| Time of quitting smoking after AMI | | CR participants (***N*** = 133) | | Non-CR-participants (***N*** = 119) | |
|---|---|---|---|---|---|
| | | quitter[b] n (%) | Backslider[c] n (%) | n (%) quitter (incl. temporary) | n (%) backslider |
| During hospitalisation | | 69 (51.9) | 4 (5.8) | 50 (42.0) | 12 (24.0) |
| within 6 weeks after hospital discharge | before CR[a] | 4 (3.0) | 3 (75.0) | 12 (10.1) | 7 (58.3) |
| | during CR[a] | 7 (5.3) | 3 (42.9) | | |

*CR* cardiac rehabilitation
[a] only for those who attended CR
[b] those who did not smoke six weeks after discharge
[c] among the quitter those who restarted smoking after six weeks

**Abbreviations**
AMI: Acute myocardial infarction; CABG: Coronary artery bypass graft; CATI: Computer assisted telephone interview; CR: Cardiac rehabilitation; PCI: Percutaneous coronary intervention; RC1: RHESA-care 1; RC3: RHESA-care 3; RHESA: Regional myocardial infarction registry; STEMI: ST-elevation myocardial infarction

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**Authors' contributions**
JH drafted the manuscript. ASP, JH conducted and coordinated the study. JH and CF conducted the literature search on the topic. JH, UJ, CF, and RM contributed to the analysis and to the interpretation of the data. All authors read and approved the final manuscript.

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**Availability of data and materials**
The datasets used and/or analysed during the current study are available from the corresponding author on request.

**Ethics approval and consent to participate**
RHESA was approved by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg and by the State Data Protection and Privacy Commissioner of Saxony-Anhalt. The ethics for the RHESA-CARE Study are included in those of the RHESA. All patients gave their written informed consent to participate in the study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note

# Publication 2

**Title:**

Participation in disease management programs and major adverse cardiac events in patients after acute myocardial infarction: a longitudinal study based on registry data

**Personal contribution:**

Conduction of subject interviews (RHESA-Care 2), development of questionnaire (RHESA-Care 3), writing amendment for Ethics Committee, data cleaning, partial conception of the analysis, revision of the manuscript

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RESEARCH ARTICLE Open Access

# Participation in disease management programs and major adverse cardiac events in patients after acute myocardial infarction: a longitudinal study based on registry data

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## Abstract

**Background:** Cardiovascular diseases are still the main cause of death in the western world. However, diminishing mortality rates of acute myocardial infarction (AMI) are motivating the need to investigate the process of secondary prevention after AMI. Besides cardiac rehabilitation, disease management programs (DMPs) are an important component of outpatient care after AMI in Germany. This study aims to analyze outcomes after AMI among those who participated in DMPs and cardiac rehabilitation (CR) in a region with overall increased cardiovascular morbidity and mortality.

**Methods:** Based on data from a regional myocardial infarction registry and a 2-year follow-up period, we assessed the occurrence of major adverse cardiac events (MACE) in relation to participation in CR and DMP, risk factors for complications and individual healths well as lifestyle characteristics. Multivariable Cox regression was performed to compare survival time between participants and non-participants until an adverse event occurred.

**Results:** Of 1094 observed patients post-AMI, 272 were enrolled in a DMP. An association between DMP participation and lower hazard rates for MACE compared to non-enrollees could not be proven in the crude model (hazard ratio = 0.93; 95% confidence interval = 0.65–1.33). When adjusted for possible confounding variables, these results remained virtually unchanged (1.03; 0.72–1.48). Furthermore, smokers and obese patients showed a distinctly lower chance of DMP enrollment. In contrast, those who participated in CR showed a lower risk for MACE in crude (0.52; 0.41–0.65) and adjusted analysis (0.56; 0.44–0.71).

**Conclusions:** Participation in DMP was not associated with a lower risk of MACE, but participation in CR showed beneficial effects. Adjustment only slightly changed effect estimates in both cases, but it is still important to consider potential effects of additional confounding variables.

**Keywords:** Myocardial infarction, Heart attack, DMP, Rehabilitation, MACE, Outpatient, Health care, Coronary heart disease, Secondary prevention

## Background

Cardiovascular diseases are still the main cause of death in the western world. In 2017, 37% of all deaths in Germany were caused by diseases directly affecting the cardiovascular system [1]. The two most frequent death-related diagnoses were coronary heart disease (CHD) and

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acute myocardial infarction (AMI) [2]. Due to standardized acute revascularization management by interventional cardiology, AMI mortality rate has been decreasing in the last three decades [3]. However, AMI survivors are a high-risk group for death or another severe health event, especially if they are affected by additional risk factors such as smoking, obesity or diabetes [4]. To avoid subsequent severe health events, secondary prevention is needed [5].

