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Risk of abnormal serum potassium levels for cardiovascular events with specific attention to drugs affecting potassium excretion

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Für meine Eltern

Niemals wird dir ein Wunsch gegeben,
ohne dass dir auch die Kraft verliehen wurde, ihn zu verwirklichen.
Es mag allerdings sein, dass du dich dafür anstrengen musst.
(Richard Bach)

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LIST OF ABBREVIATIONS

ACB	anticholinergic cognitive burden
ACE	angiotensin-converting enzyme
ADP	adenosine diphosphate
AF	atrial fibrillation
AMI	acute myocardial infarction
ARB	angiotensin II receptor blocker
ATC	anatomical therapeutic chemical
ATP	adenosine triphosphate
AV	atrioventricular
BMI	body mass index
CCI	Charlson Comorbidity Index
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CK-MB	creatinine kinase-myocardial band
CS	cross-sectional
CV	cardiovascular
CVD	cardiovascular disease
CVM	cardiovascular mortality
DBP	diastolic blood pressure
ECG	electrocardiography
eGFR	estimated glomerular filtration rate
ESTHER	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
FUP	follow-up
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HR	hazard ratio
ICD	international classification of diseases
K^+	potassium cation
LDL	low-density lipoprotein
MEANS	Modular Electrocardiography Analysis System
MESA	Multi-Ethnic Study of Atherosclerosis
Mesh	medical subject heading
MI	myocardial infarction
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
N.A.	not applicable
N.R.	not reported
Na^+	sodium cation
Na^+/ K^+-ATPase	sodium–potassium adenosine triphosphate synthase
nPNA	normalized protein nitrogen appearance

NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OTC	over-the-counter
P	phosphate
PDV/BSA	peritoneal dialysis volume per unit of body surface area
PS	propensity score
PVC	premature ventricular contraction
RAAS	Renin-Angiotensin-Aldosterone System
RR	risk ratio
SBP	systolic blood pressure
SCD	sudden cardiac death
SD	standard deviation
SVA	supraventricular arrhythmias
Tiab	title and abstract
TIBC	total iron-binding capacity
UK	United Kingdom
USA	United States of America
VA	ventricular arrhythmias
VF	ventricular fibrillation
VPC	ventricular premature complex
VT	ventricular tachycardia
WHO	World Health Organization

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1 INTRODUCTION

1.1 Cardiovascular disease: definition and prevalence

"Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, and includes coronary heart disease (CHD, disease of the blood vessels supplying the heart muscle), cerebrovascular disease (disease of the blood vessels supplying the brain), peripheral arterial disease (disease of blood vessels supplying the arms and legs), rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria), congenital heart disease (malformations of heart structure existing at birth), deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs)" (World Health Organization, 2017, http://www.who.int/mediacentre/factsheets/fs317/en/). According to the World Health Organization (WHO), CVD is the most common cause of death worldwide. An estimated 17.9 million people died from CVD in 2016, representing 31 % of all global deaths (World Health Organization, 2017). Of these deaths, 85 % were due to acute CVD events, namely myocardial infarction and stroke (World Health Organization, 2017). In Europe, CVD accounts for 45 % of all deaths whereof 70 % were attributed to CHD and cerebrovascular disease (Townsend *et al.*, 2016). Similarly, the vast majority of deaths in Germany in 2013 was caused by CVD (39.7 %) (Robert-Koch-Institut, 2015). Results of the German Health Update from 2009 to 2012 showed that the overall prevalence of major CVD events (namely myocardial infarction, angina pectoris, heart failure, and stroke) was 12.0 % in the German population (Dornquast *et al.*, 2016).

1.2 Cardiovascular disease: risk factors and prevention

There are numerous risk factors of CVD, which, according to the World Heart Federation, can be categorized into non-modifiable and modifiable risk factors (World Health Federation, 2017).

The non-modifiable risk factors of CVD include age, male sex (with gender advantage disappearing after menopause), positive CVD history of a first-degree relative, and African or Asian origin. Socioeconomic factors, such as education level, income, and poverty status, are increasingly considered "maybe modifiable risk factors" of CVD and thus strongly targeted by health politics and public health initiatives (Lennon *et al.*, 2018, p. 2).

Modifiable risk factors comprise lifestyle factors such as tobacco use, physical inactivity, obesity, unhealthy diet, stress, and excessive alcohol use, as well as diseases of the metabolic syndrome, such as hypertension, diabetes or pre-diabetes, and hyperlipidaemia (Lennon *et al.*, 2018).

Primary prevention activities focus on these modifiable risk factors by targeting early detection of people at risk, as well as education and promotion of a healthier lifestyle. For example, the Global Action Plan, which was agreed by the World Health Assembly in May 2012, launched the fight against the major risk factors of non-communicable diseases (CVD, chronic respiratory diseases, cancers, and diabetes), namely tobacco use, hypertension, unhealthy diet, physical inactivity, and harmful use of alcohol (World Health Organization, 2013). Amongst prevalence reduction of these risk factors, the global action plan aims to reduce premature mortality due to non-communicable diseases by 25 % by the year 2025. If the risk factor targets are met, a reduction of 34 % of deaths from CVD is predicted by then. This would result in 11.4 million delayed deaths in those aged 30 to 69 years and even 15.9 million prevented deaths in those aged 70 years and older (Kontis *et al.*, 2014).

The reduction of CVD deaths requires not only the modification of risk factors in order to prevent primary events, but also the use of therapeutic approaches to prevent recurrent events within the framework of secondary prevention. The latter is particularly important for managing acute CVD events such as myocardial infarction or stroke, but also in addition to prevention of primary events if several CVD risk factors concomitantly exist (Leong *et al.*, 2017).

First-line drugs for the treatment of stable CVD include aspirin, statins, and antihypertensive drugs, such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARB). All of these have shown to improve the clinical course (Fihn *et al.*, 2014; McAlister, 2012). Given that hypertension is a major risk factor of CVD, antihypertensive therapy with β-blockers, ACE inhibitors, ARBs, calcium channel blockers, and diuretics has shown to positively impact on CVD and mortality. It is expected, for instance, that a reduction of 10 mmHg in systolic blood pressure reduces the stroke risk by 41 % and the CHD risk by 22 % (Law *et al.*, 2009).

1.3 Potassium: definition, hypokalemia, and hyperkalemia

Beyond the background of CVD and CVD risk factors, I would like to draw attention to the chemical element potassium, which plays an important role in heart function and heart rhythm. It is an essential mineral for the body, which must be supplied through food, as the body cannot produce it itself. Potassium-rich food comprises vegetables and fruits, such as apricots, avocados, bananas, carrots, kohlrabi, potatoes, spinach and tomatoes. Also hazelnuts, cashew nuts, peanuts and almonds as well as dark chocolate and some types of flour (spelt, rye, buckwheat wholemeal flour) are good sources of potassium (Deutsche Gesellschaft für Ernährung e.V., 2016). As a reference value for the daily potassium intake of an adult, the Deutsche Gesellschaft für Ernährung recommends 4000 milligrams, which corresponds to about 7 bananas or 1200 grams of potatoes (Deutsche Gesellschaft für Ernährung e. V., 2017). Approximately 80 % of potassium from food is absorbed (Holbrook *et al.*, 1984). In the body, potassium is present as a positively charged electrolyte, the potassium cation (K^+), as it is dissolved in extracellular and mainly intracellular fluids. As one of the major electrolytes in the body, potassium is involved in maintaining osmotic pressure, electrolyte homeostasis and acid-base balance and thus regulates blood pressure. Potassium is further important for the transmission of nerve impulses and therefore plays a crucial role in muscle contractions, such as those of the heart muscle (Deutsche Gesellschaft für Ernährung e.V., 2016).

Under physiological conditions and as a requirement for physiological function, extracellular serum potassium levels are in the range of 3.5 to 5.1 mmol/L (Lerma, 2014). Adequate levels are maintained by renal elimination and by the activity of an enzyme called sodium–potassium adenosine triphosphate synthase (Na^+/ K^+-ATPase) (Palmer and Clegg, 2016). By hydrolysing adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and phosphate (P) these enzymes generate energy which they can use to actively (meaning against the concentration gradient) transport potassium cations (K^+) from extracellular fluids into the cells. In exchange, sodium cations (Na^+) are pumped from inside the cells to outside. (Glitsch, 2001). Nevertheless, if these mechanisms fail to compensate potassium imbalances, this can result in abnormal serum potassium levels. Hypokalemia defines the condition when serum potassium levels fall below 3.5 mmol/L (Greenlee *et al.*, 2009; Zacchia *et al.*, 2016), whereas hyperkalemia is characterized by serum potassium levels above 5.1 mmol/L (Lerma, 2014). Although often asymptomatic, hypokalemia can be associated with weakness, muscle pain or cramps, constipation, and arrhythmias (ventricular fibrillation) (Elliott and Braun, 2017; Marti *et al.*, 2014). Similarly, hyperkalemia can be associated with unspecific symptoms such as palpitations, nausea, paraesthesia, and muscle pain, but also even fatal cardiac arrhythmias (Elliott and Braun, 2017; Lehnhardt and Kemper, 2011).

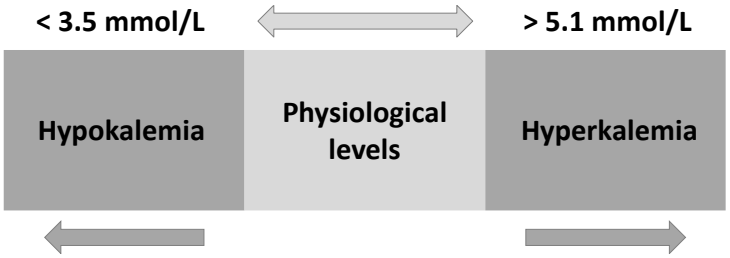

Figure 1. Simplified graphical display of physiological and abnormal serum potassium levels.

Sensitivity towards abnormal serum potassium levels seems to be important for the prognosis of CVD and may be different according to the patient's history of morbidity. In patients with acute myocardial infarction (AMI), for instance, an intracellular shift of potassium is stimulated by excessively released catecholamines during this acute condition. This results in potassium depletion, which in turn can increase the risk of ventricular fibrillation (Brown *et al.*, 1983; Obeid *et al.*, 1978). Moreover, patients with chronic kidney disease (CKD) are prone to experience imbalances in serum potassium levels (mainly hyperkalemia), due to impaired renal clearance and subsequent decreased excretion of serum potassium (Kovesdy, 2014).

1.4 Drugs affecting potassium excretion: diuretics

On the other hand, there are also drugs that have the potential to influence potassium excretion and thus to promote imbalances of serum potassium concentration. Diuretics are prescription drugs that initially block sodium reabsorption by acting at different tubular sites of the nephron, and thereby modulate the homeostasis of sodium and water in the body (diuresis) (Roush *et al.*, 2014). Therefore, diuretics are successfully used to treat oedema, high blood pressure and heart failure (Brater, 1998; Ernst and Moser, 2009). Other electrolytes, such as potassium, are also affected by diuretic effects, because finally the reabsorption of sodium is increased via an exchange with potassium. According to the type of diuresis they induce and their effects on serum potassium, diuretics can be classified into two groups: potassium-sparing and non-potassium-sparing diuretics.

Potassium-sparing diuretics induce retention of serum potassium by decreased sodium re-absorption via the exchange with potassium. These diuretics comprise the substances amiloride and triamterene, which directly block apical sodium channels, so-called ENaC channels, and the ARBs spironolactone, canrenone and eplerenone, which inhibit the effects of aldosterone by competitively binding to its receptor. Aldosterone primarily promotes the synthesis of ENaC channels to re-absorb sodium and secondarily the secretion of potassium. In contrast to ARBs, amiloride and

triamterene affect sodium re-absorption and thus the retention of potassium independently of aldosterone (Tamargo *et al.*, 2014b).

Non-potassium-sparing diuretics, in contrast, promote diuresis by inhibiting re-absorption of sodium without the retention of potassium and thus decrease serum potassium levels. This group of diuretics comprises thiazides, such as hydrochlorothiazide, and sulphonamides, such as clopamide, chlortalidone, indapamide, furosemide, bumetanide, and torasemide (Brater, 1998; Tamargo *et al.*, 2014a; Tamargo *et al.*, 2014b). While thiazide diuretics block the apical electroneutral sodium–chloride co-transporter, sulphonamides block the apical sodium–potassium–chloride co-transporter of the thick ascending limb of Henle's loop. Due to this specific site of action within the nephron, sulphonamides are also called loop diuretics (Tamargo *et al.*, 2014a; Tamargo *et al.*, 2014b). Given their mechanisms of action, non-potassium-sparing diuretics ultimately result in an increased secretion of potassium due to up-regulation of transporters that exchange potassium in favour of sodium, such as the sodium-potassium ATPase pump (Tamargo *et al.*, 2014a; Tamargo *et al.*, 2014b).

According to current guidelines of the European Society for Cardiology, diuretics, with the exception of loop diuretics, are among the first-line drugs in hypertension as they have shown to improve the clinical course and to reduce mortality (Williams *et al.*, 2018). Loop diuretics are in turn part of guideline recommendations for heart failure treatment as they offer great benefits for patients with symptoms of congestion (Ponikowski *et al.*, 2016).

1.5 Drugs affecting potassium excretion: laxatives

Not only prescription drugs but also over-the-counter (OTC) drugs can have major effects on potassium excretion and thus result in imbalances of serum potassium concentration. OTC drugs are medications that can be bought without a prescription, which consequently often happens without a physician's advice or knowledge. Older individuals, in particular, frequently use OTC drugs (Malone *et al.*, 2005; Thesing-Bleck and Hinneburg, 2012).

One prominent example is laxatives. These OTC drugs are used to treat constipation, a symptom not only characterized by reduced bowel movement frequency, but also by "excessive straining, a sense of incomplete evacuation, failed or lengthy attempts to defecate, use of digital manoeuvres for evacuation of stool, abdominal bloating, and hard consistency of stools" (Sharma and Rao, 2017). Available OTC laxatives can be classified into softeners, osmotic laxatives, and stimulant laxatives (Sharma and Rao, 2017, p. 3).

Softeners comprise natural fibres, such as bran and psyllium, methylcellulose, and polycarbophil. These substances act by binding water and thereby increase motility and transfer of stool through the colon (Xing and Soffer, 2001).

Osmotic laxatives include lactulose, polyethylene glycol, and magnesium-containing substances, such as magnesium citrate or magnesium sulphate. This group of laxatives retains water into the stool in order to restore normal osmolality (Sharma and Rao, 2017; Xing and Soffer, 2001).

Stimulants, such as senna, bisacodyl, and sodium picosulfate, are the most effective, but also the most aggressive types of laxatives. They inhibit water absorption in the colon, instead strongly stimulate water secretion, and thus result in a rapid transit through the colon (Sharma and Rao, 2017). Increased water secretion simultaneously causes increased electrolyte secretion, which in a dose-dependent manner may result in hypokalemia (Ewe, 1987).

In particular, the abuse of laxatives, i.e., overdosing or chronic use, can lead to hypokalemia, which in turn can decrease intestinal motility. As a consequence, the symptom of constipation may worsen and thus result in a need to continuously increase the effective dose of the laxative. This vicious circle can finally lead to a laxatives addiction (Dörr, 2010).

Not lastly due to age-related factors, such as decreased intestinal motility, inadequate fluid and fibre intake, physical inactivity or use of constipating drugs (e.g. opioids and anticholinergic drugs), approximately 20 % of the elderly suffer from chronic constipation and therefore regularly use laxatives (Werth *et al.*, 2017).

1.6 Current state of scientific knowledge

Given the high prevalence of CVD and the importance of adequate serum potassium levels for physiological heart function, many observational studies have assessed the association between serum potassium levels and cardiovascular outcomes. However, due to the diverse populations studied (e.g. AMI population, dialysis patients) and the various cardiovascular outcomes investigated (e.g. arrhythmias, sudden cardiac death), results are contradictory and therefore comparisons are challenging. Neither a systematic review of this study type nor a statistical synthesis of the results has been done so far. A summary of these findings, though, could present a long-lasting reference work in the field of CVD risk factors and CVD mortality reduction.

In addition, further strategies to reduce and prevent CVD mortality could include avoiding the combination of drugs that affect potassium excretion and thus serum potassium levels. Using two

or more drugs at the same time bears the potential risk of a drug-drug interaction (Becker *et al.*, 2007). Concurrent use of prescription and OTC drugs is present in 46 % of community-residing individuals aged 57 to 85 years, as reported by a study from the United States (Qato *et al.*, 2008). Laxatives, for instance, could interact with non-potassium-sparing diuretics, which are prescribed to one in five of the elderly (Si *et al.*, 2018), because both drug classes can decrease serum potassium levels by affecting potassium excretion (Brater, 1998; Lacy *et al.*, 2014). Due to the narrow range of physiological serum potassium levels (3.5 to 5.1 mmol/L), potassium depletion may result in hypokalemia (Greenlee *et al.*, 2009; Zacchia *et al.*, 2016), which subsequently can cause arrhythmias and even cardiac death (Krijthe *et al.*, 2013; Lai *et al.*, 2015). Previous cohort studies have already shown an increased cardiovascular risk by non-potassium-sparing diuretics, which was explained by drug-induced hypokalemia (Ahmed *et al.*, 2006; Cohen *et al.*, 2001; Cooper *et al.*, 1999). On the other hand, there is a lack of studies investigating the risk of regular laxatives use (Kubota *et al.*, 2016), especially in combination with non-potassium-sparing diuretics. A reason might be that most studies on drug exposure are based on medication claims databases, which do not record OTC drugs. Therefore, the risk of potentially serious drug-drug interactions may be underestimated by these studies (Bjorkman *et al.*, 2002), and should preferably rather be estimated from observational studies, which often have information on both prescription and OTC drugs.

1.7 Aims of the dissertation

The first aim of this dissertation was to conduct a systematic review of observational studies reporting on the association of abnormal serum potassium levels with cardiovascular outcomes, namely supraventricular arrhythmias (SVA), ventricular arrhythmias (VA), cardiovascular mortality (CVM), and composite cardiovascular (CV) outcomes. Meta-analyses for the data synthesis of each association were conducted separately for the older general population, and populations with a history of hypertension, AMI, heart failure, CKD, and dialysis.

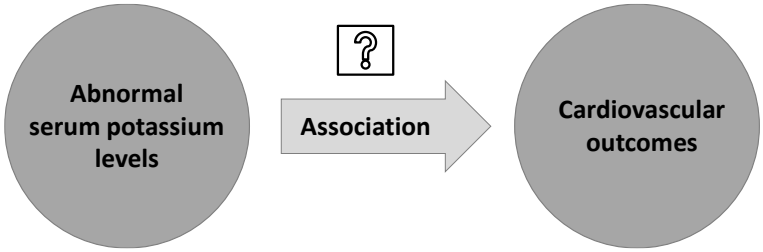

Figure 2. Simplified visual illustration presenting the research question of the systematic review and meta-analysis.

Based on the assumption that serum potassium levels in cardiovascular patients might be affected by drug treatment, I secondly aimed to investigate the cardiovascular risk of drugs affecting potassium excretion in an observational study setting. More precisely, I analysed the associations of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives use with CVM in participants receiving antihypertensive treatment, which includes individuals with hypertension or heart failure. For this purpose, the drug classes were first analysed distinctly and then jointly in order to detect potential drug-drug interactions between the aforementioned prescription and OTC drugs. Analyses were conducted separately in two large-scale cohort studies. While the German ESTHER study (**E**pidemiologische **S**tudie zu Chancen der Verhütung, Früherkennung und optimierten **Th**erapie chronischer **Er**krankungen in der älteren Bevölkerung [German]) was used as a derivation cohort to generate hypotheses, the larger UK Biobank served as replication cohort to confirm the findings. Results from both studies were then combined in an individual patient-data meta-analysis.

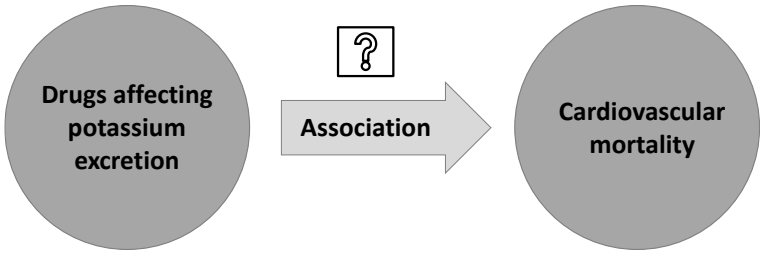

Figure 3. Simplified visual illustration presenting the research question of the original analyses in two large observational studies.

2 SYSTEMATIC REVIEW

This dissertation provides the first systematic overview about the association of abnormal serum potassium levels and cardiovascular outcomes, namely supraventricular arrhythmias and ventricular arrhythmias, CVM, and composite CV outcomes. The content of the following chapters on material and methods (2.1), results (2.2), and discussion (2.3) has previously been published by myself and co-workers in the scientific article "Hoppe, L. K., Muhlack, D. C., Koenig, W., Carr, P. R., Brenner, H. and Schöttker, B. (2018). Association of Abnormal Serum Potassium Levels with Arrhythmias and Cardiovascular Mortality: a Systematic Review and Meta-Analysis of Observational Studies. Cardiovasc Drugs Ther 32, 197-212, doi: 10.1007/s10557-018-6783-0".

2.1 Material and methods

This systematic review and meta-analysis was performed in accordance to the reporting guidelines for **M**eta-analysis **O**f **O**bservational **S**tudies in **E**pidemiology (MOOSE) (Stroup *et al.*, 2000). The MOOSE checklist (**Table 1**) shows that specifications for reporting, which include background, search strategy, methods, results, discussion, and conclusions, were appropriately followed.

Table 1. Applied MOOSE checklist for meta-analyses of observational studies.

Reporting of background should include	
Problem definition	Introduction (1.1, 1.2, 1.3, 1.6)
Hypothesis statement	Introduction (1.6, 1.7)
Description of study outcome(s)	Introduction (1.7)
Type of exposure or intervention used	Introduction (1.7)
Type of study designs used	Introduction (1.7)
Study population	Introduction (1.7)
Reporting of search strategy should include	
Qualifications of searchers (e.g. librarians and investigators)	Methods (2.1.1, 2.1.2)
Search strategy, including time period included in the synthesis and keywords	Methods (2.1.1)
Effort to include all available studies, including contact with authors	Methods (2.1.2, 2.1.4)
Databases and registries searched	Methods (2.1.1)
Search software used, name and version, including special features used (e.g. explosion)	Methods (2.1.1), Table 2
Use of hand searching (e.g. reference lists of obtained articles)	Methods (2.1.2), Discussion (2.3.4)
List of citations located and those excluded, including justification	Table A1, Tables 12 to 17

Method of addressing articles published in languages other than English	Methods (2.1.1)
Method of handling abstracts and unpublished studies	Methods (2.1.2, 2.1.4)
Description of any contact with authors	Methods (2.1.4)
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Introduction (1.6, 1.7), Results (2.2.2), Tables 3 to 5
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	Results (2.2.3, 2.2.4), Table 10, Tables 12 to 17
Documentation of how data were classified and coded (e.g. multiple evaluators, blinding, and interrater reliability)	Methods (2.1.2, 2.1.3), Results (2.2.3), Tables 7 to 9
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	Methods (2.1.3), Results (2.2.3), Tables 7 to 9
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Methods (2.1.3), Results (2.2.4)
Assessment of heterogeneity	Methods (2.1.4)
Description of statistical methods (e.g. complete description of fixed-effect or random-effects models, justification of whether the chosen models account for predictors of study results, dose-response models or cumulative meta-analysis) in sufficient detail to be replicated	Methods (2.1.4), Results (2.2.5), Table 18
Provision of appropriate tables and graphics	Tables 3 to 5, Tables 7 to 9, Table 10, Tables 12 to 17, Table 18, Figures 4 to 6
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Figure 5, Figure 6, Table 10, Table 18
Table giving descriptive information for each study included	Tables 3 to 5
Results of sensitivity testing (e.g. subgroup analysis)	Results (2.2.5), Table 18
Indication of statistical uncertainty of findings	Discussion (2.3.3)
Reporting of discussion should include	
Quantitative assessment of bias (e.g. publication bias)	Discussion (2.3.3)
Justification for exclusion (e.g. exclusion of non-English-language citations)	Results (2.2.4), Tables 12 to 17
Assessment of quality of included studies	Tables 7 to 9, Discussion (2.3.4)
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Discussion (2.3.2)
Generalization of the conclusions (meaning appropriate for the data presented and within the domain of the literature review)	Discussion (2.3.5)
Guidelines for future research	Discussion (2.3.3, 2.3.5)
Disclosure of funding source	Not applicable, as no funding received

MOOSE, Meta-analysis Of Observational Studies in Epidemiology.

2.1.1 Data sources and search strategy

First of all, I conducted a systematic literature search using the databases *Medline* (Ovid Technologies, New York) and *Web of Science* (Clarivate Analytics© 2018, Boston) from inception until November 24, 2017. No language or publication date restrictions were imposed. After having consulted a librarian, I developed the search strategy. It combined synonymous and related terms which describe the exposure (potassium), the outcomes (arrhythmias, and CVM), and the study type (observational study). In addition, the terms included different spellings as well as singular and plural forms.

A complete version of the full electronic search strategy for Medline is shown in **Table 2**. Most of the search terms were enclosed in quotation marks inducing an exact search for the enclosed term. On the other hand, adding an asterisk at the end of a search term allowed to include different endings of the search term in the search, such as singular and plural forms. Additionally, a few search terms were connected with specific search field descriptions, such as "Mesh" (enlarging the search to specific and related topics that the articles are indexed with, so-called medical subject headings (Mesh)), "tiab" (restricting the search to the title, abstract, and keywords of articles) or "Publication type" (focussing the search on specific types of material that the articles present, such as reviews, editorials, observational studies etc.) (U.S. National Library of Medicine, 2018).

The reference manager *Endnote X7* (Thomson Scientific Technical Support, New York) was used throughout the literature search and screening process.

Table 2. Details and results of the literature search in Medline until 24 November 2017.

Steps	Search term	Search string	Hits
#1	Potassium	"Potassium"[Mesh]	98,625
#2		"Potassium"[tiab]	128,526
#3	Hypokalemia	"Hypokalemia"[Mesh]	8,098
#4		"Hypokalemia"[tiab]	7,006
#5		"Hypokalemias"[tiab]	10
#6		"Hypokalaemia"[tiab]	1,935
#7		"Hypokalaemias"[tiab]	0
#8		"Hypopotassemia"[tiab]	260
#9		"Hypopotassaemia"[tiab]	25
#10		"Hypopotassaemias"[tiab]	1
#11	Hyperkalemia	"Hyperkalemia"[Mesh]	5,392
#12		"Hyperkalemia"[tiab]	5,279
#13		"Hyperkalemias"[tiab]	8
#14		"Hyperkalaemia"[tiab]	1,267
#15		"Hyperkalaemias"[tiab]	0
#16		"Hyperpotassemia"[tiab]	148
#17		"Hyperpotassaemia"[tiab]	15
#18	OR (1-17)	EXPOSURE	196,492
#19	Arrhythmias	"Arrhythmias, Cardiac"[Mesh]	188,213
#20		"Arrhythmia"[tiab]	39,259
#21		"Arrhythmias"[tiab]	48,117
#22		Cardiac dysrhythmia*[tiab]	1,035
#23		Cardiac dysrrhythmia*[tiab]	20
#24		Cardiac dysrythmia*[tiab]	11
#25		"Atrial fibrillation"[tiab]	55,816
#26		"Atrial fibrillations"[tiab]	96
#27		"Auricular fibrillation"[tiab]	1,538
#28		"Auricular fibrillations"[tiab]	7
#29		"Atrial flutter"[tiab]	5,168
#30		"Atrial flutters"[tiab]	62
#31		"Auricular flutter"[tiab]	503
#32		"Ventricular fibrillation"[tiab]	17,200
#33		"Ventricular fibrillations"[tiab]	113
#34		Ventricular flutter*[tiab]	232

Table 2 continued, page 2/4

#35	OR (19-34)		238,908
#36	Myocardial Infarction	"Myocardial Infarction"[Mesh]	161,335
#37		"Myocardial infarct"[tiab]	19,387
#38		"Myocardial infarcts"[tiab]	1,043
#39		"Myocardial infarction"[tiab]	158,678
#40		"Myocardial infarctions"[tiab]	4,956
#41		"Cardiovascular stroke"[tiab]	13
#42		Heart attack*[tiab]	4,870
#43		Non fatal myocardial infarct*[tiab]	1,712
#44		Non fatal MI*[tiab]	409
#45		Fatal myocardial infarct*[tiab]	2,145
#46		"Fatal MI" [tiab]	466
#47		"Fatal MIs" [tiab]	45
#48		Coronary death*[tiab]	1,177
#49	Heart Arrest	"Heart Arrest"[Mesh]	41,270
#50		"Heart Arrest"[tiab]	2,044
#51		"Heart Arrests"[tiab]	9
#52		"Cardiac arrest"[tiab]	27,775
#53		"Cardiac arrests"[tiab]	1,887
#54		"Asystole"[tiab]	3,313
#55		"Asystoles"[tiab]	61
#56		"Cardiopulmonary arrest"[tiab]	2,021
#57		"Cardiopulmonary arrests"[tiab]	144
#58		"Sudden cardiac death"[tiab]	12,794
#59		"Sudden cardiac deaths"[tiab]	478
#60		"Cardiac sudden death"[tiab]	160
#61		"Acute Coronary Syndrome"[Mesh]	11,907
#62		"Acute coronary syndrome"[tiab]	17,440
#63		"Angina Pectoris"[Mesh]	41,903
#64		"Angina pectoris"[tiab]	19,538
#65		"Stenocardia"[tiab]	878
#66		"Stenocardias"[tiab]	20
#67	OR (36-66)		326,154
#68	Mortality	"Mortality"[Mesh]	333,126
#69		Mortality[tiab]	623,401
#70		Mortalities[tiab]	7,890
#71		Case Fatality Rate*[tiab]	5,653

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#72	Death	"Death"[Mesh]	135,176
#73		Death[tiab]	600,845
#74	OR (68-73)		1,377,098
#75	Cardiovascular diseases	"Cardiovascular Diseases"[Mesh]	2,147,171
#76		"Cardiovascular Diseases"[tiab]	42,973
#77		"Cardiovascular Disease"[tiab]	105,662
#78		Cardiovascular[tiab]	373,239
#79		"Coronary heart disease"[tiab]	45,624
#80		"Coronary heart diseases"[tiab]	798
#81		"Coronary artery disease"[tiab]	75,152
#82		"Coronary artery diseases"[tiab]	966
#83		"Ischaemic heart disease"[tiab]	8,186
#84		"Ischaemic heart diseases"[tiab]	172
#85		"Ischemic heart disease"[tiab]	23,280
#86		"Ischemic heart diseases"[tiab]	920
#87		"Myocardial infarct"[tiab]	19,387
#88		"Myocardial infarcts"[tiab]	1,043
#89		"Myocardial infarction"[tiab]	158,678
#90		"Myocardial infarctions"[tiab]	4,956
#91		Heart attack*[tiab]	4,870
#92		"Acute coronary syndrome"[tiab]	17,440
#93	OR (75-92)		2,362,336
#94	74 AND 93		297,737
#95	Cardiovascular mortality	Coronary heart disease death*[tiab]	309
#96		Coronary artery disease death*[tiab]	24
#97		Ischaemic heart disease death*[tiab]	32
#98		Ischemic heart disease death*[tiab]	51
#99		Fatal myocardial infarct*[tiab]	2,145
#100		"Fatal MI"[tiab]	466
#101		"Fatal MIs"[tiab]	45
#102		Coronary death*[tiab]	1,177
#103	OR (95-102)		3,922
#104	94 OR 103		323,690
#105	35 OR 67 OR 104	OUTCOME	**727,386**
#106	Case-Control-Study	"Case-Control-Studies"[Mesh]	877,429
#107		"Case Control Study"	73,105
#108		"Case Control Studies"	247,030

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#109		Case Comparison Stud*	183
#110		Case Compeer Stud*	2
#111		Case Referent Stud*	546
#112		Case Base Stud*	17
#113		Nested Case Control Stud*	5,744
#114		Matched Case Control Stud*	3,192
#115	Cohort Study	"Cohort Studies"[Mesh]	1,680,207
#116		"Cohort Study"	129,890
#117		"Cohort Studies"	227,654
#118		Concurrent Stud*	293
#119		"Cohort Analysis"	5,833
#120		"Cohort Analyses"	459
#121		"Incidence Studies"	462
#122		"Incidence Study"	944
#123		"Follow up study"	33,754
#124		"Follow up studies"	585,455
#125		"Longitudinal Study"	46,975
#126		"Longitudinal Studies"	122,177
#127		"Prospective Study"	120,453
#128		"Prospective Studies"	480,442
#129		"Retrospective Study"	114,208
#130		"Retrospective Studies"	663,324
#131		"Observational Study" [Publication Type]	40,303
#132		"Observational Study"	82,800
#133		"Observational studies"	22,276
#134		"Observational Studies as Topic"[Mesh]	2,419
#135		"Observational studies as topic"	2,422
#136		"Population based Study"	24,094
#137		"Population based Studies"	6,444
#138	OR (106-137)	STUDY TYPE	**2,115,297**
#139	18 AND 105	EXPOSURE + OUTCOME	12,456
#140	139 AND 138	EXPOSURE + OUTCOME + STUDY TYPE	**1,220**

Mesh, medical subject heading; *MI*, myocardial infarction; *Tiab*, title and abstract.

