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Admission glucose level and short-term mortality in older patients with acute myocardial infarction: results from the KORA myocardial infarction registry

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Abstract

Study objectives:

To investigate the association between admission blood glucose levels and 28-day mortality as well as in-hospital complications in older patients with incident acute myocardial infarction (AMI) undergoing modern treatment.

Methods:

From a German population-based regional myocardial infarction registry, 5530 patients (2016 females), aged 65-84 years, hospitalized with an incident AMI between January 1, 2009 and December 31, 2016 were included in the study. Multivariable logistic regression models were used to assess the associations between admission blood glucose and 28-day-mortality as well as in-hospital complications after AMI. Analyses stratified according to age, diabetes, and type of infarction (ST-elevation MI/non-ST-elevation MI) were conducted.

Results:

The adjusted odds ratios for admission blood glucose predicting 28-day-mortality in young-old (65-74) and old (75-85) AMI patients were 1.41 (95% CI: 1.21-1.64) and OR 1.21 (95% CI: 1.00-1.50) per 1 SD increase in admission blood glucose, respectively. Admission blood glucose was also significantly associated with major cardiac complications in both age groups, with a higher risk in older patients. The associations were irrespective of diabetes status but not of infarction type.

Conclusion:

It seems that admission blood glucose plays a different role as a predictor of adverse short-term outcomes in certain subgroups of older AMI patients underscoring the importance of a targeted glycemic control during hospital stay.

Keywords: myocardial infarction, admission blood glucose, mortality, elderly

Strengths and limitations

This study was observational and was limited to 65-84 years old German patients with incident AMI.

The analysis was limited to admission blood glucose values only and it cannot be ruled out that some hyperglycemic patients without a history of diabetes are true diabetes cases who have not been diagnosed before.

Multivariable analysis was adjusted for several risk factors, residual confounding cannot be entirely excluded.

Data was collected within the framework of the population-based MI registry.

Important risk factors such as comorbidities, in-hospital treatment and complications were included in the analysis.

Introduction

Elevated admission blood glucose levels are common in patients hospitalized for acute myocardial infarction (AMI); the prevalence of admission hyperglycemia in epidemiological studies for these patients ranges from 40% to > 58% (1, 2). Several studies and meta-analyses further suggested that hyperglycemia upon admission is an independent risk factor for adverse outcomes and mortality among patients hospitalized with AMI (3, 4).

Trimmer at al. (5) demonstrated that higher glucose level on admission is independently associated with increased sensitivity to ischemia-reperfusion injury such as impaired initial flow in the infarct-related artery. Blood glucose level was also described as an independent prognostic factor for impaired microvascular function, or the no-reflow phenomenon (6). In addition, some studies showed that patients with hyperglycemia have a higher Killip class and thus mortality risk (7). Moreover, a larger infarct size and worse left ventricular function were linked to a higher glucose level (8), and an addition of blood glucose levels improves the predictive ability of the Global Registry of Acute Coronary Events (GRACE) risk score (9, 10).

The majority of the existing studies were conducted in the pre-reperfusion era (3, 11-13), were focused on diabetic or non-diabetic subjects (14, 15) or included the whole spectrum of acute coronary syndromes in their analysis (16). So far, only a few studies examined the association between admission blood glucose levels and short-term outcomes (including in-hospital mortality and cardiac complications) in older people (17). Furthermore, the association between admission glucose in certain subgroups of older AMI patients are missing so far. Therefore, the aim of this study including all non-selected hospitalized cases with incident AMI was to investigate the association of admission glucose on 28-day case fatality and cardiac complications in 65 to 84 years old patients undergoing non-invasive and invasive therapy. Analyses stratified according to diabetes, age, and type of infarction were conducted to determine the importance of admission blood glucose for the short-term prognosis of certain AMI patient subgroups.

Methods

Study design and data source

Data for the present observational study came from the population-based KORA (Cooperative Health Research in the Region of Augsburg) Myocardial Infarction Registry (Bavaria, Germany), which was implemented in October 1984 as part of the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project. Since then all cases of fatal and non-fatal acute myocardial infarction (AMI) occurring among the 25 to 74 years old residents of the study area (city of Augsburg and two adjacent counties), who were admitted to one out of 8 hospitals in the study area have been continuously registered. The registry was included into the KORA framework when the MONICA project was terminated in 1995. Detailed information on methods of case identification, diagnostic classification of events, and quality control of the data have been described in previous publications (18-20). Diagnostic criteria for AMI case identification were adapted to the joint statement of the European Society of Cardiology and American College of Cardiology and applied since 2001 (21). From 2009 onwards, the registry was extended for the elderly up to 84 years.

Data collection and measurements

Patients with AMI, who have survived for at least 24 hours after hospitalization were interviewed by specially trained nurses using a standardized questionnaire. Information on sociodemographic data, acute symptoms, cardiovascular risk factors, history of several diseases, and diabetes status were collected. Data on AMI characteristics, drug treatment before and during hospital stay, medication use at discharge, in-hospital adverse events, including ventricular fibrillation, cardiogenic shock, cardiac arrest, recurrent myocardial infarction, and pulmonary edema were provided by chart review. Additionally, laboratory parameters including the first blood glucose level at admission (referred as admission glucose level), the peak glucose level during hospital stay, ECG data, and the process of care in hospital were also determined. The kind of reperfusion therapy (thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting) was documented. The study has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Study population

Between January 1, 2009 and December 31, 2016, a total of 7681 patients aged 65 to 84 years were admitted to one of the hospitals in the study region due to an AMI. Of those, 1803 patients had a re-infarction and 9 patients had missing information on infarction history and were therefore excluded. Furthermore, we excluded 255 patients without data on admission glucose level and 84 patients with missing covariates information. This resulted in a total of 5530 patients (3514 men, 2016 women) with incident AMI for analysis.

Patient and public involvement

Patients and public were not involved in the research process.

Outcomes

The primary endpoint of the study was case fatality within 28 days. A multiple logistic regression model was used to assess the association between the first admission glucose level and 28-day case fatality. The secondary endpoint was a combined endpoint of in-hospital complications including cardiac arrest, recurrent infarction, pulmonary edema, cardiogenic shock, ventricular tachycardia, ventricular bradycardia and ventricular fibrillation.

Statistical analysis

Continuous data were expressed as mean values and standard deviation (SD) as well as median and interquartile range (25th and 75th quintile) in case of non-normal distribution. Categorical data were described with absolute values and percentages. Chi-square test was used to test differences in prevalences. The two-sided Welch's t-test was used to compare means.

Multivariable analyses were performed for the whole sample and also stratified by age-groups (65-74/75-85 years), diabetes status (yes/no), type of infarction (STEMI/NSTEMI), and kidney function using forward stepwise logistic regression to identify variables independently associated with 28-day case fatality after AMI. The variables age (only in the analysis including the total sample) and sex were forced into each model during the variable selection procedure. The significance criterion for staying in the final model was chosen as $p < 0.05$. The association between admission blood glucose level and the primary endpoint was adjusted for

sex and age in the first model. The second model included previous factors and any reperfusion therapy (yes/no), treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), antiplatelets during hospital stay (yes/no), insulin (yes/no), cardiac arrest during hospitalization (yes/no), any other complication during hospital stay (recurrent infarction, ventricular fibrillation, ventricular tachycardia, bradycardia, pulmonary edema and cardiogenic shock), and diabetes (yes/no).

In logistic regression analysis investigating the association between admission blood glucose level and the secondary endpoint, the first model included admission blood glucose, age and sex. The second model was adjusted additionally for diabetes (yes/no), any reperfusion therapy (yes/no), treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), antiplatelets during hospital stay (yes/no), and insulin (yes/no). Odds ratios and 95% CI interval were computed per 1 SD increase of admission blood glucose level.

We conducted a formal test to identify an interaction with sex, age, diabetes and myocardial infarction type. The test showed significant interaction with age and diabetes. Due to a significant interaction with age, the sample was stratified into two age groups: “young old” patients (65-74 years) and “old” patients (75-85 years) (Figure 1). In addition, stratified analyses were conducted for patients with and without diabetes, and for STEMI/NSTEMI patients.

We used restricted cubic splines with different numbers of knots for testing the linearity assumption of the appropriate multivariable logistic model. For all investigations, a significance level of 5% was applied. Analyses were performed using R version 3.5.2.