Cardiac rehabilitation (CR) is one of the best-known and most often recommended secondary prevention approach after AMI [5–9]. However, in light of its high costs, delayed return home (in the case of in-patient treatment), and only a short period of intervention, the search for alternatives is well justified [10–13]. One such alternative is a disease management program (DMP) which has been introduced in Germany in 2002 to improve outpatient medical treatment quality and reduce costs in the health care system [14]. DMPs are structured treatment programs, coordinated by the patient's general practitioner (GP). Since 2012, all statutory health insurance companies in Germany are required to offer DMPs based on the guidelines of the Federal Joint Committee to achieve nationwide homogeneity. Participating in a DMP is voluntary for the patients, and recommendation to a DMP is voluntary for the GPs. For patients, inclusion criteria are defined for enrollment in a DMP [15]. Patients, who meet the inclusion criteria for a specific DMP are asked by their GP or Health Insurance Company to enroll into DMP. For patients enrolled in the DMP coronary heart disease the program includes systematic control of medication, recommendations on nutrition and physical activity as well as advice on smoking cessation if relevant.

However, 18 years after the introduction of the first DMP for coronary heart disease, there is still insufficient evidence regarding the effectiveness of DMPs. Aside from the mandatory evaluations of insurance companies, only a few studies were published, and they mostly focused on DMPs related to diabetes mellitus [16–25]. Since DMPs were introduced all over Germany as a mandatory service, only observational studies can contribute further evidence on their performance [26].

In the federal state of Saxony-Anhalt, there were 75 deaths per 100,000 persons with AMI as recorded cause of death in 2016, which is 38.5% above the German average (55 deaths per 100,000 persons) [2]. In order to investigate the causes of this increased level, a regional registry of myocardial infarction in urban and rural regions of the federal state (RHESA) was established [27]. Patients who agreed to participate in RHESA are followed over time using questionnaires and health status information [28]. As one explanation of the elevated mortality could be suboptimal secondary prevention, we performed a follow-up of the RHESA participants that focused on secondary prevention programs.

Our aim was to assess the participation of AMI survivors in the secondary prevention programs and the association between the participation in secondary prevention and major cardiac outcomes including another AMI, stroke, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or death.

## Methods

### *Study design, study location, period of recruitment and participants*

We used data from follow-up of patients registered in RHESA. RHESA and its follow-up modalities were described elsewhere [27, 28]. In brief, RHESA was established to investigate the causes of the increased level of morbidity and mortality of AMI of the federal state Saxony-Anhalt [27] and collected information about all fatal and non-fatal myocardial infarctions in the city of Halle and in the rural region of the Altmark. In addition to collecting anonymous data, patients with AMI were asked during their hospital stay if they are willing to contribute their data and answer questionnaires in the future. Study instruments included hospital questionnaires filled out by medical staff, death certificates of the regionally responsible health office and documentations of emergency aid [28]. The recruitment for RHESA and its baseline information was obtained via questionnaires from physicians or study nurses in the respective hospitals since June 2013 and is ongoing. Between 2013 and 2017, a first follow-up named RHESA-Care1 (RC1) was conducted 6 weeks after hospital discharge (n = 804 patients participated); between 2015 and 2018, a second follow-up [RHESA-Care 2 (RC2)] was conducted, in which patients were contacted 2 years after their hospital discharge (n = 383) (Fig. 1). For the purpose of the current study, we conducted a third follow-up [RHESA-Care 3 (RC3)] of all patients from March to June 2019. This third follow-up focused on information about the occurrence of cardiac events: AMI, stroke, death, PCI or CABG, in addition to information regarding participation in DMPs or CR, co-morbidities, and socioeconomic factors as well as smoking/smoking cessations. In order to clarify if patients who died before the third follow-up had participated in DMPs, we contacted the doctors who signed their death certificates with a short questionnaire regarding their assessment of the cause of death and DMP participation. For the current study we included all participants, who took part in either RC1 and RC2 or RC3 (Fig. 1).