2.1.2 Literature screening and selection criteria

The literature was screened in four steps. First, publication types other than observational studies were deleted by the keyword search in Endnote (e.g. reviews, editorials, commentaries). In step two to four, the title, abstract, and full-text of studies were screened for content relevant to this review topic. Two reviewers (myself and Dana Clarissa Muhlack) independently performed the full-text screening by using the following exclusion criteria: A) no observational study design, B) study not conducted in humans, C) serum potassium levels not measured, D) no association of serum potassium levels with one of the defined outcomes (arrhythmias, CVM or composite CV outcomes) assessed, and E) intervention influencing serum potassium levels or outcome.

2.1.3 Data extraction and risk of bias assessment

Two reviewers (myself and Dana Clarissa Muhlack) independently extracted data from the studies included in the systematic review. Consensus was reached through discussion or consultation of the third reviewer (PD Dr. Ben Schöttker). Risk of bias and quality of the included studies were assessed by using a modified version of the Newcastle-Ottawa-Scale (Wells *et al.*, 2008). This practical tool for assessing the quality of non-randomised observational studies uses a scoring system to evaluate the studies in three overall topics: the study group selection, the comparability of the groups, and the determination of either the exposure (for case-control studies) or the outcome of interest (for cohort studies). For the assessment of cohort and case-control studies, the tool comprised eight categories and the studies could be rated by a maximum of nine points. The quality of cross-sectional studies was assessed by using only five categories and a maximum of six rating points. The exclusion of three categories was necessary, because evaluations of length and adequacy of follow-up as well as absence of outcome at baseline were not applicable to cross-sectional studies.

2.1.4 Statistical analysis

Studies were included in meta-analyses if 1) serum potassium [mmol/L] was investigated as a categorical variable with a cut-off for low serum potassium of ≤ 4.0 mmol/L or lower and a cut-off for high serum potassium of ≥ 4.5 mmol/L or higher, if 2) a reference category for serum potassium was used that did not include hypokalemic (< 3.5 mmol/L) or hyperkalemic (> 5.5 mmol/L) serum potassium levels, if 3) effect estimates (risk ratio, hazard ratio or odds ratio) and confidence intervals were reported, could be calculated or were provided by the authors when contacted, and if 4) sufficient information about the study outcome was provided. If a study reported effect estimates

for several categories in the hypokalemic (< 3.5 mmol/L) or the hyperkalemic (> 5.5 mmol/L) range, these estimates were pooled by fixed-effect model meta-analyses. The fixed-effect model is based on the assumption that there is one true intervention effect, which is similarly estimated by every study included in the meta-analysis (McKenzie *et al.*, 2016). As the estimates are derived from the same study, the fixed-effect model is most appropriate to use. The pooled result of one study was then used for the meta-analyses with other studies.

Meta-analyses were conducted separately for study outcome and study population, namely older general population and populations with a history of hypertension, AMI, heart failure, CKD or dialysis. For meta-analyses between studies, I applied random-effects model meta-analyses with inverse variance weighting to allow for between-study heterogeneity. The method of inverse variance weighting assigns a weight to each study that corresponds to the inverse of its variance. Thus, studies with a smaller variance (that is with a higher precision of the effect size due to a smaller standard error and consequently tighter confidence intervals around the effect size) receive a higher weight and therefore contribute more to the calculated average effect size of the meta-analysis. Cochran's Q test was used to test for statistically significant heterogeneity between studies (Whitehead and Whitehead, 1991). Additionally, the I^2 statistic was calculated as $I^2 = 100\ \% (Q - df)/ Q$, where Q represents Cochran's heterogeneity statistic and df the degrees of freedom. By definition, values of I^2 range from 0 % (indicating no observed heterogeneity) to 100 % (Higgins *et al.*, 2003). Publication bias was assessed with Kendall's tau and Egger's test of the intercept (one-tailed).

The software *Comprehensive Meta-Analysis 2.0* (Biostat, Englewood, NJ, USA) was used for all analyses.

2.2 Results

2.2.1 Screening results and study selection

A flow diagram of the literature screening and study selection process is given in **Figure 4**. After removing duplicates, the literature search revealed 1,424 articles. Further exclusions during the screenings of study type, title, and abstract resulted in 103 remaining articles for the full-text selection.

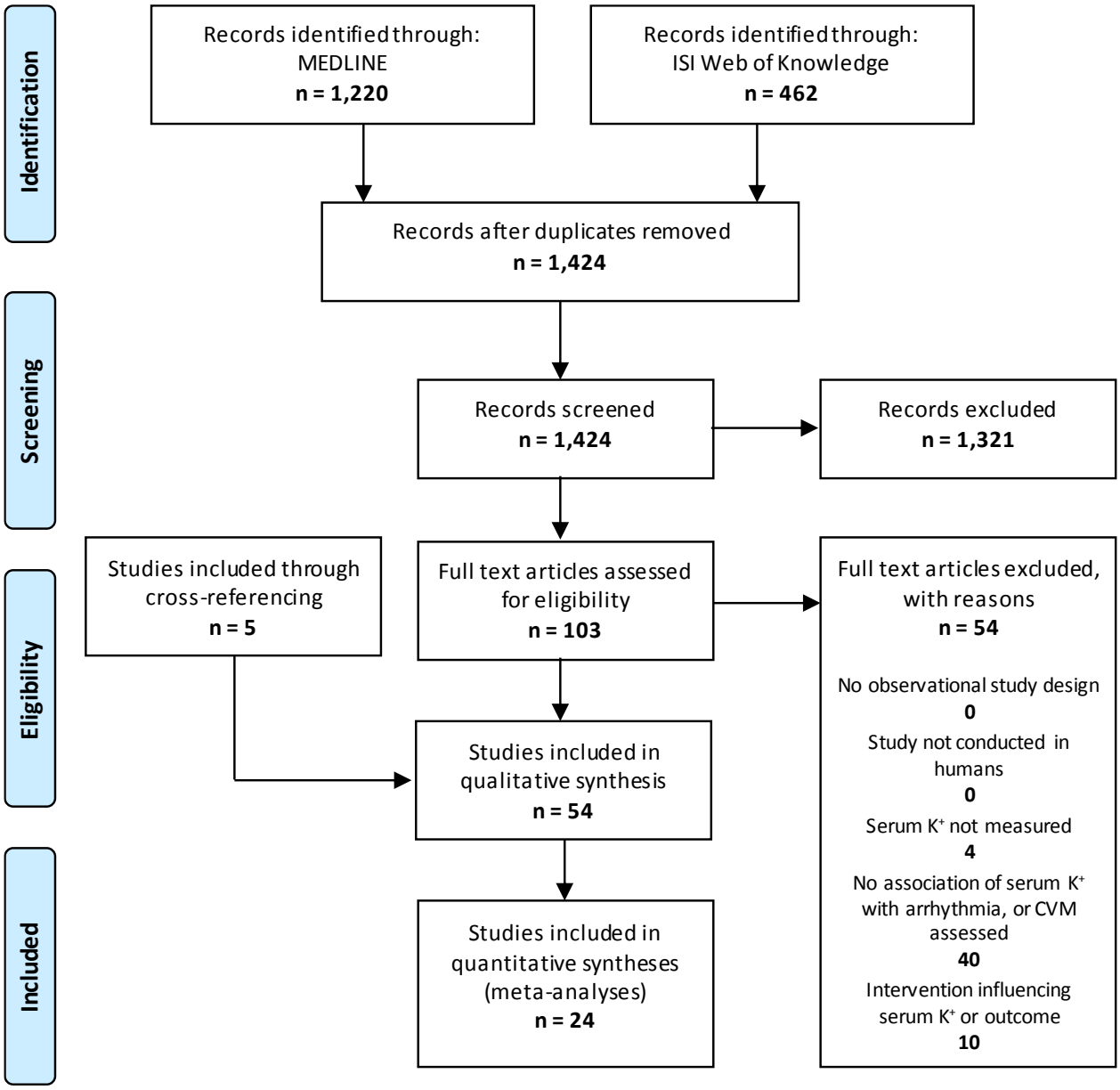

Figure 4. Flow diagram showing the systematic literature screening process.

CVM, cardiovascular mortality; K^+, potassium.

The references of studies excluded during the full-text screening are summarized in **Table A1** of the Appendix. In total, 54 studies did not meet the inclusion criteria, because 4 studies measured potassium elsewhere than in serum (e.g. in urine), another 40 studies assessed the association of serum potassium levels and other outcomes than those relevant for this systematic review, and 10 studies had interventions influencing serum potassium levels, such as surgery procedures.

Overall, this review included 54 studies (Ahmed *et al.*, 2007; Ahmed *et al.*, 2010; Aldahl *et al.*, 2017; Brezins *et al.*, 1996; Bulpitt *et al.*, 1986; Chen *et al.*, 2016; Choi *et al.*, 2014; Chow *et al.*, 2009; Cleland *et al.*, 1987; Cohen *et al.*, 2001; D'Elia *et al.*, 1988; Dargie *et al.*, 1987; Davidson

and Surawicz, 1967; Detrano *et al.*, 1984; Dyckner *et al.*, 1982; Fang *et al.*, 2000; Friedensohn *et al.*, 1991; Genovesi *et al.*, 2009; Goyal *et al.*, 2012; Gundling *et al.*, 2012; Herlitz *et al.*, 1988; Higham *et al.*, 1993; Huang *et al.*, 2015; Hughes-Austin *et al.*, 2017; Janko *et al.*, 1992; Kafka *et al.*, 1987; Karaboyas *et al.*, 2017; Keskin *et al.*, 2016; Korgaonkar *et al.*, 2010; Kovesdy *et al.*, 2007; Krijthe *et al.*, 2013; Lai *et al.*, 2015; Li *et al.*, 2015; López Castro *et al.*, 2010; Luo *et al.*, 2016; Madias *et al.*, 2000; Nielsen *et al.*, 1986; Nolan *et al.*, 1998; Nordrehaug *et al.*, 1985; Park *et al.*, 2017; Reuben and Thomas, 1982; Ribeiro *et al.*, 2015; Shlomai *et al.*, 2016; Simpson *et al.*, 2002; Su *et al.*, 2012; Thomas, 1983; Torlen *et al.*, 2012; Tsuji *et al.*, 1994; Uluganyan *et al.*, 2016; Wagner *et al.*, 2017; Walsh *et al.*, 2002; Wannamethee *et al.*, 1997; Xu *et al.*, 2014; Yusuf *et al.*, 2016). Within these 54 studies, five were identified by cross-referencing (Aldahl *et al.*, 2017; Huang *et al.*, 2015; Hughes-Austin *et al.*, 2017; Torlen *et al.*, 2012; Xu *et al.*, 2014).

Finally, 24 studies were suitable for meta-analyses (Ahmed *et al.*, 2007; Ahmed *et al.*, 2010; Aldahl *et al.*, 2017; Chen *et al.*, 2016; Chow *et al.*, 2009; Cohen *et al.*, 2001; Fang *et al.*, 2000; Goyal *et al.*, 2012; Huang *et al.*, 2015; Hughes-Austin *et al.*, 2017; Karaboyas *et al.*, 2017; Keskin *et al.*, 2016; Korgaonkar *et al.*, 2010; Kovesdy *et al.*, 2007; Krijthe *et al.*, 2013; Lai *et al.*, 2015; Luo *et al.*, 2016; Ribeiro *et al.*, 2015; Torlen *et al.*, 2012; Uluganyan *et al.*, 2016; Wagner *et al.*, 2017; Walsh *et al.*, 2002; Wannamethee *et al.*, 1997; Xu *et al.*, 2014).

2.2.2 Study design of included studies

Within the 54 included studies, I detected 28, 24 and 4 studies reporting on the association of abnormal serum potassium levels with arrhythmias (Brezins *et al.*, 1996; Choi *et al.*, 2014; Cleland *et al.*, 1987; D'Elia *et al.*, 1988; Dargie *et al.*, 1987; Davidson and Surawicz, 1967; Detrano *et al.*, 1984; Dyckner *et al.*, 1982; Friedensohn *et al.*, 1991; Goyal *et al.*, 2012; Gundling *et al.*, 2012; Herlitz *et al.*, 1988; Higham *et al.*, 1993; Janko *et al.*, 1992; Kafka *et al.*, 1987; Keskin *et al.*, 2016; Krijthe *et al.*, 2013; Madias *et al.*, 2000; Nielsen *et al.*, 1986; Nordrehaug *et al.*, 1985; Park *et al.*, 2017; Reuben and Thomas, 1982; Shlomai *et al.*, 2016; Simpson *et al.*, 2002; Su *et al.*, 2012; Thomas, 1983; Tsuji *et al.*, 1994; Uluganyan *et al.*, 2016), with cardiovascular mortality (CVM) (Ahmed *et al.*, 2007; Ahmed *et al.*, 2010; Aldahl *et al.*, 2017; Bulpitt *et al.*, 1986; Chen *et al.*, 2016; Chow *et al.*, 2009; Fang *et al.*, 2000; Genovesi *et al.*, 2009; Huang *et al.*, 2015; Hughes-Austin *et al.*, 2017; Korgaonkar *et al.*, 2010; Kovesdy *et al.*, 2007; Lai *et al.*, 2015; Li *et al.*, 2015; López Castro *et al.*, 2010; Madias *et al.*, 2000; Nolan *et al.*, 1998; Ribeiro *et al.*, 2015; Torlen *et al.*, 2012; Wagner *et al.*, 2017; Walsh *et al.*, 2002; Wannamethee *et al.*, 1997; Xu *et al.*, 2014; Yusuf *et al.*, 2016), and with composite CV outcomes (Cohen *et al.*, 2001; Karaboyas *et al.*, 2017; Korgaonkar *et al.*, 2010; Luo *et al.*, 2016), respectively. Two studies (Korgaonkar *et al.*, 2010;

Madias *et al.*, 2000) appear twice. Details of included studies sorted by study outcome (arrhythmias, CVM, and composite CV outcomes) and study population are shown in **Table 3**, **Table 4**, and **Table 5**, respectively.

Among the studies assessing arrhythmias (**Table 3**), the study of Krijthe and colleagues was the only study with a prospective cohort design (Krijthe *et al.*, 2013). All other studies reporting on arrhythmias were classified as cross-sectional studies because measurement of potassium was at the same hospital stay as the arrhythmia diagnosis, in most cases less than two days apart. Studies about "arrhythmias" were mainly performed in patients with AMI (Brezins *et al.*, 1996; Choi *et al.*, 2014; Dyckner *et al.*, 1982; Friedensohn *et al.*, 1991; Goyal *et al.*, 2012; Herlitz *et al.*, 1988; Higham *et al.*, 1993; Kafka *et al.*, 1987; Keskin *et al.*, 2016; Madias *et al.*, 2000; Nielsen *et al.*, 1986; Nordrehaug *et al.*, 1985; Reuben and Thomas, 1982; Shlomai *et al.*, 2016; Su *et al.*, 2012; Thomas, 1983; Uluganyan *et al.*, 2016). The study sizes ranged from 50 participants (Detrano *et al.*, 1984) to 38,689 participants (Goyal *et al.*, 2012) with an arrhythmia prevalence of 1.5 % (Park *et al.*, 2017; Shlomai *et al.*, 2016) to 61.0 % (Cleland *et al.*, 1987; Dargie *et al.*, 1987). With exception of one study (Krijthe *et al.*, 2013) that investigated supraventricular arrhythmias (atrial fibrillation and atrial flutter), and one other study (Madias *et al.*, 2000) that investigated both supraventricular arrhythmias (atrial fibrillation) and ventricular arrhythmias (ventricular fibrillation), all other studies investigated ventricular arrhythmias.

Table 3. Details of included studies reporting on the association of serum potassium levels and arrhythmias.

First author, (Year)	Country (Baseline)	Study type	Study population			Outcome n (%)	Type of arrhythmias[a]
			Population	Age [mean ± SD]	Female n (%)	Size n	
*Krijthe, (2013)	Netherlands (1990-1993)	Cohort	Older general	69.2 ± 8.6	2,425 (59.7)	4,059	474 (11.7)	AF, atrial flutter
Simpson, (2002)	USA (N.R)	CS	Older general	45.0 to 65.0	8,308 (55.1)	15,070	940 (6.2)	PVCs
Tsuji, (1994)	USA (1979-1983)	CS	Older general	44.0 ± 10.0	1,723 (51.8)	3,327	183 (5.5)	VPCs
Brezins, (1996)	Israel (1990-1994)	CS	AMI	64.0 ± 12.0	482 (30.3)	1,590	57 (3.6)	Primary VF
Choi, (2014)	Korea (2006-2009)	CS	AMI	64.0 ± 12.8	589 (30.6)	1,924	54 (2.8)[b]	VT, VF
Dyckner, (1982)	Sweden (1968; 1976)	CS	AMI	66.0	250 (37.0)	676	261 (38.6)	VT, VF
Friedensohn, (1991)	Israel (N.R.)	CS	AMI	62.1 ± 11.0	212 (21.0)	1,011	606 (59.9)	VT, VF
*Goyal, (2012)	USA (2000-2008)	CS	AMI	68.1 ± 14.0	15,714 (40.6)	38,689	1,707 (4.4)	VT, VF
Herlitz, (1988)	Sweden (1976-1981)	CS	AMI	61.0[c]	161 (23.7)	679[d]	25 (3.8)	VF
Higham, (1993)	UK (1982-1983)	CS	AMI	63.0 ± 10.0	164 (32.6)	504	17 (3.4)	VF
Kafka, (1987)	Canada (N.R.)	CS	AMI	N.R.	N.R.	211	110 (52.1)	VT, VF
*Keskin, (2016)	Turkey (2010-2012)	CS	AMI	58.0 ± 11.6	714 (19.0)	3,760	230 (6.1)	VA

First author, (Year)	Country (Baseline)	Study type	Study population				Outcome n (%)	Type of arrhythmias[a]
			Population	Age [mean ± SD]	Female n (%)	Size n		
Madias, (2000)	USA (1986-1989)	CS	AMI	63.1 ± 13.0	153 (29.6)	517	72 (13.9) 72 (13.9)	AF, VF
Nielsen, (1986)	Denmark (1982)	CS	AMI	63.2	47 (22.0)	214	69 (32.2)	N.R.
Nordrehaug, (1985)	Norway (N.R.)	CS	AMI	66.1 ± 9.7	6 (10.0)	60	18 (30.0)	VT, PVCs
Reuben, (1982)	UK (N.R.)	CS	AMI	≥ 65.0	128 (31.6)	405	13 (3.2)	VT
Shlomai, (2016)	Israel (N.R.)	CS	AMI	64.0 ± 13.0	286 (22.4)	1,277	22 (1.7)	Primary VF
Su, (2012)	China (2002-2007)	CS	AMI	60.0	107 (22.9)	468	44 (9.4)	Ventricular flutter, VT, VF
Thomas, (1983)	UK (1974-1980)	CS	AMI	60.1 ± 10.4	N.R.	809	17 (2.1)	VF
*****Uluganyan, (2016)	Turkey (2011-2012)	CS	AMI	59.0 ± 13.6	84 (13.8)	611	65 (10.6)	VT, VF
Davidson, (1967)	USA (1962-1966)	CS	Hospitalized	N.R.	N.R.	1,986[e]	391 (19.6)	Supraventricular or ventricular ectopic beats and rhythms
Detrano, (1984)	USA (1982)	CS	Hospitalized	59.0	13 (26.0)	50	24 (48.0)	VT, PVCs
Janko, (1992)	Austria (1989)	CS	Hospitalized	N.R.	N.R.	745	127 (17.1)	Ectopic ventricular activity
Park, (2017)	Korea (2013)	CS	Hospitalized	59.7	8,227 (46.3)	17,777	260 (1.5)	In-hospital arrhythmia (not specified)

First author, (Year)	Country (Baseline)	Study type	Study population				Outcome n (%)	Type of arrhythmias[a]
			Population	Age [mean ± SD]	Female n (%)	Size n		
Gundling, (2012)	Germany (2004-2008)	CS	Cirrhosis	62.1 ± 12.8	114 (38.9)	293	48 (16.4)	Ventricular flutter, VF
Cleland, (1987)	UK (N.R.)	CS	Heart failure	59.0 ± 9.0	24 (16.0)	152	93 (61.0)	VT
Dargie, (1987)	UK (N.R.)	CS	Heart failure	59.0	18 (21.4)	84	51 (61.0)	VT
D'Elia, (1988)	USA (1981-1984)	CS	Dialysis	50.1 ± 2.2	60 (49.2)	122	32 (26.7)	Ventricular ectopy, AV-block

***** Studies included in meta-analyses.

[a] Comprehensive list of arrhythmia outcome definitions is given in **Table 6**.

[b] Choi, (2014): Only the results of ventricular arrhythmias occurring before coronary angiography were considered.

[c] Herlitz, (1988): It was reported that of 1,318 participants in total, n = 690 were aged ≤ 61 years and n = 628 were aged > 61 years.

[d] Herlitz, (1988): Study size was derived from a randomised placebo-controlled trial including 1,318 participants in total. Of these, 679 participants were randomised to placebo and used for the arrhythmia assessment. [e] Davidson, (1967): Study size derived from 107 patients with hypokalemia and a group of 1,879 controls.

AF, atrial fibrillation; *AMI*, acute myocardial infarction; *AV*, atrioventricular; *CS*, cross-sectional; *N.R.*, not reported; *PVC*, premature ventricular contraction; *SD*, standard deviation; *UK*, United Kingdom; *USA*, United States of America; *VA*, ventricular arrhythmias; *VF*, ventricular fibrillation; *VPC*, ventricular premature complex; *VT*, ventricular tachycardia.

Among the studies assessing CVM (**Table 4**), the study of Chow and colleagues was the only one with a case-control design (Chow *et al.*, 2009), while the others were cohort studies. Most of the studies investigated populations of dialysis patients (Chow *et al.*, 2009; Genovesi *et al.*, 2009; Huang *et al.*, 2015; Kovesdy *et al.*, 2007; Li *et al.*, 2015; Ribeiro *et al.*, 2015; Torlen *et al.*, 2012; Xu *et al.*, 2014; Yusuf *et al.*, 2016), older general individuals (Chen *et al.*, 2016; Fang *et al.*, 2000; Hughes-Austin *et al.*, 2017; Lai *et al.*, 2015; Walsh *et al.*, 2002; Wannamethee *et al.*, 1997), and heart failure patients (Ahmed *et al.*, 2007; Ahmed *et al.*, 2010; Aldahl *et al.*, 2017; López Castro *et al.*, 2010; Nolan *et al.*, 1998). Additionally, there was one study in hypertensive patients (Bulpitt *et al.*, 1986), one study in AMI patients (Madias *et al.*, 2000), and another two studies in CKD patients (Korgaonkar *et al.*, 2010; Wagner *et al.*, 2017). The largest study comprised 74,219 participants (Kovesdy *et al.*, 2007), while the smallest study had 312 participants (Huang *et al.*, 2015; Li *et al.*, 2015). They were followed up for at least 0.3 years (Aldahl *et al.*, 2017) and up to a maximum of 23.5 years (Chen *et al.*, 2016). During the follow-up, the CVM rate ranged from 1.5 % (Walsh *et al.*, 2002) to 28.7 % (Ahmed *et al.*, 2010).

Table 4. Details of included studies reporting on the association of serum potassium levels and CVM.

First author, (Year)	Country (Baseline)	Study type	Study population				Outcome n (%)	Mean FUP [years]
			Population	Age [mean ± SD]	Female n (%)	Size n		
*Chen, (2016)	USA (1987-1989)	Cohort	Older general	54.2 ± 5.8	8,560 (55.1)	15,539	534 (3.4)	23.5
*Fang, (2000)	USA (1974-1975)	Cohort	Older general	46.6 ± 13.9	1,578 (55.6)	2,836	272 (9.6)	15.9
*Hughes-Austin, (2017)	USA (1989-1993) CHS (2000-2002) MESA	Cohort	Older general	66.0 ± 10.0	5,598 (58.0)	9,651	1,087 (11.3)	10.5
*Lai, (2015)	Taiwan (1999-2000)	Cohort	Older general	72.8 ± 5.9	688 (33.3)	2,065	219 (10.6)	8.0
*Walsh, (2002)	USA (1979-1983)	Cohort	Older general	43.0 ± 10.0	1,636 (51.9)	3,151	46 (1.5)	16.0
*Wannamethee, (1997)	UK (1978-1980)	Cohort	Older general	40 to 59	0 (0.0)	7,262	370 (5.1)	11.5[a]
Bulpitt, (1986)	UK (1962-1966)	Cohort	Hypertension	50.1 ± 12.2	211 (52.2)	404	52 (12.9)	15.0
Madias, (2000)	USA (1986-1989)	Cohort	AMI	63.1 ± 13.0	153 (29.6)	517	80 (15.5)	N.R.
*Ahmed A., (2007)	USA; Canada (1991-1993)	Cohort	Heart failure	63.5 ± 11.2	729 (30.7)	2,374[b]	653 (27.5)	3.1
*Ahmed M. I., (2010)	USA; Canada (1991-1993)	Cohort	Heart failure	65.0 ± 10.0	464 (21.3)	2,177[c]	625 (28.7)	3.2
*Aldahl, (2017)	Denmark (1994-2012)	Cohort	Heart failure	75.8	8,316 (42.5)	19,549	1,384 (7.1)[d]	0.3
López Castro, (2010)	Spain (1999-2002)	Cohort	Heart failure	74.8	1,111 (46.6)	2,384	79 (3.3)	4.8

First author, (Year)	Country (Baseline)	Study type	Study population				Outcome n (%)	Mean FUP [years]
			Population	Age [mean ± SD]	Female n (%)	Size n		
Nolan, (1998)	UK (1993-1995)	Cohort	Heart failure	62.0 ± 9.6	N.R.	433	48 (11.1)	1.3
*Korgaonkar, (2010)	USA (2000-2006)	Cohort	CKD	60.5 ± 15.4	372 (45.4)	820	N.R.	2.6
*Wagner, (2017)	France (2000-2012)	Cohort	CKD	58.8 ± 15.2	700 (33.7)	2078	83 (4.0)	5.0
*Chow, (2009)	China (2003-2006)	Case-Control	Dialysis	Cases: 61.4 ± 9.5 Controls: 56.2 ± 12.3	Cases: 6 (25.0) Controls: 27 (56.3)	Cases: 24 Controls: 48	24 (33.3)	3.6
Genovesi, (2009)	Italy (2003)	Cohort	Dialysis	20.0 to > 70.0	199 (41.8)	476	67 (14.1)	3.0
*Huang, (2015)	Taiwan (2006)	Cohort	Dialysis	60.0 ± 15.0	163 (52.2)	312	31 (9.9)	4.8
*Kovesdy, (2007)	USA (2001)	Cohort	Dialysis	61.2 ± 15.2[e]	26,417 (46.4)[e]	74,219	8,679 (11.7)	3.0
Li, (2015)	China (2007-2012)	Cohort	Dialysis	50.3 ± 15.7	163 (45.7)	357	49 (13.7)	3.1
*Ribeiro, (2015)	Brazil (2004)	Cohort	Dialysis	59.3 ± 15.9	1,145 (63.0)	1,817	169 (9.3)	7.0[f]
*Torlén, (2012)	USA (2001-2006)	Cohort	Dialysis	56.0 ± 16.0	4,920 (47.0)	10,468	N.R.	2.3
*Xu, (2014)	China (2006-2010)	Cohort	Dialysis	48.5 ± 15.4	380 (42.9)	886	69 (7.8)	2.6
Yusuf, (2016)	USA (2010)	Cohort	Dialysis	62.9 ± 14.6	16,231 (44.0)	36,888	1,604 (4.4)	0.8

***** Studies included in meta-analyses.
[a] Wannamethee, (1997): Length of follow-up was reported as overall study duration instead of mean.
[b] Ahmed A., (2007): The study size indicated was obtained by propensity score matching within a cohort of 6,845 patients. Hypokalemic participants (n = 1,187) were matched to normokalemic participants (n = 1,187).
[c] Ahmed M. I., (2010): The study size indicated was obtained by propensity score matching within a cohort of 7,788 patients. Hyperkalemic participants (n = 548) were matched to normokalemic participants (n = 1,829).
[d] Aldahl, (2017): Number indicates the total number of deaths.
[e] Kovesdy, (2007): Indicated numbers were only reported for a subset of patients (n = 55,984).
[f] Ribeiro, (2015): Length of follow-up was reported as overall study duration instead of mean.