Results

In total, the study sample consisted of 5530 women and men aged 65-84 years. There were 292 (7.9%) deaths within 28 days among 3709 patients aged 65-74 years and 209 (11.5%) deaths among 1821 patients aged 75-84 years. The median admission glucose level was 94.0 mg/dl (interquartile range 68.0 to 138.0 mg/dl) and 37.9% of the patients in the total sample had diabetes.

The baseline characteristics of the patients according to the age groups are shown in Table 1. The older age group was associated with a higher proportion of female patients and a higher frequency of patients with a history of hypertension. In the younger age group a higher prevalence of ST-elevation myocardial infarction type as well as non-ST-elevation myocardial infarction type than in the older age group was observed. Patients in the younger age group showed a higher prevalence of lipid disorders in comparison to the older age group.

Treatment during hospital stay according to the age groups is shown in Table 2. More young old patients less likely received ACE inhibitors, beta-blockers and nitrates. On the other hand, older patients were more often treated with calcium channel blockers and angiotensin II antagonists. There was no difference in treatment with lipid lowering drugs, anticoagulants and insulin. At least one recanalization therapy (PCI, CABG or thrombolysis) was more likely performed in the younger old compared to the older patients.

Major complications in AMI patients occurring during hospital stay are listed in Table 3. Frequency of in-hospital cardiac arrest was significantly higher in the older patients' group. Regarding other in-hospital complications including cardiogenic shock, pulmonary edema, ventricular fibrillation, tachycardia and re-infarction there was no significant difference between the two age groups.

In the whole sample, as it is presented in Table 4, admission blood glucose was significantly associated with 28-day case fatality: per 1 SD increase in admission blood glucose level the OR for 28-day mortality was 1.33 (95% CI: 1.21-1.63). In the younger old group there was also a significant relationship; per 1 SD increase of blood glucose the OR for 28-day case fatality was 1.41 (95% CI: 1.21-1.64). Among the older patients, there was no significant association in the fully adjusted model (OR 1.21; 95% CI: 1.00-1.50).

In addition, blood glucose levels at admission were independently associated with major in-hospital complications in the total sample and in both age groups (Table 4). Among all patients the OR for any major complication was 1.26 (95% CI: 1.17-1.35) per 1 SD increase of blood glucose level; among the patients aged 65-74 years and 75-84 years the OR was 1.23 (95% CI: 1.13-1.34) and 1.31 (95% CI: 1.16-1.48) per 1 SD increase of blood glucose level, respectively.

The increased admission glucose level was significantly associated with higher 28-day mortality and hospital complications, irrespective of diabetes status in both the younger old and old group. However, the observed associations were stronger in AMI patients without diabetes (Table 4). In patients with STEMI but not with NSTEMI a significant association with 28-day case-fatality could be observed for both, young old and old patients. Regarding in-hospital complications, in STEMI patients a significant relationship could be found for the older patients (OR 1.67; 95% CI: 1.24-2.26). In NSTEMI patients a significant association with in-hospital complications could be shown for both the younger old (OR 1.16; 95% CI 1.03-1.30) and old group (OR 1.24; 95% CI 1.04-1.47).

Discussion

In this real-world study including all consecutive hospitalized, unselected cases with incident AMI in patients 65 to 84 years of age, 28-day case fatality was associated with increasing blood glucose concentrations measured at hospital admission. The risk of death in the younger old patients (65-74 years) increased significantly with increasing blood glucose levels, but in the older patients' group (75-84 years) no independent association was found. In addition, admission glucose was significantly associated with a higher 28-day mortality in the total sample of patients with and without diabetes, and in STEMI patients. The risk of major in-hospital complications after incident AMI was also related to higher admission blood glucose levels in both age groups, in patients with and without diabetes, STEMI and NSTEMI patients.

Previous studies have demonstrated that elevated blood glucose on admission is common in patients with AMI and is independently associated with a higher risk of in-hospital mortality and in-hospital complications, such as cardiac arrest, cardiogenic shock, and pulmonary edema regardless of diabetes status (22-24). Although numerous studies have documented this association (17, 25-27), the impact of admission blood glucose on short-term mortality and in-hospital complications in older patients with AMI remains underappreciated so far.

In a large population-based study including AMI patients aged 65 years and older (17), glucose levels were associated with 30-day case fatality in patients without known diabetes (referent: glucose ≤ 110 mg/dl; range from glucose >110 to 140 mg/dl: HR 1.17; 95% CI: 1.11–1.24; to glucose >240 mg/dl: HR 1.87; 95% CI: 1.75–2.00). In a nationally representative study of patients (median age 67 years) hospitalized with AMI in China, Zhao et al. (27) reported that both moderate and severe hyperglycemia (blood glucose ≥ 11.1 mmol/L) on admission were associated with an elevated risk for in-hospital mortality among both nondiabetic and diabetic patients. Fujino et al. (26) analyzed the short-term outcome of acute hyperglycemia on admission (≥ 200 mg/dL) and chronic hyperglycemia defined by an HbA1C ≥ 6.5% in a small sample of acute AMI patients and reported that acute hyperglycemia but not chronic hyperglycemia was an independent predictor of in-hospital mortality.

Several prior studies examined the association between hyperglycemia on admission and complications of AMI. Dziewierz et al. (22) analyzed data of elderly AMI patients of the Poland's Krakow Registry and found that hyperglycemia on admission was related to an

increased risk of pulmonary edema and heart rhythm/conduction disturbances in both diabetic and nondiabetic patients. In another study Kim et al. (24) found a significant association between hyperglycemia and life-threatening complications during hospitalization such as cardiogenic shock, decreased hemoglobin level (hemoglobin ≥ 5g/dL), atrioventricular block, ventricular tachycardia, and atrial fibrillation. Besides, they observed that a higher age of patients (≥ 75 years), female sex, STEMI, low LV function, low revascularization ratio, larger infarct size and inflammation were related to hyperglycemia on admission.

The results of the present study confirm the findings regarding a strong association between admission blood glucose and short-term mortality as well as in-hospital complications in AMI patients independent of diabetes status. Contrary to our study, prior studies did not evaluate how the relationship between admission glucose and outcomes varies between different age groups or other AMI subgroups in higher aged patients. The present study therefore expands the current understanding of the relevance of admission glucose regarding adverse outcomes in subgroups of older AMI patients. Further studies on this issue are necessary to confirm or refute our findings.

The present data indicated that admission glucose had different impacts on adverse short-term outcomes in elderly STEMI versus NSTEMI patients. Prior studies investigating the relevance of admission glucose on outcomes were mostly conducted in STEMI patients (28-30) or included both STEMI and NSTEMI patients (17, 31, 32); only a few studies were conducted in NSTEMI-samples (33). In addition, studies on this issue conducted in elderly AMI patients are scarce (34). For example, a meta-analysis including six cohort studies reported that elevated admission glucose (≥6.1-11.1 mmol/L) was significantly associated with short-term mortality in STEMI patients without diabetes (RR 4.38; 95% CI 3.23-5.94) (35). In another study conducted in NSTEMI patients undergoing PCI, admission blood glucose was a predictor of 30-day major adverse cardiovascular events (MACE), irrespective of diabetes status (33). Our results suggested that admission glucose might be a predictor of short-term mortality and in-hospital complications in older STEMI patients, while in NSTEMI patients it was associated with in-hospital complications only.

The increased mortality related to high admission glucose levels in AMI patients has been linked to different pathophysiologic mechanisms. There is evidence for the toxic effects of hyperglycemia on cell function, because acute high blood glucose might induce oxidative

stress, most likely via generation of free radicals (2). Moreover, hyperglycemia inhibits metabolic processes in the myocardium and induces apoptosis in cardiomyocytes. Chang et al. (36) showed an association between high glucose level and sFas serum levels, which is a valuable biomarker of the physiological response to ischemia.

Stress hyperglycemia in myocardial infarction patients could also be associated with adverse outcomes due to its ability to increase systemic inflammation and activation of stress responsive kinases. Recently, Marfella et al. (37) demonstrated an association between inflammatory markers and functional cardiac outcome in patients with an incident myocardial infarction. In that study hyperglycemia was associated with amplified inflammatory immune reactions and worse functional cardiac outcome.

Moreover, hyperglycemia is strongly associated with impaired coronary flow before reperfusion and has been related to enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis. Hyperglycemia has been linked to increased sensitivity to ischemia-reperfusion injury (5, 38). These pathological processes may vary with age, that could explain, at least in part, our results.