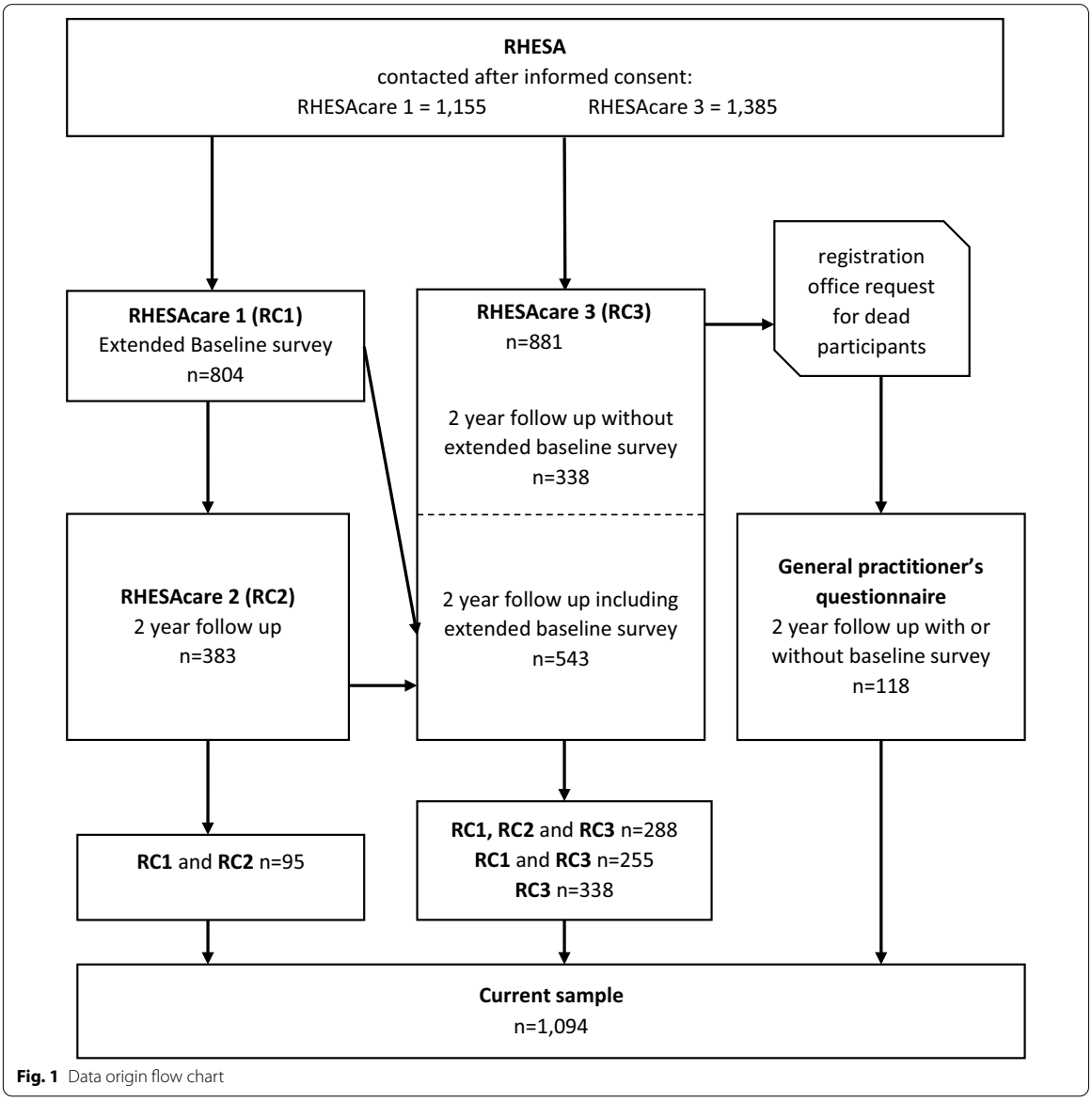


**Fig. 1** Data origin flow chart

***Exposure and covariates***

In the current study we compared the long-term survival and cardiac health of AMI patients in terms of their participation in secondary prevention programs. We furthermore used the variables of obesity ($\geq 30$ kg/m$^2$ vs. $< 30$ kg/m$^2$ at the time of the initial AMI), hypertension (elevated arterial blood pressure diagnosed before or at the time of the initial AMI), and ST-elevated myocardial infarction (STEMI) versus non-ST-elevated myocardial infarction (NSTEMI) based on baseline questionnaire of RHESA as covariates in the cox regression models. To examine the factors that influence the participation in secondary prevention, we also used baseline information from the hospital questionnaires for each patient's history with on smoking, diabetes, STEMI/NSTEMI, sex, obesity hypertension and age at the initial AMI as independent variables. Since analysis of age as a categorical variable did not indicate any nonlinearity, age was modelled as a continuous variable.

### Ethical approval

All participants provided written informed consent for participation in RHESA. The Ethics Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg approved the initial study and the follow-up questionnaires.

### End points

The primary endpoint was survival time, starting 15 days after the initial AMI, until the occurrence of the first major adverse cardiac event (MACE) with a maximum of 24 months of observation time. In the composite endpoint, we included: AMI, stroke, PCI, CABG, and death (all-cause mortality and cardiac death were analyzed separately). As 2 weeks after AMI is the usual period for starting a subsequent cardiac rehabilitation according to Volume V of the German Social Code (SGB V) and to avoid immortal time bias [32], only those events which occurred at least fifteen days after the initial AMI were included in the study. In case of multiple outcomes, only the first was considered. Occurrence for all MACE as well as the beginning of participation in DMPs were self-reported by the patient or reported by the patient's GP with an exact date. However, due to many participants only reporting the month, every event was recorded to have happened on the 15$^{th}$ of the respective month. In the case of discordant information in different follow-up questionnaires, we used the information which was collected most closely following the reported event. Since enrollment into a DMP can occur at various times after the AMI, we considered DMP as a time-dependent exposure.

A known risk of using composite endpoints are dilution effects [29]. Thus, we defined two subtypes of MACE: MACE1 included only AMI, stroke, and death. MACE2 included AMI, stroke and death in addition to PCI and CABG. In the analyses of determinants for participation in secondary prevention, the endpoint was participation in a DMP or CR, respectively.

### Statistical analysis

Descriptive characteristics of the sample were reported as percentages and mean values with 95% confidence intervals (CI).

In order to identify determinants of DMP and CR, we obtained multivariable relative risks from a Poisson model with robust error variance as alternative to a logistic regression analysis for frequent outcomes [30]. In these models, participation in either DMP or CR was considered the main exposure while the outcomes were the ones specified above. We adjusted the model for all included covariates (smoking, diabetes mellitus, STEMI, sex, obesity, hypertension, and age). Since investigated covariates were potentially correlated, we tested for their multicollinearity, but no covariates needed to be excluded [31].

