Is the risk of cardiovascular disease increased in living kidney donors? A Danish population-based cohort study

Research year report

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Preface

This report is based on a study conducted during my research year at Department of Clinical Epidemiology (DCE) at Aarhus University Hospital from February 2019 to January 2020.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CRS	Civil Registry System
CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
DNPR	Danish National Patient Registry
DNR	Danish National Prescription Registry
HR	Hazard ratio
HT	Hypertension
IQR	Interquartile range
IR	Incidence rate
ICD-8	International Classification of Disease, 10th edition
ICD-10	International Classification of Disease, 8th edition
NSCP	NOMESCO Classification of Surgical Procedures
SCANDAT	Scandinavian Donations and Transfusions
SIR	Standardized incidence ratio
TIA	Transient ischemic attack

Table of Contents

Manuscript *1*

Introduction **1**

Methods **2**

Results **8**

Discussion **10**

Supplementary *15*

Background **15**

Methodological considerations **16**

Systematic and random error **19**

Generalizability **24**

References *27*

Tables and figures *29*

Abstract

Objective: To examine the risk of cardiovascular disease (CVD), hypertension (HT) and death in living kidney donors.

Methods: In this nationwide cohort study, we included individuals who underwent living donor nephrectomy in the period from 1996 to 2018 and followed them for acute myocardial infarction, angina pectoris, ischemic stroke, transient ischemic attack, atrial fibrillation/flutter, hypertension and death through medical registries. We included two different comparison cohorts: 1) a cohort of sex- and age-matched individuals from the general population and 2) an external cohort of blood donors. We compared the risks of CVD, HT and death in kidney donors with those in the general population cohort by computing hazard ratios (HRs) using Cox-regression, while we compared with the external blood donor cohort by computing standardized incidence ratios (SIRs).

Results: We identified 1,325 living kidney donors and followed them for a median of 8 years. Compared with the general population, kidney donors had a similar risk of the composite endpoint of acute myocardial infarction, angina pectoris, ischemic stroke and transient ischemic attack (5.9 events v 6.9 per 1000 person years; HR = 0.85 (95% confidence interval (CI), 0.64-1.12)). Kidney donors had a lower risk of atrial fibrillation/flutter (HR = 0.59 (95% CI, 0.38-0.94)) and death (HR = 0.58 (95% CI, 0.41-0.81)), while the risk of HT was similar (HR = 1.11 (95% CI, 0.93-1.32)). Compared with blood donors, kidney donors had a similar risk of the composite endpoint of acute myocardial infarction, angina pectoris, ischemic stroke and transient ischemic attack (Observed events/expected events (O/E)= 53/47.3; SIR = 1.12 (95% CI, 0.85–1.47)), of death (O/E = 29/26.1; SIR = 1.11 (95% CI, 0.77-1.61)), and of atrial fibrillation/flutter (O/E = 18/21.4; SIR = 0.84 (95% CI, 0.52–1.33)) and an increased risk of HT (O/E= 135/96.4; SIR = 1.40 (95% CI, 1.18–1.67)).

Conclusion: We did not find a clearly higher risk of CVD or death after living kidney donation. This supports the safety of living kidney donation based on current principles involving rigorous medical examination and strict requirements for living kidney donation. The potentially increased risk of HT emphasizes the importance of subsequent regular follow-up care of kidney donors.