Another possible explanation for the findings in our study is related to the importance of age in this context, because it as a strong risk factor for cardiovascular disease and an independent risk factor for mortality and adverse outcomes after AMI. For example, Shechter et al. (39) demonstrated that AMI patients over 80 years had more major adverse cardiac events (including re-infarction, post-infarction angina, ischemic stroke, high-degree atrioventricular block, acute renal failure, and major bleeding) in-hospital and a four- to five-fold higher mortality rate than younger patients. Furthermore, age is related to frequent complications and side effects of treatment interventions and pharmacotherapy (40). Additionally, the hemodynamic impact of a given infarct size may be more pronounced in the elderly as a result of reduced cardiac reserve (41). There is also a greater likelihood of comorbid illnesses with advancing age, which contribute to poorer outcomes (42).

Strengths and limitations

Several important limitations of the present study should be acknowledged. First, our study was observational and nonrandomized by nature. Second, the analysis was limited to admission blood glucose values. Thus, there is a lack of information on the effect of in hospital

treatment regarding hyperglycemia and hypoglycemia, and how glucose levels during hospital stay affected adverse outcomes. Third, it cannot be ruled out that some hyperglycemic patients without a history of diabetes are true diabetes cases who have not been diagnosed before. Fourth, although our multivariable analysis was adjusted for several risk factors, residual confounding cannot be entirely excluded. Finally, our study was limited to 65-84 years old German patients with incident AMI, therefore it remains uncertain if our results apply to other populations and age subgroups of patients.

The present study is characterized by several strengths. Data was collected within the framework of a population-based MI registry, and the consecutively admitted patients included from the general population presenting with first AMIs were registered according to a standardized protocol. Furthermore, important risk factors such as comorbidities, in-hospital treatment and complications were included in our analysis.

Conclusions

High admission blood glucose significantly increased the risk of short-term mortality and complications among older patients hospitalized with incident AMI independent of diabetes status. It could be shown, that admission glucose has a relatively small effect on 28-day-mortality among 75-84 years old patients compared to patients aged 65-74 years. Additionally, admission glucose seems to play a different role as predictor of 28-day mortality and in-hospital complications in older STEMI/NSTEMI patients. These findings underscore the importance of a closely glycemic control during hospital stay particularly in certain subgroups of older AMI patients. More studies based on large samples are needed to further confirm this conclusion.

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Conflicts of interest

No conflict of interest to declare.

Clinical trial name

No trial name/ URL/ registration number assigned (observational study from a population-based registry)

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Table 1. Characteristics of the AMI patients by age groups.

	Age groups		p-value	Total sample
	65-74 (n=3709)	75-84 (n=1821)		(n=5530)
Female sex	1185 (31.9%)	831 (45.6%)	<0.001	2016 (36.5%)
Hypertension	3060 (82.5%)	1602 (88.0%)	<0.001	4662 (84.3%)
Lipid disorder	2238 (60.3%)	906 (49.8%)	<0.001	3144 (56.9%)
Smoking status				
Smoker	674 (18.2%)	121 (6.6%)		795 (14.4%)
Ex-smoker	1245 (33.6%)	533 (29.3%)		1778 (32.2%)
Never-smoker	1291 (34.8%)	792 (43.5%)		2083 (37.7%)
Missing	499 (13.5%)	375 (20.6%)		874 (15.8%)

Glucose level on admission (mg/dl) [Median (IQR)]	92.0 (71.0)	97.0 (71.0)	0.52	94.0 (70.0)
Peak glucose level (mg/dl) [Median (IQR)]	98.0 (60.0)	95.0 (81)	0.01	97.0 (87.0)
Cardiac arrest before hospitalization	147 (4.0%)	41 (2.3%)		188 (3.4%)
Missing	220 (5.9%)	159 (8.7%)		379 (6.9%)
LVEF < 30%	197 (5.3%)	169 (9.3%)		366 (6.6%)
Missing	987 (26.6%)	288 (15.8%)		1275 (23.1%)
Diabetes	1376 (37.1%)	721 (39.6%)	0.07	2097 (37.9%)
STEMI				
STEMI	1189 (32.1%)	440 (24.2%)	0.01	1629 (29.5%)
NSTEMI	1967 (53.0%)	898 (49.3%)		2865 (51.8%)

Bundle branch block	316 (8.5%)	220 (12.1%)	536 (9.7%)
Not defined	237 (6.4%)	263 (14.4%)	500 (9.0%)
Typical symptoms	2896 (78.1%)	1218 (66.9%)	4114 (74.4%)
Missing	54 (1.5%)	29 (1.6%)	83 (1.5%)

AMI – acute myocardial infarction, IQR – interquartile range, STEMI – ST-segment elevation myocardial infarction, NSTEMI – Non-ST-segment elevation myocardial infarction

Table 2. Treatment of AMI patients during hospital stay by age groups

	Age groups			Total sample
	65-74 (n=3709)	75-84 (n=1821)	p-value	(n=5530)
Drug treatment of AMI patients				
Anticoagulants	3661 (98.7%)	1806 (99.1%)	0.1	5467 (98.8%)
Ca-antagonists	1343 (36.2%)	748 (41.1%)	<0.001	2091 (37.8%)
ACE inhibitors	3007 (81.1%)	1337 (73.4%)	<0.001	4344 (78.5%)
Beta-blockers	3492 (94.1%)	1683 (92.4%)	0.016	5175 (93.6%)
Nitrates	2948 (79.5%)	1237 (67.9%)	<0.001	4185 (75.7%)
Angiotensin II antagonists	404 (10.9%)	327 (17.9%)	<0.001	731 (13.2%)
Other antihypertensives	635 (17.1%)	395 (21.7%)	<0.001	1030 (18.6%)
Statins	3284 (88.5%)	1614 (88.6%)	0.966	4898 (88.6%)
Insulin	1250 (33.7%)	610 (33.5%)	0.904	1860 (33.6%)
Recanalization therapy of AMI-patients				
At least one recanalization therapy	2941 (79.3%)	1271 (69.8%)	<0.001	4212 (76.2%)
PCI	2294 (61.8%)	1064 (58.4%)	0.015	3358 (60.7%)

Bypass	672 (18.1%)	236 (13.0%)	<0.001	908 (16.4%)
Thrombolytic therapy	160 (4.3%)	8 (0.4%)	<0.001	168 (3.0%)

AMI – acute myocardial infarction, ACE – Angiotensin-converting enzyme, ASS - PTCA – Percutaneous transluminal coronary angioplasty

Table 3. Complications in AMI patients by age groups.

Major complications	Age groups		p-value	Total sample
	65-74 (n=3709)	75-84 (n=1821)		(n=5530)
Cardiac arrest in hospital	403 (10.9%)	256 (14.1%)	<0.001	659 (11.9%)
Cardiogenic shock	253 (6.8%)	149 (8.2%)	0.01	402 (7.3%)
Pulmonary edema	172 (4.6%)	85 (4.7%)	1	257 (4.6%)
Bradycardia	225 (6.1%)	99 (5.4%)	0.330	324 (5.9%)
Ventricular fibrillation	121 (3.3%)	50 (2.7%)	0.336	171 (3.1%)
Ventricular tachycardia	149 (4.0%)	82 (4.5%)	0.477	231 (4.2%)
Re-infarction	92 (2.5%)	33 (1.8%)	0.130	125 (2.3%)
28-day case fatality	292 (7.9%)	209 (11.5%)	<0.001	501(9.1%)

AMI – acute myocardial infarction

Table 4. Association of admission blood glucose levels (per 1 SD increase) with 28-day case fatality and major complications.