AMI, acute myocardial infarction; *CHS*, Cardiovascular Health Study; *CKD*, chronic kidney disease; *CVM*, cardiovascular mortality; *FUP*, follow-up; *MESA*, Multi-Ethnic Study of Atherosclerosis; *N.R.*, not reported; *SD*, standard deviation; *UK*, United Kingdom; *USA*, United States of America.

The four studies with composite CV outcomes (**Table 5**) were prospective cohort studies in patients with hypertension (Cohen *et al.*, 2001), CKD (Korgaonkar *et al.*, 2010; Luo *et al.*, 2016), and dialysis (Karaboyas *et al.*, 2017) and had study sizes of 7,653 participants (Cohen *et al.*, 2001), 820 participants (Korgaonkar *et al.*, 2010), 55,266 participants (Luo *et al.*, 2016), and 45,511 participants (Karaboyas *et al.*, 2017), respectively.

Table 5. Details of included studies reporting on the association of serum potassium levels and composite CV outcomes.

First author, (Year)	Country (Baseline)	Study type	Study population				Outcome n (%)	Mean FUP [years]
			Population	Age [mean ± SD]	Female n (%)	Size n		
*Cohen, (2001)[a]	USA (1973-1996)	Cohort	Hypertension	53.1 ± 9.5	2,960 (38.7)	7,653	470 (6.1)	6.7
*Korgaonkar, (2010)[b]	USA (2000-2006)	Cohort	CKD	60.5 ± 15.4	372 (45.4)	820	190 (23.2)	2.6
*Luo, (2016)[c]	USA (2009-2013)	Cohort	CKD	74.5 ± 11.3	32,353 (58.5)	55,266	N.R.	2.76
*Karaboyas, (2017)[d]	USA (1996-2001)	Cohort	Dialysis	62.5 ± 15.2	23,221 (42.1)	45,511	3,300 (7.3)	1.4

* Studies included in meta-analyses.

[a] Cohen (2001): Definition of composite CV outcome: Admissions to hospital because of myocardial infarction, angioplasty or coronary bypass surgery, cerebrovascular disease, unstable angina, congestive heart failure, and deaths from all causes of cardiovascular disease.

[b] Korgaonkar (2010): Definition of composite CV outcome: Death or any cardiovascular event defined as pre-specified coronary disease-, cerebrovascular disease- or peripheral vascular disease-related events that required hospitalization or revascularization procedures in any of the named three major arterial beds.

[c] Luo (2016): Definition of composite CV outcome: Arrhythmia, myocardial infarction, stroke, and heart failure exacerbation.

[d] Karaboyas (2017): Definition of composite CV outcome: Death due to either hyperkalemia, hypokalemia, cardiac arrhythmia or cardiac arrest (cause unknown); inpatient hospitalization due to atrial fibrillation or other arrhythmia; or a procedure for cardioversion or automatic implantable cardioverter-defibrillator or pacemaker placement.

CKD, chronic kidney disease; *CV*, cardiovascular; *FUP*, follow-up; *N.R.*, not reported; *SD*, standard deviation; *USA*, United States of America.

A comprehensive list of outcome definitions of the included studies is provided in **Table 6**. The definitions in the second column of the table are original texts from the corresponding publications (see first column for the first author and publication year).

Outcome definitions for ventricular arrhythmias mainly included ventricular tachycardia (VT), ventricular fibrillation (VF), and premature ventricular contractions (PVC) or ventricular premature complexes (VPC). CVM was mostly defined as deaths due to CVD or as sudden cardiac death (SCD). The definition of the composite CV outcome in all three studies included major CVD events as well as cardiovascular death.

Table 6. Detailed outcome definitions of studies included in this systematic review.

Definitions of arrhythmias	
Krijthe, (2013)	AF and atrial flutter diagnosed by electrocardiography (ECG) processing with the Modular ECG Analysis System (MEANS) and manual verification by two blinded specialists.
Simpson, (2002)	A single PVC was one PVC on the 2-minute ECG without a short coupling interval between the PVC and the preceding beat. A short coupling interval was arbitrarily defined as the upper 5 % of the distribution for the entire population of coupling intervals. Frequent PVCs are defined as 2 or more PVCs without consecutive PVCs or short-coupled PVCs. Complex PVCs are consecutive PVCs, multiple morphologic features of at least 2 PVCs, or the presence of a short coupled PVC on the 2-minute ECG.
Tsuji, (1994)	Definition included VPCs, multiform VPCs, and repetitive (≥ 2) VPCs. The primary outcome was complex or frequent VPCs, defined as > 30 VPCs/hour, multiform VPCs, or repetitive VPCs.
Brezins, (1996)	Primary VF.
Choi, (2014)	VT or VF. VT was further categorized into sustained and non-sustained VT, depending on the occurrence or not of tachycardia lasting more than 30 s and leading to haemodynamic collapse. Left ventricular ejection fraction was evaluated by echocardiogram that performed in 98 % patients at 1.08 ± 2.10 days after admission.
Dyckner, (1982)	VF, VT, defined as a rhythm with 3 or more consecutive ventricular ectopic beats, and asystole.
Friedensohn, (1991)	Non-sustained VT (3-15 consecutive ventricular beats at a rate greater than 110 beats per minute), or sustained VT (more than 15 consecutive ventricular beats at a rate greater than 110 beats per minute), or VF (rapid irregular cardiac rhythm), or other VA requiring antiarrhythmic treatment (multiple ventricular premature beats, bigeminy or R-on-T) or high degree conduction disturbances (second degree block, Mobitz type II and third degree AV-block).
Goyal, (2012)	In-hospital VF or ventricular flutter (International Classification of Diseases (ICD)-9-Clinical Modification (CM) codes 427.4, 427.41 or 427.42) or cardiac arrest (ICD-9-CM code 427.5).
Herlitz, (1988)	VF.

Table 6 continued, page 2/4

Higham, (1993)	VF defined as irregular, rapid, non-coherent ECG activity associated with haemodynamic collapse.
Kafka, (1987)	Major VA defined as consisting of VF, VT (more than three premature ventricular beats in sequence), and complex premature ventricular beats (consisting of frequent premature beats (more than six per minute)).
Keskin, (2016)	VA.
Madias, (2000)	AF and VF.
Nielsen, (1986)	Definition of arrhythmias followed E. Sandøe and B. Sigurd (1980).
Nordrehaug, (1985)	Definition included VT, defined as three or more consecutive ventricular complexes at a rate of greater than 120 beats/min and PVCs, sub-classed as frequent (> 5 isolated uni-focal beats/min), bigeminy (alternate sinus and ventricular beats), multifocal (multifocal beats in the same hour of recording), couplets (two consecutive ventricular beats, R-on-T according to R -R' R- T < 0.85), and overall frequency (total number of PVCs in the recording divided by the number of analysable hours and expressed as the number per hour).
Reuben, (1982)	VT defined as 10 or more consecutive ventricular ectopic beats occurring at a rate of 120 per minute or more. Multiple ventricular ectopic beats were regarded as being significant if they occurred at a rate greater than 5 per minute.
Shlomai, (2016)	Primary VF.
Su, (2012)	Malignant VA including VF, ventricular flutter or VT.
Thomas, (1983)	VF.
Uluganyan, (2016)	VT and VF.
Davidson, (1967)	Supraventricular or ventricular, or both, ectopic beats and rhythms.
Detrano, (1984)	Runs of VT, number of ventricular couplets, and PVCs.
Janko, (1992)	Ectopic ventricular activity.
Park, (2017)	In-hospital arrhythmias.
Gundling, (2012)	VF or ventricular flutter (or both in combination), AV-block, AV node re-entry-tachycardia or supraventricular and ventricular extrasystoles (> Lown IIIa).
Cleland, (1987)	VT defined as > 3 consecutive ventricular extrasystoles at > 120 beats/minute.
Dargie, (1987)	Ventricular extrasystoles, couplets or salvoes of ventricular extrasystoles, or VT.
D'Elia, (1988)	Abnormal ambulatory ECG defined by second-degree or greater AV-block or by Lown grade 3 or greater ventricular ectopy.
Definitions of cardiovascular mortality (CVM)	
Chen, (2016)	SCD, defined as definite or possible arrhythmic death adjudicated by a panel of physicians who reviewed all fatal CHD events.
Fang, (2000)	Death due to CVD (codes 390-459).
Hughes-Austin, (2017)	Death from atherosclerotic CVD, stroke, atherosclerotic disease other than CHD or stroke (e.g. aortic aneurysm), or other CVD death (e.g. valvular heart disease).

Table 6 continued, page 3/4

Lai, (2015)	Death caused by diabetes (ICD-9:250), hypertension (ICD-9: 401-405), ischemic heart disease (ICD-9: 410-414), heart failure (ICD-9: 428), and stroke (ICD-9: 430-438).
Walsh, (2002)	Death from CVD events including angina pectoris, coronary insufficiency, myocardial infarction, stroke, intermittent claudication, and death due to CHD or stroke.
Wannamethee, (1997)	Death from CVD received from the National Health Service registries.
Bulpitt, (1986)	Death from ischaemic heart disease.
Madias, (2000)	Death from pump failure, cardiac standstill, or VT and VF.
Ahmed A., (2007)	CVM does not include: progressive heart failure, even if the final event was an arrhythmia, deaths presumed to result from arrhythmia without evidence of progressive heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery, and deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid endarterectomy.
Ahmed M.I., (2010)	See Ahmed A., (2007).
Aldahl, (2017)	Cardiac death.
López Castro, (2010)	Not reported.
Nolan, (1998)	Death classified as SCD if it occurred within 1 hour of a change in symptoms or if it occurred during sleep or while unobserved, if circumstantial evidence pointed to death from cardiovascular causes in the absence of clinical or post-mortem evidence of AMI or increasing heart failure, death due to progressive heart failure if death occurred after a documented period of symptomatic or haemodynamic deterioration, and other cardiovascular death if it did not occur suddenly and was not associated with progressive heart failure.
Korgaonkar, (2010)	Death due to CVD events defined as pre-specified coronary disease-, cerebrovascular disease- or peripheral vascular disease-related events that required hospitalization or revascularization procedures in any of the named three major arterial beds.
Wagner, (2017)	Cardiovascular causes of death including ischemic heart disease, cerebrovascular disease, heart failure, dysrhythmia, peripheral arterial disease, SCD, and valvular disease.
Chow, (2009)	SCD defined as unexpected non-traumatic death occurring within 1 hour of the onset of symptoms and without any previous condition that would seem fatal. Also death during sleep and un-witnessed death occurring at home.
Genovesi, (2009)	Death due to causes including documented heart diseases. SCD was defined as unexpected natural death occurring within 1 h after the onset of symptoms.
Huang, (2015)	Death classified as SCD.
Kovesdy, (2007)	Not reported.
Li, (2015)	Death from acute heart failure, myocardial infarction, fatal arrhythmia, stroke, peripheral artery disease or SCD.
Ribeiro, (2015)	Death attributed to CVD.
Torlén, (2012)	Not reported.

Table 6 continued, page 4/4

Xu, (2014)	Death from acute heart failure, myocardial infarction, fatal arrhythmia, stroke, peripheral artery disease or SCD.
Yusuf, (2016)	Cardiovascular events as causes of death.
Definitions of the composite cardiovascular (CV) outcome	
Cohen, (2001)	Hospital admissions due to myocardial infarction, angioplasty or coronary bypass surgery, cerebrovascular disease, unstable angina, congestive heart failure and death from all causes of CVD.
Korgaonkar, (2010)	Death or any cardiovascular event defined as pre-specified coronary disease-, cerebrovascular disease- or peripheral vascular disease-related events requiring hospitalization or revascularization procedures.
Luo, (2016)	Arrhythmia, myocardial infarction, stroke, and heart failure exacerbation.
Karaboyas, (2017)	Death due to hyperkalemia, hypokalemia, cardiac arrhythmia or cardiac arrest; inpatient hospitalization due to AF or other arrhythmia; procedure for cardioversion or automatic implantable cardioverter-defibrillator or pacemaker placement.

AMI, acute myocardial infarction; *AF*, atrial fibrillation; *AV*, atrioventricular; *CHD*, coronary heart disease; *CM*, clinical modification; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality; *ECG*, electrocardiography; *ICD*, international classification of diseases; *MEANS*, Modular Electrocardiography Analysis System; *PVC*, premature ventricular contraction; *SCD*, sudden cardiac death; *VA*, ventricular arrhythmias; *VF*, ventricular fibrillation; *VPC*, ventricular premature complex, *VT*, ventricular tachycardia.

2.2.3 Risk of bias and quality assessment of included studies

Results of the risk of bias and quality assessment of the included studies are shown in **Table 7**, **Table 8**, and **Table 9**.

For the evaluation of cross-sectional studies I used a modified version of the Newcastle-Ottawa-Scale restricted to five categories and a maximum of six accessible points (**Table 7**). The 27 cross-sectional studies on "arrhythmias" were on average rated with 3.3 points (range: 1 to 5 points).

Cohort studies (**Table 8**) and the case-control study (**Table 9**) were evaluated in eight categories and could be awarded a maximum of nine points. While the cohort study on supraventricular arrhythmias was awarded 9.0 points (Krijthe *et al.*, 2013), the average number of points per study was 6.9 (range: 5 to 9 points) and 6.8 (range: 5 to 8 points) for studies assessing CVM and studies assessing composite CV outcomes, respectively.

Table 7. Risk of bias assessment of included cross-sectional studies according to a modified Newcastle-Ottawa-Scale.

	First author, (Year)	Representativeness of the exposed cohort[a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Comparability of cohorts on the basis of the design or analysis[c]	Assessment of outcome[d]	Total score[e]
SVA	Madias, (2000)	1	1	1	0	1	**4**
VA	Simpson, (2002)	1	1	1	0	1	**4**
	Tsuji, (1994)	1	1	0	1	1	**4**
	Brezins, (1996)	1	1	0	0	1	**3**
	Choi, (2014)	1	1	0	0	1	**3**
	Dyckner, (1982)	1	1	0	0	0	**2**
	Friedensohn, (1991)	1	1	1	0	1	**4**
	*****Goyal, (2012)	1	1	0	1	1	**4**
	Herlitz, (1988)	1	1	1	0	0	**3**
	Higham, (1993)	1	1	1	0	1	**4**
	Kafka, (1987)	1	1	1	0	1	**4**

	First author, (Year)	Representativeness of the exposed cohort[a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Comparability of cohorts on the basis of the design or analysis[c]	Assessment of outcome[d]	Total score[e]
VA	*Keskin, (2016)	1	1	1	1	1	**5**
	Madias, (2000)	1	1	1	0	1	**4**
	Nielsen, (1986)	1	1	1	0	0	**3**
	Nordrehaug, (1985)	1	1	1	0	1	**4**
	Reuben, (1982)	1	0	0	0	1	**2**
	Shlomai, (2016)	1	1	0	0	0	**2**
	Su, (2012)	1	1	0	0	1	**3**
	Thomas, (1983)	1	1	1	0	0	**3**
	*Uluganyan, (2016)	1	1	1	2	0	**5**
	Davidson, (1967)	0	0	0	0	1	**1**
	Detrano, (1984)	1	1	1	0	0	**3**
	Janko, (1992)	1	1	1	0	1	**4**

	First author, (Year)	Representativeness of the exposed cohort[a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Comparability of cohorts on the basis of the design or analysis[c]	Assessment of outcome[d]	Total score[e]
VA	Gundling, (2012)	1	1	0	0	1	**3**
	Cleland, (1987)	1	1	0	0	1	**3**
	Dargie, (1987)	1	1	0	0	1	**3**
	D'Elia, (1988)	1	1	0	0	0	**2**
N.R.	Park, (2017)	1	1	1	1	0	**4**

***** Studies included in meta-analyses.

[a] If the analysed study population was representative, a point was assigned. No point was assigned to studies conducted in claims data of specific health insurance companies.

[b] One point was assigned if serum potassium measurements were collected at baseline or derived from medical records and descriptions about the methods applied for the measurements were provided.

[c] If the study was adjusted for both age and sex, one point was assigned. Further, if the analyses were adjusted for at least five out of six important potential confounders (namely body mass index (BMI) or other weight measure, smoking, diabetes, history of CVD, hypertension, and kidney disease), an additional point was assigned.

[d] If authors explained how the outcome was assessed, a point was assigned.

[e] A study can be awarded a maximum of six points.

BMI, body mass index; *CVD*, cardiovascular disease; *N.R.*, not reported; *SVA*, supraventricular arrhythmias; *VA*, ventricular arrhythmias.

Table 8. Risk of bias assessment of included cohort studies according to a modified Newcastle-Ottawa-Scale.

	First author, (Year)	Representativeness of the exposed cohort [a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Demonstration that outcome of interest was not present at the start of study[c]	Comparability of cohorts on the basis of the design or analysis[d]	Assessment of outcome[e]	Was FUP long enough for outcomes to occur[f]	Adequacy of FUP of cohorts[g]	Total score[h]
SVA	*Krijthe, (2013)	1	1	1	1	2	1	1	1	**9**
CVM	*Chen, (2016)	1	1	1	1	1	1	1	1	**8**
	*Fang, (2000)	1	1	1	1	1	1	1	0	**7**
	*Hughes-Austin, (2017)	1	1	1	1	1	1	1	1	**8**
	*Lai, (2015)	1	1	1	1	2	1	1	0	**8**
	*Walsh, (2002)	1	1	1	1	2	1	1	0	**8**
	*Wannamethee, (1997)	1	1	1	1	2	1	1	1	**9**
	Bulpitt, (1986)	1	1	0	1	0	1	1	1	**6**
	Madias, (2000)	1	1	1	1	0	1	0	0	**5**
	*Ahmed A., (2007)	1	1	0	1	1	1	1	1	**7**
	*Ahmed M. I., (2010)	1	1	0	1	2	1	1	1	**8**

	First author, (Year)	Representativeness of the exposed cohort [a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Demonstration that outcome of interest was not present at the start of study[c]	Comparability of cohorts on the basis of the design or analysis[d]	Assessment of outcome[e]	Was FUP long enough for outcomes to occur[f]	Adequacy of FUP of cohorts[g]	Total score[h]
CVM	***** Aldahl, (2017)	1	1	1	1	1	1	0	1	**7**
	López Castro, (2010)	1	1	0	1	0	1	1	0	**5**
	Nolan, (1998)	1	1	0	1	0	1	1	0	**5**
	*****Korgaonkar, (2010)	1	1	0	1	1	1	1	0	**6**
	*****Wagner, (2017)	1	1	1	1	1	1	1	1	**8**
	Genovesi, (2009)	1	1	0	1	0	1	1	0	**5**
	*****Huang, (2015)	1	1	1	1	1	1	1	0	**7**
	*****Kovesdy, (2007)	1	1	1	1	1	1	1	0	**7**
	Li, (2015)	1	1	0	1	1	1	1	1	**7**
	*****Ribeiro, (2015)	1	1	0	1	1	0	1	0	**5**
	*****Torlén, (2012)	1	1	1	1	2	0	1	1	**8**
	*****Xu, (2014)	1	1	1	1	1	1	1	0	**7**

	First author, (Year)	Representativeness of the exposed cohort [a]	Selection of the non-exposed cohort	Ascertainment of exposure[b]	Demonstration that outcome of interest was not present at the start of study[c]	Comparability of cohorts on the basis of the design or analysis[d]	Assessment of outcome[e]	Was FUP long enough for outcomes to occur[f]	Adequacy of FUP of cohorts[g]	Total score[h]
CVM	Yusuf, (2016)	0	1	1	1	1	1	0	1	**6**
Composite CV outcome	*****Cohen, (2001)	1	1	1	1	2	1	1	0	**8**
	*****Korgaonkar, (2010)	1	1	0	1	1	1	1	0	**6**
	*****Luo, (2016)	0	1	0	1	1	1	1	0	**5**
	*****Karaboyas, (2017)	1	1	1	1	2	1	1	0	**8**

***** Studies included in meta-analyses.

[a] If the analysed study population was representative, a point was assigned. No point was assigned to studies conducted in claims data of specific health insurance companies.

[b] One point was assigned, if serum potassium measurements were collected at baseline or derived from medical records and descriptions about the methods applied for the measurements were provided.

[c] Regarding CVM, it is obvious, that this outcome is not present at the start of study. Therefore, all the studies assessing "CVM" were awarded one point.

[d] If the study was adjusted for both age and sex, one point was assigned. Further, if the analyses were adjusted for at least five out of six important potential confounders (namely BMI or other weight measure, smoking, diabetes, history of CVD, hypertension, and kidney disease) an additional point was assigned.

[e] If authors explained how the outcome was assessed, a point was assigned.

[f] One point was assigned if the length of follow-up was at least 1 year.

[g] If FUP rate was ≥ 90 % or information was ascertained through registration or other administrative offices, a point was assigned.

[h] A study can be awarded a maximum of nine points.

BMI, body mass index; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality; *FUP*, follow-up; SVA, supraventricular arrhythmias.

Table 9. Risk of bias assessment of the included case-control study according to a modified Newcastle-Ottawa-Scale.

	First author, (Year)	Is the case definition adequate?[a]	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis[b]	Ascertainment of exposure[c]	Same method of ascertainment for cases and controls	Non-Response rate	Total score[d]
CVM	*Chow, (2009)	1	1	1	1	1	0	1	0	**6**

***** Studies included in meta-analyses.

[a] One point was assigned when there was some independent validation (e.g. > 1 person/record/time/process to extract information or reference to primary record source such as medical/hospital records).

[b] If the study was adjusted for both age and sex, one point was assigned. Further, if the analyses were adjusted for at least five out of six important potential confounders (namely BMI or other weight measure, smoking, diabetes, history of CVD, hypertension, and kidney disease) an additional point was assigned.

[c] One point was assigned if serum potassium measurements were collected at baseline or derived from medical records and descriptions about the methods applied for the measurements were provided.

[d] A study can be awarded a maximum of nine points.

BMI, body mass index; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality.

2.2.4 Outcome details of included studies

Results of 24 studies, which comprised 310,825 participants, were suitable for meta-analyses and are presented in **Table 10**. The studies are sorted by study outcome and study population. Risk ratios (RR) and confidence intervals (CI) are shown separately for the low and high serum potassium category with preferably levels of < 3.5 and ≥ 5.5 mmol/L, but alternatively, cut-offs up to ≤ 4.0 and ≥ 4.5 mmol/L, respectively, were also accepted if no stricter cut-offs were applied in the studies. If a study reported effect estimates for several categories in the hypokalemic (< 3.5 mmol/L) or the hyperkalemic (≥ 5.5 mmol/L) range, pooled estimates are shown. The risk categories were compared to a reference category that was not allowed to include abnormal serum potassium values < 3.5 or > 5.5 mmol/L. All studies were adjusted for age and sex. However, only 2 studies (Cohen *et al.*, 2001; Krijthe *et al.*, 2013) out of 23 studies were adjusted for all eight covariates that I deemed important to consider in a model for the association of serum potassium levels and cardiovascular outcomes as they are themselves risk factors for CVD: age, sex, body mass index (BMI) or other weight measure, smoking, diabetes, history of CVD, hypertension, and kidney disease.

Table 10. Details of included studies for meta-analysis about the association of serum potassium levels and cardiovascular outcomes.

	First author, (Year)	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates								
			n (%)	Definition [mmol/L]	Definition [mmol/L]	RR (95%-CI)	Definition [mmol/L]	RR (95%-CI)	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others[a]
SVA	Krijthe, (2013)[b]	Older general	474 (11.7)	3.5 to 5.0	< 3.5	1.62 (1.02; 2.55)	> 5.0	0.96 (0.24; 3.91)	X	X	X	X	X	X	X	X	X
VA	Goyal, (2012)[c]	AMI	1,707 (4.4)	3.5 to < 4	< 3.5	1.13 (0.82; 1.55)	≥ 5.5	2.65 (1.70; 4.13)	X	X			X	X	X	X	X
	Keskin, (2016)[d]	AMI	230 (6.1)	4.0 to < 4.5	< 3.5	3.54 (1.79; 7.02)	≥ 5.5	1.82 (0.95; 4.18)	X	X			X	X	X	X	X
	Uluganyan, (2016)[e]	AMI	65 (10.6)	3.5 to < 4	< 3.5	2.70 (0.93; 7.80)	≥ 5.0	1.38 (0.34; 5.50)	X	X		X	X	X	X	X	X
CVM	Chen, (2016)	Older general	534 (3.4)	3.5 to < 5.5	< 3.5	1.38 (0.94; 2.03)	≥ 5.5	1.25 (0.67; 2.32)	X	X			X	X	X	X	X
	Fang, (2000)	Older general	272 (9.6)	3.8 to < 4.5	< 3.8	0.96 (0.61; 1.50)	≥ 4.5	1.54 (1.03; 2.31)	X	X		X		X	X	X	X
	Hughes-Austin, (2017)	Older general	1,087 (11.3)	4.0 to < 4.5	< 3.5	0.84 (0.63; 1.12)	≥ 5.0	1.50 (1.00; 2.26)	X	X		X	X		X	X	X
	Lai, (2015)	Older general	219 (10.6)	3.9 to < 4.5	< 3.5	1.60 (0.70; 3.40)	≥ 4.5	1.30 (1.00; 1.80)	X	X	X		X	X	X	X	X

	First author, (Year)	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates									
			n (%)	Definition [mmol/L]	Definition [mmol/L]	RR (95%-CI)	Definition [mmol/L]	RR (95%-CI)	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others[a]
CVM	Walsh, (2002)	Older general	46 (1.5)	> 4.0 to < 5.2	≤ 4.0	1.40 (0.30; 5.90)	≥ 5.2	1.30 (0.70; 2.60)	X	X	X	X	X		X	X	X
	Wannamethee, (1997)	Older general	370 (5.1)	> 4.5 to < 4.9	< 4.0	0.77 (0.52; 1.15)	≥ 5.2	1.15 (0.52; 2.80)	X	X	X	X	X	X	X		X
	Ahmed A., (2007)	Heart failure	653 (27.5)	4.0 to 5.5	< 4.0	1.27 (1.06; 1.51)	N.A.	N.A.	X	X	X		X	X	X		X
	Ahmed, M.I., (2010)	Heart failure	625 (28.7)	4.0 to < 5.0	N.A.	N.A.	≥ 5.0	1.08 (0.89; 1.30)	X	X	X		X	X	X	X	X
	Aldahl, (2017)	Heart failure	N.R.	4.2 to < 4.5	< 3.5	2.86 (2.10; 3.89)	> 5.5	3.24 (2.49; 4.23)	X	X			X	X		X	X
	Korgaonkar, (2010)	CKD	N.R.	> 4.0 to < 5.5	≤ 4.0	0. 97 (0.62; 1.54)	≥ 5.5	1.49 (0.91; 2.45)	X	X			X	X	X	X	X
	Wagner, (2017)	CKD	83 (4.0)	4.0 to 5.0	< 4	1.01 (0.52; 1.95)	> 5	1.47 (0.67; 3.24)	X	X	X	X	X			X	X
	Chow, (2009)	Dialysis	24 (33.3)	N.R.	< 3.5	3.36 (0.59; 19.04)	N.A.	N.A.	X	X		X	X		X	X	X
	Huang, (2015)	Dialysis	31 (9.9)	4.0 to 5.0	< 4.0	2.82 (0.52; 15.40)	> 5.0	4.11 (1.62; 10.41)	X	X	X		X	X		X	X
	Kovesdy, (2007)	Dialysis	8,679 (11.7)	4.6 to < 5.0	< 4.0	1.11 (1.01; 1.20)	≥ 5.6	1.25 (1.17; 1.33)	X	X	X	X	X			X	X
	Ribeiro, (2015)	Dialysis	169 (9.3)	4.0 to 4.5	< 3.5	1.49 (1.01; 2.21)	N.A.	N.A.	X	X	X		X			X	X

	First author, (Year)	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates									
			n (%)	Definition [mmol/L]	Definition [mmol/L]	RR (95%-CI)	Definition [mmol/L]	RR (95%-CI)	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others[a]
CVM	Torlén, (2012)	Dialysis	N.R.	4.0 to < 4.5	< 3.5	1.05 (0.88; 1.25)	≥ 5.5	1.27 (1.05; 1.52)	X	X	X	X	X	X		X	X
	Xu, (2014)	Dialysis	69 (7.8)	4.0 to < 4.5	< 3.5	1.10 (0.63; 1,94)	≥ 5,5	2.29 (0.80; 6.53)	X	X	X		X			X	X
Composite CV outcome	Cohen, (2001)[f]	Hypertension[g]	470 (6.1)	> 3.5 to < 5.1	≤ 3.5	2.57 (1.51; 4.36)	≥ 5.1	1.65 (1.02; 2.67)	X	X	X	X	X	X	X	X	X
	Korgaonkar, (2010)[h]	CKD	190 (23.2)	> 4.0 to < 5.5	≤ 4.0	1.13 (0.76; 1.67)	≥ 5.5	1.69 (1.09; 2.60)	X	X			X	X	X	X	X
	Luo, (2016)[i]	CKD	N.R.	4.5 to < 5.0	< 3.5	1.89 (1.72; 2.09)	≥ 5.5	1.26 (1.19; 1.34)	X	X			X	X		X	X
	Karaboyas, (2017)[j]	Dialysis	3,300 (7.3)	4.0 to 5.0	< 4.0	0.94 (0.83; 1.05)	> 5.5	1.12 (1.03; 1.23)	X	X	X		X	X	X	X	X

[a] A comprehensive list of covariates, which the studies were adjusted for, is given in **Table 11**.

[b] Krijthe, (2013): Definition of arrhythmia: atrial fibrillation and atrial flutter diagnosed by ECG processing with the Modular ECG Analysis System and manual verification by two blinded specialists.

[c] Goyal, (2012): Definition of arrhythmia: In-hospital ventricular fibrillation or ventricular flutter (documented by ICD-9-CM codes 427.4, 427.41 or 427.42) or cardiac arrest (ICD-9-CM code 427.5).

[d] Keskin, (2016): Definition of arrhythmia: Ventricular arrhythmias were evaluated by a trained study coordinator. However, ventricular arrhythmias were not categorized by the respect of time and long-term ventricular arrhythmias were not included.

[e] Uluganyan, (2016): Definition of arrhythmia: ventricular arrhythmias.

[f] Cohen, (2001): Definition of composite CV outcome: Admissions to hospital because of myocardial infarction, angioplasty or coronary bypass surgery, cerebrovascular disease, unstable angina, congestive heart failure and deaths from all causes of CVD.

[g] Cohen, (2001): hypertensive study population treated with mainly non-potassium-sparing diuretics (thiazides).

[h] Korgaonkar, (2010): Definition of composite CV outcome: Death or any cardiovascular event defined as pre-specified coronary disease-, cerebrovascular disease- or peripheral vascular disease-related events that required hospitalization or revascularization procedures in any of the named three major arterial beds.
[i] Luo, (2016): Definition of composite CV outcome: Arrhythmia, myocardial infarction, stroke, and heart failure exacerbation.
[j] Karaboyas, (2017): Definition of composite CV outcome: Death due to hyperkalemia, hypokalemia, cardiac arrhythmia or cardiac arrest; inpatient hospitalization due to atrial fibrillation or other arrhythmia; procedure for cardioversion or automatic implantable cardioverter-defibrillator or pacemaker placement.