We analyzed the effects of CR or DMP participation on the occurrence of MACE using Cox proportional hazard regression models. We assessed assumption of proportional hazards for the Cox model by inspecting respective Kaplan–Meier plots (Additional file 1: Fig. 1).

Covariates for adjustment were selected based on the literature and directed acyclic graphs theory. They were: diabetes mellitus (diagnosed before or at the time of the initial AMI), smoking status (being smoker at the time of the initial AMI), sex, obesity, and age at the time of initial AMI. The models for CR and DMP participation were also mutually adjusted for these variables. Adjusting our analysis by socioeconomic status was not applicable, because of missing data, especially due to the GP's questionnaire not including the corresponding items.

Some patients participated in DMP before their AMI—this time was censored to create a proper "time zero" of the time-dependent covariate [33]. In a sensitivity analysis, those who started participating in a DMP before AMI were excluded from the analysis.

Since the sample size was predefined, we investigated how strong the observed effects have to be, to provide statistically significant results. We estimated that a risk reduction of 18% or more could be detected at the significance level of $p < 0.05$ with 80% power. A risk reduction of 18% would be considered clinically relevant.

Besides social characteristics, patients taking part in either DMPs or CR could have a stronger motivation to change their lifestyle than those, who do not choose to participate. In such way, the participants of secondary prevention programs could be those with stronger motivation and likely better outcomes. This internal motivation is difficult to study. In an earlier analysis [44], we found that patients who stopped smoking after AMI (before CR) also had a higher probability of attending CR. Smoking cessation and attending CR were both possibly resulting from a higher internal motivation, which might also reduce MACE independently of CR. We compared effects of CR on MACE in those, who stopped smoking before CR and those who stopped later or did not stop.

All statistical analyzes were performed with SAS 9.4.

## Results

### *Sample characteristics*

Of the 1385 participants who provided informed consent for the follow-up and were alive in May 2019, 881 (63.6%) participated in the third follow-up of RHESA and filled out the corresponding questionnaire after up to two reminders. Additionally, there were 95 people who participated in the follow-up 2 years after AMI but did

not participate in the third follow-up. Still, because they provided the relevant information for the current analysis in the earlier questionnaire they were also included in the analysis. Furthermore, we received information about 118 patients who died before their second follow-up through a questionnaire filled out by their respective GPs. The median duration of follow-up for all patients was 24 months. For patients, who experienced an event, the median duration of follow-up was 8 months.

Of the 1,094 participants that were included in our study, about one quarter (24.9%) had been enrolled in a DMP while 58.5% took part in CR after treatment of the initial AMI, 189 patients (17.3%) participated both in DMPs and CR. Of all patients, 33.9% did not participate in either CR or a DMP (Table 1). CR participants were more likely to be also enrolled in DMP and vice versa. Of all DMP participants, 18.3% were enrolled in a DMP before the registered AMI. The remaining participants enrolled in median in the second month after hospital discharge.

Those who participated in CR were younger and more often smokers at the time of AMI than those who did not participate (Table 1). In contrast, those who participated in a DMP were less often smokers than those who did not. STEMI was most common among CR participants.

About one third of all participants experienced MACE within 2 years of follow up and 9% experienced a reinfarction (Table 2). Those who participated in DMP had experienced more MACE than those who participated in CR, as evidenced by the deaths in the group of 83 DMP participants that did not take part in CR. The mean age of this subgroup was 71 years and therefore much higher than the average age of all DMP participants.

#### *Determinants of DMP enrollment and participation in CR*

In the multivariable model, smoking at the time point of AMI was associated with lower participation in DMP, but not with lower participation in CR (Figs. 2 and 3, Additional file 1: Supplemental Table 1). In contrast, higher age was associated with lower participation in CR but not in DMP. STEMI was also associated with increased participation in CR.

#### *Association between participation in DMP or CR after AMI and outcomes during follow up*

The comparison of MACE1 and MACE2 showed higher absolute numbers of events and narrower CI for MACE2