	28-day case fatality				In-hospital complications			
	OR* (95% CI)	p-value	OR** (95% CI)	p-value	OR* (95% CI)	p-value	OR*** (95%CI)	p-value
Total sample	1.59 (1.48-1.70)	<0.0001	1.33 (1.21-1.63)	<0.0001	1.39 (1.31-1.47)	<0.0001	1.26 (1.17-1.35)	<0.0001
65-74 years	1.66 (1.51-1.82)	<0.0001	1.41 (1.21-1.64)	<0.0001	1.35 (1.26-1.45)	<0.0001	1.23 (1.13-1.34)	<0.0001
75-84 years	1.47 (1.29-1.66)	<0.0001	1.21 (1.00-1.50)	0.1	1.45 (1.31-1.61)	<0.0001	1.31 (1.16-1.48)	<0.0001
Diabetes								
Total sample	1.42 (1.23-1.57)	<0.0001	1.33 (1.18-1.50)	<0.0001	1.45 (1.30-1.63)	<0.0001	1.26 (1.11-1.43)	0.0003
65-74 years	1.44 (1.26-1.63)	<0.0001	1.28 (1.06-1.55)	<0.001	1.36 (1.18-1.57)	<0.0001	1.18 (1.01-1.37)	0.0310
75-84 years	1.37 (1.14-1.63)	<0.001	1.09 (0.83-1.45)	0.1	1.64 (1.36-1.99)	<0.0001	1.43 (1.15-1.79)	0.0014
No diabetes								
Total sample	2.68 (2.31-3.13)	<0.0001	1.75 (1.41-2.17)	<0.0001	1.49 (1.38-1.60)	<0.0001	1.34(1.24-1.45)	<0.0001
65-74 years	2.83 (2.34-3.44)	<0.0001	1.88 (1.45-2.46)	<0.0001	1.47 (1.35-1.61)	<0.0001	1.36 (1.24-1.49)	<0.0001
75-84 years	2.45 (1.91-3.15)	<0.0001	1.50 (1.03-2.19)	<0.01	1.50 (1.31-1.73)	<0.0001	1.49(1.18-1.88)	<0.0001
STEMI								

Total sample	1.87 (1.62-2.16)	<0.0001	1.83(1.43-2.36)	<0.0001	1.35 (1.22-1.50)	<0.0001	1.24 (1.09-1.41)	0.0010
65-74 years	1.91 (1.61-2.27)	<0.0001	1.96 (1.46-2.66)	<0.0001	1.25 (1.11-1.41)	<0.0001	1.13 (0.98-1.31)	0.0828
75-84 years	1.79 (1.38-2.34)	<0.0001	1.73 (1.06-2.88)	<0.01	1.75 (1.39-2.20)	<0.0001	1.67 (1.24-2.26)	0.0007
NSTEMI								
Total sample	1.54 (1.39-1.71)	<0.0001	1.16 (0.98-1.37)	0.05	1.37 (1.26-1.48)	<0.0001	1.19 (1.08-1.31)	0.0004
65-74 years	1.60 (1.40-1.82)	<0.0001	1.22 (0.99-1.51)	0.05	1.32 (1.20-1.46)	<0.0001	1.16 (1.03-1.30)	0.0136
75-84 years	1.45 (1.22-1.72)	<0.0001	1.04 (0.77-1.42)	0.1	1.46 (1.26-1.68)	<0.0001	1.24 (1.04-1.47)	0.0129

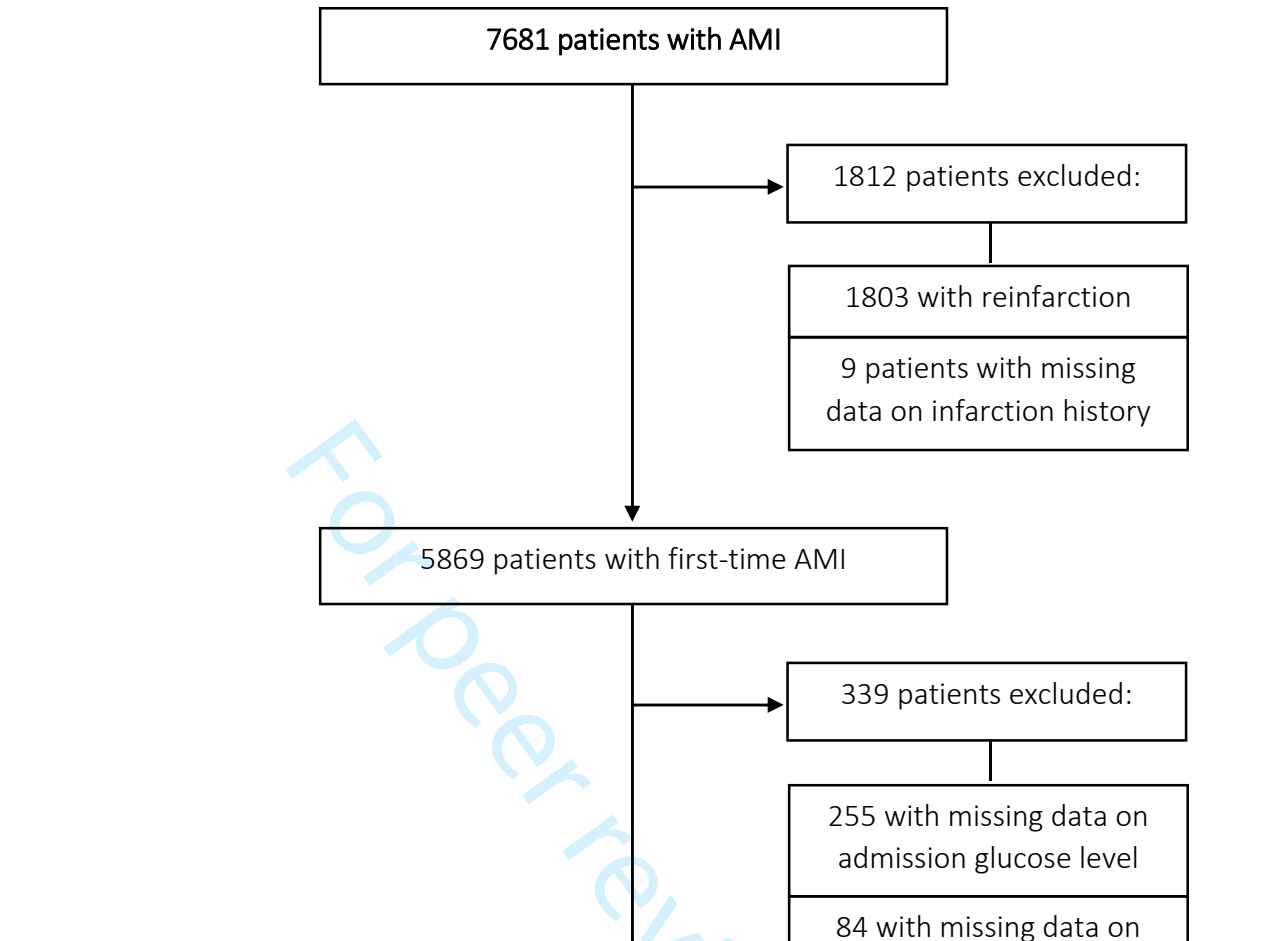
OR* - adjusted for sex, age

OR** - adjusted for sex, age, diabetes, reperfusion therapy, drug treatment (treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), and antiplatelets during hospital stay (yes/no), insulin (yes/no), complications (recurrent infarction, ventricular fibrillation, ventricular tachycardia, bradycardia, pulmonary edema and cardiogenic shock, cardiac arrest during hospital stay).

OR*** - adjusted for sex, age, diabetes, reperfusion therapy, drug treatment (treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), and antiplatelets during hospital stay (yes/no), insulin (yes/no).

Figure 1. Flow chart diagram of study sample selection

Inclusion process for study sample with numbers and reasons for excluding patients from the original data set.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	25
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Admission glucose level and short-term mortality in older patients with acute myocardial infarction: results from the KORA myocardial infarction registry

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Keywords:	Cardiac Epidemiology < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, EPIDEMIOLOGY

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Admission glucose level and short-term mortality in older patients with acute myocardial infarction: results from the KORA myocardial infarction registry

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Abstract

Study objectives:

To investigate the association between admission blood glucose levels and 28-day mortality as well as in-hospital complications in older patients with incident acute myocardial infarction (AMI) undergoing modern treatment.

Methods:

From a German population-based regional myocardial infarction registry, 5530 patients (2016 females), aged 65-84 years, hospitalized with an incident AMI between January 1, 2009 and December 31, 2016 were included in the study. Multivariable logistic regression models were used to assess the associations between admission blood glucose and 28-day-mortality as well as in-hospital complications after AMI. Analyses stratified according to age, diabetes, and type of infarction (ST-elevation MI/non-ST-elevation MI) were conducted.