AMI, acute myocardial infarction; *BMI*, body mass index; *CI*, confidence interval; *CKD*, chronic kidney disease; *CM*, clinical modification; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality; *ECG*, electrocardiography; *ICD*, international classification of diseases; K^+, potassium; *N.A.*, not applicable, *N.R.*, not reported; *RR*, risk ratio; *SVA*, supraventricular arrhythmias; *VA*, ventricular arrhythmias.

An overview about the covariates, which the studies of the meta-analyses were adjusted for, is given in **Table 11**. In the first column, the studies are identified by the name of their first author and publication year, while the comprehensive lists of their covariates (original texts from the corresponding publications) are presented in the second column. Moreover, the structure of the table is as follows: the studies are first sorted by study outcome and then by study population.

Table 11. Comprehensive list of covariates of the studies included in meta-analyses.

Outcome: Supraventricular arrhythmias / Population: Older general	
Krijthe, (2013)	Age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), ACE inhibitors, low-ceiling diuretics, high-ceiling diuretics, β-blocker and other blood pressure lowering drugs, BMI, total and high-density lipoprotein (HDL)-cholesterol, current smoking, past smoking, history of myocardial infarction, presence of heart failure, presence of diabetes, estimated glomerular filtration rate (eGFR), P-wave duration, and serum magnesium.
Outcome: Ventricular arrhythmias / Population: AMI	
Goyal, (2012)	Age, sex, race, comorbidities (diabetes, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia, dialysis), admission GFR, potassium, glucose, white blood cell count, haematocrit, peak troponin level, number of potassium checks, presence of cardiogenic shock and acute respiratory failure on admission, cardiac catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery, acute kidney injury, length of hospital stay, medications (fibrinolytic therapy, aspirin, clopidogrel, ticlopidine, β-blockers, ACE inhibitors or sartans, calcium channel blockers, nitrates, diuretics, bronchodilators, statins, insulin, oral antihyperglycemic agents, and clustering by hospital site.
Keskin, (2016)	Age, sex, first measurement during hospitalization of the following laboratory values (admission GFR calculated by Cockcroft Gault, C-reactive protein, potassium, glucose, white blood cell count, hematocrit), peak troponin level, presence of cardiogenic shock and acute respiratory failure on admission, procedures during hospitalization, acute kidney injury during hospitalization, comorbidities (diabetes, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dialysis), medications during hospitalization.
Uluganyan, (2016)	Age, sex, eGFR, Killip class, left, ventricular ejection fraction, past history (hypertension, diabetes mellitus, coronary artery disease, hyperlipidaemia, and smoking status), diagnosis (anterior ST-elevation myocardial infarction (STEMI)), cardiac enzymes (peak creatinine kinase-myocardial band (CK-MB) levels during hospitalization), and medication before hospitalization.

Table 11 continued, page 2/4

Outcome: CVM / Population: Older general	
Chen, (2016)	Age, sex, race, study centre, eGFR, diabetes, hypertension, history of CVD, use of ACE inhibitors, potassium-wasting diuretics (loop diuretics, thiazide and thiazide-like diuretics), potassium-sparing diuretics (aldosterone antagonists, triamterene and amiloride), β-blockers and non-steroidal anti-inflammatory drugs (NSAIDs).
Fang, (2000)	Age, sex, race, blood pressure, cholesterol, smoking status, diuretic use, renal function, renal disease, and heart disease.
Hughes-Austin, (2017)	Age, sex, race, eGFR, diabetes mellitus, SBP, current smoking, pack-years smoking, ever having cancer, study cohort, ACE inhibitors/ ARBs, potassium-sparing diuretics, other diuretics, NSAIDs, potassium supplements, β-blockers, β-agonists, and other antihypertensive medications.
Lai, (2015) (Lai *et al.*, 2015)	Age, sex, BMI, serum low-density lipoprotein (LDL)-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, glucose, uric acid, creatinine, and sodium, SBP, DBP, hypertension, diabetes medication, self-reported heart disease, kidney disease, and stroke.
Walsh, (2002)	Age, sex, SBP, DBP, hypertension treatment, diabetes mellitus, cigarette smoking, alcohol consumption, serum creatinine level, BMI, total cholesterol and HDL.
Wannamethee, (1997)	Age, social class, smoking, alcohol intake, BMI, physical activity, diabetes mellitus, blood glucose, pre-existing ischemic heart disease, heart rate, forced expiratory volume in 1 second (FEV1), SBP.
Outcome: CVM / Population: Heart failure	
Ahmed A., (2007)	Age, sex, non-white, BMI, duration of heart failure, primary cause of heart failure (ischaemic, hypertensive, idiopathic, others), prior myocardial infarction, current angina, hypertension, diabetes, medications (pre-trial digoxin use, trial use of digoxin, ACE inhibitors, hydralazine and nitrates, diuretics, potassium sparing diuretics, potassium supplements), symptoms and signs of heart failure, NYHA functional class I-IV, heart rate, SBP, DBP, chest radiograph findings, and serum creatinine.
Ahmed M. I., (2010)	Age, sex, non-white, BMI, duration of heart failure, aetiology of heart failure (ischaemic, hypertensive), prior myocardial infarction, current angina pectoris, hypertension, diabetes mellitus, CKD, medications (pre-trial digoxin use, trial use of digoxin, ACE inhibitors, hydralazine and nitrates, diuretics, potassium sparing diuretics, potassium supplements), symptoms and signs of heart failure, NYHA functional class III-IV, heart rate, SBP, DBP, chest radiograph findings, serum creatinine, and left ventricular ejection fraction.
Aldahl, (2017)	Age, sex, AMI, chronic obstructive pulmonary disease, diabetes, atrial fibrillation, ventricular fibrillation, AV-block (2nd and 3rd degree), relevant concomitant pharmacotherapy (β-blockers, mineralocorticoid receptor antagonists, thiazides, digoxin and potassium supplements) and a high serum creatinine level.

Table 11 continued, page 3/4

Outcome: CVM / Population: CKD	
Korgaonkar, (2010)	Age, sex, race, diabetes status, history of CVD, hypertension, eGFR, and serum albumin.
Wagner, (2017)	Age, sex, centre, ethnicity, smoking status, BMI, diabetes, baseline GFR, albuminemia, urinary potassium, log albumin/creatinine ratio, medication that may decrease plasma potassium (non-potassium-sparing diuretics, bicarbonate treatment, potassium-binding resins), and medication that may increase plasma potassium (potassium-sparing diuretics, ACE inhibitors or ARBs, β-blockers)
Outcome: CVM / Population: Dialysis	
Chow, (2008)	Age, sex, smoking history, diabetes mellitus, DBP, corrected QT interval, Kt/V (total), residual GFR, aspirin, blood transfusion within 1 month and within 1 year, and units of red blood cells transfused within 1 year.
Huang, (2015)	Age, sex, dialysis vintage, BMI, exposure to 1.0 mEq/L potassium or 2.5 mEq/L calcium dialysate, coronary artery disease, diabetes mellitus, Kt/V, serum levels of albumin, haemoglobin, potassium, creatinine, phosphate and alkaline phosphatase.
Kovesdy, (2007)	Age, sex, race, ethnicity, diabetes, vintage categories, primary insurance (Medicare, Medicaid, private and other), marriage status (married, single, divorced, widowed and other), standardized mortality status of the dialysis clinic during entry quarter, comorbid conditions, tobacco smoking, residual renal function during entry quarter, Kt/V (single pool), 10 indicators of nutritional state and inflammation, including normalized protein nitrogen appearance (nPNA) and serum albumin, bicarbonate, total iron-binding capacity (TIBC), ferritin and creatinine, white blood cell count, lymphocyte percentage, haemoglobin level, and BMI.
Ribeiro, (2015)	Age, BMI, centre experience, Davies score, diabetes, family income, sex, literacy, peritoneal dialysis modality, race, previous haemodialysis, duration of pre-dialysis care, and year of initiation of peritoneal dialysis.
Torlén, (2012)	Age, sex, race, diabetes, dialysis vintage, primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, BMI, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, haemoglobin, white blood cell count, and percentage lymphocyte count.
Xu, (2014)	Age, sex, BMI, diabetic status, Charlson Comorbidity Index (CCI), haemoglobin, serum albumin level, high-sensitivity C-reactive protein, and peritoneal dialysis volume per unit of body surface area (PDV/BSA).
Outcome: Composite CV outcome / Population: Hypertension	
Cohen, (2001)	Age, sex, race, history of CVD, diabetes, previous treatment, smoking status, left ventricular hypertrophy, blood sugar, cholesterol, uric acid, serum creatinine, BMI, SBP, and diuretic use.

Table 11 continued, page 4/4

Outcome: Composite CV outcome / Population: CKD	
Korgaonkar, (2010)	Age, sex, race, diabetes status, history of CVD, hypertension, eGFR, and serum albumin.
Luo, (2016)	Age, sex, race, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, β-blocker use, RAAS blocker use, non-di-hydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and estimated GFR.
Outcome: Composite CV outcome / Population: Dialysis	
Karaboyas, (2017)	Age, sex, dialysis vintage, comorbid conditions (cancer, other CVDs, cerebrovascular disease, heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurologic disease, psychiatric disorder, peripheral vascular disease, recurrent cellulitis, gangrene), vascular access, BMI, albumin level, normalized protein catabolic rate, serum calcium level, serum phosphorus level, serum phosphorus squared, serum bicarbonate level, dialysate bicarbonate concentration, haemoglobin level, session duration, and Kt/V.

ACE, angiotensin-converting enzyme; *AMI*, acute myocardial infarction; *ARB*, angiotensin II receptor blocker; *AV*, atrioventricular; *BMI*, body mass index; *CCI*, Charlson Comorbidity Index; *CKD*, chronic kidney disease; *CK-MB*, creatinine kinase-myocardial band; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *FEV1*, forced expiratory volume in one second; *GFR*, glomerular filtration rate; *HDL*, high-density lipoprotein; *Kt/V*, formula to calculate the efficacy of dialysis (K, Clearance; t, time of dialysis; V, volume of 60 % of body mass); *LDL*, low-density lipoprotein; *nPNA*, normalized protein nitrogen appearance; *NSAID*, non-steroidal anti-inflammatory drug; *NYHA*, New York Heart Association; *PDV/BSA*, peritoneal dialysis volume per unit of body surface area; *RAAS*, Renin-Angiotensin-Aldosterone System; *SBP*, systolic blood pressure; *STEMI*, ST-elevation myocardial infarction; *TIBC*, total iron-binding capacity.

Results from 30 studies could not be included in the meta-analyses and are summarized in **Tables 12 to 17**. The studies statistically compared either frequencies of outcomes in serum potassium categories (Brezins *et al.*, 1996; Choi *et al.*, 2014; D'Elia *et al.*, 1988; Davidson and Surawicz, 1967; Dyckner *et al.*, 1982; Friedensohn *et al.*, 1991; Gundling *et al.*, 2012; Herlitz *et al.*, 1988; Janko *et al.*, 1992; Kafka *et al.*, 1987; Madias *et al.*, 2000; Nielsen *et al.*, 1986; Reuben and Thomas, 1982; Shlomai *et al.*, 2016; Thomas, 1983) (**Table 12**) or mean serum potassium levels in case and control groups (Bulpitt *et al.*, 1986; Detrano *et al.*, 1984; Higham *et al.*, 1993) (**Table 13**). Other studies either assessed the correlation of serum potassium with an outcome (Cleland *et al.*, 1987; Dargie *et al.*, 1987) (**Table 14**), or modelled serum potassium as a continuous variable in a regression analysis (Kafka *et al.*, 1987; Nolan *et al.*, 1998; Nordrehaug *et al.*, 1985; Tsuji *et al.*, 1994) (**Table 15**). Additionally, six studies (Genovesi *et al.*, 2009; Li *et al.*, 2015; López Castro *et al.*, 2010; Simpson *et al.*, 2002; Su *et al.*, 2012; Yusuf *et al.*, 2016), which included either hypo- or hyperkalemic values in the reference group, were excluded from meta-analyses (**Table 16**). One study (Park *et al.*, 2017) could not be included in meta-analyses, as the corresponding outcome “in-hospital arrhythmia” was not further specified (**Table 17**). The results of these 30 studies are not regarded further in this review.

Table 12. Results of studies comparing outcome frequencies in defined potassium categories.

	First author, (Year)	Population	Study size	Low serum K^+		Reference serum K^+		High serum K^+		p-value	Statistical test
				Definition [mmol/L]	Frequency outcome n (%)	Definition [mmol/L]	Frequency outcome n (%)	Definition [mmol/L]	Frequency outcome n (%)		
SVA	Madias, (2000)	AMI	517	< 3.5	6 (14.6)	≥ 3.5	66 (13.9)	N.R.	N.R.	0.89	Chi^2-test
VA	Brezins, (1996)	AMI	1,590	< 4.0	26 (14.1)	≥ 4.0	31 (2.2)	N.R.	N.R.	< 0.001	Chi^2-test
	Choi, (2014)	AMI	1,924	< 3.5	3 (3.1)	3.5 to < 4.0	21 (2.7)	≥ 5.0	2 (8.7)	0.447	Chi^2-test or Fisher's exact test
	Dyckner, (1982)	AMI	676	< 3.6	46 (50.0)	3.6 to < 4.4	158 (39.0)	> 5.1	11 (50.0)	< 0.01[a]	Chi^2-test
	Friedensohn, (1991)	AMI	1,011	< 3.6	N.R. (68.5)	3.6 to < 4.4	N.R. (60.7)	> 5.1	N.R. (50.2)	N.R.	Chi^2-test
	Herlitz, (1988)	AMI	679	< 3.5	3 (10.0)	≥ 3.5	22 (3.5)	N.R.	N.R.	N.R.	Pitman's non-parametric test
	Kafka, (1987)	AMI	211	< 3.5	22 (62.0)	3.5 to 4.8	79 (49.0)	> 4.8	6 (43.0)	< 0.03	Univariate logistic regression
	Madias, (2000)	AMI	517	< 3.5	10 (24.4)	≥ 3.5	62 (13.0)	N.R.	N.R.	0.04	Chi^2-test
	Nielsen, (1986)	AMI	214	< 3.6	12 (27.9)	3.6 to 5.0[b]	57 (33.3)	N.R.	N.R.	N.S.	Chi^2-test
	Reuben, (1982)	AMI	405	< 4.0	12 (6.9)	≥ 4.0	1 (0.43)	N.R.	N.R.	< 0.001	N.R.
	Shlomai, (2016)	AMI	1,277[c]	< 3.9	8 (2.4)	3.9 to 4.2	5 (1.6)	> 4.5	7 (2.2)	0.26	Chi^2-test

	First author, (Year)	Population	Study size	Low serum K^+		Reference serum K^+		High serum K^+		p-value	Statistical test
				Definition [mmol/L]	Frequency outcome n (%)	Definition [mmol/L]	Frequency outcome n (%)	Definition [mmol/L]	Frequency outcome n (%)		
VA	Thomas, (1983)	AMI	809	< 4.0	14 (3.7)	≥ 4.0	3 (0.70)	N.R.	N.R.	< 0.005	Chi^2-test
	Davidson, (1967)	Hospitalized	1,986	≤ 3.2	53 (49.5)	> 3.2	338 (18.0)	N.R.	N.R.	N.R.	Chi^2-test
	Janko, (1992)	Hospitalized	745	< 2.5	13 (21.0)	2.6 to 3.5	73 (17.33)	> 3.5	41 (15.6)	N.S.	Chi^2-test
	Gundling, (2012)	Cirrhosis	293	< 3.0	16 (12.5)	3.5 to 5.0	21 (19.4)	> 5.0	6 (33.3)	N.R.	Chi^2-test
	D'Elia, (1988)	Dialysis	122	< 3.6	9 (29.0)[d]	3.6 to 5.4	23 (25.8)	> 5.4	9 (29.0)[d]	N.S.	Chi^2-test
CVM	Madias, (2000)	AMI	517	< 3.5	7 (17.1)	≥ 3.5	73 (15.3)	N.R.	N.R.	0.52	Chi^2-test

[a] Dyckner, (1982): The p-value refers to the difference between the hypokalemic group and the group with a high normal serum potassium concentration.
[b] Nielsen, (1986): Of 171 patients in the normokalemic group 169 had serum potassium values within the reference category. In addition, two patients were included with hyperkalemic serum potassium values of 5.1 and 5.6 mmol/L.
[c] Shlomai, (2016): Only patients with serum potassium levels within the range of 3.5 to 5.2 mmol/L at presentation were included in the study.
[d] D'Elia, (1988): Only a combined category of abnormal serum potassium levels was used and the frequency shown in the table was reported for the combined group.

AMI, acute myocardial infarction; *CVM*, cardiovascular mortality; K^+, potassium; *N.R.*, not reported; *N.S.*, not significant; *SVA*, supraventricular arrhythmias; *VA*, ventricular arrhythmias.

Table 13. Results of studies comparing mean serum potassium values in case and control group.

	First author, (Year)	Population	Study size	Outcome		Case	Control	p-value	Statistical method
				n	(%)	Serum K^+ mean [mmol/L]	Serum K^+ mean [mmol/L]		
VA	Higham, (1993)	AMI	504	17	(3.4)	3.58 ± 0.41	3.89 ± 0.61	< 0.05	Wilcoxon rank sum test
	Detrano, (1984)	Heart disease	50	24	(48.0)	4.40[a] 4.33[c]	4.35[a] 4.44[c]	0.30[a] 0.44[c]	Wilcoxon rank sum test[b]
CVM	Bulpitt, (1986)	Hypertension[d]	404	52	(12.9)	3.93 ± 0.05	3.85 ± 0.03	N.R.	Nonparametric test of Lee & Desu (1972)

[a] Detrano, (1984): Outcome: Ventricular tachycardia runs > 0.
[b] Detrano, (1984): Additional results of the Spearman rank test: R = -0.34, p = 0.02.
[c] Detrano, (1984): Outcome: Couplets > 0. [d] Bulpitt, (1986): Study population with untreated hypertension.

AMI, acute myocardial infarction; *CVM*, cardiovascular mortality; *K^+*, potassium; *N.R.*, not reported; *VA*, ventricular arrhythmias.

Table 14. Results of studies assessing the correlation of serum potassium levels and ventricular arrhythmia case status.

First author, (Year)	Population	Study size	Outcome		Serum K^+ as continuous variable			Covariates								
			n	(%)	SD [mmol/L]	R-value[a]	p-value	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others
Cleland, (1987)	Heart failure	152	93	(61.0)	N.R.	- 0.38	< 0.001					N.R.				
Dargie, (1987)	Heart failure	84	51	(61.0)	N.R.	- 0.44	< 0.001					N.R.				

[a] R-value calculated by method of Spearman or Pearson.

BMI, body mass index; *CVD*, cardiovascular disease; K^+, potassium; *N.R.*, not reported; *SD*, standard deviation.

Table 15. Results of studies modelling serum potassium as a continuous variable in a regression analysis.

	First author, (Year)	Population	Study size	Outcome		Association per 1 SD increase of serum K^+			Covariates								
				n	(%)	SD [mmol/L]	RR (95%-CI)	p-value	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others
VA	Tsuji, (1994)	Older general	3,327	183	(5.5)	0.48	1.27 (1.06; 1.51)	0.008	X	X		X					X[a]
VA	Kafka, (1987)	AMI	211	110	(52.1)	0.57	N.R.	0.020					N.R.				
VA	Nordrehaug, (1985)	AMI	60	18	(30.0)	N.R.	N.R.	0.016					N.R.				
CVM	Nolan, (2015)	Heart failure	433	48	(11.1)	0.49	1.64 (1.03; 2.63)	0.039	X								X[b]

[a] Tsuji, (1994): Age, sex, systolic blood pressure, cigarette smoking, caffeinated coffee consumption, alcohol consumption, diuretic use, and left ventricular mass.

[b] Nolan, (2015): Age, NYHA functional class, furosemide dose, LVESD (Left ventricular end-systolic diameter), LVEDD (Left ventricular end-diastolic diameter), FSI (Fractional shortening index), serum sodium, cardiothoracic ratio, heart rate, sNN50 (the number of increases in successive normal-to-normal RR intervals > 50ms in the 24-hour recording, an index of parasympathetic activity), rMSSD (the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals in the 24-hour recording, a complementary index of parasympathetic activity), SDNN (the SD of all normal-to-normal RR intervals in the entire 24-hour recording, an index of the total amount of heart rate variability present in the 24-hour recording period, which is modulated by multiple factors).

AMI, acute myocardial infarction; *BMI*, body mass index; *CI*, confidence interval; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality; K^+, potassium; *N.R.*, not reported; *NYHA*, New York Heart Association; *RR*, risk ratio; *SD*, standard deviation; *VA*, ventricular arrhythmias.

Table 16. Results of studies using a reference category for serum potassium that included low (< 3.5 mmol/L) or high (> 5.5 mmol/L) levels.

	First author, (Year)	Population	Outcome		Reference serum K^+	Low serum K^+		High serum K^+		Covariates								
			n	(%)	Definition [mmol/L]	Definition [mmol/L]	RR (95%-CI)	Definition [mmol/L]	RR (95%-CI)	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others[a]
VA	Simpson, (2002)[b]	Older general	940	(6.2)	≥ 3.5	< 3.5	1.76 (1.43; 2.09)	N.A.	N.A.	X								
VA	Su, (2012)[c]	AMI	44	(9.4)	≥ 3.5	< 3.5	6.21 (2.67; 14.44)	N.A.	N.A.	X		X		X	X	X		X
CVM	López Castro, (2010)	Heart failure	79	(3.3)	< 4.0	N.A.	N.A.	≥ 4.0	3.07 (1.25; 7.53)	X					X		X	X
CVM	Genovesi, (2009)	Dialysis	67	(14.1)	< 6.0	N.A.	N.A.	≥ 6.0	2.70 (1.28; 5.85)	X				X	X	X		X
CVM	Li, (2015)	Dialysis	49	(13.7)	≥ 4.0	< 4.0	1.50 (0.78; 2.89)	N.A.	N.A.	X	X	X		X				X
CVM	Yusuf, (2016)	Dialysis	1,604	(4.4)	< 5.5	N.A.	N.A.	≥ 5.5	1.00 (0.86; 1.17)	X	X	X		X	X			X

[a] A comprehensive list of covariates, which the studies were adjusted for, is given in **Table 11**.

[b] Simpson, (2002): Definition of arrhythmia: Single, frequent or complex premature ventricular contractions.

[c] Su, (2012): Definition of arrhythmia: Malignant ventricular arrhythmias included ventricular fibrillation, ventricular flutter or ventricular tachycardia.

AMI, acute myocardial infarction; *BMI*, body mass index; *CI*, confidence interval; *CVD*, cardiovascular disease; *CVM*, cardiovascular mortality; K^+, potassium; *N.A.*, not applicable; *RR*, risk ratio; *VA*, ventricular arrhythmias.

Table 17. Results of studies with study outcomes not possible to assign to a specific arrhythmia category.

	First author, (Year)	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates									
			n (%)	Definition [mmol/L]	Definition [mmol/L]	RR (95%CI)	Definition [mmol/L]	RR (95%CI)	Age	Sex	BMI / Weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney Disease	Others[a]
N.R.	Park, (2017)	Hospitalized	260 (1.5)	3.6 to 4.0	N.A.	N.A.	> 5.5	4.85 (2.16; 10.84)	X	X			X		X	X	X

[a] Park, (2017): Age, sex, history of cancer, ischemic heart disease, heart failure, hypertension, diabetes mellitus, baseline estimated GFR and total carbon dioxide, presence of hypoalbuminemia, anaemia, and baseline use of ACE inhibitors/ ARBs, β-blockers, diuretics and NSAIDs.

ACE, angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *BMI*, body mass index; *CI*, confidence interval; *CVD*, cardiovascular disease; *GFR*, glomerular filtration rate; K^+, potassium; *N.A.*, not applicable; *N.R.*, not reported; *NSAID*, non-steroidal anti-inflammatory drug; *RR*, risk ratio.

2.2.5 Results of meta-analyses by study outcome and specific population

Pooled effect estimates and 95%-confidence intervals of study results for low and high serum potassium levels are shown separately by study outcome and study population in **Table 18**. Pooled estimates and corresponding heterogeneity statistics are presented if there was more than one study per meta-analysis.

Additionally, meta-analyses of studies are presented in forest plots sorted by study outcome and study population in **Figure 5**. Moreover, the associations of hypokalemia (coloured in blue) and hyperkalemia (coloured in ochre) are illustrated in one plot for each outcome and population. The effect estimates of the single studies and the pooled effect estimates of the meta-analyses (summary measures) originate from **Table 10** and **Table 18**, respectively.

No publication bias was detected in any of the meta-analyses (all $p > 0.05$).

Table 18. Effect estimates for the association of serum potassium levels and cardiovascular outcomes.

	Population	Low serum K^+					High serum K^+				
		No. of studies	**n_{total}**	**n_{cases}**	**RR (95%-CI)**	**Heterogeneity Q; *P;* I^2 [%]**	**No. of studies**	**n_{total}**	**n_{cases}**	**RR (95%-CI)**	**Heterogeneity Q; *P;* I^2 [%]**
SVA	Older general	1[a]	4,059	474	**1.62 (1.02; 2.55)**	N.A.	1[a]	4,059	474	0.96 (0.24; 3.91)	N.A.
VA	AMI	3[b]	43,060	2,002	2.08 (0.89; 4.85)	10.23; 0.01; 80.4	3[b]	43,060	2,002	**2.33 (1.60; 3.38)**	1.24; 0.54; 0.0
CVM	Older general	6[c]	40,504	2,528	1.00 (0.79; 1.26)	7.26; 0.20; 31.1	6[c]	40,504	2,528	**1.38 (1.14; 1.66)**	0.89; 0.97; 0.0
	Heart failure	2[d]	21,932	653[e]	1.87 (0.85; 4.18)	20.04; 0.00; 95.0	2[f]	21,726	625[g]	1.86 (0.64; 5.47)	43.70; 0.00; 97.7
	CKD	2[h]	2,898	83[i]	0.98 (0.68; 1.43)	0.01; 0.92; 0.0	2[h]	2,898	83[i]	1.48 (0.98; 2.26)	0.00; 0.98; 0.0
	Dialysis	6[j]	87,774	8,972[k]	**1.11 (1.02; 1.21)**	5.33; 0.38; 6.1	4[l]	85,885	8,779[k]	**1.36 (1.10; 1.68)**	7.53; 0.06; 60.2
Composite CV outcome	Hypertension[m]	1[n]	7,653	470	**2.57 (1.51; 4.36)**	N.A.	1[n]	7,653	470	**1.65 (1.02; 2.67)**	N.A.
	CKD	2[o]	56,086	190[p]	1.52 (0.92; 2.50)	6.18; 0.01; 83.8	2[o]	56,086	190[p]	**1.34 (1.06; 1.71)**	1.72; 0.19; 41.9
	Dialysis	1[q]	45,511	3,300	0.94 (0.83; 1.05)	N.A.	1[q]	45,511	3,300	**1.12 (1.03; 1.23)**	N.A.

A pooled effect estimate is shown if there is more than one study per population.
Bold printed effect estimates indicate statistically significant results ($P < 0.05$).
[a] Krijthe, (2013).
[b] Goyal, (2012); Keskin, 2016; Uluganyan, (2016).
[c] Chen, (2016); Fang, (2000); Hughes-Austin, (2017); Lai, (2015); Walsh, (2002); Wannamethee, (1997).
[d] Ahmed A., (2007); Aldahl (2017).
[e] Ahmed A., (2007): n_{cases} = 653; Aldahl (2017): n_{cases} = N.R.
[f] Ahmed, M. I., (2010); Aldahl (2017).
[g] Ahmed, M. I., (2010): n_{cases} = 625; Aldahl (2017): n_{cases} = N.R.
[h] Korgaonkar, (2010); Wagner, (2017).
[i] Korgaonkar, (2010): n_{cases} = N.R.; Wagner, (2017): n_{cases} = 83.
[j] Chow, (2008); Huang, (2015); Kovesdy, (2007); Ribeiro, (2015); Torlén, (2012); Xu, (2014).
[k] Torlén, (2012): n_{cases} = N.R.
[l] Huang, (2015); Kovesdy, (2007); Torlén, (2012); Xu, (2014).
[m] Cohen, (2001): Hypertensive study population treated with mainly non-potassium-sparing diuretics (thiazides).
[n] Cohen, (2001).
[o] Korgaonkar, (2010); Luo, (2016).
[p] Korgaonkar, (2010): n_{cases} = 190; Luo, (2016): n_{cases} = N.R.
[q] Karaboyas, (2017).

AMI, acute myocardial infarction; *CI*, confidence interval; *CKD*, chronic kidney disease; *CV*, cardiovascular; *CVM*, cardiovascular mortality; K^+, potassium; *N.A.*, not applicable; *RR*, risk ratio; *SVA*, supraventricular arrhythmias; *VA*, ventricular arrhythmias.

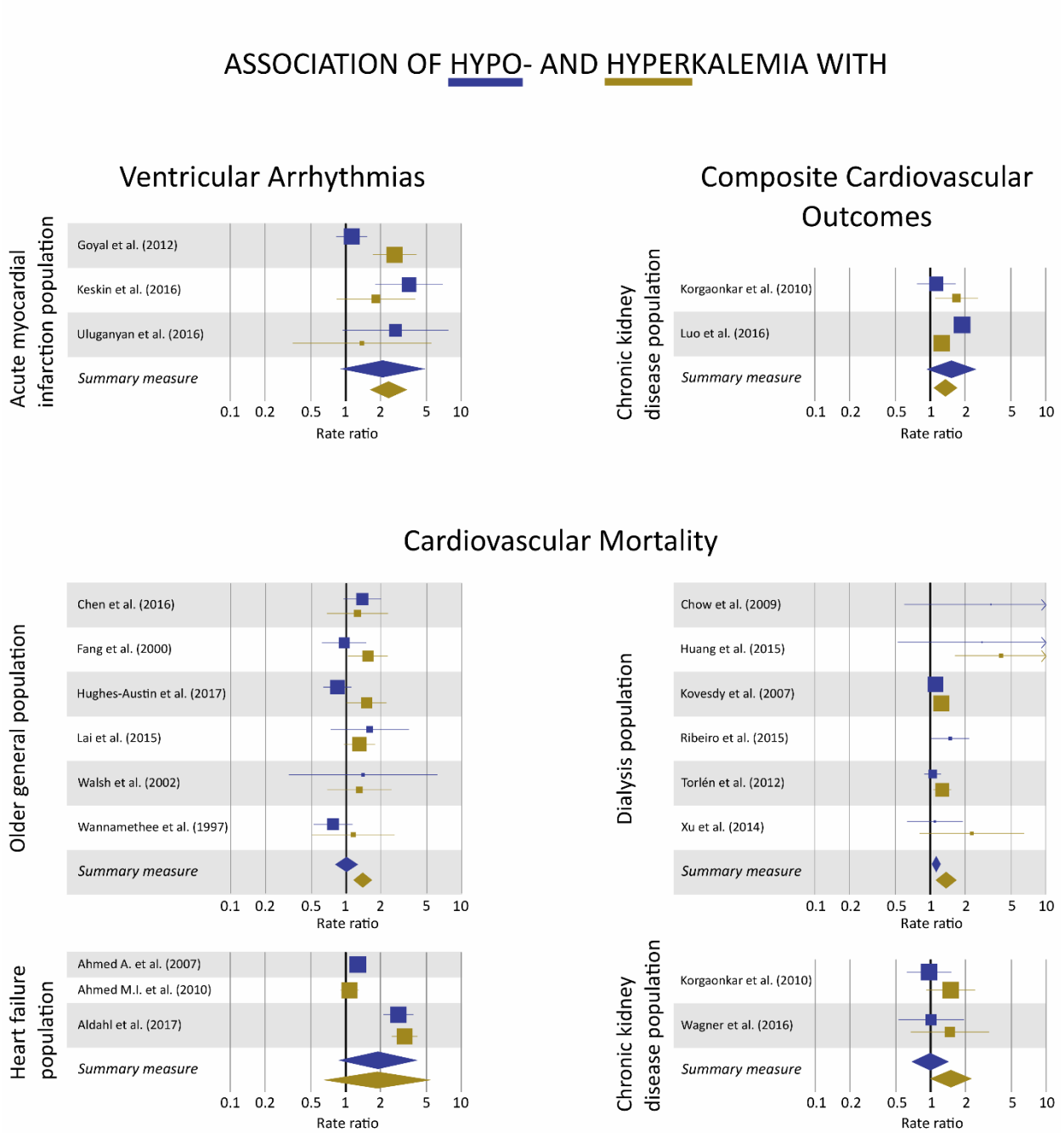

Figure 5. Forest plots of studies assessing the association of abnormal serum potassium levels with ventricular arrhythmias, cardiovascular mortality, and composite cardiovascular outcomes in specific populations.