**Table 1 Characteristics of the study population**

| | | DMP only N = 83 | CR only N = 451 | Both N = 189 | None N = 371 | Total N = 1094 |
|---|---|---|---|---|---|---|
| Age (mean) | Years | 70.9 | 64.9 | 64.5 | 69.9 | 67.0 |
| | (95% CI) | (68.5–73.2) | (63.8–66.0) | (62.9–66.1) | (68.6–71.2) | (66.2–67.7) |
| Age groups | pct | | | | | |
| 25–49 | | 3.6 | 11.5 | 12.2 | 6.2 | 9.2 |
| 50–59 | | 16.9 | 25.1 | 22.2 | 18.9 | 21.9 |
| 60–69 | | 19.3 | 28.2 | 27.5 | 20.5 | 24.8 |
| 70–79 | | 42.2 | 23.7 | 33.3 | 31.0 | 29.3 |
| 80+ | | 18.1 | 11.5 | 4.8 | 23.5 | 14.9 |
| Male sex | pct | 77.1 | 71.8 | 68.3 | 69.5 | 70.8 |
| | (95% CI) | (66.6–85.6) | (67.4–76.0) | (61.1–74.8) | (64.6–74.2) | (68.1–73.5) |
| Diabetes | pct | 27.7 | 18.6 | 9.5 | 14.8 | 16.5 |
| | (95% CI) | (18.5–38.6) | (15.1–22.5) | (5.7–14.6) | (11.4–18.9) | (14.3–18.8) |
| Smoker | pct | 19.3 | 38.1 | 30.2 | 28.0 | 31.9 |
| | (95% CI) | (11.4–29.4) | (33.6–42.8) | (23.7–37.2) | (23.5–32.9) | (29.2–34.8) |
| Hypertension | pct | 91.6 | 83.2 | 79.4 | 83.8 | 83.4 |
| | (95% CI) | (85.6–97.4) | (79.4–86.5) | (72.9–84.9) | (79.7–87.4) | (81.0–85.5) |
| Obesity | pct | 20.5 | 25.9 | 17.5 | 18.9 | 21.7 |
| | (95% CI) | (12.4–30.8) | (22.0–30.3) | (12.3–23.6) | (15.0–23.2) | (19.3–24.2) |
| STEMI | Pct | 28.9 | 51.0 | 48.7 | 34.0 | 43.1 |
| | (95% CI) | (19.5–39.9) | (46.3–55.7) | (41.4–56.0) | (29.2–39.0) | (40.2–46.1) |

*DMP* disease management program, *CR* cardiac rehabilitation; smoker and diabetes only relevant if being current at the time of the initial myocardial infarction registered in the data base

age/age groups = age in years at the time of the initial acute myocardial infarction

**Table 2 Proportion of patients experiencing negative relevant outcomes within 2 years after AMI**

| | DMP only N = 83 | CR only N = 451 | Both N = 189 | None N = 371 | Total N = 1094 |
|---|---|---|---|---|---|
| MACE1 | 45.8 | 14.6 | 19.1 | 27.5 | 22.1 |
| | 35.0–57.1 | 11.5–18.2 | 13.7–25.4 | 23.0–32.3 | 19.7–24.7 |
| MACE2 | 51.8 | 24.6 | 31.2 | 35.0 | 31.4 |
| | 40.6–62.9 | 20.7–28.9 | 24.6–37.8 | 30.2–40.1 | 28.6–34.2 |
| Reinfarction | 10.8 | 8.9 | 7.4 | 10.2 | 9.2 |
| | 5.1–19.6 | 6.4–11.9 | 4.1–12.1 | 7.4–13.8 | 7.6–11.1 |
| Stroke | 1.2 | 3.3 | 2.7 | 3.0 | 2.9 |
| | 0.0–6.5 | 1.9–5.4 | 0.9–6.1 | 1.5–5.2 | 2.0–4.1 |
| PCI | 9.6 | 8.7 | 11.1 | 10.0 | 9.6 |
| | 4.3–18.1 | 6.1–11.2 | 7.0–16.5 | 7.1–13.5 | 7.9–11.5 |
| CABG | 0.0 | 5.8 | 5.8 | 3.0 | 4.4 |
| | 0.0–4.3 | 3.8–8.3 | 2.5–9.2 | 1.5–5.2 | 3.3–5.8 |
| Cardiac death | 13.3 | 0.7 | 2.7 | 5.7 | 3.7 |
| | 6.8–22.5 | 0.1–1.9 | 0.9–6.1 | 3.5–8.5 | 2.6–5.0 |
| Death (other) | 25.3 | 2.9 | 9.0 | 11.3 | 8.5 |
| | 16.4–36.0 | 1.5–4.9 | 5.3–14.0 | 8.3–15.0 | 6.9–10.3 |

MACE 1 = composite endpoint including Reinfarction, Stroke and Death (cardiac / other), MACE 2 = composite endpoint including MACE 1 plus percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)

*DMP* disease management program, *CR* cardiac rehabilitation

without dilution effects. Thus, MACE2 was used as the primary endpoint in all cox regression analyses.

Participation in DMP was not associated with improved outcomes (crude hazard ratio = 0.93; 95% CI 0.65–1.33), while participation in CR was associated with risk reduction of about 50% (0.52; 0.41–0.65). These results were virtually unchanged after adjustment for age, sex, several diseases and a mutual adjustment for DMP and cardiac rehabilitation (Fig. 4).

Overall, the effects of stratification for the considered subgroups were small indicating that selection of participants according to these variables did not strongly affect the impact of either CR or DMP.

Age, sex and obesity did not show an association with change in survival time in our 2-year observation. Smokers showed a lower hazard rate with the confidence interval still containing the null effect (HR = 0.76; 95% CI 0.55–1.05), similarly there was a slightly increased risk of MACE in participants with diabetes, but the confidence interval included 1 (HR = 1.21; 95% CI 0.88–1.67).

Sensitivity analysis with 77.6% of all DMP participants who began their program after the AMI did not change the outcome noticeably. The HRs for DMP and CR were 0.98 (0.62–1.57) and 0.55 (0.43–0.71), respectively.