Results:

The adjusted odds ratios (OR) for the association between admission blood glucose and 28-day-mortality in young-old (65-74) and old (75-85) AMI patients were 1.40 (95% CI: 1.21-1.62) and OR 1.21 (95% CI: 0.98-1.50) per 1 SD increase in admission blood glucose, respectively. Furthermore, higher admission blood glucose was related to case-fatality irrespective of the diabetes status and type of infarction only in the under-75 group. For the patients aged 75-84 years it was only true for those without diabetes and STEMI infarctions. Admission blood glucose was also associated with major cardiac complications in both age-groups.

Conclusion:

Admission blood glucose was significantly associated with 28-day case fatality in AMI patients aged 65-74 years but not 75-84 years; furthermore, in both age-groups there was an increased risk of major complications. It seems that admission glucose may play a rather minor role in terms of case-fatality in higher-aged AMI patients.

Keywords: myocardial infarction, admission blood glucose, mortality, elderly

Strengths and limitations

This study was observational and was limited to 65-84 years old German patients with incident AMI.

The analysis was limited to admission blood glucose values only and it cannot be ruled out that some hyperglycemic patients without a history of diabetes are true diabetes cases who have not been diagnosed before.

Multivariable analysis was adjusted for several risk factors, residual confounding cannot be entirely excluded.

Data was collected within the framework of the population-based MI registry.

Important risk factors such as comorbidities, in-hospital treatment and complications were included in the analysis.

Introduction

Elevated admission blood glucose levels are common in patients hospitalized for acute myocardial infarction (AMI); the prevalence of admission hyperglycemia in epidemiological studies for these patients ranges from 40% to > 58% (1, 2). Several studies and meta-analyses further suggested that hyperglycemia upon admission is an independent risk factor for adverse outcomes and mortality among patients hospitalized with AMI (3, 4).

Timmer at al. (5-9) demonstrated that higher glucose level on admission is independently associated with increased sensitivity to ischemia-reperfusion injury such as impaired initial flow in the infarct-related artery. Blood glucose level was also described as an independent prognostic factor for impaired microvascular function, or the no-reflow phenomenon (10). In addition, some studies showed that patients with hyperglycemia have a higher Killip class and thus mortality risk (11). Moreover, a larger infarct size and worse left ventricular function were linked to a higher glucose level (12), and an addition of blood glucose levels improves the predictive ability of the Global Registry of Acute Coronary Events (GRACE) risk score (13, 14).

The majority of the existing studies were conducted in the pre-reperfusion era (3, 15-17), were focused on patients with or without diabetes (18, 19) or included the whole spectrum of acute coronary syndromes in their analysis (20). So far, only a few studies examined the association between admission blood glucose levels and short-term outcomes (including in-hospital mortality and cardiac complications) in older people (21). Furthermore, the association between admission glucose in certain subgroups of older AMI patients are missing so far. Therefore, the aim of this study including all non-selected hospitalized cases with incident AMI was to investigate the association of admission glucose on 28-day case fatality and cardiac complications in 65 to 84 years old patients undergoing non-invasive and invasive therapy. Analyses stratified according to diabetes, age, and type of infarction were conducted to determine the importance of admission blood glucose for the short-term prognosis of certain AMI patient subgroups.

Methods

Study design and data source

Data for the present observational study came from the population-based KORA (Cooperative Health Research in the Region of Augsburg) Myocardial Infarction Registry (Bavaria, Germany), which was implemented in October 1984 as part of the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project. Since then all cases of fatal and non-fatal acute myocardial infarction (AMI) occurring among the 25 to 74 years old residents of the study area (city of Augsburg and two adjacent counties), who were admitted to one out of 8 hospitals in the study area have been continuously registered. The registry was included into the KORA framework when the MONICA project was terminated in 1995. Detailed information on methods of case identification, diagnostic classification of events, and quality control of the data have been described in previous publications (22-24). Diagnostic criteria for AMI case identification were adapted to the joint statement of the European Society of Cardiology and American College of Cardiology and applied since 2001 (25). From 2009 onwards, the registry was extended for the elderly up to 84 years.

Data collection and measurements

Patients with AMI, who have survived for at least 24 hours after hospitalization were interviewed by specially trained nurses using a standardized questionnaire. Information on sociodemographic data, acute symptoms, cardiovascular risk factors, and history of several diseases was collected. Diabetes status (yes/no) was based on what was known on admission only. Data on AMI characteristics, drug treatment before and during hospital stay, medication use at discharge, in-hospital adverse events, including ventricular fibrillation, cardiogenic shock, cardiac arrest, recurrent myocardial infarction, and pulmonary edema were provided by chart review. Additionally, laboratory parameters including the first blood glucose level at admission (referred as admission glucose level), ECG data, and the process of care in hospital were also determined. The kind of reperfusion therapy (thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting) was documented. The study has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Study population

Between January 1, 2009 and December 31, 2016, a total of 7681 patients aged 65 to 84 years were admitted to one of the hospitals in the study region due to an AMI. Of those, 1803 patients had a re-infarction and 9 patients had missing information on infarction history and were therefore excluded. Furthermore, we excluded 255 patients without data on admission glucose level and 84 patients with missing covariates information. This resulted in a total of 5530 patients (3514 men, 2016 women) with incident AMI for analysis.

Patient and public involvement

Patients and public were not involved in the research process.

Outcomes

The primary endpoint of the study was case fatality within 28 days. A multiple logistic regression model was used to assess the association between the first admission glucose level and 28-day case fatality (yes/no). The secondary endpoint was a combined endpoint of in-hospital complications including cardiac arrest, recurrent infarction, pulmonary edema, cardiogenic shock, ventricular tachycardia, ventricular bradycardia and ventricular fibrillation.

Statistical analysis

Continuous data were expressed as mean values and standard deviation (SD) as well as median and interquartile range (25th and 75th quintile) in case of non-normal distribution. Categorical data were described with absolute values and percentages. Chi-square test was used to test differences in prevalences. The two-sided Welch's t-test was used to compare means.

Due to the large number of missing values presented in Table 1, we used multiple imputation before regression. Since the missing mechanism was not completely at random, this approach minimized bias of the effect estimates and increased statistical power. Multivariable analyses were performed for the whole sample and also stratified by age-groups (65-74/75-85 years), diabetes status (yes/no), and type of infarction (STEMI/NSTEMI) using forward stepwise logistic regression to identify variables independently associated with 28-day case fatality (yes/no) after AMI. The variables age (only in the analysis including the total sample) and sex were forced into each model during the variable selection procedure. The significance

criterion for staying in the final model was chosen as $p < 0.05$. The association between admission blood glucose level and the primary endpoint was adjusted for sex and age in the first model. The second model included previous factors and any reperfusion therapy (yes/no), treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), antiplatelets during hospital stay (yes/no), insulin (yes/no), cardiac arrest during hospitalization (yes/no), any other complication during hospital stay (recurrent infarction, ventricular fibrillation, ventricular tachycardia, bradycardia, pulmonary edema and cardiogenic shock), and diabetes (yes/no).

In logistic regression analysis investigating the association between admission blood glucose level and the secondary endpoint, the first model included admission blood glucose, age and sex. The second model was adjusted additionally for diabetes (yes/no), any reperfusion therapy (yes/no), treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), antiplatelets during hospital stay (yes/no), and insulin (yes/no). Odds ratios and 95% CI interval were computed per 1 SD increase of admission blood glucose level.

We conducted a formal test to identify an interaction with sex, age, diabetes and myocardial infarction type. The test showed significant interaction with age and diabetes. Due to a significant interaction with age, the sample was stratified into two age groups: “young old” patients (65-74 years) and “old” patients (75-85 years) (Figure 1). In addition, stratified analyses were conducted for patients with and without diabetes, and for STEMI/NSTEMI patients.

We used restricted cubic splines with different numbers of knots for testing the linearity assumption of the appropriate multivariable logistic model. For all investigations, a significance level of 5% was applied. Analyses were performed using R version 3.5.2.

Results

In total, the study sample consisted of 5530 women and men aged 65-84 years. There were 292 (7.9%) deaths within 28 days among 3709 patients aged 65-74 years and 209 (11.5%) deaths among 1821 patients aged 75-84 years. The median admission glucose level was 94.0 mg/dl (interquartile range 68.0 to 138.0 mg/dl) and 37.9% of the patients in the total sample had known diabetes.