Dansk resumé

Formål: at undersøge risikoen for kardiovaskulær sygdom (CVD), hypertension (HT) og død hos levende nyredonorer.
Metode: I dette populationsbaseret kohortestudie inkluderede vi individer, som fik foretaget levende donornefrektomi i perioden fra 1996 til 2018. Gennem danske registre fulgte vi nyredonorerne for akut myokardieinfarkt, angina pectoris, iskæmisk apopleksi, transitorisk cerebral iskæmi, atrieflimren/flagren, hypertension og død. Vi inkluderede to forskellige sammenligningskohorter: 1) en kohorte bestående af køns- og aldersmatchede individer fra baggrundsbefolkningen og 2) en ekstern kohorte bestående af bloddonorer. Vi sammenlignede risikoerne for CVD, HT og død hos nyredonorer med dem i baggrundsbefolkningskohorten ved at beregne hazardratioer (HRs) via en Cox-regression, mens vi sammenlignede med bloddonorerne ved at beregne standardiserede incidensratioer (SIRs).
Resultat: Vi identificerede 1.325 levende nyredonorer og fulgte dem i en median tid på 8 år. Sammenlignet med baggrundsbefolkningskohorten havde nyredonorerne samme risiko for komposit endepunktet bestående af akut myokardieinfarkt, angina pectoris, iskæmisk apopleksi og transitorisk cerebral iskæmi (5,9 tilfælde vs 6,9 per 1000 person-år; HR = 0,85 (95% sikkerhedsinterval (CI), 0,64-1,12)). Nyredonorer havde en lavere risiko for atrieflimren/flagren (HR = 0,59 (95% CI, 0,38-0,94)) og død (HR = 0,58 (95% CI, 0,41-0,81)), mens risikoen for hypertension var den samme (HR = 1,11 (95% CI, 0,93-1,32)). Sammenlignet med bloddonorerne havde nyredonorer den samme risiko for komposit endepunktet bestående af akut myokardieinfarkt, angina pectoris, iskæmisk apopleksi og transitorisk cerebral iskæmi (Observerede tilfælde/forventede tilfælde (O/E) = 53/47,3; SIR = 1,12 (95% CI, 0,85–1,47)), for død (O/E = 29/26,1; SIR = 1,11 (95% CI, 0,77-1,61)) og for atrieflimren/flagren (O/E = 18/21,4; SIR = 0,84 (95% CI, 0,52–1,33)) og en forhøjet risiko for HT (O/E= 135/96,4; SIR = 1,40 (95% CI, 1,18–1,67)).

Konklusion: Vi fandt ikke en klart forhøjet risiko for CVD eller død efter levende nyredonation. Dette fund understøtter sikkerheden ved levende nyredonation. Den potentielt forhøjede risiko for hypertension understreger vigtigheden af efterfølgende opfølgning af nyredonorer.

Manuscript

Introduction

For most patients with end stage renal disease, kidney transplantation is considered the best treatment because it is associated with lower mortality and morbidity compared with chronic dialysis [1]. Kidney transplantation from a living donor is associated with longer graft survival than from a deceased donor [2]; however, it also involves the risk associated with surgery and removal of a kidney from an otherwise healthy individual. Although the remaining kidney to some extent compensates for the loss of nephron mass by hyperfiltration, the nephrectomy in living kidney donors will lead to a reduction in renal function [3] and a risk of increased urinary protein excretion [3, 4]. It is well-established that reduced renal function and proteinuria are associated with increased risk of cardiovascular disease in the general population [5, 6], but the effect of reduced renal function and increased protein excretion on risk of cardiovascular disease in the otherwise healthy kidney donors is less clear.

Previous studies have investigated the risk of cardiovascular disease after living kidney donation [7-12]. The majority of these studies did not find an increased risk of cardiovascular disease among kidney donors [7-11], while a single study found a 40% increased cardiovascular mortality in kidney donors during a median follow-up of 15.1 years compared with a cohort consisting of self-proclaimed healthy individuals [12]. To our knowledge, none of the studies have investigated the risk of atrial fibrillation or flutter after living kidney donation. Identifying a relevant comparison group, however, remains a major challenge in observational studies examining the outcomes in living kidney donors, since kidney donors are highly selected and inherently healthy. Thus, the results of these studies might be

confounded by a greater baseline risk of cardiovascular disease in the comparison cohort leading to an underestimation of the relative risk in kidney donors.