The associations of hypokalemia (coloured in blue) and hyperkalemia (coloured in ochre) are shown in the same plot for each study outcome and population.

2.2.5.1 Supraventricular and ventricular arrhythmias

In the older general population, the low serum potassium group had an increased risk of supraventricular arrhythmias by 62 % (1.62 [1.02; 2.55]). When an AMI was diagnosed, risk of ventricular arrhythmias was increased by even 108 % (2.08 [0.89; 4.85]). However, this result was not statistically significant. In addition, there was a 133 % increased risk of ventricular arrhythmias in AMI patients with high serum potassium levels (2.33 [1.60; 3.38]). Contrarily, no increased risk of supraventricular arrhythmias was observed for hyperkalemia in the older general population (0.96 [0.24; 3.91]).

2.2.5.2 Cardiovascular mortality

In contrast to supraventricular arrhythmias, high serum potassium levels in the older general population were associated with a 1.4-fold increased CVM [1.38 (1.14; 1.66)], while no association was detected for low serum potassium levels and CVM. Furthermore, CVM was significantly increased in dialysis patients for both low (1.11 [1.02; 1.21]) and high (1.36 [1.10; 1.68]) serum potassium levels. The same pattern of increased CVM for low or high serum potassium levels was observed in heart failure patients but effect estimates were not statistically significant.

2.2.5.3 Composite CV outcome

In hypertensive patients, the risk of composite CV outcomes was significantly increased by 157 % (2.57 [1.51; 4.36]) and 65 % (1.65 [1.02; 2.67]) for the low and the high serum potassium category, respectively. Moreover, both CKD patients (1.34 [1.06; 1.71]) and dialysis patients (1.12 [1.03; 1.23]) with high serum potassium had an increased risk of composite CV outcomes.

2.2.6 Shape of the relationship of serum potassium levels and cardiovascular outcomes

For a visual assessment of the associations of serum potassium levels and cardiovascular outcomes, the risk ratios and confidence intervals reported in **Table 18** have been illustrated in **Figure 6**. The plots are sorted by study population, namely older general population, and populations with hypertension, AMI, heart failure, CKD, and dialysis.

A U-shaped relationship was found in a population with hypertension for a composite CV outcome (**3C**), in patients with AMI for ventricular arrhythmias (**3D**), in heart failure patients for CVM (**3E**), in a population with CKD for a composite CV outcome (**3F**), and in patients receiving dialysis for CVM (**3H**). However, it should be noted that some risk ratios were not statistically significant as their confidence intervals included the value 1.

No U-shaped association was found for the risk of supraventricular arrhythmias in the older general population. Instead, there was an increased risk for individuals in the low serum potassium category only (**3A**).

In contrast, only the high serum potassium category was associated with increased CVM in both the older general population (**3B**) and in CKD patients (**3G**). Likewise, high serum potassium was associated with a composite CV outcome in dialysis patients (**3I**).

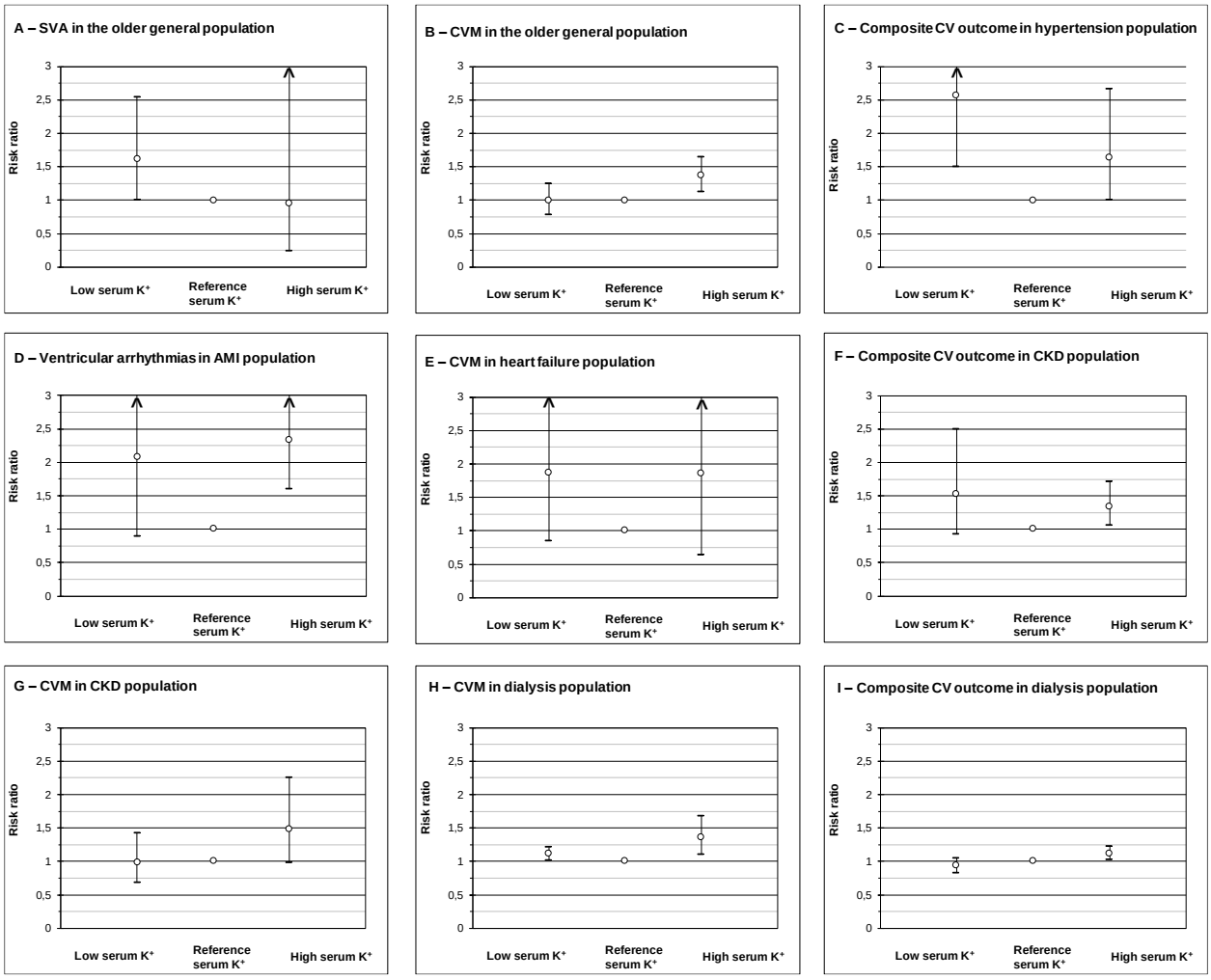

Figure 6. Risk ratios of cardiovascular outcomes for low and high serum potassium levels in specific populations.

Cardiovascular outcomes are shown for the older general population (A, B), and populations with hypertension (C), acute myocardial infarction (D), heart failure (E), chronic kidney disease (F, G), and dialysis treatment (H, I). A pooled estimate is shown if there is more than one study per population.

AMI, acute myocardial infarction; *CKD*, chronic kidney disease; *CV*, cardiovascular; *CVM*, cardiovascular mortality; K^+, potassium; *SVA*, supraventricular arrhythmias.

2.3 Discussion

2.3.1 Summary of the findings

This systematic review and meta-analysis examined the association of abnormal serum potassium levels with cardiovascular outcomes in the older general population and populations with hypertension, AMI, heart failure, CKD, and dialysis treatment. Results showed partly strong associations of abnormal serum potassium levels with supraventricular and ventricular arrhythmias, CVM and composite CV outcomes.

2.3.2 Discussion of results of the meta-analyses

2.3.2.1 Older general population

While hypokalemia was associated with an increased risk of supraventricular arrhythmias (defined as atrial flutter and atrial fibrillation) (Krijthe *et al.*, 2013) in the older general population, it was not associated with CVM. Therefore, I presume that hypokalemia-induced arrhythmias, especially atrial arrhythmias, rarely have a fatal course in the older general population.

In contrary, hyperkalemia was not associated with an increased risk of supraventricular arrhythmias defined as atrial flutter and atrial fibrillation in one small study (Krijthe *et al.*, 2013). As no other study assessed the association of hyperkalemia and arrhythmias, it cannot be ruled out that hyperkalemia is possibly associated with ventricular arrhythmias in the older general population. In fact, it is well-known that hyperkalemia can cause fatal cardiac arrhythmias (Dunn *et al.*, 2015; Rossignol *et al.*, 2016; Weisberg, 2008). Moreover, ventricular fibrillation represents the main cause of sudden cardiac death (John *et al.*, 2012; Koplan and Stevenson, 2009). Consistent with this, is the observation that hyperkalemia was associated with increased CVM. Hence, the observed increased CVM could result at least partly from fatal ventricular arrhythmias in the course of hyperkalemia.

2.3.2.2 Participants with acute myocardial infarction (AMI)

A different systematic review identified low serum potassium levels as a risk factor for primary ventricular fibrillation during AMI (Gheeraert *et al.*, 2006). Even if only on the border to statistical significance, analyses similarly revealed an increased risk of ventricular arrhythmias in hypokalemic patients with AMI (Goyal *et al.*, 2012; Keskin *et al.*, 2016; Uluganyan *et al.*, 2016). During AMI, hypokalemia-induced arrhythmias are known to result from the effects of highly released

catecholamines, which cause an intracellular shift of potassium (Brown *et al.*, 1983). Interestingly, the risk of ventricular arrhythmias during AMI was also increased under hyperkalemic conditions. This result supports my aforementioned hypothesis that the association between hyperkalemia and the risk of arrhythmias might be restricted to specific arrhythmias.

2.3.2.3 Participants with heart failure

Two studies evaluated the association between hypokalemia and CVM in heart failure patients (Ahmed *et al.*, 2007; Aldahl *et al.*, 2017). Both studies individually reported statistically significantly increased associations of hypokalemia and CVM, while the pooled result was not statistically significant. This was due to high heterogeneity (I^2 = 95.0 %) between the two studies, which could originate from different serum potassium categories used. The study of Ahmed A. and colleagues reported a slightly increased CVM (1.27 [1.06, 1.51]) in patients with chronic heart failure who had serum potassium levels below 4.0 mmol/L (Ahmed *et al.*, 2007), whereas the study of Aldahl and colleagues reported a very strongly increased CVM (2.86 [2.10; 3.89]) in heart failure patients with serum potassium levels below 3.5 mmol/L (Aldahl *et al.*, 2017). Moreover, in the first study, the majority of the study population received ACE inhibitors and mainly non-potassium-sparing diuretics, such as thiazides and loop diuretics. However, these diuretics, especially if used in higher doses, are able to lower serum potassium levels, which then may induce fatal arrhythmias and ultimately increase CVM through this mechanism.

Similarly, the meta-analysis of the two studies on the association of hyperkalemia and CVM also showed high heterogeneity (I^2 = 97.7 %) and the pooled result lacked statistical significance (1.86 [0.64; 5.47]). While Ahmed M. I. and colleagues (Ahmed *et al.*, 2010) did not observe an increased CVM in a group with serum potassium levels above 5.0 mmol/L (1.08 [0.89; 1.30]), the study of Aldahl and colleagues showed statistically significant associations with CVM for serum potassium levels above 4.5 mmol/L, with the strongest association in a group with levels above 5.5 mmol/L (3.24 [2.49; 4.23] (Aldahl *et al.*, 2017). Therefore, further studies are needed for the endpoint CVM in heart failure patients because of the high heterogeneity of the limited number of studies.

According to current guidelines of the European Society of Cardiology (ESC) (Ponikowski *et al.*, 2016), first-choice drugs in heart failure patients include ACE inhibitors, β-blockers, ARBs, and aldosterone antagonists. Apart from β-blockers, these disease-modifying drugs all retain serum

potassium. Low-dose (non-potassium-sparing) diuretics are additionally used for symptomatic relief in patients with signs and/or symptoms of congestion. Thus, theoretically, instead of hypokalemia rather hyperkalemia becomes the more serious problem in heart failure patients.

2.3.2.4 Participants with chronic kidney disease (CKD)

As renal elimination is crucial to maintain physiological serum potassium levels, individuals with impaired kidney function are at increased risk of hyperkalemia (Kovesdy, 2014; Lehnhardt and Kemper, 2011). Consequently, hyperkalemia can be regarded as a symptom of progressive CKD, which is known to be a risk factor for CVD (Gansevoort *et al.*, 2013). Accordingly, non-significant increased CVM (1.48 [0.98, 2.26]) and a significantly increased risk for composite CV outcomes (1.34 [1.06, 1.71]) were detected for hyperkalemic participants with CKD in this review. In contrast, while no significant association of hypokalemic conditions and CVM was found, the association with an increased risk of composite CV outcomes was on the border to statistical significance (1.52 [0.92, 2.50]).

2.3.2.5 Participants receiving dialysis

In patients with end-stage renal disease, dialysis is used to imitate kidney function. During dialytic procedures, waste products and excessive substances from the blood are filtered into an individually mixed dialysate solution. Due to a concentration gradient between the dialysate potassium and the serum potassium, excessive potassium is removed and the serum potassium level normalizes. Many studies have already assessed the association between dialysate potassium and risk of cardiovascular outcomes, such as sudden cardiac death (Abuelo, 2015; Al-Ghamdi *et al.*, 2010; Bleyer *et al.*, 2006; Hung and Hakim, 2015; Karaboyas *et al.*, 2017; Karnik *et al.*, 2001; Kovesdy *et al.*, 2007; Pun *et al.*, 2011). Although low dialysate potassium is needed to normalize pre-dialysis hyperkalemia, excessive filtering of serum potassium can result in hypokalemia. Therefore, individuals on dialysis are at an increased risk of both hypo- and hyperkalemia, which both may cause arrhythmias leading even to sudden cardiac death. Accordingly, the results from the meta-analyses showed that both low and high serum potassium levels were statistically significantly associated with increased CVM in patients on dialysis.

2.3.2.6 Participants with hypertension

Amongst other drugs, (non-potassium-sparing) diuretics are used as a first-line treatment in patients with hypertension (Williams *et al.*, 2018). One study (Cohen *et al.*, 2001) specifically focused on individuals with hypertension receiving diuretic treatment and observed a highly increased risk of a composite CV outcome for both hypo- and hyperkalemia. Moreover, this study detected that diuretic use was more prevalent in hypokalemic participants and less prevalent in hyperkalemic participants when compared to participants with normokalemic levels. This finding supports the assumption that hypertensive individuals who receive diuretic treatment have a particularly high risk of hypokalemia. However, it should be considered, that the aforementioned observational study covered more than 20 years (1973 to 1996) with crucial changes concerning the usage and dosage of (non-potassium-sparing) diuretics. Nowadays, treatment of hypertension includes only low-dose hydrochlorothiazides, which have minor potential effects on serum potassium.

In addition, the increased cardiovascular risk by hyperkalemia in hypertension might be explained by renal co-morbidity, which is frequent in hypertensive patients because high blood pressure can damage renal blood vessels (American Heart Association, 2016). Therefore, also in patients with hypertension, the association of hyperkalemia and cardiovascular endpoints may not be causal because hyperkalemia could be a symptom of progressive CKD, which is known to be a risk factor for CVD (Gansevoort *et al.*, 2013).

2.3.3 Research gaps and implications for future studies

Due to various outcomes and populations, a maximum of six studies was pooled per meta-analysis. Future research should therefore continue to add studies on populations and outcomes where statistically significant results are currently lacking in the meta-analyses or where no study has been conducted so far. In addition, future studies on arrhythmias should have a prospective design by performing regular follow-up investigations with ECG recordings. New studies on abnormal serum potassium levels and cardiovascular outcomes are still needed to close these gaps of evidence in literature.

2.3.4 Strengths and limitations

2.3.4.1 Literature search

As I only searched two medical databases, I could have missed potentially relevant studies. However, as only five additional studies were identified through a thorough cross-referencing, I am confident that no important study was missed.

2.3.4.2 Reported study results

Many studies included were quite old and lacked adequate statistical analyses and reporting of results. In particular, many studies on arrhythmias originate from the 1980s and had low scores in the risk of bias assessment. Moreover, in former studies among patients receiving diuretics, higher doses of non-potassium-sparing diuretics were prescribed until the late 1980s, which may explain the high arrhythmia rate and possibly resulting cardiovascular deaths. Furthermore, cut-off values for low, reference, and high serum potassium levels differed between the included studies. However, by including only studies with appropriate reference categories of serum potassium levels in the meta-analyses, I managed to make the studies mostly comparable and similar to the limits proposed by the American Heart Association (3.5 to 5.1 mmol/L (Lerma, 2014)). New studies should categorise serum potassium levels according to recommended clinical cut-off values and thoroughly report risk estimates and confidence intervals.

2.3.4.3 Control of confounding

The studies included in the meta-analyses were quite heterogeneous with regard to covariate adjustment. While all of the studies were adjusted for at least age and sex, only few studies had comparable additional adjustments for important confounders. Therefore, I suggest a set of key covariates, which future studies on this topic could use, namely age, sex, BMI or other weight measure, smoking, diabetes, hypertension, history of CVD, and kidney disease.

2.3.4.4 Heterogeneity

Despite the differences in study designs described, heterogeneity was low in most of the meta-analyses. However, significant heterogeneity ($p < 0.05$) was detected among the three studies assessing the association of low serum potassium levels and ventricular arrhythmias in AMI patients ($I^2 = 80.4$ %), the two studies on CVM in hypokalemic heart failure patients ($I^2 = 95.0$ %) and the two studies on CVM and hyperkalemic heart failure patients ($I^2 = 97.7$ %). Furthermore, there was

significant heterogeneity among the two studies investigating the association of low serum potassium levels and a composite CV outcome in CKD patients (I^2 = 83.8 %). Of note is that all four meta-analyses revealed non-significant increased associations of abnormal serum potassium levels and the corresponding outcome. One possible explanation of the heterogeneity in the latter meta-analysis is that definitions of the composite CV outcomes were quite different in the studies included (**Table 6**).

2.3.4.5 Composite outcomes

In addition, atherosclerotic events, namely myocardial infarction and non-specified stroke, were part of the composite CV outcomes. Although there is no plausible association for low serum potassium levels and myocardial infarction, the latter was part of the search strategy in order to identify cardiovascular deaths due to myocardial infarction. However, I did not explicitly implement "cerebrovascular diseases" in the search strategy, as except for embolic stroke, which may develop in the course of hypokalemia-induced atrial fibrillation, abnormal serum potassium levels have not been reported to be risk factors for cerebrovascular disease events. Therefore, I suspect that the studies with composite CV outcomes included might have underestimated the risk of hypo- and hyperkalemia. Thus, I suggest that future studies with composite CV endpoints should consider excluding atherosclerotic events, such as myocardial infarction and ischemic stroke, from their endpoint definitions.

Similarly, the definitions of ventricular arrhythmias were heterogeneous between the studies included (**Table 6**). While some studies investigated ventricular tachycardia, ventricular flutter or ventricular fibrillation, others measured abnormal ectopic ventricular activity or premature ventricular complexes. Consequently, the percentages of participants experiencing ventricular arrhythmias ranged widely in the studies included. I intended to do arrhythmia subtype-specific meta-analyses, but this was not completely possible, because only three studies had sufficient data for meta-analysis and used composite arrhythmia outcomes (Goyal *et al.*, 2012; Keskin *et al.*, 2016; Uluganyan *et al.*, 2016). These three studies had quite comparable arrhythmia rates (4.4 %, 6.1 %, and 10.6 %, respectively) and were finally pooled in a meta-analysis. Future studies should be large enough to address clearly defined arrhythmia subtypes instead of composite arrhythmia definitions.

2.3.5 Clinical implications for maintaining serum potassium levels in specific ranges

As recommended by experts with an affiliation to the American Heart association (Lerma, 2014), serum potassium levels should be maintained between 3.5 and 5.1 mmol/L in the older general population in order to prevent supraventricular arrhythmias and ventricular arrhythmias, as well as CVM. For patients with hypertension or heart failure, a higher cut-off of 4.0 mmol/L has been suggested for hypokalemia (Cohn *et al.*, 2000; Hunt *et al.*, 2005). This recommendation is supported by the observed increased cardiovascular risk for low serum potassium levels in these two aforementioned patient groups sometimes treated with non-potassium-sparing diuretics. As the corresponding studies had been conducted before current guidelines for the management of hypertension (Mancia and Fagard, 2013; Williams *et al.*, 2018) and heart failure (Ponikowski *et al.*, 2016) were published, the study results need to be interpreted with caution. In patients with hypertension, non-potassium-sparing diuretics are nowadays used in low doses and often in combination with potassium-sparing agents. In patients with heart failure, the aforementioned cardiovascular risk for hypokalemia should no longer exist since they receive ACE inhibitors, ARBs or aldosterone antagonists, all retaining serum potassium. However, it seems to be important to cautiously monitor serum potassium levels when thiazide or even loop diuretics, especially in higher doses, are prescribed for patients with hypertension or heart failure.

For patients with AMI, an even higher threshold for hypokalemia has been suggested, namely 4.5 mmol/L during or shortly after AMI (Macdonald and Struthers, 2004). As I detected a borderline significant 2-fold increased risk of arrhythmias in AMI patients with low serum potassium levels, I agree with this recommendation to target serum potassium levels in the high-normal range in these patients. However, hyperkalemia could also be a threat because AMI patients showed a strongly increased arrhythmia risk with serum potassium levels ≥ 5.5 mmol/L (Goyal *et al.*, 2012).

For patients with CKD or end-stage renal disease requiring dialysis, it is difficult to reach serum potassium levels ≤ 5.1 mmol/L. Therefore, some studies suggested a higher cut-off of > 5.5 mmol/L for hyperkalemia in these patients (Abuelo, 2015; Van Harrison *et al.*, 2014). However, this systematic review included large cohort studies in patients with impaired kidney function (Luo *et al.*, 2016) and dialysis treatment (Kovesdy *et al.*, 2007), which assessed the shape of the association of serum potassium levels and cardiovascular outcomes and did observe an increased risk for serum potassium levels above 5.0 mmol/L (Kovesdy *et al.*, 2007; Luo *et al.*, 2016). In addition, it should be noted that another large observational study with almost 100,000 CKD patients (Collins *et al.*, 2017) showed in a spline analysis that all-cause mortality of CKD patients already started to increase at serum potassium levels above 5.0 mmol/L.

2.3.6 Conclusion

My findings from this systematic review and meta-analysis highlight the clinical relevance of monitoring serum potassium levels especially in cardiac patients at high risk of hypokalemia, such as patients with hypertension or heart failure, who frequently receive diuretic treatment. Controlled clinical trials are needed to determine if these patient populations may profit from more frequent potassium-monitoring and subsequent interventions, such as change or withdrawal of potassium-influencing drugs, in order to restore normal values and prevent cardiovascular outcomes.

3 ORIGINAL STUDY

In summary, the results of the systematic review and meta-analysis showed that the association of hypokalemia and CVM appears to be restricted to subpopulations with hypertension or heart failure (Hoppe *et al.*, 2018). Both conditions are frequently treated with diuretics (Williams *et al.*, 2018), which is why hypokalemia due to use of non-potassium-sparing diuretics might explain the increased CVM in these patients (Schulman and Narins, 1990). Therefore, the second aim of this dissertation was to investigate the association of drugs affecting potassium excretion and CVM. More precisely, I analysed the associations of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives use with CVM in individuals receiving antihypertensive treatment, including individuals with hypertension or heart failure. For this purpose, the drug classes were first analysed distinctly and then jointly in order to detect potential drug-drug interactions between these two potassium-influencing drug classes.

The content of the following chapters on material and methods (3.1), results (3.2), and discussion (3.4) are currently under consideration for publication in the scientific article "Hoppe, L. K., Muhlack, D. C., Koenig, W., Brenner, H. and Schöttker, B. (2019). The Associations of Diuretics and Laxatives Use with Cardiovascular Mortality. An Individual Patient-Data Meta-Analysis of Two Large Cohort Studies. (Submitted)".

3.1 Material and methods

3.1.1 Design and setting

The ESTHER study (**E**pidemiologische **S**tudie zu Chancen der Verhütung, Früherkennung und optimierten **Th**erapie chronischer **Er**krankungen in der älteren Bevölkerung [German]) is an ongoing epidemiological cohort study performed in the older general population of the federal state of Saarland, Germany (Löw *et al.*, 2004). At baseline (2000 to 2002), 9,940 men and women, aged 50 to 75 years, were recruited by their general practitioner when presenting for a routine health check-up (Muhlack *et al.*, 2018). Data collection at baseline included physical measurements and blood sampling. Additionally, both the general practitioner and the participant provided information via detailed standardized questionnaires. Follow-up contacts were realized after 2, 5, 8, 11, and 14 years, of which the latter was used for the current analysis.

The UK Biobank is also a general population cohort study and recruited participants aged between 40 and 69 years (Collins, 2012). Recruitment of 502,616 individuals took place from 2006 to 2010

throughout the United Kingdom (UK) (Sudlow *et al.*, 2015). Data collection included a self-completed touchscreen questionnaire, a computer-assisted interview, physical and functional measures, and biological samples, as described in detail elsewhere (Sudlow *et al.*, 2015). A follow-up after 7 years was realised through linked population-level UK medical and other health-related records (Palmer, 2007; Sudlow *et al.*, 2015).

3.1.2 Mortality ascertainment

Vital status of ESTHER participants was collected until the end of 2015 by querying the residents' registration offices resulting in a completeness of follow-up for all-cause mortality of 99.7 %. Death certificates were available from public health departments for 98.9 % of ESTHER participants who had died. In the UK Biobank, almost complete mortality follow-up until 15 February 2016 was guaranteed by embedding the study within the UK's National Health Service (Collins, 2012). The primary cause of death was available for all but six UK Biobank participants (99.99 % completeness).

The International Statistical Classification of Diseases and Related Health Problems (ICD) is the most important globally acknowledged classification system for medical diagnoses (World Health Organization, 2019). According to the 10th revision of the ICD, deaths coded with ICD-10 codes I00-I99, which comprise diseases of the circulatory system, were considered as cardiovascular deaths. Hereinafter these deaths are collectively considered and also referred to as cardiovascular mortality (CVM).

3.1.3 Medication assessment

In the ESTHER study, prescribed drugs were collected from the physician's questionnaire. In the UK Biobank, an interview of the study participants with a trained nurse was conducted to get information on drug utilization. The Anatomical Therapeutic Chemical (ATC) classification system, developed and maintained by the WHO Collaborating Centre for Drug Statistics Methodology, systematically classifies drugs according to their anatomical, therapeutic, pharmacological, and chemical properties into five levels (WHO Collaborating Centre for Drug Statistics Methodology, 2018). An ATC code presented in one to four levels defines a group of drugs acting on the same organ, treating the same disease, having the same pharmacological effect, and showing the same chemical structure, respectively. An ATC code in five levels identifies exactly one specific active substance. To define the study population of individuals treated with antihypertensive drugs, I used the following drug classes with their corresponding ATC codes: Agents acting on the renin-

angiotensin system (C09), calcium channel blockers (C08), β-blocking agents (C07), diuretics (C03), and miscellaneous antihypertensive agents (C02).

Diuretics were studied in two groups: (i) non-potassium-sparing diuretics (C03AA, C03AH, C03AX, C03BA, C03BC, C03BD, C03BK, C03BX, C03CA, C03CC, and C03CX), and (ii) potassium-sparing diuretics (C03D), combinations of non-potassium-sparing diuretics with potassium (C03AB, C03BB, and C03CB) or combinations of non-potassium-sparing diuretics with potassium-sparing diuretics (C03E).

Laxatives use was assessed with the following question in the participant questionnaire of the ESTHER study: "Do you sometimes or regularly take laxatives?" The answering options "Yes, sometimes" and "Yes, regularly" were used to identify regular laxatives users. The UK Biobank assessed laxatives use via the touchscreen questionnaire with the following question: "Do you regularly take any of the following? (You can select more than one answer)". Answering options included "Laxatives (e.g. Dulcolax, Senokot)" and other OTC drugs.

3.1.4 Covariate assessment

Socio-demographic characteristics and lifestyle factors were assessed as self-reported information with detailed standardized participant questionnaires in the ESTHER study and with touchscreen questionnaires in the UK Biobank.

The smoking status was assessed by questions about the participant's past and current tobacco smoking history and finally defined via the following three categories: "never", "previous" or "current". Physical activity was measured in hours of vigorous physical activity per week in the ESTHER study. Participants doing any amount of vigorous physical activity per week were defined as physically active. In the UK Biobank, physical activity was assessed as the number of days per week of at least 10 minutes of vigorous physical activity. Participants who had answered with one to seven days were defined as physically active. Alcohol consumption was assessed by questions about the participants' weekly and monthly consumption of pints of beer, glasses of wine, and measures of spirits. I used the amounts of beverages to estimate grams of consumed ethanol per day and subsequently grouped participants into the WHO drinking categories as follows: Abstainers, category I (mild) including women with an alcohol consumption of 0-19.99 g/d or men with 0-39.99 g/d, and category II/III (moderate/ heavy) including women with ≥ 20 g/d or men with ≥ 40 g/d (Rehm *et al.*, 2003).