The baseline characteristics of the patients according to the age groups are shown in Table 1. The older age group was associated with a higher proportion of female patients and a higher frequency of patients with a history of hypertension. In the younger age group a higher prevalence of ST-elevation myocardial infarction type as well as non-ST-elevation myocardial infarction type than in the older age group was observed. Patients in the younger age group showed a higher prevalence of lipid disorders in comparison to the older age group.

Treatment during hospital stay according to the age groups is shown in Table 2. More young old patients less likely received ACE inhibitors, beta-blockers and nitrates. On the other hand, older patients were more often treated with calcium channel blockers and angiotensin II antagonists. There was no difference in treatment with lipid lowering drugs, antiplatelets and insulin. At least one recanalization therapy (PCI, CABG or thrombolysis) was more likely performed in the younger old compared to the older patients.

Major complications in AMI patients occurring during hospital stay are listed in Table 3. Frequency of in-hospital cardiac arrest was significantly higher in the older patients' group. Regarding other in-hospital complications including cardiogenic shock, pulmonary edema, ventricular fibrillation, tachycardia and re-infarction there was no significant difference between the two age groups.

In the whole sample, as it is presented in Table 4, admission blood glucose was significantly associated with 28-day case fatality: per 1 SD increase in admission blood glucose level the OR for 28-day mortality was 1.33 (95% CI: 1.19-1.50). In the younger old group there was also a significant relationship; per 1 SD increase of blood glucose the OR for 28-day case fatality was 1.40 (95% CI: 1.21-1.62). Among the older patients, there was no significant association in the fully adjusted model (OR 1.21; 95% CI: 0.98-1.50).

In addition, blood glucose levels at admission were independently associated with major in-hospital complications in the total sample and in both age groups (Table 4). Among all patients the OR for any major complication was 1.25 (95% CI: 1.17-1.35) per 1 SD increase of blood glucose level; among the patients aged 65-74 years and 75-84 years the OR was 1.24 (95% CI: 1.13-1.35) and 1.29 (95% CI: 1.14-1.47) per 1 SD increase of blood glucose level, respectively.

Admission glucose level was significantly associated with higher 28-day mortality and hospital complications, irrespective of diabetes status in both the younger old and old group (except the association with the 28-day mortality in the older group) (Table 4). In patients with STEMI but not with NSTEMI a significant association with 28-day case-fatality could be observed for both, young old and old patients. Regarding in-hospital complications, in STEMI patients a significant relationship could be found for the older patients (OR 1.68; 95% CI: 1.24-2.27). In NSTEMI patients a significant association with in-hospital complications could be shown for both the younger old (OR 1.17; 95% CI 1.04-1.33) and old group (OR 1.20; 95% CI 1.01-1.43).

Discussion

In this real-world study including all consecutive hospitalized, unselected cases with incident AMI in patients 65 to 84 years of age, 28-day case fatality was associated with increasing blood glucose concentrations measured at hospital admission. The risk of death in the younger old patients (65-74 years) increased significantly with increasing blood glucose levels, but in the older patients' group (75-84 years) no independent association was found. In addition, admission glucose was significantly associated with a higher 28-day mortality in the total sample of patients with and without diabetes, and in STEMI patients. The risk of major in-hospital complications after incident AMI was also related to higher admission blood glucose levels in both age groups, in the total sample of patients with and without diabetes, STEMI and NSTEMI patients.

Previous studies have demonstrated that elevated blood glucose on admission is common in patients with AMI and is independently associated with a higher risk of in-hospital mortality and in-hospital complications, such as cardiac arrest, cardiogenic shock, and pulmonary edema regardless of diabetes status (26-28). Although numerous studies have documented this association (21, 29-31), the impact of admission blood glucose on short-term mortality and in-hospital complications in older patients with AMI remains underappreciated so far.

In a large population-based study including AMI patients aged 65 years and older (21), glucose levels were associated with 30-day case fatality in patients without known diabetes (referent: glucose ≤ 110 mg/dl; range from glucose >110 to 140 mg/dl: HR 1.17; 95% CI: 1.11–1.24; to glucose >240 mg/dl: HR 1.87; 95% CI: 1.75–2.00). In a nationally representative study of patients (median age 67 years) hospitalized with AMI in China, Zhao et al. (31) reported that both moderate and severe hyperglycemia (blood glucose ≥ 11.1 mmol/L) on admission were associated with an elevated risk for in-hospital mortality among both patients without and with diabetes. Fujino et al. (30) analyzed the short-term outcome of acute hyperglycemia on admission (≥ 200 mg/dL) and chronic hyperglycemia defined by an HbA1C ≥ 6.5% in a small sample of acute AMI patients and reported that acute hyperglycemia but not chronic hyperglycemia was an independent predictor of in-hospital mortality.

Several prior studies examined the association between hyperglycemia on admission and complications of AMI. Dziewierz et al. (26) analyzed data of elderly AMI patients of the

Poland's Krakow Registry and found that hyperglycemia on admission was related to an increased risk of pulmonary edema and heart rhythm/conduction disturbances in both patients with and without diabetes. In another study Kim et al. (28) found a significant association between hyperglycemia and life-threatening complications during hospitalization such as cardiogenic shock, decreased hemoglobin level (hemoglobin ≥ 5g/dL), atrioventricular block, ventricular tachycardia, and atrial fibrillation. Besides, they observed that a higher age of patients (≥ 75 years), female sex, STEMI, low LV function, low revascularization ratio, larger infarct size and inflammation were related to hyperglycemia on admission.

The results of the present study confirm the findings regarding a strong association between admission blood glucose and short-term mortality as well as in-hospital complications in AMI patients independent of diabetes status. Contrary to our study, prior studies did not evaluate how the relationship between admission glucose and outcomes varies between different age groups or other AMI subgroups in higher aged patients. The present study therefore expands the current understanding of the relevance of admission glucose regarding adverse outcomes in subgroups of older AMI patients. Further studies on this issue are necessary to confirm or refute our findings.

The present data indicated that admission glucose had different impacts on adverse short-term outcomes in elderly STEMI versus NSTEMI patients. Prior studies investigating the relevance of admission glucose on outcomes were mostly conducted in STEMI patients (32-34) or included both STEMI and NSTEMI patients (21, 35, 36); only a few studies were conducted in NSTEMI-samples (37). In addition, studies on this issue conducted in elderly AMI patients are scarce (38). For example, a meta-analysis including six cohort studies reported that elevated admission glucose (≥6.1-11.1 mmol/L) was significantly associated with short-term mortality in STEMI patients without diabetes (RR 4.38; 95% CI 3.23-5.94) (39). In another study conducted in NSTEMI patients undergoing PCI, admission blood glucose was a predictor of 30-day major adverse cardiovascular events (MACE), irrespective of diabetes status (37). Our results suggested that admission glucose might be a predictor of short-term mortality and in-hospital complications in 65-84 year old STEMI patients, while in NSTEMI patients it was associated with in-hospital complications only.

The increased mortality related to high admission glucose levels in AMI patients has been linked to different pathophysiologic mechanisms. There is evidence for the toxic effects of

hyperglycemia on cell function, because acute high blood glucose might induce oxidative stress, most likely via generation of free radicals (2). Moreover, hyperglycemia inhibits metabolic processes in the myocardium and induces apoptosis in cardiomyocytes. Chang et al. (40) showed an association between high glucose level and sFas serum levels, which is a valuable biomarker of the physiological response to ischemia.

Stress hyperglycemia in myocardial infarction patients could also be associated with adverse outcomes due to its ability to increase systemic inflammation and activation of stress responsive kinases. Recently, Marfella et al. (41) demonstrated an association between inflammatory markers and functional cardiac outcome in patients with an incident myocardial infarction. In that study hyperglycemia was associated with amplified inflammatory immune reactions and worse functional cardiac outcome.

Moreover, hyperglycemia is strongly associated with impaired coronary flow before reperfusion and has been related to enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis. Hyperglycemia has been linked to increased sensitivity to ischemia-reperfusion injury (9, 42). These pathological processes may vary with age, that could explain, at least in part, our results.