When stratified by the time point of smoking cessation, the effect was somewhat stronger in those CR-participants, who stopped smoking before the CR, when compared to those who did not stop smoking before CR or

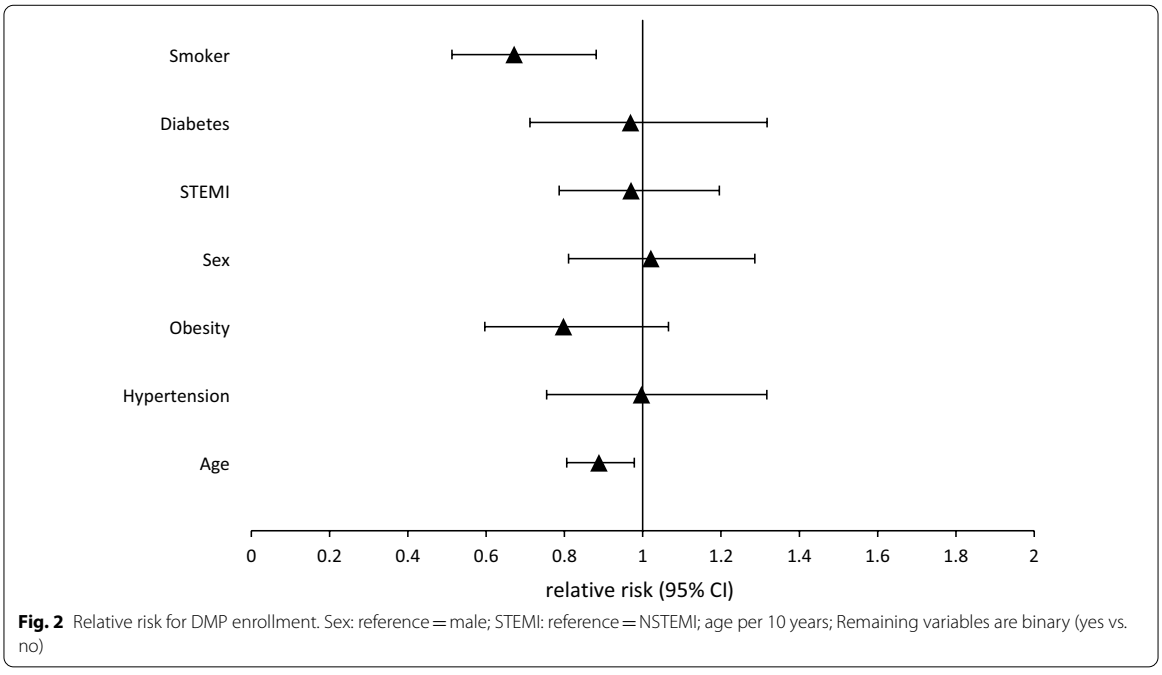


**Fig. 2** Relative risk for DMP enrollment. Sex: reference = male; STEMI: reference = NSTEMI; age per 10 years; Remaining variables are binary (yes vs. no)

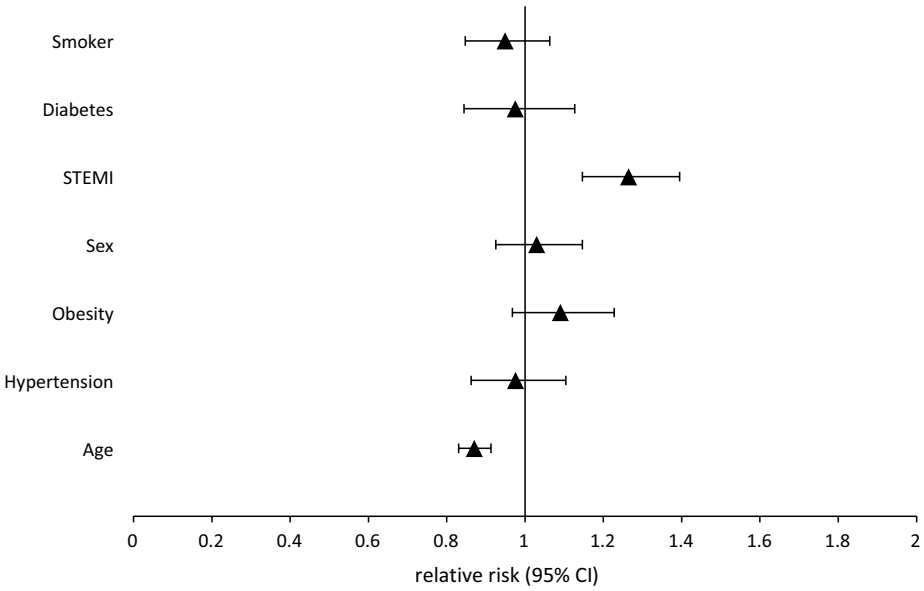


**Fig. 3** Relative risk for participating in cardiac rehabilitation. Sex reference = male; STEMI = ST-elevation myocardial infarction with reference = non-STEMI; Age = age in years continuously in 10 year steps; Remaining variables are binary (yes vs. no)