In the ESTHER study, measurements of systolic blood pressure (in mmHg) were available from the physician's medical conditions report of the health check-up. In the UK Biobank, systolic blood pressure measurements were conducted by automated reading at the left upper arm (range returned by the Omron device is 0-255 mmHg). BMI (in kg/m^2) was calculated based on weight [kg] and height [m] and categorized according to a slightly modified version of the WHO standards as follows: < 25, 25 to < 30, and ≥ 30 kg/m^2 (World Health Organization, 2000). Potential kidney damage was defined by urinary albumin levels ≥ 20 mg/L. In the ESTHER study, urinary albumin was measured by nephelometry with the BN II system using OSAL N antiserum against albumin (both Siemens, Marburg, Germany). In the UK Biobank, urinary albumin was determined with immunoturbidimetry on a Beckman Coulter AU5400 (Brea, United States).

Information on diseases (diabetes mellitus, heart failure, and CHD) and a history of cardiovascular events (myocardial infarction and stroke) were based on physician-reported information in the ESTHER study and on self-reported information from a verbal interview in the UK Biobank. To identify participants with diabetes mellitus, I additionally used the reported information on antidiabetic drugs (physician-reported in the ESTHER study and self-reported in the UK Biobank). CHD was defined as a composite of angina pectoris and myocardial infarction. The heart failure prevalence in the UK Biobank was implausibly low (0.03 %) most probably because of self-reporting and was therefore not used in these analyses.

Anticholinergic drug use included use of drugs classified as having a moderate (score 2) or severe (score 3) anticholinergic potential according to the anticholinergic cognitive burden (ACB) scoring (Cai *et al.*, 2013). The ACB score was developed in the course of a systematic review summarizing the results of 27 studies about the association of anticholinergic activities of drugs and cognition. Subsequently, a list of those anticholinergic drugs identified to affect cognition was presented to an interdisciplinary expert panel, who finally classified the drugs into three ordered groups (1 = mild, 2 = moderate, 3 = severe) (Boustani *et al.*, 2008; Campbell *et al.*, 2009).

Opioid use was identified via the ATC codes N02A (opioids) and N07BC (drugs used in opioid dependence).

3.1.5 Statistical analysis

To have a more comparable baseline age in the two studies, n = 117,894 participants younger than 50 years were excluded from the total UK Biobank sample of n = 502,616. Furthermore, in order to have a comparable baseline cardiovascular risk of diuretics users and a control group, only users of antihypertensive drugs were included in the current analysis ($n_{excluded}$ = 279,348). A further 15

participants were excluded as their causes of death were unknown (ICD-10 codes R98 and R99) or missing. Finally, the analytical sample size for the UK Biobank was n = 105,359.

Likewise, participants of the ESTHER study (n = 9,940 at baseline) were excluded if they had no antihypertensive treatment ($n_{excluded}$ = 5,622), an unknown cause of death ($n_{excluded}$ = 56) or a loss to follow-up ($n_{excluded}$ = 9), leaving an analytical sample size of n = 4,253 participants.

Figure 7 graphically shows the aforementioned inclusions and exclusions of the study participants to determine the final analysis samples.

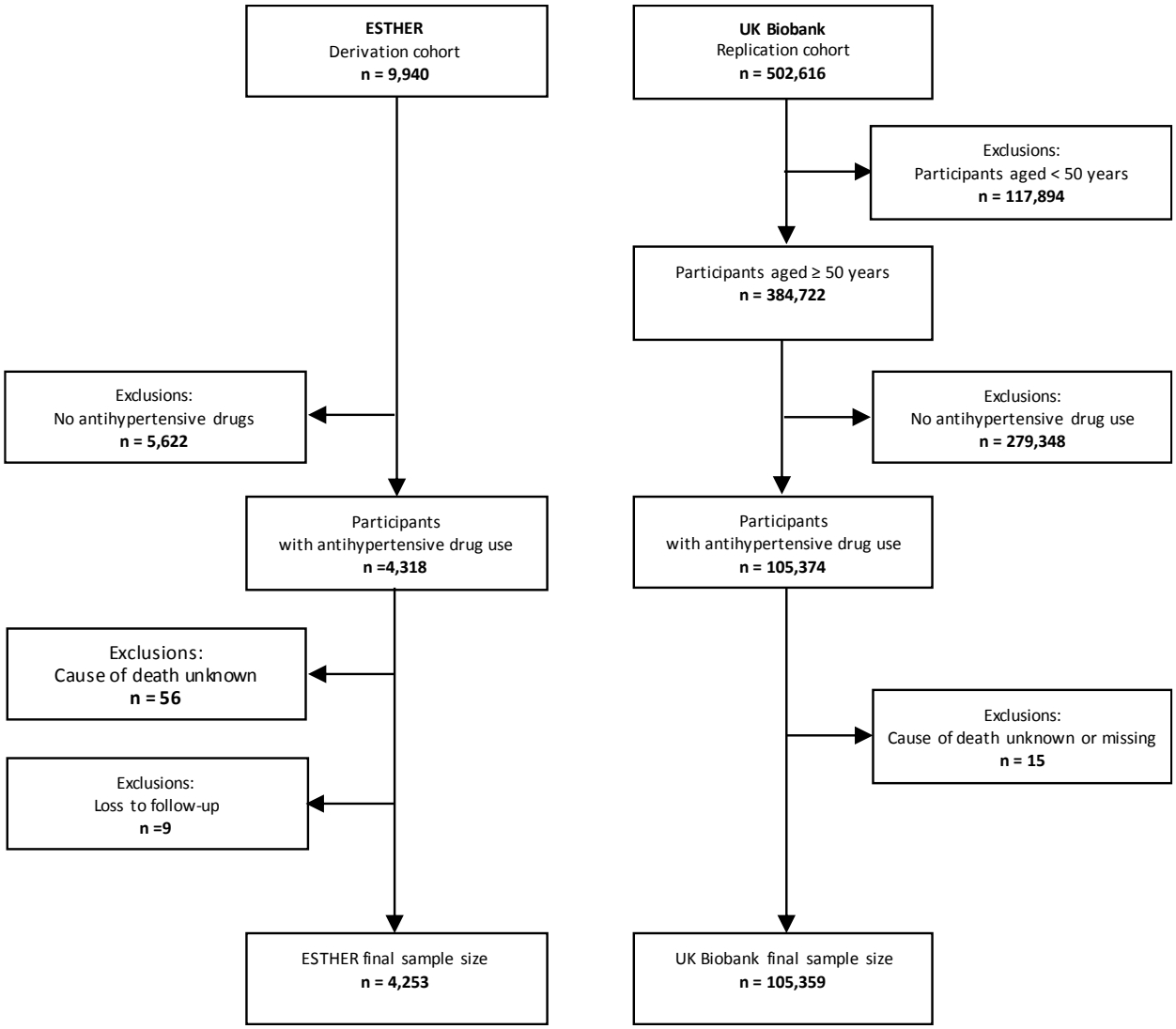

Figure 7. Flow chart showing the study populations of the ESTHER study (baseline: 2000-2002) and the UK Biobank (baseline: 2006-2010) with inclusion and exclusion procedures that resulted in the final analytical sample sizes.

Exposure to diuretics and laxatives was assessed in two ways: distinctly and jointly. In distinct analyses, laxatives and diuretics were put separately into models. Furthermore, I analysed diuretics use overall and more specifically sub-divided into two groups:

(1) Users of non-potassium-sparing diuretics
(2) Users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

In a sensitivity analysis conducted in the large UK Biobank only, the second group was further divided into its three subgroups.

For joint analyses of concurrent diuretics and laxatives use, study participants were allocated to six mutually exclusive treatment groups (**Figure 8**):

(1) Non-potassium-sparing diuretics and laxatives
(2) Non-potassium-sparing diuretics and no laxatives
(3) Potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics and laxatives
(4) Potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics and no laxatives
(5) No diuretics and laxatives
(6) No diuretics and no laxatives.

Where characteristics were described by dichotomous or categorical variables, Chi^2-tests were used to assess differences in baseline characteristics in selected drug user groups.

Moreover, the associations of the aforementioned drug exposure groups with CVM were assessed in a time-to-event analysis using Cox proportional hazard regression models to estimate hazard ratios and 95%-confidence intervals. All analyses were adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, BMI, potential kidney damage, diabetes mellitus, heart failure (in the ESTHER study only), CHD, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids. I adjusted for the latter two drug classes because they can cause chronic constipation and are known to be associated with mortality (Ray *et al.*, 2016; Ruxton *et al.*, 2015). Age and systolic blood pressure were modelled continuously and all other co-variables with the categorizations shown in **Table 19**.

In a further sensitivity analysis, the aforementioned covariates were combined in propensity scores and the Cox models of the distinct analyses were adjusted for the propensity scores.

Furthermore, subgroup analyses were conducted for age (≥ 65 years vs. < 65 years), sex (men vs. women), potential kidney damage (urinary albumin ≥ 20 mg/L vs. < 20 mg/L), CHD (Yes vs. No), and heart failure (Yes vs. No).

Results of both studies were combined by random-effects model meta-analyses with inverse variance weighting to allow for between-study heterogeneity. Data synthesis was performed by using the software Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ, USA).

In another sensitivity analysis, the follow-up time of the ESTHER study (14 years) was restricted to the follow-up time of the UK Biobank (7 years) to check whether the different lengths of follow-up had a significant influence on the results.

All analyses were performed with the software package SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). Missing values were imputed using the MCMC algorithm of the SAS procedure PROC MI. Finally, five imputed datasets were created and analyses of these five datasets were combined by the SAS procedure PROC MIANALYZE. All statistical tests were two-sided with an α-level of 0.05.

3.2 Results

3.2.1 Characteristics of the study population

Baseline characteristics of antihypertensive medication users of both study populations are shown in **Table 19**. The mean age of the 4,253 ESTHER participants and the 105,359 UK Biobank participants was 64 years (Standard deviation (SD) = 6 years) and 62 years (SD = 5 years), respectively. Sexes (men/women) were almost equally distributed within each study, while there was a higher proportion of men in the UK Biobank (52.9 %) than in the ESTHER study (45.1 %). The proportions of physically active participants and moderate/heavy drinkers (WHO category II/III) were higher in the UK Biobank. The prevalence of diseases and cardiac events was higher in the ESTHER study, while elevated urinary albumin levels (≥ 20 mg/L) were more prevalent in the UK Biobank indicating a higher proportion of participants with potential kidney damage in this cohort.

Table 19. Baseline characteristics of the analysed participants with antihypertensive treatment of the ESTHER study (Germany, baseline: 2000-2002) and the UK Biobank (UK, baseline: 2006-2010).

	ESTHER (n = 4,253)					**UK BIOBANK** (n = 105,359)				
Characteristics	**n_{total}[a]**	**n_{char}**	**(%)**	**Mean**	**(SD)**	**n_{total}[a]**	**n_{char}**	**(%)**	**Mean**	**(SD)**
Age (years)	4,253			64	(6)	105,359			62	(5)
Age ≥ 65 years	4,253	2,024	(47.6)			105,359	38,203	(36.3)		
Sex (male)	4,253	1,917	(45.1)			105,359	55,751	(52.9)		
Smoking	4,128					104,621				
Never		2,136	(51.7)				50,280	(48.1)		
Former		1,440	(34.9)				45,054	(43.1)		
Current		552	(13.4)				9,287	(8.9)		
Vigorous physical activity[b]	4,240					96,972				
No		2,455	(57.9)				44,401	(45.8)		
Yes		1,785	(42.1)				52,571	(54.2)		
Alcohol consumption[c]	3,803					88,913				
Abstainer		1,381	(36.3)				10,804	(12.2)		
WHO category I		2,196	(57.7)				55,816	(62.8)		
WHO category II/III		226	(5.9)				22,293	(25.1)		
SBP (mmHg)	4,246			145	(20)	98,147			147	(19)
BMI (kg/m^2)	4,253			28.9	(4.5)	104,683			29.5	(5.2)
< 25		771	(18.1)				18,823	(18.0)		
25 to < 30		1,996	(47.0)				44,376	(42.4)		
≥ 30		1,483	(34.9)				41,484	(39.6)		
Urinary albumin (mg/L)	4,220					41,488				
< 20		3,303	(78.3)				27,495	(66.3)		
≥ 20		917	(21.7)				13,993	(33.7)		
Diabetes mellitus	4,192	944	(22.5)			105,359	11,375	(10.8)		
Heart failure	4,206	748	(17.8)			104,935	N.A.[d]			
CHD	4,252	946	(22.3)			104,935	17,627	(16.8)		
History of MI	4,079	417	(10.2)			104,935	9,345	(8.9)		
History of stroke	4,066	222	(5.5)			104,935	2,940	(2.8)		
Anticholinergic drug use	4,253	224	(5.3)			105,359	7,160	(6.8)		
Opioid use	4,253	35	(0.8)			105,359	9,615	(9.1)		
Laxatives use	4,253	352	(8.2)			105,359	4,322	(4.1)		
Diuretics use	4,253	897	(21.1)			105,359	38,227	(36.3)		

Characteristics	ESTHER (n = 4,253)					UK BIOBANK (n = 105,359)				
	n_{total}[a]	n_{char}	(%)	Mean	(SD)	n_{total}[a]	n_{char}	(%)	Mean	(SD)
Non-potassium-sparing diuretics		455	(10.7)				35,821	(34.0)		
Potassium-sparing diuretics or combinations[e]		442	(10.4)				2,406	(2.3)		

[a] Does not always add up to the total study sizes (n) due to missing values.
[b] Vigorous physical activity was measured in hours per week (ESTHER) or in the number of days per week of at least 10 min of activity (UK Biobank): "No": Participants not doing any amount of vigorous physical activity, "Yes": Participants doing any amount of vigorous physical activity.
[c] Alcohol consumption in categories of the WHO (Rehm *et al.*, 2003): Category I including women with an alcohol consumption of 0-19.99 g/d or men with 0-39.99 g/d, category II including women with an alcohol consumption of 20-39.99 g/d or men with 40-59.99 g/d, and category III including women with an alcohol consumption of ≥ 40 g/d or men with ≥ 60 g/d.
[d] Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.
[e] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

BMI, body mass index; *CHD*, coronary heart disease; *MI*, myocardial infarction; *N.A.*, not applicable; n_{char}, number of participants with the characteristics; n_{total}, number of participants with data for the characteristic; *SBP*, systolic blood pressure; *SD*, standard deviation; *UK*, United Kingdom; *WHO*, World Health Organization

Further, **Table 19** shows that self-reported, regular laxatives use was higher in the ESTHER study (8.2 %) than in the UK Biobank (4.1 %). In addition, one out of five ESTHER participants used diuretics (21.1 %), whereas in the UK Biobank more than every third participant did (36.3 %). The difference can mostly be explained by lower β-blocker use in the UK Biobank (30.6 %) compared to 49.3 % in the ESTHER study (**Table 20**). One might conclude that treatment of hypertension in the UK is preferably managed by use of diuretics as they are much cheaper than β-blockers. All other antihypertensive drug classes (calcium channel blockers, ACE inhibitors, and ARBs) were similarly frequently used (**Table 20**). Interestingly, **Table 19** shows that the diuretics users in the ESTHER study (n = 897) consisted to equal parts of non-potassium-sparing diuretics users (50.7 %) and potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics users (49.3 %), while the diuretics users in the UK Biobank (n = 38,227) mainly took non-potassium-sparing diuretics (93.7 %) and only few diuretics users (6.3 %) had potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

Table 20. Use of antihypertensive drug classes at baseline in the ESTHER study (Germany, baseline: 2000-2002, mean baseline age: 64 years) and the UK Biobank (UK, baseline: 2006-2010, mean baseline age: 62 years).

Drug class	**ESTHER** (n = 4,253)		**UK BIOBANK** (n = 105,359)	
	n	**(%)**	**n**	**(%)**
Diuretics	897	(21.1)	38,227	(36.3)
β-blockers	2,095	(49.3)	32,193	(30.6)
Calcium channel blockers	1,168	(27.5)	33,463	(31.7)
Angiotensin-converting enzyme (ACE) inhibitors	1,660	(39.0)	46,001	(43.7)
Angiotensin II receptor blockers (ARBs)	513	(12.1)	19,963	(19.0)

UK, United Kingdom.

Population characteristics that were statistically significantly associated with regular laxatives use in both studies were age ≥ 65 years, female sex, mild alcohol consumption (category I), history of stroke, anticholinergic drug use, opioid use, and diuretics use (**Table 21**).

Table 21. Baseline characteristics of laxatives users compared to non-users of laxatives of the analysed participants with antihypertensive treatment in the ESTHER study (Germany, baseline: 2000-2002) and the UK Biobank (UK, baseline: 2006-2010).

	ESTHER (n = 4,253)			**UK BIOBANK** (n = 105,359)		
Laxatives use	**Yes** (n = 345)	**No** (n = 3,908)		**Yes** (n = 4,322)	**No** (n = 101,037)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
Age ≥ 65 years	57.1	46.8	< **0.001**	41.6	36.0	< **0.001**
Sex (male)	25.8	46.8	< **0.001**	32.3	53.8	< **0.001**
Smoking			0.181			< **0.001**
Never	54.8	51.5		46.1	48.1	
Former	30.4	35.3		42.6	43.1	
Current	14.9	13.2		11.4	8.8	
Vigorous physical activity[a]			0.218			< **0.001**
No	61.1	57.6		57.5	45.3	
Yes	39.0	42.4		42.6	54.7	
Alcohol consumption[b]			< **0.001**			< **0.001**
Abstainer	48.0	35.3		22.5	11.7	
WHO category I	47.3	58.6		57.3	63.0	
WHO category II/III	4.7	6.1		20.2	25.3	

Laxatives use	**ESTHER** (n = 4,253)			**UK BIOBANK** (n = 105,359)		
	Yes (n = 345)	**No** (n = 3,908)		**Yes** (n = 4,322)	**No** (n = 101,037)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
SBP (mmHg)			0.176			**< 0.001**
< 140	34.3	32.4		44.2	35.9	
140 to < 160	44.3	41.6		36.4	39.6	
≥ 160	21.4	26.0		19.4	24.6	
BMI (kg/m^2)			0.060			**< 0.001**
< 25	20.6	17.9		20.8	17.9	
25 to < 30	40.9	47.5		38.2	42.6	
≥ 30	38.6	34.6		41.0	39.6	
Urinary albumin (mg/L)			0.575			0.615
< 20	79.5	78.2		66.9	66.3	
≥ 20	20.5	21.8		33.2	33.8	
Diabetes mellitus	26.3	22.2	0.080	10.9	10.8	0.788
Heart failure[c]	25.4	17.1	**< 0.001**	N.A.	N.A.	N.A.
CHD	25.5	22.0	0.129	21.3	16.6	**< 0.001**
History of MI	12.6	10.0	0.138	9.6	8.9	0.130
History of stroke	8.9	5.2	**0.005**	3.9	2.8	**< 0.001**
Anticholinergic drug use	9.0	4.9	**0.001**	18.5	6.3	**< 0.001**
Opioid use	2.0	0.7	**0.010**	26.1	8.4	**< 0.001**
Diuretics use	29.6	20.3	**< 0.001**	43.6	36.0	**< 0.001**
Non-potassium-sparing diuretics	15.4	10.3	**0.004**	39.3	33.8	**< 0.001**
Potassium-sparing diuretics or combinations[d]	14.2	10.1	**0.016**	4.3	2.2	**< 0.001**

Bold printed: statistically significant ($p < 0.05$).

[a] Vigorous physical activity was measured in hours per week (ESTHER study) and in the number of days per week of at least 10 min of activity (UK Biobank): "No": Participants not doing any amount of vigorous physical activity, "Yes": Participants doing any amount of vigorous physical activity.

[b] Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/d or men with 0-39.99 g/d, category II including women with an alcohol consumption of 20-39.99 g/d or men with 40-59.99 g/d, and category III including women with an alcohol consumption of ≥ 40 g/d or men with ≥ 60 g/d.

[c] Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

[d] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

BMI, body mass index; *CHD*, coronary heart disease; *MI*, myocardial infarction; *N.A.*, not applicable; *SBP*, systolic blood pressure; *UK*, United Kingdom; *WHO*, World Health Organization.

The use of diuretics was statistically significantly positively associated with older age (≥ 65 years), female sex, lower alcohol consumption, higher BMI, history of stroke, opioid use, and laxatives use in both cohorts (**Table 22**).

Table 22. Baseline characteristics of diuretics users compared to non-users of diuretics of the analysed participants with antihypertensive treatment in the ESTHER study (Germany, baseline: 2000-2002) and the UK Biobank (UK, baseline: 2006-2010).

	ESTHER (n = 4,253)			**UK BIOBANK** (n = 105,359)		
Diuretics use	**Yes** (n = 897)	**No** (n = 3,356)		**Yes** (n = 38,227)	**No** (n = 67,132)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
Age ≥ 65 years	56.6	45.2	**< 0.001**	38.9	34.8	**< 0.001**
Sex (male)	40.5	46.3	**0.002**	42.7	58.7	**< 0.001**
Smoking			0.251			**< 0.001**
Never	54.0	51.2		49.2	47.4	
Former	34.0	35.1		42.2	43.6	
Current	12.1	13.7		8.6	9.0	
Vigorous physical activity[a]			0.094			**< 0.001**
No	60.4	57.3		48.7	44.2	
Yes	39.6	42.8		51.4	55.8	
Alcohol consumption[b]			**< 0.001**			**< 0.001**
Abstainer	42.6	34.7		13.6	11.4	
WHO category I	53.7	58.8		61.2	63.6	
WHO category II/III	3.7	6.5		25.2	25.0	
SBP (mmHg)			0.797			**< 0.001**
< 140	33.4	32.3		34.9	36.9	
140 to < 160	41.0	42.1		40.2	39.0	
≥ 160	25.6	25.6		25.0	24.1	
BMI (kg/m^2)			**< 0.001**			**< 0.001**
< 25	12.7	19.6		15.1	19.6	
25 to < 30	40.9	48.6		39.5	44.0	
≥ 30	46.4	31.8		45.4	36.4	
Urinary albumin (mg/L)			**0.007**			**< 0.001**
< 20	75.0	79.2		67.4	65.7	
≥ 20	25.1	20.8		32.6	34.3	

Diuretics use	**ESTHER** (n = 4,253)			**UK BIOBANK** (n = 105,359)		
	Yes (n = 897)	**No** (n = 3,356)		**Yes** (n = 38,227)	**No** (n = 67,132)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
Diabetes mellitus	30.9	20.3	< **0.001**	10.2	11.2	< **0.001**
Heart failure[c]	28.5	15.0	< **0.001**	N.A.	N.A.	N.A.
CHD	31.2	19.9	< **0.001**	11.0	20.1	< **0.001**
History of MI	15.4	8.9	< **0.001**	5.8	10.7	< **0.001**
History of stroke	8.2	4.7	< **0.001**	3.2	2.6	< **0.001**
Anticholinergic drug use	5.5	5.2	0.768	7.4	6.5	< **0.001**
Opioid use	1.6	0.6	**0.006**	11.1	8.0	< **0.001**
Laxatives use	11.4	7.2	< **0.001**	4.9	3.6	< **0.001**

Bold printed: statistically significant ($p < 0.05$).

[a] Vigorous physical activity was measured in hours per week (ESTHER study) and in the number of days per week of at least 10 min of activity (UK Biobank): "No": Participants not doing any amount of vigorous physical activity, "Yes": Participants doing any amount of vigorous physical activity.

[b] Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/d or men with 0-39.99 g/d, category II including women with an alcohol consumption of 20-39.99 g/d or men with 40-59.99 g/d, and category III including women with an alcohol consumption of ≥ 40 g/d or men with ≥ 60 g/d.

[c] Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

BMI, body mass index; *CHD*, coronary heart disease; *MI*, myocardial infarction; *N.A.*, not applicable; *SBP*, systolic blood pressure; *UK*, United Kingdom; *WHO*, World Health Organization.

Comparing more specifically users of non-potassium-sparing diuretics and users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics, most characteristics were comparable (**Table 23**). Interestingly, participants with potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics more frequently had blood pressure < 140 mmHg in both cohorts. However, a different pattern in the two studies was observed for the CVD burden. Whereas CHD and a history of myocardial infarction in users of non-potassium-sparing diuretics were more prevalent in the ESTHER study, these CVDs were statistically significantly substantially less prevalent in the UK Biobank.

Table 23. Baseline characteristics of users of non-potassium-sparing diuretics compared to users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics of the analysed participants with antihypertensive treatment in the ESTHER study (Germany, baseline: 2000-2002) and the UK Biobank (UK, baseline: 2006-2010).

	ESTHER (n = 4,253)			**UK BIOBANK** (n = 105,359)		
Users of	**Non-potassium-sparing diuretics** (n = 455)	**Potassium-sparing diuretics or diuretics combinations**[a] (n = 442)		**Non-potassium-sparing diuretics** (n = 35,821)	**Potassium-sparing diuretics or diuretics combinations**[a] (n = 2,406)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
Age ≥ 65 years	58.2	55.0	0.324	38.8	40.4	0.112
Sex (male)	43.7	37.1	0.043	42.8	41.0	0.074
Smoking			0.054			**< 0.001**
Never	52.6	55.4		49.5	45.6	
Former	37.2	30.6		42.1	43.9	
Current	10.1	14.0		8.5	10.5	
Vigorous physical activity[b]			0.976			**< 0.001**
No	60.3	60.4		47.9	59.4	
Yes	39.7	39.6		52.1	40.6	
Alcohol consumption[c]			0.880			**< 0.001**
Abstainer	41.7	43.4		13.1	20.9	
WHO category I	54.5	53.0		61.5	56.5	
WHO category II/III	3.8	3.6		25.4	22.7	
SBP (mmHg)			**0.013**			**< 0.001**
< 140	29.0	38.0		33.8	51.0	
140 to < 160	42.7	39.2		40.6	33.2	
≥ 160	28.3	22.8		25.6	15.8	
BMI (kg/m^2)			0.479			**< 0.001**
< 25	12.1	13.4		15.1	15.7	
25 to < 30	39.6	42.3		39.8	34.5	
≥ 30	48.4	44.3		45.1	49.9	

	ESTHER (n = 4,253)			**UK BIOBANK** (n = 105,359)		
Users of	**Non-potassium-sparing diuretics** (n = 455)	**Potassium-sparing diuretics or diuretics combinations**[a] (n = 442)		**Non-potassium-sparing diuretics** (n = 35,821)	**Potassium-sparing diuretics or diuretics combinations**[a] (n = 2,406)	
Characteristics	**n [%]**	**n [%]**	**p-value**	**n [%]**	**n [%]**	**p-value**
Urinary albumin (mg/L)			**0.002**			0.124
< 20	70.4	79.6		67.6	65.1	
≥ 20	29.6	20.4		32.4	34.9	
Diabetes mellitus	35.3	26.3	**0.004**	10.0	12.7	**< 0.001**
Heart failure[d]	31.5	25.4	**0.046**	N.A.	N.A.	N.A.
CHD	35.2	27.2	**0.010**	10.1	24.0	**< 0.001**
History of MI	17.2	13.4	0.119	5.1	15.5	**< 0.001**
History of stroke	9.0	7.4	0.393	3.2	3.5	0.305
Anticholinergic drug use	4.8	6.1	0.401	7.2	10.6	**< 0.001**
Opioid use	1.3	1.8	0.553	10.7	17.1	**< 0.001**
Laxatives use	11.7	11.1	0.791	4.7	7.8	**< 0.001**

Bold printed: statistically significant ($p < 0.05$).

[a] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

[b] Vigorous physical activity was measured in hours per week (ESTHER study) and in the number of days per week of at least 10 min of activity (UK Biobank): "No": Participants not doing any amount of vigorous physical activity, "Yes": Participants doing any amount of vigorous physical activity.

[c] Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/d or men with 0-39.99 g/d, category II including women with an alcohol consumption of 20-39.99 g/d or men with 40-59.99 g/d, and category III including women with an alcohol consumption of ≥ 40 g/d or men with ≥ 60 g/d.

[d] Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

BMI, body mass index; *CHD*, coronary heart disease; *MI*, myocardial infarction; *N.A.*, not applicable; *SBP*, systolic blood pressure; *UK*, United Kingdom; *WHO*, World Health Organization.

3.2.2 Associations of laxatives and diuretics use with CVM in distinct analyses

During a median follow-up time of 14 years, 476 cardiovascular deaths were observed in the ESTHER study (rate per 1,000 person-years: 8.7). In the UK Biobank, 1,616 cardiovascular deaths were observed during a median follow-up of 7 years (rate per 1,000 person-years: 2.2). Hazard ratios (HR) and 95%-confidence intervals (95%-CI) for the associations of laxatives and diuretics use with CVM are shown in **Table 24**.

3.2.2.1 Laxatives

In both studies, no statistically significantly increased CVM was observed in laxatives users compared to non-users. The association of laxatives use and CVM was also not statistically significant when combining the results of both studies by random-effects model meta-analysis (HR [95%-CI]: 1.13 [0.94; 1.36]).

3.2.2.2 Diuretics

I observed a statistically significantly increased CVM in users of diuretics overall in both studies. The corresponding pooled effect estimate revealed a 1.6-fold increased CVM of diuretics users compared to non-users, who used other antihypertensive drugs (HR [95%-CI]: 1.57 [1.29; 1.90]). Furthermore, there was a statistically significant association of non-potassium-sparing diuretics use and CVM in both studies and the pooled hazard ratio [95%-CI] was 1.39 [1.26; 1.53]. Results of the ESTHER study and UK Biobank diverged for users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics and when pooling these results of both studies by random-effects model meta-analysis, the hazard ratio point estimate was not statistically significant (HR [95%-CI]: 1.84 [0.68; 4.96]). The strong, statistically significant association for this group in the UK Biobank (HR [95%-CI]: 3.03 [2.52; 3.64]) was based on both participants taking potassium-sparing diuretics only and participants using potassium-sparing diuretics in combination with non-potassium-sparing diuretics (**Table 25**). Users of a combination of non-potassium-sparing diuretics and potassium had no statistically significantly increased CVM (**Table 25**).

Table 24. Associations with CVM comparing users and non-users of laxatives, diuretics overall, and diuretics in specific in the ESTHER study (Germany, baseline: 2000-2002, mean baseline age: 64 years, 14 years of mortality follow-up), in the UK Biobank (UK, baseline: 2006-2010, mean baseline age: 62 years, 7 years of mortality follow-up) and in a meta-analysis of the two studies.