It is well known that age is a risk factor for cardiovascular disease and an independent risk factor for mortality and adverse outcomes after AMI. For example, Shechter et al. (43) demonstrated that AMI patients over 80 years had more major adverse cardiac events (including re-infarction, post-infarction angina, ischemic stroke, high-degree atrioventricular block, acute renal failure, and major bleeding) in-hospital and a four- to five-fold higher mortality rate than younger patients. Furthermore, age is related to frequent complications and side effects of treatment interventions and pharmacotherapy (44). Additionally, the hemodynamic impact of a given infarct size may be more pronounced in the elderly as a result of reduced cardiac reserve (45). There is also a greater likelihood of comorbid illnesses with advancing age, which contribute to poorer outcomes (46). The non-significant association between admission glucose levels and 28-day mortality in the age group 75-84 years in our study may be attributed to the fact, that these patients suffered more often from comorbidities and were more severely ill (e.g. higher complication rate, a higher proportion of patients with an LVEF <30%) compared to the younger age-group; it might be thinkable that admission glucose values might not have a major influence on the case-fatality in this group.

Strengths and limitations

Several important limitations of the present study should be acknowledged. First, our study was observational and non-randomized by nature and therefore, causality could not be evaluated. Second, the analysis was limited to admission blood glucose values. In patients without diabetes, admission blood glucose alone without HbA1c values to test for undiagnosed diabetes or prediabetes and without post-discharge tests to assess the glycaemic state after the drop of stress during hospital admission, the meaning and interpretation of admission hyperglycaemia in clinical practice is difficult (47-50). We cannot exclude the possibility that the outcome in the group without diabetes was driven by prediabetes or undiagnosed diabetes. Furthermore, there is a lack of information on the effect of in hospital treatment regarding hyperglycemia and hypoglycemia, and how glucose levels during hospital stay affected adverse outcomes. Additionally, in our study, we did not assess major comorbidities, which can increase the risk of death (e.g. lung disease, chronic renal failure or peripheral vascular disease) and for this reason our results should be interpreted with caution. Although our multivariable analysis was adjusted for several risk factors, residual confounding cannot be entirely excluded. Finally, our study was limited to 65-84 years old German patients with incident AMI, therefore it remains uncertain if our results apply to other populations and age subgroups of patients.

The present study is characterized by several strengths. Data was collected within the framework of a population-based MI registry, and the consecutively admitted patients included from the general population presenting with first AMIs were registered according to a standardized protocol. Furthermore, important risk factors such as in-hospital treatment, complications and types of infarction were included in our analysis.

Conclusions

Admission blood glucose was significantly associated with 28-day case fatality in AMI patients aged 65-74 years but not 75-84 years; furthermore, in both age-groups there was an increased risk of major complications. After stratification for diabetes and type of infarction admission blood glucose was significantly related to case-fatality irrespective of the diabetes status and type of infarction only in the patients aged 65-74 years. Thus, it is likely that admission glucose

plays only a minor role in terms of case-fatality in higher-aged AMI patients. The older the patients are the more comorbidities they may have and the sicker these patients may be when admitted to hospital. The probability that these patients die from these conditions seems to be higher than that they die as a result of increased admission glucose.

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Contributors: MT, VK, MC conceived the study. DF, MT, VK performed the statistical analysis and interpreted the results with feedback from MC, LJ, UA, KB, HM, PA, CT. MT, VK drafted and revised the manuscript based on comments, which were provided by all authors. MC, HM, KB, PA and CT contributed to data acquisition. All authors revised the manuscript critically for important intellectual content and approved the final version.

Data availability statement: Project agreements to use and access KORA data can be requested from national and international researchers via the KORA-PASST tool under https://epi.helmholtz-muenchen.de/

Ethic statement

Ethics approval: The study has been approved by the ethics committee of the Bavarian Medical Association (Ethik-Kommission Nr. 08064) and the study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Patients consent for publication: Not required

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Table 1. Characteristics of the AMI patients by age groups.

	Age groups		p-value	Total sample
	65-74 (n=3709)	75-84 (n=1821)		(n=5530)
Female sex	1185 (31.9%)	831 (45.6%)	<0.001	2016 (36.5%)
Hypertension	3060 (82.5%)	1602 (88.0%)	<0.001	4662 (84.3%)
Lipid disorder	2238 (60.3%)	906 (49.8%)	<0.001	3144 (56.9%)
Smoking status				
Smoker	674 (18.2%)	121 (6.6%)		795 (14.4%)
Ex-smoker	1245 (33.6%)	533 (29.3%)		1778 (32.2%)
Never-smoker	1291 (34.8%)	792 (43.5%)		2083 (37.7%)
Missing	499 (13.5%)	375 (20.6%)		874 (15.8%)

Glucose level on admission (mg/dl) [Median (IQR)]	92.0 (71.0)	97.0 (71.0)	0.52	94.0 (70.0)
Peak glucose level (mg/dl) [Median (IQR)]	98.0 (60.0)	95.0 (81)	0.01	97.0 (87.0)
Cardiac arrest before hospitalization	147 (4.0%)	41 (2.3%)		188 (3.4%)
Missing	220 (5.9%)	159 (8.7%)		379 (6.9%)
LVEF < 30%	197 (5.3%)	169 (9.3%)		366 (6.6%)
Missing	987 (26.6%)	288 (15.8%)		1275 (23.1%)
Diabetes	1376 (37.1%)	721 (39.6%)	0.07	2097 (37.9%)
STEMI				
STEMI	1189 (32.1%)	440 (24.2%)	0.01	1629 (29.5%)
NSTEMI	1967 (53.0%)	898 (49.3%)		2865 (51.8%)

Bundle branch block	316 (8.5%)	220 (12.1%)	536 (9.7%)
Not defined	237 (6.4%)	263 (14.4%)	500 (9.0%)
Typical symptoms	2896 (78.1%)	1218 (66.9%)	4114 (74.4%)
Missing	54 (1.5%)	29 (1.6%)	83 (1.5%)

AMI – acute myocardial infarction, IQR – interquartile range, STEMI – ST-segment elevation myocardial infarction, NSTEMI – Non-ST-segment elevation myocardial infarction

Table 2. Treatment of AMI patients during hospital stay by age groups

	Age groups			Total sample
	65-74 (n=3709)	75-84 (n=1821)	p-value	(n=5530)
Drug treatment of AMI patients				
Antiplatelets	3661 (98.7%)	1806 (99.1%)	0.1	5467 (98.8%)
Ca-antagonists	1343 (36.2%)	748 (41.1%)	<0.001	2091 (37.8%)
ACE inhibitors	3007 (81.1%)	1337 (73.4%)	<0.001	4344 (78.5%)
Beta-blockers	3492 (94.1%)	1683 (92.4%)	0.016	5175 (93.6%)
Nitrates	2948 (79.5%)	1237 (67.9%)	<0.001	4185 (75.7%)
Angiotensin II antagonists	404 (10.9%)	327 (17.9%)	<0.001	731 (13.2%)
Other antihypertensives	635 (17.1%)	395 (21.7%)	<0.001	1030 (18.6%)
Statins	3284 (88.5%)	1614 (88.6%)	0.966	4898 (88.6%)
Insulin	1250 (33.7%)	610 (33.5%)	0.904	1860 (33.6%)
Recanalization therapy of AMI-patients				
At least one recanalization therapy	2941 (79.3%)	1271 (69.8%)	<0.001	4212 (76.2%)
PCI	2294 (61.8%)	1064 (58.4%)	0.015	3358 (60.7%)

Bypass	672 (18.1%)	236 (13.0%)	<0.001	908 (16.4%)
Thrombolytic therapy	160 (4.3%)	8 (0.4%)	<0.001	168 (3.0%)

AMI – acute myocardial infarction, ACE – Angiotensin-converting enzyme, ASS - PTCA – Percutaneous transluminal coronary angioplasty

Table 3. Complications in AMI patients by age groups.

Major complications	Age groups		p-value	Total sample
	65-74 (n=3709)	75-84 (n=1821)		(n=5530)
Cardiac arrest in hospital	403 (10.9%)	256 (14.1%)	<0.001	659 (11.9%)
Cardiogenic shock	253 (6.8%)	149 (8.2%)	0.01	402 (7.3%)
Pulmonary edema	172 (4.6%)	85 (4.7%)	1	257 (4.6%)
Bradycardia	225 (6.1%)	99 (5.4%)	0.330	324 (5.9%)
Ventricular fibrillation	121 (3.3%)	50 (2.7%)	0.336	171 (3.1%)
Ventricular tachycardia	149 (4.0%)	82 (4.5%)	0.477	231 (4.2%)
Re-infarction	92 (2.5%)	33 (1.8%)	0.130	125 (2.3%)
28-day case fatality	292 (7.9%)	209 (11.5%)	<0.001	501(9.1%)

AMI – acute myocardial infarction

Table 4. Association of admission blood glucose levels (per 1 SD increase) with 28-day case fatality and major complications.