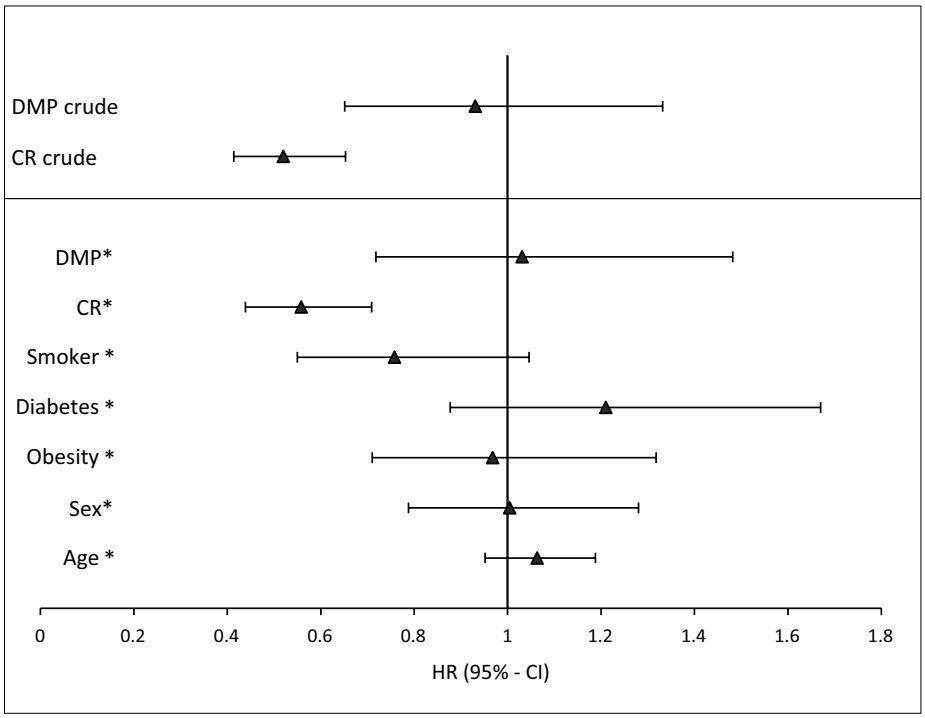


**Fig. 4** Association between secondary prevention or patient's risk factors and MACE. Sex: reference = male; STEMI: reference = NSTEMI; Age = age in years continuously. Remaining variables are binary (yes vs. no); * = adjusted model

**Table 3 Effects of participation in cardiac rehabilitation on occurrence of MACE1 stratified by smoking status**

| Model<br>Effects of rehabilitation in those who | Hazard ratio[a] (95% CI) |
|---|---|
| …did not smoke at time point of AMI | 0.59 (0.45–0.78) |
| … smoked at time point of AMI | 0.45 (0.27–0.74) |
| … smoked at time point of AMI, but stopped before rehabilitation | 0.39 (0.18–0.83) |
| … smoked at time point of AMI, but did not stop smoking before rehabilitation | 0.51 (0.26–1.01) |

[a] Participation in cardiac rehabilitation vs. no participation regarding MACE1 occurrence

did not smoke (Table 3). However, a strong association between smoking status and CR effect was not found.

## Discussion

Using data from the regional myocardial infarction registry RHESA, there was no evidence that participating in DMPs does result in lower rates of cardiac events. On the other hand, participation in CR after discharge from the hospital was associated with a distinctly lower hazard rate of MACE compared to non-participants.

The potential explanation for the lack of specific effect of DMPs could be that patients participating in DMPs did not receive similar care. It could be either that DMPs are not fully implemented, or that patients outside of DMPs benefit from the fact that their GPs employ the rules of DMPs also to them. DMPs have been repeatedly adapted since their establishment in 2003, so there may be a spillover effect on the outpatient treatment by GPs on all patients regardless of being actively enrolled in a DMP or not [17, 20].

We expected to see a higher prevalence of diabetes mellitus, obesity and smoking in DMP participants, due to DMPs targeting the reduction of those risk factors for cardiac events [15]. In contrast to our expectations, in our cohort patients with risk factors like smokers and obese people were found to have a lower likelihood to be enrolled in DMPs. On this account, several key components of the DMPs probably could not achieve their full effect, because patients who would likely benefit the most were participating less often in DMPs. The slightly lower hazard ratio for MACE in the crude model is probably due to the DMP participants being already healthier before the DMP than the control group.

It is also remarkable, that the proportion of enrollment in DMPs of about one quarter is substantially lower than the 77% participantion rate found 8 years ago in a comparable study in the region of Augsburg by Laxy et al. [16]. Röttger et al. [23] found similar results (enrollment rate of 72%) throughout Germany in 2013 in patients with CHD. Possible explanations could be regional socioeconomic differences [43] and health characteristics of the respective cohorts as well as the time span between the studies [21, 23]. In conclusion, it is apparent that the DMPs are currently ineffective in reaching their required target group in Saxony-Anhalt. While only about one third of all RHESA registered patients took part in the baseline survey with 70% answering in the respective follow-up, often those who participated were more health conscious.

Thus, our results indicate that the process of DMP participant acquisition, which does not reach the high-risk population, may be one of the reasons for the lack of effects on MACE in patients after myocardial infarction. This is especially important, considering the higher rates of cardiac mortality, risk factor distribution and demographic structure in our regional study population [37]. These observations are in line with a study by Schäfer et al. about selection effects in current DMP research [35]. While our results match the conclusions of similar studies [16, 17], health insurance evaluations repeatedly described protective effects [36]. The explanation could be a different comparison group.