Drug class	**ESTHER** (n = 4,253; 476 cases)			**UK BIOBANK** (n = 105,359 1,616 cases)			**META-ANALYSIS** (n = 109,612; 2,092 cases)		
	n[a]	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[c]**
Laxatives									
Non-users	3,890	433	Ref.	101,003	1,526	Ref.	104,893	1,959	Ref.
Users	363	43	0.99 (0.70; 1.41)	4,356	90	1.19 (0.96; 1.48)	4,719	133	1.13 (0.94; 1.36)
Diuretics overall									
Non-users	3,356	327	Ref.	67,132	887	Ref.	70,488	1,214	Ref.
Users	897	149	**1.39 (1.13; 1.70)**	38,227	729	**1.70 (1.53; 1.88)**	39,124	878	**1.57 (1.29; 1.90)**
Diuretics in specific									
Non-users	3,356	327	Ref.	67,132	887	Ref.	70,448	1,214	Ref.
Users of non-potassium-sparing diuretics	455	90	**1.49 (1.17; 1.89)**	35,821	597	**1.37 (1.23; 1.52)**	36,276	687	**1.39 (1.26; 1.53)**
Users of potassium-sparing diuretics or combinations[d]	442	59	1.10 (0.83; 1.46)	2,406	132	**3.03 (2.52; 3.64)**	2,848	191	1.84 (0.68; 4.96)

Bold printed: statistically significant ($\rho < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1.

[b] Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure (in ESTHER study only), coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

[c] Results of the two studies combined by random-effects model meta-analysis.

[d] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CI, confidence interval; *CVM*, cardiovascular mortality; *HR*, hazard ratio; *Ref.*, reference; *UK*, United Kingdom.

Table 25. Associations with CVM in users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics compared to non-users of diuretics in the UK Biobank (UK, baseline: 2006-2010, mean baseline age: 62 years, 7 years of mortality follow-up).

Drug class	**UK BIOBANK** (n = 105,359; 1,616 cases)		
	n[a]	**n_{cases}**[b]	**HR (95%-CI)**[c]
Non-users of diuretics	67,132	887	Ref.
Users of potassium-sparing diuretics	490	26	**2.76 (1.87; 4.07)**
Users of non-potassium-sparing diuretics combined with potassium-sparing diuretics	1,675	101	**3.15 (2.56; 3.87)**
Users of non-potassium-sparing diuretics combined with potassium	241	5	1.51 (0.63; 3.62)

Bold printed: statistically significant ($p < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1.

[b] Case numbers do not add up to the total study case number (n=1,616) due to 597 cases within the users of non-potassium-sparing diuretics (not shown).

[c] Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

CI, confidence interval*; CVM*, cardiovascular mortality; *HR*, hazard ratio; *Ref.*, reference; *UK*, United Kingdom.

3.2.2.3 Subgroup analyses

I further assessed the aforementioned associations of laxatives and diuretics use with CVM in subgroups by age, sex, urinary albumin levels, CHD, and heart failure (**Table 26**). The subgroup analysis for heart failure was only carried out in the ESTHER study because of an insufficient heart failure assessment in the UK Biobank (unreliable self-reports).

The lack of an association of laxatives use and CVM was also observed in all subgroups after pooling the two studies by meta-analyses. In analyses on diuretics, participants aged 65 and older as well as study participants with potential kidney damage (urinary albumin levels ≥ 20 mg/L) did not have substantially stronger associations of diuretics use and CVM. However, males, participants with CHD, and participants with heart failure had substantially stronger associations with CVM in all diuretics analyses with only one exception (sex-stratified analysis in the UK Biobank for users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics).

Table 26. Associations with CVM comparing users and non-users of laxatives, diuretics overall, and diuretics in specific assessed in subgroups by age, sex, urinary albumin levels and heart failure (the latter only in the ESTHER study).

Users of laxatives compared to non-users of laxatives

		ESTHER (n = 4,253; n_{cases} = 476)			**UK BIOBANK** (n = 105,359; n_{cases} = 1,616)			**META-ANALYSIS** (n = 109,612; n_{cases} = 2,092)		
Characteristic	**Subgroup**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[c]**
Age (years)	< 65	2,229	126	0.94 (0.46; 1.92)	67,156	818	**1.55 (1.16; 2.06)**	69,385	944	1.35 (0.87; 2.09)
	≥ 65	2,024	350	0.97 (0.65; 1.46)	38,203	798	0.88 (0.63; 1.25)	40,227	1,148	0.92 (0.71; 1.19)
Sex	Female	2,336	207	0.93 (0.56; 1.52)	49,608	365	1.11 (0.77, 1.60)	51,944	572	1.04 (0.78; 1.40)
	Male	1,917	269	1.09 (0.66; 1.78)	55,751	1,251	1.23 (0.93, 1.62)	57,668	1,520	1.20 (0.94; 1.52)
Albumin (mg/L)	< 20	3,328	316	1.02 (0.68; 1.54)	64,433	820	1.25 (0.90; 1.74)	67,761	1,136	1.15 (0.89; 1.49)
	≥ 20	925	160	0.90 (0.48; 1.69)	40,926	796	1.13 (0.80; 1.60)	41,851	956	1.07 (0.79; 1.45)
CHD	No	3,307	304	1.07 (0.70; 1.64)	87,731	967	1.23 (0.91; 1.66)	91,038	1,271	1.17 (0.92; 1.50)
	Yes	946	172	0.82 (0.47; 1.45)	17,628	649	1.17 (0.84; 1.62)	18,574	821	1.06 (0.77; 1.45)
Heart failure	No	3,489	326	1.07 (0.71; 1.61)	-	-	-	-	-	-
	Yes	764	150	0.83 (0.46; 1.49)	-	-	-	-	-	-

Table 26 continued, page 2/4

Users of diuretics overall compared to non-users of diuretics

		ESTHER (n = 4,253; n_{cases} = 476)			UK BIOBANK (n = 105,359; n_{cases} = 1,616)			META-ANALYSIS (n = 109,612; n_{cases} = 2,092)		
Characteristic	**Subgroup**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[c]**
Age (years)	< 65	2,229	126	**1.52 (1.01; 2.29)**	67,156	818	**1.69 (1.46; 1.95)**	69,385	944	**1.67 (1.46; 1.91)**
	≥ 65	2,024	350	**1.38 (1.09; 1.75)**	38,203	798	**1.71 (1.48; 1.97)**	40,227	1,148	**1.57 (1.28; 1.93)**
Sex	Female	2,336	207	1.20 (0.88; 1.64)	49,608	365	**1.34 (1.09; 1.66)**	51,944	572	**1.29 (1.09; 1.54)**
	Male	1,917	269	**1.55 (1.18; 2.03)**	55,751	1,251	**1.84 (1.64; 2.07)**	57,668	1,520	**1.77 (1.53; 2.04)**
Albumin (mg/L)	< 20	3,328	316	**1.33 (1.03; 1.72)**	64,433	820	**1.68 (1.41; 2.00)**	67,761	1,136	**1.52 (1.22; 1.91)**
	≥ 20	925	160	**1.53 (1.08; 2.17)**	40,926	796	**1.72 (1.46; 2.03)**	41,851	956	**1.68 (1.45; 1.95)**
CHD	No	3,307	304	1.11 (0.84; 1.46)	87,731	967	**1.33 (1.17; 1.51)**	91,038	1,271	**1.27 (1.09; 1.48)**
	Yes	946	172	**1.85 (1.36; 2.54)**	17,628	649	**2.53 (2.15; 2.98)**	18,574	821	**2.23 (1.65; 3.01)**
Heart failure	No	3,489	326	1.08 (0.82; 1.41)	-	-	-	-	-	-
	Yes	764	150	**2.15 (1.53; 3.02)**	-	-	-	-	-	-

Table 26 continued, page 3/4

Users of non-potassium-sparing diuretics compared to non-users of diuretics

		ESTHER (n = 3,811; n_{cases} = 417)			UK BIOBANK (n = 102,953; n_{cases} = 1,484)			META-ANALYSIS (n = 106,764; n_{cases} = 1,901)		
Characteristic	**Subgroup**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[c]**
Age (years)	< 65	2,030	115	**2.01 (1.24; 3.24)**	65,722	752	**1.48 (1.27; 1.72)**	67,752	867	**1.58 (1.24; 2.02)**
	≥ 65	1,781	302	**1.48 (1.11; 1.97)**	37,231	732	**1.53 (1.32; 1.78)**	39,012	1,034	**1.52 (1.33; 1.74)**
Sex	Female	2,058	182	**1.46 (1.00; 2.12)**	48,188	339	**1.26 (1.02; 1.57)**	50,246	521	**1.31 (1.08; 1.58)**
	Male	1,753	235	**1.63 (1.17; 2.28)**	54,765	1,145	**1.61 (1.42; 1.82)**	56,518	1,380	**1.61 (1.44; 1.81)**
Albumin (mg/L)	< 20	2,977	272	**1.47 (1.07; 2.03)**	62,978	750	**1.47 (1.22; 1.76)**	65,955	1,022	**1.47 (1.25; 1.72)**
	≥ 20	834	145	**1.84 (1.24; 2.73)**	39,975	734	**1.55 (1.30; 1.84)**	40,809	879	**1.59 (1.36; 1.87)**
CHD	No	2,985	270	1.15 (0.81; 1.64)	85,895	908	**1.21 (1.06; 1.39)**	88,880	1,178	**1.20 (1.06; 1.36)**
	Yes	826	147	**2.27 (1.58; 3.27)**	17,058	576	**2.22 (1.87; 2.65)**	17,884	723	**2.23 (1.91; 2.61)**
Heart failure	No	3,161	294	1.14 (0.80; 1.61)	-	-	-	-	-	-
	Yes	650	123	**2.60 (1.76; 3.84)**	-	-	-	-	-	-

Table 26 continued, page 4/4

Users of potassium-sparing diuretics or diuretics combinations[d] compared to non-users of diuretics										
		ESTHER (n = 3,798; n_{cases} = 386)			**UK BIOBANK** (n = 69,538; n_{cases} = 1,019)			**META-ANALYSIS** (n = 73,336; n_{cases} = 1,405)		
Characteristic	**Subgroup**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[c]**
Age (years)	< 65	2,039	103	1.03 (0.54; 1.95)	45,221	532	**3.68 (2.82; 4.82)**	47,260	635	2.02 (0.58; 7.01)
	≥ 65	1,759	283	1.24 (0.90; 1.72)	24,317	487	**3.51 (2.67; 4.60)**	26,076	770	2.09 (0.76; 5.81)
Sex	Female	2,080	167	0.92 (0.59; 1.43)	29,134	203	**2.22 (1.45; 3.39)**	31,214	370	1.43 (0.60; 3.40)
	Male	1,718	219	**1.47 (1.01; 2.14)**	40,404	816	**1.40 (1.10; 1.78)**	42,122	1,035	**1.42 (1.16; 1.74)**
Albumin (mg/L)	< 20	3,007	264	1.16 (0.83; 1.63)	42,145	530	**3.91 (2.95; 5.19)**	45,152	794	2.14 (0.65; 7.03)
	≥ 20	791	122	1.13 (0.65; 1.96)	27,393	489	**3.37 (2.52; 4.51)**	28,184	611	2.00 (0.69; 5.84)
CHD	No	3,012	262	1.03 (0.71; 1.50)	55,521	593	**3.28 (2.49; 4.33)**	58,533	855	1.85 (0.60; 5.76)
	Yes	786	124	1.39 (0.88; 2.18)	14,017	426	**3.95 (3.02; 5.18)**	14,803	550	2.38 (0.86; 6.63)
Heart failure	No	3,178	285	1.01 (0.70; 1.46)	-	-	-	-	-	-
	Yes	620	101	**1.61 (1.00; 2.59)**	-	-	-	-	-	-

Bold printed: statistically significant ($\rho < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1.

[b] Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure (in ESTHER study only), coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

[c] Results of the two studies combined by random-effects model meta-analysis.

[d] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CHD, coronary heart disease; *CI*, confidence interval*; CVM*, cardiovascular mortality; *HR*, hazard ratio.

3.2.3 Association of laxatives and diuretics use with CVM in joint analyses

Figure 8 provides a flow diagram showing the categorization of the study participants into six mutually exclusive treatment groups of possible combinations of non-potassium-sparing diuretics, potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics, and laxatives. Concurrent use of non-potassium-sparing diuretics and laxatives was comparably rare in both cohorts (56 participants (1.3 %) in the ESTHER study and 1,709 participants (1.6 %) in the UK Biobank).

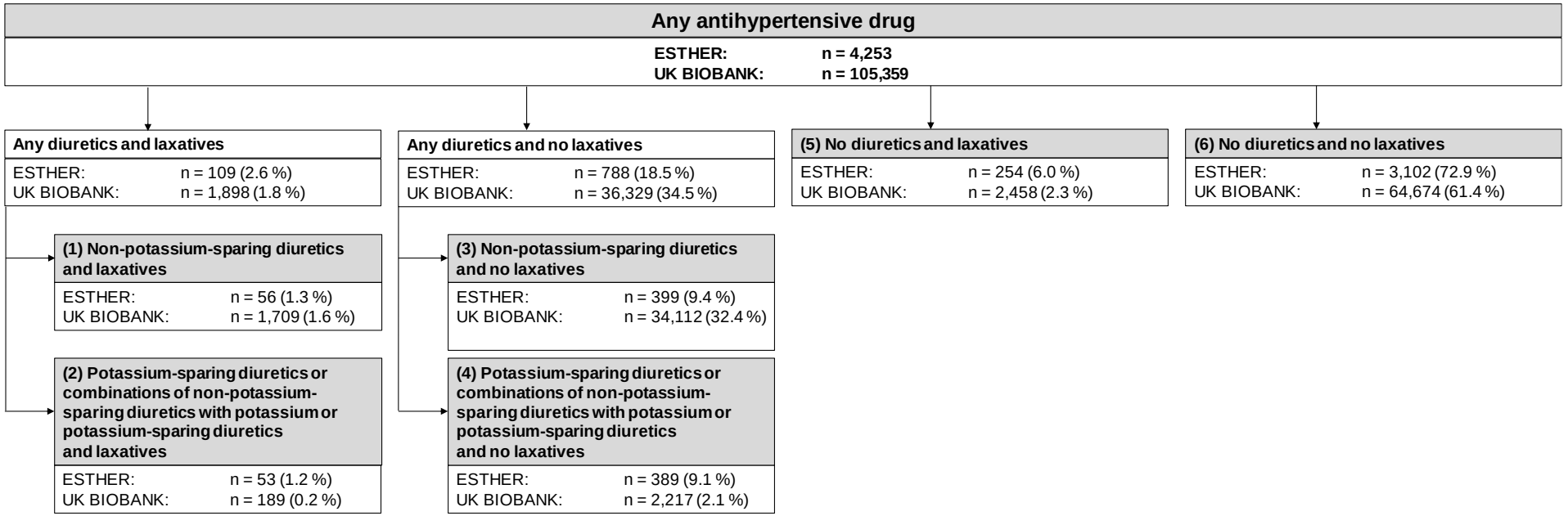

Figure 8. Flow chart showing the categorization of the study participants into six mutually exclusive treatment groups within the ESTHER study and the UK Biobank.

The associations of the comparisons between the mutually exclusive treatment groups with CVM, using study participants taking neither diuretics nor laxatives (group 6) as the control group, are presented in **Table 27**.

Concurrent users of non-potassium-sparing diuretics and laxatives had a higher CVM in both studies (HR [95%-CI] for meta-analysis: 2.05 [1.55; 2.71]) than those who only used non-potassium-sparing diuretics (HR [95%-CI] for meta-analysis: 1.50 [1.36; 1.66]), which speaks for a drug-drug interaction. However, the difference between these groups was not statistically significant. Similarly, a test for interaction of the variables "non-potassium-sparing diuretics use" and "laxatives use" was not statistically significant either (β, p for meta-analysis: +0.718, 0.075) but not far from the cut-off for statistical significance (p=0.05).

Additional laxatives use of participants taking potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics resulted in lower CVM (HR [95%-CI] for meta-analysis: 1.43 [0.33; 6.22]) than no additional laxatives use (HR [95%-CI] for meta-analysis: 2.19 [0.79; 6.08]). Although confidence intervals overlapped widely, the p-value for an interaction test was again not far from a statistically significant finding (β, p for meta-analysis: -0.580, 0.076).

The different directions of the β-coefficients for the two interaction terms are biologically plausible because they suggest an additional risk by comparing laxatives and non-potassium-sparing diuretics and a protective effect by comparing laxatives and potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics. In the latter group, the hypokalemic effects of laxatives may counteract diuretic-induced hyperkalemia.

Table 27. Associations with CVM in mutually exclusive treatment groups in the ESTHER study (Germany, baseline: 2000-2002, mean age: 64 years) and the UK Biobank (UK, baseline: 2006-2010, mean age: 62 years).

	ESTHER (n = 4,253; 476 cases)			**UK BIOBANK** (n = 105,359; 1,616 cases)			**META-ANALYSIS** (n = 109,612; 2,092 cases)		
Treatment group	**n[a]**	**n_{cases} (%)**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases} (%)**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases} (%)**	**HR (95%-CI)[c]**
Non-potassium-sparing diuretics and laxatives	56	15 (26.8)	**2.26 (1.31; 3.90)**	1,709	39 (2.3)	**1.98 (1.43; 2.75)**	1,765	54 (3.1)	**2.05 (1.55; 2.71)**
Non-potassium-sparing diuretics and no laxatives	399	75 (18.8)	**1.44 (1.10; 1.87)**	34,112	558 (1.6)	**1.51 (1.35; 1.68)**	34,511	633 (1.8)	**1.50 (1.36; 1.66)**
Potassium-sparing diuretics or combinations[d] and laxatives	53	3 (5.7)	0.59 (0.15; 2.33)	189	9 (4.8)	**2.70 (1.39; 5.23)**	242	12 (5.0)	1.43 (0.33; 6.22)
Potassium-sparing diuretics or combinations[d] and no laxatives	389	56 (14.4)	1.29 (0.95; 1.75)	2,217	123 (5.6)	**3.66 (3.01; 4.44)**	2,606	179 (6.9)	2.19 (0.79; 6.08)
No diuretics and laxatives	254	25 (9.8)	0.93 (0.61; 1.42)	2,458	42 (1.7)	1.15 (0.84; 1.58)	2,712	67 (2.5)	1.07 (0.83; 1.37)
No diuretics and no laxatives	3,102	302 (9.7)	Ref.	64,674	845 (1.3)	Ref.	67,776	1,147 (1.7)	Ref.

Bold printed: statistically significant ($\rho < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1.

[b] Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure (in ESTHER study, only), coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

[c] Results of the two studies combined by random-effects model meta-analysis.

[d] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CI, confidence interval*; CVM*, cardiovascular mortality; *HR*, hazard ratio; *Ref.*; reference; *UK*, United Kingdom.

3.2.4 Sensitivity analyses

In a sensitivity analysis using only data from the first 7 years of follow-up of the ESTHER study, the effect estimates were comparable or slightly stronger than those from the analysis with the complete follow-up time of 14 years (**Table 28**).

In a further sensitivity analysis, the Cox models for distinct analyses of laxatives and diuretics were adjusted for a propensity score (propensity to use drug class of interest), but results did not change substantially (**Table 29**). Methods, results, and discussion of the sensitivity analysis using propensity scores are presented in greater detail in chapter 3.3 (Excursus: Propensity scores).

Table 28. Associations with CVM comparing users and non-users of laxatives, diuretics overall, and diuretics in specific in the ESTHER study using only the first 7 years of follow-up or the complete follow-up of 14 years.

Drug class	ESTHER (7 years of FUP) (n = 4,253; 169 cases)			ESTHER (14 years of FUP) (n = 4,253; 476 cases)		
	n[a]	**n_{cases}**	**HR (95%-CI)[b]**	**n[a]**	**n_{cases}**	**HR (95%-CI)[b]**
Laxatives						
Non-users	3,890	153	Ref.	3,890	433	Ref.
Users	363	16	1.09 (0.64; 1.87)	363	43	0.99 (0.70; 1.41)
Diuretics overall						
Non-users	3,356	109	Ref.	3,356	327	Ref.
Users	897	60	**1.45 (1.06; 2.06)**	897	149	**1.39 (1.13; 1.70)**
Diuretics in specific						
Non-users	3,356	109	Ref.	3,356	327	Ref.
Users of non-potassium-sparing diuretics	455	40	**1.75 (1.21; 2.53)**	455	90	**1.49 (1.17; 1.89)**
Users of potassium-sparing diuretics or combinations[c]	442	20	0.96 (0.59; 1.54)	442	59	1.10 (0.83; 1.46)

Bold printed: statistically significant ($p < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1.

[b] Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure, coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

[c] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CI, confidence interval*; CVM*, cardiovascular mortality; *FUP*, follow-up*; HR*, hazard ratio; *Ref.*; reference.

3.3 Excursus: Propensity scores

Before presenting the methods, results, and discussion of the sensitivity analysis using propensity scores, this chapter briefly provides an introduction to propensity scores.

3.3.1 Introduction to propensity scores

3.3.1.1 Aiming for internal validity in observational studies (i.e., to avoid confounding)

There is widespread agreement in medical research that treatment efficacy and more generally causality should be tested primarily in randomised controlled trials. A reason is that only randomisation guarantees an even distribution of all known and unknown patient characteristics between a treatment group and a control group, and thus allows causal statements about treatment effects (Kuss *et al.*, 2016).

Although randomised controlled trials are the gold standard to assess causality, they are in some instances "unnecessary, inappropriate, impossible or inadequate" (Black, 1996, p. 1), such as when assessing the effect of smoking on lung cancer or mortality. Moreover, lack of external validity (generalisability) is a major criticism of randomised controlled trials, as the patients included often do not represent the average patient regarding age and health (McKee *et al.*, 1999; Rothwell, 2005). Therefore, observational studies may present an important alternative in specific research settings, such as in a study population of elderly or children, or when investigating a potential risk factor. Nevertheless, observational studies have the problem of missing internal validity. This means that, instead of randomly, physicians variably select treatment with regard to the individual patient characteristics. Consequently, treatment and control group can be systematically different with regard to their baseline characteristics (Kuss *et al.*, 2016).

Given that these systematically different characteristics do not only influence the decision for treatment but also increase the risk of experiencing the outcome, this is where confounding comes into play. Consequently, a characteristic or covariate is then considered a confounder if it is associated with both the treatment and the outcome. Therefore, the relationship between treatment and outcome is not independent, and is finally mixed up by these confounding factors. Due to confounding, "the observed effect measure will differ from the true causal effect measure of the treatment" (Kurth and Seeger, 2008, p. 2).

According to Kurth and Seeger, confounding is often graphically presented as a triangle with each corner representing one variable (treatment, outcome, and confounder) (**Figure 9**). The association

of interest (treatment and outcome) is shown as the arrow representing the base of the triangle, whereas other associations, such as confounder to treatment or confounder to outcome, are presented by the two other sides (arrows) of the triangle (Kurth and Seeger, 2008, p. 2).

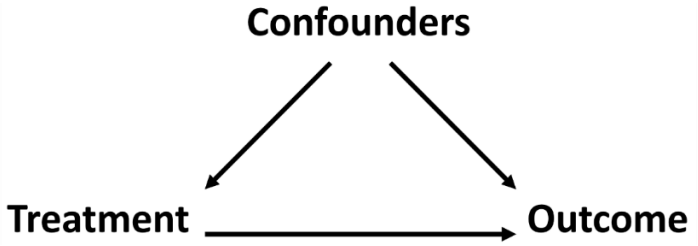

Figure 9. Confounding in observational studies illustrated as a triangle with each corner representing a variable, namely treatment, outcome, and confounder.

Although challenged by confounding, the congruence of findings in randomised controlled trials and observational studies is one major goal in epidemiologic research (Williamson and Forbes, 2014). To accomplish this aim, design and analytic techniques that create balance among characteristics of the treatment and control group at baseline are of extraordinary importance in order to remove confounding as far as possible (Weinberg, 1993). For this purpose, analyses in real-world data could be restricted, adjusted, matched, stratified or weighted on a small number of variables (Norgaard *et al.*, 2017). Graphically spoken, these techniques address confounding by aiming to remove the confounder–treatment arrow in observational settings (Williamson and Forbes, 2014). However, if the number of potential confounders is large, this becomes nearly impossible. The reason is that methods, such as restriction, regression adjustment, matching, stratification or weighting, can only handle a restricted number of covariates per outcome to be included in the analysis (Harrell *et al.*, 1984; Harrell *et al.*, 1996). To address this issue, methods have been suggested that combine multiple covariates into one variable, such as comorbidity scores summarizing several comorbidities into one score (Schneeweiss *et al.*, 2001). Another such technique is the propensity score, which collapses multiple confounders associated with the treatment into a single score.

3.3.1.2 Definition and estimation of a propensity score

A patient's propensity to be treated (propensity score) is defined as his/her predicted probability to receive the treatment of interest with respect to his/her available baseline characteristics (Rosenbaum and Rubin, 1983). This consequently means that the propensity score is a number ranging from 0 to 1, inclusively. While a patient's probability to receive the treatment in a 1:1 randomised controlled trial is 0.5, this probability remains unknown in an observational non-randomised study

in which the probability to be treated depends on a patient's individual characteristics (Kuss *et al.*, 2016). These baseline characteristics, however, can be collapsed into one new variable, the propensity score, by using a logistic regression model with the exposure variable (treatment) as dependent variable and the available baseline variables (possible confounders) as independent explanatory variables.

When building a propensity score model, the first step involves the selection of variables to be included in the propensity score. The model should preferably include variables that represent indications or contraindications for the treatment, risk factors for the outcome, most common diagnosis and procedures, as well as drugs with the potential to predict treatment (Kurth and Seeger, 2008). Variable selection for propensity score estimation should focus on characteristics which influence the outcome rather than the exposure, because this decreases the variance of an estimated exposure effect without increasing bias (Brookhart *et al.*, 2006). Consequently, this means that variables included should be associated with the outcome or both the exposure and the outcome. If, however, a variable is a strong predictor of only the exposure, this might result in a loss of efficiency, and thus should be avoided (Kurth and Seeger, 2008). The propensity score, of course, can only be estimated from measured baseline variables. As a consequence, confounding by unmeasured factors (so-called residual confounding) will not be removed by use of propensity score techniques.

3.3.1.3 Methods to use with propensity scores

After estimating the propensity score (propensity for treatment) as a function of covariates in a first step, it is then used to account for treatment selection in a second step. For this purpose, four methods are available: matching, stratification, regression adjustment, and weighted regression adjustment.

Matching on the propensity score

In propensity score matching, each treated patient is assigned one ("one-to-one matching") untreated patient or several ("one-to-many matching") untreated patients with the same propensity score or with a propensity score that deviates only minimally within predefined limits. The matched population is then used to estimate the treatment effect taking into account the matching (Austin, 2009). Propensity score matching is most often and preferably used as it is quite intuitive and comprehensible. For instance, balancing of covariates becomes obvious, when baseline characteristics of the treatment and control group are being compared before and after matching in a descriptive table that resembles the typical Table 1 of a randomised controlled study (Austin, 2013). A disadvantage of matching is, that the sample size might be substantially reduced because unmatched participants are being excluded (Kurth and Seeger, 2008).

Stratification on the propensity score

Stratification on the propensity score can be seen as a coarser propensity score matching, because participants are grouped into subsets according to their propensity score (Austin, 2011). Then, the entire population is ranked by the propensity score and divided into equal parts, preferably into quintiles as proposed by Rosenbaum and Rubin (Rosenbaum and Rubin, 1984), because the use of five strata has shown to remove 90 % of the bias for most continuous distributions (Cochran, 1968). In each of these parts, a treatment effect is estimated by using conventional methods to compare outcomes between treated and untreated participants. The resulting treatment effects are then summarised into an overall effect using meta-analytical approaches (Austin, 2011). In contrast to matching, stratification on the propensity score does not exclude unmatched participants from the analyses, but uses all study participants to estimate the treatment effect (Kurth and Seeger, 2008).

Regression adjustment

Covariate adjustment using the propensity score involves the calculation of a conventional regression model with the outcome variable of interest used as the dependent variable and the treatment effect and the propensity score used as the independent variables. The association of treatment and outcome variable is thereby adjusted for the propensity score and thus for all baseline patient characteristics included in the propensity score (Stuart *et al.*, 2009). It is therefore important "to model the association between the propensity score and the outcome correctly" (Kurth and Seeger, 2008, p. 7) by carefully selecting all important variables to estimate the propensity score. Regression adjustment has the advantage that all participants can be included in the analyses, and that many researchers are quite familiar with this approach. "On the other hand, regression adjustment is less intuitive as matching or stratification, and is prone to error through misspecifying the association between the propensity score and the outcome in the model in which the treatment effect is estimated" (Kurth and Seeger, 2008, p. 7).

Weighted regression adjustment based on the propensity score

Inverse probability of treatment weighting (IPTW) using the propensity score (PS) involves that each patient is assigned the inverse of the probability of receiving their actual treatment as a statistical weight. A treated patient receives the weight 1/PS, an untreated patient the weight 1/ (1-PS). This means that a treated patient with a low propensity score (for treatment) receives a high weight, because he/she resembles the untreated patients in terms of their characteristics (expressed by their low propensity score) and therefore enables a valid comparison with these. Treatment effects are then evaluated using participants according to their statistical weights (Austin, 2011). Nevertheless, the IPTW approach causes difficulties when some treated participants have very low propensity scores (low propensity to receive treatment, but treated) and some untreated participants, in turn, have very high propensity scores (high propensity to receive treatment, but untreated). These participants from the so-called tails of the propensity scores distribution receive extremely high weights due to inverse probability weighting. In case that the risk to experience the outcome is significantly different for those participants in the tails, this will highly influence the treatment effect in the total cohort (Kurth and Seeger, 2008). While the weighting method comes along with the advantage that the total study population can be used to estimate the treatment effect, it is less intuitive than other approaches, such as matching or stratification.

3.3.2 Methods of the sensitivity analysis using propensity scores

3.3.2.1 Variable selection

In addition to the basic covariates, age and sex, my variable selection to build the propensity score model included smoking status, physical activity, alcohol consumption, systolic blood pressure, BMI, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure (in the ESTHER study only), CHD, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids. Age and systolic blood pressure were modelled continuously and all other co-variables with the categorizations shown in **Table 19**. In brief, the propensity score model included the same variables as the Cox regression models in the main analyses.

3.3.2.2 Regression adjustment for the propensity score

Once the propensity scores had been estimated, I applied the approach of regression adjustment for the propensity score in order to estimate the treatment effects with respect to CVM for the following three user groups of:

- Laxatives
- Diuretics overall
- Non-potassium-sparing diuretics in specific
- Potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics

Although adjusting for the propensity score is less intuitive than matching, for instance, I decided in favour of this approach in order to avoid exclusions due to un-matched participants, which would have resulted in a reduced sample size. Given the partly already small group sizes of the drug user groups, matching on the propensity score would have caused a substantial loss of statistical power. Therefore, I used regression adjustment in the context of a sensitivity analysis.