	28-day case fatality				In-hospital complications			
	OR* (95% CI)	p-value	OR** (95% CI)	p-value	OR* (95% CI)	p-value	OR*** (95%CI)	p-value
Total sample	1.56 (1.45-1.68)	<0.0001	1.33 (1.19-1.50)	<0.0001	1.39 (1.31-1.48)	<0.0001	1.25 (1.17-1.35)	<0.0001
65-74 years	1.63 (1.49-1.79)	<0.0001	1.40 (1.21-1.62)	<0.0001	1.36 (1.27-1.46)	<0.0001	1.24 (1.13-1.35)	<0.0001
75-84 years	1.44 (1.26-1.63)	<0.0001	1.21 (0.98-1.50)	0.0773	1.46 (1.31-1.62)	<0.0001	1.29 (1.14-1.47)	<0.0001
Diabetes								
Total sample	1.38 (1.25-1.52)	<0.0001	1.22 (1.06-1.41)	0.0067	1.28 (1.18-1.38)	<0.0001	1.16 (1.07-1.26)	0.0004
65-74 years	1.40 (1.24-1.57)	<0.0001	1.29 (1.08-1.53)	0.0045	1.22 (1.11-1.34)	<0.0001	1.12 (1.01-1.24)	0.0251
75-84 years	1.34 (1.12-1.59)	0.0011	1.10 (0.83-1.46)	0.5063	1.42 (1.23-1.63)	<0.0001	1.25 (1.07-1.45)	0.0040
No diabetes								
Total sample	2.87 (2.44-3.37)	<0.0001	1.82 (1.45-2.30)	<0.0001	2.06 (1.81-2.36)	<0.0001	1.72(1.49-1.99)	<0.0001
65-74 years	3.18 (2.58-3.91)	<0.0001	1.98 (1.49-2.63)	<0.0001	2.12 (1.80-2.49)	<0.0001	1.83 (1.53-2.18)	<0.0001
75-84 years	2.50 (1.91-3.27)	<0.0001	1.55 (1.03-2.32)	0.0359	1.97 (1.56-2.47)	<0.0001	1.52(1.18-1.95)	0.0012
STEMI								

Total sample	1.87 (1.61-2.17)	<0.0001	1.76(1.37-2.26)	<0.0001	1.39 (1.24-1.56)	<0.0001	1.26 (1.10-1.45)	0.0011
65-74 years	1.86 (1.56-2.22)	<0.0001	1.86 (1.38-2.51)	<0.0001	1.29 (1.13-1.47)	0.0001	1.16 (0.99-1.35)	0.0625
75-84 years	1.88 (1.341-2.51)	<0.0001	1.82 (1.08-3.06)	0.0250	1.75 (1.39-2.22)	<0.0001	1.68 (1.24-2.27)	0.0008
NSTEMI								
Total sample	1.51 (1.36-1.68)	<0.0001	1.17 (0.99-1.38)	0.0697	1.37 (1.26-1.50)	<0.0001	1.19 (1.07-1.31)	0.0009
65-74 years	1.58 (1.39-1.81)	<0.0001	1.24 (1.01-1.52)	0.0446	1.34 (1.21-1.49)	<0.0001	1.17 (1.04-1.33)	0.0114
75-84 years	1.40 (1.17-1.66)	<0.0001	1.06 (0.77-1.45)	0.7373	1.45 (1.24-1.69)	<0.0001	1.20 (1.01-1.43)	0.0425

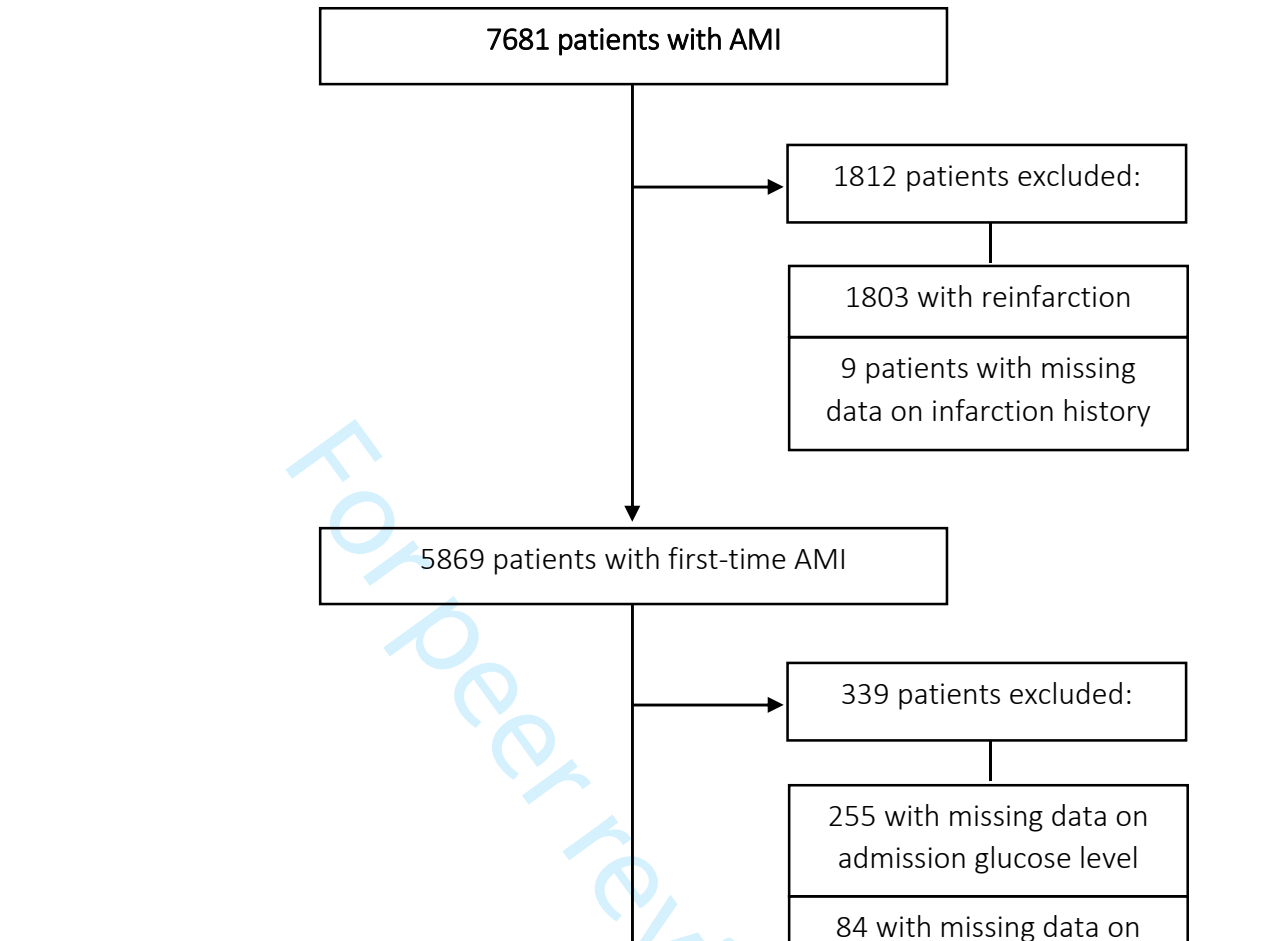
OR* - adjusted for sex, age

OR** - adjusted for sex, age, diabetes, reperfusion therapy, drug treatment (treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), and antiplatelets during hospital stay (yes/no), insulin (yes/no), complications (recurrent infarction, ventricular fibrillation, ventricular tachycardia, bradycardia, pulmonary edema and cardiogenic shock, cardiac arrest during hospital stay).

OR*** - adjusted for sex, age, diabetes, reperfusion therapy, drug treatment (treatment with angiotensin-converting enzyme (ACE) inhibitor (yes/no), beta-blocker (yes/no), lipid-lowering drug (yes/no), and antiplatelets during hospital stay (yes/no), insulin (yes/no).

Figure 1. Flow chart diagram of study sample selection

Inclusion process for study sample with numbers and reasons for excluding patients from the original data set.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	27
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.