In contrast, participation in CR after discharge from hospital resulted in a distinctly lower hazard rate of MACE compared to non-participants. There is a possibility that this effect may be related to self-selection of the participants of CR. On the one hand, we found that many of those who smoked at the time of AMI, stopped smoking before starting CR. This could indicate that there is an underlying motivation for lifestyle changes resulting in the participation in CR. Such motivation rather than the CR itself could be responsible for the positive effect attributed to CR. Consistently, there was an indication of more beneficial effects of CR in this subgroup. On the other hand, adjusting for the relevant risk factors did not pertinently change the estimated effect of CR in the direction of the null. We conclude that selection is likely present in CR participation and enhancing the observed effect, but it does not explain it fully.

According to our results, smoking at the time of the initial AMI shows a weak association with prolonged survival time. This well-known 'smoker's paradox' has been reported in several studies [38, 39]. The main suspected reason is that smokers experience AMI at younger age, and thus the relation with mortality is diluted.

### Strengths and limitations

The strength of this study lies in the prospective, population-based design with a cohort of patients severely affected by the elevated risk of multiple complications after their myocardial infarction. In addition, the

time-dependent covariate design in survival time analysis as well as the possibility to adjust the regression to multiple important co-morbidities and patient's characteristics with relevant influence on the total effect adds to the novelty and importance in current research.

Immortal time bias is common in prospective cohort studies, but our method of implementing DMP status as a time dependent covariate in the analysis can strongly reduce biased treatment effect estimates [32, 42]. This enables our analysis to account for DMP time whether or not the patient enrolled before or after the time of the initial AMI. Hence, our study is not limited by a time-fixed control group status which would ignore late onset DMP enrollment.

The findings of our study are limited by the follow-up time of only 2 years, and thus later outcomes are not considered. A longer follow-up period with greater, Germany-wide data could add to our results. Also, the main source of our data are self-reported questionnaires and telephone interviews which allow for recall bias or erroneous answers [40]. In order to investigate if the observed effects of either DMP or CR were influenced by selection of participants in those programs, we conducted multivariable analysis [21, 41]. Although we selected the covariates for the analysis by directed acyclic graphs, this choice was also limited by the availability of data. Adjusting our analysis for socioeconomic status was not possible, because of 118 patients who died and did not previously provide this information. Various mechanisms could affect the representativeness of the sample of AMI survivors in our study. First, the proportion of those included in RHESA in comparison to all AMIs in the study regions was at maximum 85% in 2016 and substantially lower in subsequent years. Second, only patients who agreed to the follow up were included (38% of patients who were alive at discharge). We do not have information to what degree this participation was a random process. The patients included in RHESA who agreed to follow up were on average about 4 years younger than those for whom agreement to follow up was not available, but for most other characteristics we saw no difference between participants and non-participants (Additional file 1: Supplental Table 2).

## Conclusions

Within the framework of the regional AMI registry in urban and rural regions of the federal state (RHESA), we could not confirm a benefit from participating in DMP for AMI survivors with respect to MACE. The present findings suggest that the reason for the lack of effects of DMPs may be the insufficient inclusion of those who would benefit from the DMP. In contrast, we observed a positive effect of CR, although it is possible that these results are confounded due to differences in personal motivation to participation. Thus, selection effects should be considered.

## Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-020-01832-3.

**Additional file 1. Table 1**. Relative Risk for participation in DMP or CR with corresponding 95% Confidence Intervals. **Table 2.** Characteristic of participants and non-participants of RHESA follow up.

### Abbreviations

AMI: Acute myocardial infarction; CABG: Coronary artery bypass graft; CHD: Coronary heart disease; CI: Confidence interval; CR: Cardiac rehabilitation; GP: General practitioner; MACE: Major adverse cardiac events; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; RC1: RHESA-CARE 1; RC3: RHESA-CARE 3; RHESA: Regional Myocardial Infarction Registry; STEMI: ST-elevation myocardial infarction.

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### Authors' contributions

CF designed the analysis, drafted the manuscript, conducted the literature search, performed statistical analysis and interpreted the data. JH co-designed the analysis. JH, RM, MN and SH contributed to the analysis and interpretation of the data. RM and JH conducted and coordinated the RHESA CARE 3 study. JH and CF developed the RHESA CARE 3 questionnaire. All authors have read and approved the manuscript. RHESA is conducted by the Institute of Medical Epidemiology, Biometrics and Informatics (IMEBI) of the Medical Faculty of Martin Luther University Halle-Wittenberg (head: Prof. Mikolajczyk). All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg approved the RHESA study and the follow up questionnaires RHESA CARE 1 and 2, and recently RHESA CARE 3. Written informed consent was obtained from all RHESA participants by the doctors working in the collaborating hospitals of the RHESA registry.

### Consent to publication

Not applicable.

**Competing interests**
Michael Noutsias declares that he serves on the editorial board of BMC Cardiovascular Disorders. All other authors declare that they have no competing interests.

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