3.3.3 Results of the sensitivity analysis using propensity scores

The results of the sensitivity analysis using regression adjustment for a propensity score are shown in **Table 29**. Both statistical significance and magnitude of the hazard ratios (HR) and the confidence intervals (CI) did not substantially change, when compared to the main analysis using Cox regression with adjustment for all potential confounders as separate variables (**Table 24**). Again, laxatives use was not associated with CVM (HR [95%-CI] for meta-analysis: 1.04 [0.74; 1.46]),

while use of diuretics overall and the use of non-potassium-sparing diuretics in specific again showed 1.6-fold (HR [95%-CI] for meta-analysis: 1.58 [1.19; 2.09]), and 1.5-fold (HR [95%-CI] for meta-analysis: 1.46 [1.32; 1.61]) increased CVM, respectively. The group of users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics showed the same pattern of association as observed in the Cox regression: no statistically significantly increased CVM in the users of the ESTHER study, a significantly 3-fold increased CVM in the users of the UK Biobank, and no significantly increased estimate in the meta-analysis of the two studies.

3.3.4 Discussion of the sensitivity analysis using propensity scores

The fact that both approaches, traditional Cox regression and regression adjustment for a propensity score, yielded similar results is not surprising, because the logistic regression model to estimate the propensity score used exactly the same variables as were used for covariate adjustment in the Cox regression. Therefore, the propensity score approach could not manage to remove more confounding than the traditional Cox model did. Given the small number of only 15 covariates for the ESTHER study and 14 covariates for the UK Biobank that were collapsed into the propensity score, it becomes obvious that variable selection was not at its maximum. Unfortunately, the extent to enlarge variable selection was restricted by the fact that only a limited set of diseases and disease risk factors was assessed in the UK Biobank and the ESTHER study, and there were no more eligible variables that were assessed in both studies. For example, other important variables, such as NYHA grade to evaluate the severity of heart failure had not been assessed in both studies, and were therefore not available for a propensity score estimation.

Inclusion of further baseline covariates into the propensity score might have removed confounding to a larger extent. As a result, this would have yielded weaker effect size estimates than the traditional Cox regression with a limited set of adjusting factors. Nevertheless, I am confident that the major potential confounders were adjusted for in the main analyses and that this limitation of the data sources led only to a small overestimation of treatment effects and did not substantially bias the results of the analyses.

Table 29. Associations with CVM comparing users and non-users of laxatives, diuretics overall, and diuretics in specific in the ESTHER study (Germany, baseline: 2000-2002, mean baseline age: 64 years, 14 years of mortality follow-up), in the UK Biobank (UK, baseline: 2006-2010, mean baseline age: 62 years, 7 years of mortality follow-up) by use of propensity scores, and in a meta-analysis of the two studies

Drug class	ESTHER (n = 4,253; 476 cases)			UK BIOBANK (n = 105,359 1,616 cases)			META-ANALYSIS (n = 109,612; 2,092 cases)		
	n^a	n_{cases}	HR (95%-CI)[b]	n^a	n_{cases}	HR (95%-CI)[b]	n^a	n_{cases}	HR (95%-CI)[c]
Laxatives									
Non-users	3,890	433	Ref.	101,003	1,526	Ref.	104,893	1,959	Ref.
Users	363	43	0.85 (0.61; 1.20)	4,356	90	1.21 (0.97; 1.51)	4,719	133	1.04 (0.74; 1.46)
Diuretics overall									
Non-users	3,356	327	Ref.	67,132	887	Ref.	70,488	1,214	Ref.
Users	897	149	**1.34 (1.08; 1.68)**	38,227	729	**1.79 (1.61; 1.98)**	39,124	878	**1.58 (1.19; 2.09)**
Diuretics in specific									
Non-users	3,356	327	Ref.	67,132	887	Ref.	70,448	1,214	Ref.
Users of non-potassium-sparing diuretics	455	90	**1.56 (1.19; 2.04)**	35,821	597	**1.44 (1.29; 1.60)**	36,276	687	**1.46 (1.32; 1.61)**
Users of potassium-sparing diuretics or combinations[d]	442	59	1.02 (0.75; 1.38)	2,406	132	**3.15 (2.61; 3.81)**	2,848	191	1.80 (0.60; 5.45)

Bold printed: statistically significant ($\rho < 0.05$).

[a] Sample sizes exemplarily taken from imputed data set no. 1. [b] Adjusted for a propensity score created based on the variables age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure (in ESTHER study, only), coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids. [c] Results of the two studies combined by random-effects model meta-analysis. [d] Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CI, confidence interval*; CVM*, cardiovascular mortality; *HR*, hazard ratio; *Ref.*; reference; *UK*, United Kingdom.

3.4 Discussion

3.4.1 Summary of the findings

In this meta-analysis of elderly users of antihypertensive drugs from two large cohort studies, the use of diuretics overall, but not regular use of laxatives, was associated with CVM. Subgroup analyses suggested a particularly strongly increased CVM in users of diuretics overall who were male, had CHD or heart failure. There were no statistically significant differences among the specific diuretics classes in the results of the meta-analyses. However, signs for a potential drug-drug interaction of non-potassium-sparing diuretics and concurrent regular laxatives use were observed but tests for interaction did not reach statistical significance.

3.4.2 Association of laxatives use with CVM

This is the first observational study on cardiovascular risk of regular laxatives use in a European population. Regular laxatives use was not associated with CVM in any of the analyses. This did not support my hypothesis that hypokalemia by regular laxatives use (Kokot and Hyla-Klekot, 2008; Xing and Soffer, 2001) may result in an increased risk for CVM as a consequence of ventricular arrhythmias, for instance (Faggioni and Knollmann, 2015; John *et al.*, 2012). One reason for the observed null association might be that most laxatives users had taken laxatives for a long time and tolerated them well without developing arrhythmias (prevalent users). Individuals with very high laxatives use, who are prone to arrhythmias, may have died before the study initiation. This phenomenon known as healthy-user/sick-stopper bias is common in studies with a prevalent user design (Ray, 2003) and may have biased my result towards a null association. A second explanation may be that discontinuation of laxatives use could have happened during follow-up. Those study participants, however, remained assigned to the user group in my analysis and could have attenuated the effect estimate for the exposure group. The only other comparable cohort study investigating laxatives use and CVM also used a single assessment of laxatives at baseline only. This study from Japan observed statistically significantly increased associations with CHD mortality and ischemic stroke mortality in men and women (Kubota *et al.*, 2016). Besides different outcomes, the ethnic difference as well as the younger (age-range: 40-79 years) and healthier (free of history of CVD and cancer) population of the Japanese study may explain the different results. Therefore, more studies on laxatives use and CVM are needed to elucidate the divergent findings. These studies should have a new user design (with start of follow-up at the first initiation of drug exposure) and include repeated assessments of laxatives use.

3.4.3 Association of diuretics use with CVM

With respect to non-potassium-sparing diuretics, I observed a 1.4-fold increased CVM in the meta-analysis of the results from the two studies. This is in line with the results of Cooper and colleagues (population: patients with left ventricular dysfunction; outcome: arrhythmic death) (Cooper *et al.*, 1999), Ahmed A. and colleagues (population: Heart failure patients; outcome: long-term mortality) (Ahmed *et al.*, 2006) and Alharbi and colleagues (population: Cases with cardiac arrest and controls from the general population; outcome: cardiac arrest) (Alharbi *et al.*, 2017). Interestingly, the latter study observed a comparably increased risk (about 40 %) of cardiac arrest for individuals receiving non-potassium-sparing diuretics. In addition, this hazard ratio point estimate was not higher than for individuals using a combination of antihypertensives with hypo- and hyperkalemic effects. I observed a similar pattern, when comparing users of non-potassium-sparing diuretics and users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

However, a network meta-analysis of clinical trials did not show higher cardiovascular risks of low-dose diuretics as first-line antihypertensive treatment compared to β-blockers, ACE inhibitors, calcium channel blockers, alpha-blockers, and ARBs; rather the opposite was observed (Psaty *et al.*, 2003).

The divergent results can have several reasons: the efficacy-effectiveness gap of clinical trials (Amler *et al.*, 2015), non-comparable study populations or an insufficient control of confounding in observational studies. The last point is supported by the fact that my analyses were limited by insufficient control for confounders, such as heart failure and CHD, both presenting a higher baseline cardiovascular risk for the affected patients. In practice, diuretics are often prescribed in combination with other antihypertensive drug classes for patients with high cardiovascular risk or a blood pressure that cannot be controlled by one agent (Williams *et al.*, 2018). An intensive blood pressure control with two or more antihypertensive drugs is particularly important in individuals with a history of myocardial infarction or other cardiovascular events (Wang *et al.*, 2018; Williams *et al.*, 2018). In addition, loop diuretics are most often used as part of the guideline-treatment in symptomatic heart failure patients (New York Heart Association (NYHA) class II to IV) (Ponikowski *et al.*, 2016). Therefore, it was not surprising that diuretics users more frequently had heart failure, CHD and histories of myocardial infarction and stroke compared to non-users (**Table 22**).

A better adjustment for heart failure and CHD would have been desirable, but NYHA classification and CHD severity were not available in both the UK Biobank and the ESTHER study. Therefore, the particularly strongly increased CVM in diuretics users with CHD or heart failure should be

interpreted with caution. This strong association might be rather due to the fact that individuals receiving diuretics probably had more severe stages of CHD or heart failure than non-users. Consequently, further observational studies are needed with more detailed information on these two diseases.

Confounding by indication for severe stages of CHD or heart failure may also explain some other findings. First, both heart diseases were more prevalent in males than females (data not shown), which can explain the observed stronger associations in all analyses for male diuretics users than female users. Second, a 3-fold CVM was detected in the UK Biobank for users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics. Analyses in the UK Biobank showed that users of these diuretics frequently had a CHD and a previous myocardial infarction but lower systolic blood pressure than users of non-potassium-sparing diuretics only (**Table 23**). According to the guideline for the management of arterial hypertension (Wang *et al.*, 2018; Williams *et al.*, 2018), British physicians may attempt to intensively control blood pressure in these high-risk cardiovascular patients with potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics. This data, however, cannot answer the question whether the reason for this strongly increased CVM is the aforementioned diuretics use or the underlying high cardiovascular risk of this patient group.

Users of exclusively potassium-sparing diuretics in the UK Biobank also had a statistically significantly increased CVM. However, this drug exposure was rather rare in the UK Biobank population and this finding was based on 26 cases only (**Table 25**). As prescriptions of potassium-sparing diuretics were more frequent in the ESTHER population and no increased CVM was observed, the UK Biobank result might have been a finding by chance.

Finally, because poor renal function is associated with hyperkalemia (Drawz *et al.*, 2012) and increased CVM (Hayes *et al.*, 2012; Kovesdy *et al.*, 2018), it was of interest whether results for diuretics use differed according to kidney function. However, diuretics users with potential kidney damage (urinary albumin levels $\geq$ 20 mg/L) did not show a stronger association with CVM. An explanation may be that I mainly focused on non-potassium-sparing diuretics users who are rather prone to hypokalemia than to hyperkalemia. The group with a possible risk of hyperkalemia (users of potassium-sparing diuretics), however, was not separately investigated in subgroups by urinary albumin.

3.4.4 Potential drug-drug interaction of non-potassium-sparing diuretics and laxatives

Signs for a potential drug-drug interaction of non-potassium-sparing diuretics and concurrent regular laxatives use were observed, but tests for interaction did not reach statistical significance. This can mainly be explained by the low statistical power of this analysis because exposure to concurrent use of both drug classes was rare (1.3 % and 1.6 % among antihypertensive drug users in the ESTHER study and the UK Biobank, respectively). In addition, the likely underestimation of the cardiovascular risk of regular laxatives users in my analysis due to the healthy-user/sick-stopper bias discussed earlier and a prevalent user design will have limited the chance for a detection of a statistically significant interaction.

3.4.5 Strengths and limitations

The major limitations of my analyses and their potential impact on the results have been discussed earlier and include the prevalent user design, no repeated drug assessment, and a limited extent to control for confounding (in particular for the severity of heart failure and CHD).

Furthermore, serum potassium measurements were not available from the two analysed cohort studies. In addition to information on potassium-influencing drug use, such measurements would have been quite informative to provide evidence that the increased CVM observed in my analysis was indeed related to a drug-induced electrolyte disorder. However, this is already evident from previous cohort studies, which I summarised in the systematic review about potassium measurements and cardiovascular outcomes in chapter 2 (Hoppe *et al.*, 2018). The study included of Cohen and colleagues, for instance, observed a 2.6-fold increased risk for a composite cardiovascular outcome in diuretic-treated hypertensive patients with low serum potassium levels compared to individuals with adequate potassium levels (Cohen *et al.*, 2001). Furthermore, the risk of hypokalemia by chronic laxative use has been well-documented by Xing and colleagues (Xing and Soffer, 2001) as well as Kokot and colleagues (Kokot and Hyla-Klekot, 2008).

The major strength of my study is that the analyses followed the same protocol in two large cohort studies with a long follow-up for CVM. Thus, statistically significant results from a derivation cohort (ESTHER) were confirmed in a replication cohort (UK Biobank). Moreover, this is the first investigation about the concurrent use of non-potassium-sparing diuretics and laxatives, which was only feasible due to a thorough medication assessment of OTC drugs, which are not available in claims databases.

3.4.6 Conclusion

This is the first individual patient-data meta-analysis of two large cohort studies about the association of potassium-influencing drugs and CVM. Concurrent use of non-potassium-sparing diuretics and laxatives was associated with a 2-fold increased CVM in participants with antihypertensive treatment. Physicians and pharmacists should ask patients using non-potassium-sparing diuretics about additional laxatives use, and inform them about the cardiovascular risk of concurrent use of these potassium-influencing drug classes. Furthermore, in these patients, the monitoring of serum potassium in shorter intervals may be an opportunity for cardiovascular risk prevention.

4 CONCLUSION

With my dissertation in the field of cardiovascular disease epidemiology, I provide the first systematic review and meta-analysis about the association of abnormal serum potassium levels and cardiovascular outcomes in specific populations. In summary, I observed associations of low serum potassium levels with supraventricular arrhythmias and associations of high serum potassium levels with CVM in the older general population. Associations of abnormal serum potassium levels and cardiovascular outcomes were even more pronounced in populations with hypertension, AMI, heart failure, CKD or dialysis. Although the observational studies included in the systematic review cannot ascertain causality of the aforementioned significant associations, their results highlight the clinical relevance of maintaining serum potassium levels within the reference range of 3.5 to 5.1 mmol/L. More frequent potassium-monitoring and subsequent interventions, such as change or withdrawal of potassium-influencing drugs, might help to restore normal values and prevent cardiovascular events.

The cardiovascular risk of potassium-influencing drugs was subject of further investigations within the course of my dissertation. To address this issue, I focused on the exposure to diuretics overall, non-potassium-sparing diuretics in specific, and laxatives, and investigated their associations with CVM. A potential drug-drug interaction of non-potassium-sparing diuretics and laxatives was of special interest. The analyses in two large cohort studies from Germany and the United Kingdom yielded consistent results with respect to an association of diuretics use but not regular laxatives use with CVM among older adults treated with antihypertensive drugs. Signs for a drug-drug interaction of non-potassium-sparing diuretics and laxatives were detected. Interactions, however, were not statistically significant, mainly because concurrent use was rare in the two studies. Nevertheless, a statistically significant 2-fold increased CVM rate was observed in concurrent users of non-potassium-sparing diuretics and laxatives.

Therefore, pharmacists should be vigilant about the concurrent use of drugs affecting potassium excretion, and make patients aware of this risk when they regularly purchase laxatives in a pharmacy. Similarly, I strongly recommend physicians to ask their patients who use non-potassium-sparing diuretics about additional laxatives use, to inform them about the cardiovascular risk of concurrent use of these drug classes, and to monitor serum potassium levels in shorter intervals in patients using laxatives on a regular basis. Of course, serum potassium levels are already being routinely checked in cardiac patients (1-2 weeks after initiation of a therapy, after dosage increase, and every 6 months), but the risk of additional self-medication may have been underestimated in

clinical practice so far. Hence, a closer monitoring with shorter intervals (e.g. every 3 months) could provide an opportunity for cardiovascular prevention. However, before implemented in clinical routine, controlled clinical trials are needed to evaluate if tighter potassium-monitoring intervals have an advantage for cardiovascular patients using non-potassium-sparing diuretics and laxatives.

5 SUMMARIES

5.1 English summary

This dissertation provides the first systematic review and meta-analysis of observational studies on the association of abnormal serum potassium levels (< 3.5 or > 5.1 mmol/L) and cardiovascular outcomes within specific populations. For this purpose, the medical databases *Medline* and *Web of Science* were systematically searched from inception until November 24, 2017. Data synthesis of 24 relevant studies was performed using random-effects model meta-analyses, which finally comprised the data of 310,825 participants.

In the older general population, low serum potassium was associated with a 1.6-fold increased risk of supraventricular arrhythmias (hazard ratio [95%-confidence interval]: 1.62 [1.02; 2.55]). Contrarily, high serum potassium was associated with increased cardiovascular mortality (1.38 [1.14; 1.66]). In patients with acute myocardial infarction, the risk of ventricular arrhythmias was increased for high serum potassium (2.33 [1.60; 3.38]). A U-shaped association was observed both with a composite cardiovascular outcome in hypertensive patients (2.6-fold increased risk with hypokalemia and 1.7-fold increased risk with hyperkalemia), and with cardiovascular mortality in dialysis patients (1.1-fold increased risk with hypokalemia and 1.4-fold increased risk with hyperkalemia) as well as in heart failure patients (not statistically significant). Further, only hyperkalemia was associated with an increased risk of a composite cardiovascular outcome in dialysis patients (1.12 [1.03; 1.23]) and also in chronic kidney disease patients (1.34 [1.06; 1.71]).

Due to both a lack of studies and a variety of investigated outcomes and populations, a maximum of six studies was pooled per meta-analysis. The studies included also partly differed with regard to statistical analyses, reporting of results, and cut-off values for serum potassium. However, by using explicit inclusion and exclusion criteria with respect to design, statistical methods and definition of serum potassium cut-off values, the studies pooled in meta-analyses were mostly comparable and similar to the cut-off values proposed by the American Heart Association (reference range: 3.5 to 5.1 mmol/L). Given the heterogeneous covariate adjustment among the studies included, I suggest a key set of covariates, which future studies on this topic could use, namely age, sex, body mass index or other weight measure, smoking, diabetes, hypertension, history of cardiovascular disease, and kidney disease.

In conclusion, these results suggest that some populations, especially patients with hypertension or heart failure, might profit from more frequent potassium-monitoring and subsequent interventions, such as change or withdrawal of potassium-influencing drugs, in order to restore normal values and prevent cardiovascular outcomes.

Secondly, this dissertation presents the first investigation about the associations of use of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives with cardiovascular mortality in participants with antihypertensive treatment. The drug classes were first analysed distinctly and then jointly to detect potential drug-drug interactions in two large-scale cohort studies. While the German ESTHER study served as a derivation cohort to generate hypotheses, the larger UK Biobank was used as a replication cohort to confirm the findings. Methodologically, Cox proportional hazard regression models were applied to estimate hazard ratios and 95%-confidence intervals in each study. Results from both studies were then combined in an individual patient-data meta-analysis using the random-effects model.

Analyses included 4,253 participants, aged 50 to 75 years, from the ESTHER study and 105,359 participants, aged 50 to 69 years, from the UK Biobank. During 14 and 7 years of follow-up, 476 and 1,616 cardiovascular mortality cases were observed in the ESTHER study and the UK Biobank, respectively. Compared to non-users, a 1.6-fold (1.57 [1.29; 1.90]), a 1.4-fold (1.39 [1.26; 1.53]), and no statistically significantly increased [1.13 [0.94; 1.36]) cardiovascular mortality rate was observed in users of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives, respectively. Concurrent use of non-potassium-sparing diuretics and laxatives was associated with a 2-fold increased cardiovascular mortality (2.05 [1.55; 2.71]) when compared to users of neither diuretics nor laxatives. However, a test for interaction slightly missed statistical significance (p=0.075).

The major limitations of these analyses include the prevalent user design with regard to laxatives users, no repeated drug assessments, and a limited extent to control for confounding, in particular for the severity of heart failure and coronary heart disease.

Nevertheless, an interaction of non-potassium-sparing diuretics and laxatives appears plausible. Therefore, physicians are highly recommended to clarify additional laxatives use and monitor serum potassium levels more closely (e.g. every 3 months) in concurrent users.

5.2 Deutsche Zusammenfassung

Diese Dissertation beinhaltet die erste systematische Übersichtsarbeit und Meta-Analyse von Beobachtungsstudien über den Zusammenhang von abnormalen Kaliumwerten (< 3,5 oder > 5,1 mmol/L) und kardiovaskulären Ereignissen in spezifischen Bevölkerungsgruppen. Dazu wurden die medizinischen Datenbanken *Medline* und *Web of Science* systematisch durchsucht. Die Recherche deckte den Zeitraum bis einschließlich 24. November 2017 ab. Die Zusammenfassung von 24 relevanten Studien wurde mittels Meta-Analysen nach dem Random-Effects-Modell durchgeführt und enthält die Daten von 310.825 Teilnehmern.

In der älteren Allgemeinbevölkerung waren niedrige Kaliumwerte mit einem 1,6-fach erhöhten Risiko für supraventrikuläre Arrhythmien assoziiert (Risikoverhältnis [95%-Konfidenzintervall]: 1,62 [1,02-2,55]). Im Gegensatz dazu gingen hohe Kaliumwerte mit einer erhöhten kardiovaskulären Mortalität einher (1,38 [1,14-1,66]). Bei Patienten mit akutem Myokardinfarkt war das Risiko von ventrikulären Arrhythmien bei hohen Kaliumwerten erhöht (2,33 [1,60-3,38]). Ein U-förmiger Zusammenhang zeigte sich sowohl für kardiovaskuläre Ereignisse bei hypertensiven Patienten (2,6-fach erhöhtes Risiko bei Hypokaliämie und 1,7-fach erhöhtes Risiko bei Hyperkaliämie) als auch für kardiovaskuläre Mortalität bei Dialysepatienten (1,1-fach erhöhtes Risiko bei Hypokaliämie und 1,4-fach erhöhtes Risiko bei Hyperkaliämie) ebenso wie bei Patienten mit Herzinsuffizienz (nicht statistisch signifikant). Darüber hinaus erhöhte eine Hyperkaliämie das Risiko für kardiovaskuläre Ereignisse bei Dialysepatienten (1,12 [1,03-1,23]) sowie bei Patienten mit chronischer Nierenerkrankung (1,34 [1,06-1,71]).

Aufgrund fehlender Studien sowie einer Vielzahl an untersuchten Endpunkten und Studienpopulationen konnten maximal sechs Studien pro Meta-Analyse zusammengefasst werden. Die Studien unterschieden sich zudem teilweise bezüglich der statistischen Auswertung, der Ergebnispräsentation sowie der verwendeten Grenzwerte für Serumkalium. Die Verwendung expliziter Ein- und Ausschlusskriterien ermöglichte jedoch, dass die in Meta-Analysen zusammengefassten Studien weitestgehend vergleichbar waren und mit den Grenzwerten der American Heart Association (Referenzbereich: 3,5 bis 5,1 mmol/L) übereinstimmten. Angesichts der Unterschiede in der Variablenadjustierung erscheint ein Keyset von Kovariablen sinnvoll, welches in zukünftigen Studien verwendet werden sollte: Alter, Geschlecht, Body-Maß-Index oder andere Gewichtsmessungen, Rauchen, Diabetes, Bluthochdruck, Vorgeschichte von Herz-Kreislauf-Erkrankungen und Nierenerkrankungen.

Abschließend deuten diese Ergebnisse darauf hin, dass einige Populationen, insbesondere Patienten mit Bluthochdruck oder Herzinsuffizienz, von engmaschigeren Kontrollen des Kaliumwertes

und nachfolgenden Interventionen, wie beispielsweise der Wechsel oder das Absetzen kaliumbeeinflussender Medikamente, profitieren könnten, um Normalwerte wiederherzustellen und Herz-Kreislauf-Ereignisse zu verhindern.

Im Weiteren behandelte diese Dissertation die Assoziationen von Diuretika im Allgemeinen, von nicht-kaliumsparenden Diuretika im Spezifischen und von Abführmitteln mit kardiovaskulärer Mortalität. Die Analysen wurden zwecks Herstellung eines vergleichbaren kardiovaskulären Grundrisikos bei Patienten mit antihypertensiver Therapie beschränkt.

Die Wirkstoffklassen wurden zunächst einzeln und dann gemeinsam in zwei großen Kohortenstudien analysiert, um mögliche Interaktionen zu erkennen. Während die deutsche ESTHER-Studie als Ableitungskohorte zur Generierung von Hypothesen fungierte, diente die UK Biobank zur Validierung der Ergebnisse. Die Ergebnisse beider Studien wurden anschließend in einer individuellen Patientendaten-Meta-Analyse nach dem Random-Effects-Model zusammengefasst.

Die Analysen umfassten 4.253 ESTHER-Teilnehmer im Alter von 50 bis 75 Jahren und 105.359 Teilnehmer im Alter von 50 bis 69 Jahren aus der UK Biobank. Innerhalb einer Nachbeobachtungszeit von 14 Jahren wurden in der ESTHER-Studie 476 kardiovaskuläre Todesfälle beobachtet und innerhalb von 7 Jahren 1.616 kardiovaskuläre Todesfälle in der UK Biobank. Im Vergleich zu Nichtanwendern war die kardiovaskuläre Mortalität bei Anwendern von Diuretika im Allgemeinen 1,6-fach (1,57 [1,29-1,90]), bei Anwendern nicht-kaliumsparender Diuretika im Spezifischen 1,4-fach (1,39 [1,26-1,53]) und bei Anwendern von Abführmitteln nicht statistisch signifikant (1,13 [0,94-1,36]) erhöht. Die gleichzeitige Verwendung von nicht-kaliumsparenden Diuretika und Abführmitteln zeigte eine 2-fach erhöhte kardiovaskuläre Mortalität (2,05 [1,55-2,71]) im Vergleich zu Nichtanwendern beider Substanzgruppen. Ein Interaktionstest verfehlte jedoch knapp ein statistisch signifikantes Ergebnis (p=0,075).

Die Limitationen dieser Analysen beinhalten das Prevalent-User-Design in Bezug auf Anwender von Abführmitteln, fehlende wiederholte Arzneimittelabfragen sowie ein begrenztes Maß zur Adjustierung für wichtige Kovariablen, wie beispielsweise den Schweregrad der Herzinsuffizienz sowie der koronaren Herzkrankheit.

Insgesamt legen diese Ergebnisse dennoch den Schluss nahe, dass eine Arzneimittelinteraktion zwischen nicht-kaliumsparenden Diuretika und Abführmitteln plausibel erscheint. Deshalb ist Ärzten unbedingt zu empfehlen, die zusätzliche Einnahme von Abführmitteln bei ihren Patienten stets zu erfragen und bei gleichzeitiger Anwendung mit nicht-kaliumsparenden Diuretika eine engmaschigere Überwachung der Kaliumwerte (beispielsweise alle 3 Monate) vorzunehmen.

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7 OWN CONTRIBUTIONS AND PUBLICATIONS

The data collection for the systematic review (literature screening and data extraction) was carried out together with my co-doctoral fellow Dana Clarissa Muhlack. The project setup and management, the development of the search strategy as well as the evaluation and preparation of the data was carried out entirely by myself and is a central result of this dissertation.

The basis for the second central result of this work was derived from data of the German ESTHER study ("Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung") and the UK Biobank. In both studies, the preparation, analysis, and evaluation of the data as well as the presentation of the results were carried out entirely by myself. The coding of reasonable variables from the large UK Biobank data set and harmonizing the coding with the ESTHER study variables, in particular, was challenging and time-consuming and was done entirely by myself.

Results of the present dissertation were or will be published in the following articles:

1. Hoppe, L. K., Muhlack, D. C., Koenig, W., Carr, P. R., Brenner, H. and Schöttker, B. (2018). Association of Abnormal Serum Potassium Levels with Arrhythmias and Cardiovascular Mortality: a Systematic Review and Meta-Analysis of Observational Studies. Cardiovasc Drugs Ther *32*, 197-212, doi: 10.1007/s10557-018-6783-0.
2. Hoppe, L. K., Muhlack, D. C., Koenig, W., Brenner, H. and Schöttker, B. (2019). The Associations of Diuretics and Laxatives Use with Cardiovascular Mortality. An Individual Patient-Data Meta-Analysis of Two Large Cohort Studies. (Submitted).

The dissertation chapters 2.1 (Material and methods), 2.2 (Results), and 2.3 (Discussion) originate from **Publication 1**. My contributions to this publication include data collection (together with my co-doctoral fellow Dana Clarissa Muhlack), data analysis, interpretation of the results, and writing of the manuscript (revised by my supervisor PD Dr Ben Schöttker).

Manuscript 2 provides the content for chapters 3.1 (Material and methods), 3.2 (Results), and 3.4 (Discussion) of this dissertation. My contributions to this publication include the preparation, analysis, and presentation of the study data as well as interpretation of the results, and writing of the manuscript (revised by my supervisor PD Dr Ben Schöttker).

In addition, parts of chapters 1 (Introduction) and 4 (Conclusions) of this dissertation have also been previously published in the aforementioned articles.

Further own and co-authored publications:

3. Hoppe, L. K., Schöttker, B., Holleczek, B., Stegmaier, C. and Brenner, H. (2017). Die ESTHER-Studie: Aktuelle Erkenntnisse zur Arzneimitteltherapiesicherheit im Alter. Saarländisches Ärzteblatt *12*, 21-25.

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Oral presentations at scientific conferences:

34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management
22-26 August 2018, Prague, Czech Republic
Drug-drug interaction of non-potassium-sparing diuretics and laxatives is associated with cardiovascular mortality in hypertension-treated subjects [After Call for Papers]
Hoppe L. K., Muhlack D. C., Koenig W., Brenner H. and Schöttker B.

Workshop on pharmacoepidemiology of the Deutsche Gesellschaft für Epidemiologie (DGEpi)
6-7 June, 2018, Bremen, Germany
The Associations of Diuretics and Laxatives Use with Cardiovascular Mortality in Subjects Treated with Antihypertensive Drugs: An Individual Patient-Data Meta-Analysis of Two Large Cohort Studies
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Association of serum potassium with arrhythmias and cardiovascular mortality: a systematic review and meta-analysis of observational studies [After Call for Papers]
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APPENDIX

Table A1. Reference list of studies excluded from the systematic review about abnormal serum potassium levels and cardiovascular outcomes during full-text selection.

A) No observational study design

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B) Study not conducted in humans

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C) Serum potassium levels not measured

1. Abraham, A. S., Rosenmann, D., Zion, M. M. and Eylath, U. (1988). Lymphocyte potassium and magnesium concentrations as prognostic factors after acute myocardial infarction. Cardiology 75, 194-199, doi: 10.1159/000174370.
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D) No association of serum potassium levels and relevant outcomes assessed

1. Abraham, A. S., Rosenman, D., Meshulam, Z., Zion, M. and Eylath, U. (1986). Serum, lymphocyte, and erythrocyte potassium, magnesium, and calcium concentrations and their relation to tachyarrhythmias in patients with acute myocardial infarction. Am J Med 81, 983-988.
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E) Intervention influencing serum potassium levels or outcome

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EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

   Risk of abnormal serum potassium levels for cardiovascular events with specific attention to drugs affecting potassium excretion

   handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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