The aim of this study was to examine the risk of ischemic cerebrovascular disease, ischemic heart disease, atrial fibrillation or flutter, hypertension, and death after living kidney donation in Denmark. To address the problem of a relevant comparison cohort, we included two different comparison cohorts: 1) a cohort of individuals from the general population and 2) a cohort of blood donors. Because of the similarities in the requirements for living kidney and blood donation, we *a priori* expected blood donors to be more comparable to the healthy kidney donors than to the comparison cohorts in previous studies.

Methods

Study design and setting

We designed this study as a nation-wide cohort study, based on prospectively collected data retrieved from the Danish National Patient Registry (DNPR), the Danish Civil Registration System (CRS), the Danish National Prescription Registry (DPR) and the Scandinavian Donations and Transfusions (SCANDAT) database. The Danish National Health service provides tax-supported health care for the entire Danish population (5.8 million inhabitants), ensuring free access to general practitioner and hospitals. All Danish residents are assigned a unique personal identifier (the CPR-number) at birth or upon immigration which permits unambiguous individual linkage between each Danish registry [13].

Data sources

DNPR contains data on all inpatient visits at somatic departments since 1977. Visits at hospital outpatient clinics and emergency rooms are included since 1995. It contains both administrative and clinical data on admissions and discharges,

diagnoses, examinations and surgical procedures [14]. Diagnoses are classified according to the International Classification of Diseases, Eight revision [ICD-8] through 1993, and Tenth Revision [ICD-10] thereafter. Surgical procedures are classified according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP).

DPR contains data on all prescriptions redeemed by Danish residents at community pharmacies since 1995. It includes information on the drug type according to the Anatomical Therapeutic Chemical (ATC) codes and the dispensing date [15].

The SCANDAT database includes detailed information on virtually all Danish (and Swedish) blood donors and transfusion recipients since 1982. It contains data on the type of donations (whole blood, plasma and other types) and dates of donations/transfusions [16].

CRS contains data on vital status and migration to and from Denmark [17].

Study population

Kidney donors:

Through DNPR, we identified living kidney donors in Denmark from 1996-2018 using procedure codes for removal of kidney from a living donor. In order to increase the specificity, we additionally required all identified individuals to have either a diagnosis code indicating a contact related to the donation of a kidney or a code representing the examination of a potential organ or tissue donor registered between 1994 and the recorded date of nephrectomy. The date of nephrectomy served as index date for the kidney donors.

We excluded kidney donors with a diagnosis of one or more of the following cardiovascular diseases registered in DNPR before index date: atrial fibrillation or flutter, angina pectoris, myocardial infarction, ischemic stroke, intracranial hemorrhage, transient ischemic attack (TIA), or heart failure. In addition, we

excluded individuals with a redeemed prescription of any antihypertensive drugs within one year prior to index date (see Supplementary table 1 for codes).

In the comparison with the general population cohort we furthermore excluded kidney donors with a registered diagnosis of chronic liver disease, diabetes, chronic obstructive pulmonary disease (COPD), cancer or autoimmune disease before index date or donors who redeemed prescriptions of antidiabetic drugs within one year prior to index date (see Supplementary table 1 for codes).

When comparing with blood donors we excluded kidney donors with age <25 years because of a very low number of kidney donors below this age and kidney donors with age >65 years because of the upper age limit for blood donation.

General population cohort:

Trough CRS, we identified sex- and age- matched comparisons from the general population. The date of nephrectomy of the corresponding kidney donor served as index date for the general population cohort. Each kidney donor was matched to 10 comparisons without any diagnoses of the abovementioned cardiovascular diseases, chronic liver disease, chronic kidney disease, diabetes, COPD, cancer, or autoimmune disease before index date and without any redeemed prescriptions of antihypertensive or antidiabetic drugs within one year prior to index date (see Supplementary table 1 for codes).

Blood donor cohort:

Unfortunately, we did not have SCANDAT data included in our dataset with kidney donors as SCANDAT data were stored at a server at Statistics Denmark. Therefore, we constructed a secondary external comparison cohort consisting of donors of whole blood. We identified all donors from 1995-2017 in SCANDAT database who had donated blood a minimum of four times with the fourth blood donation date serving as their index date. We required four blood donations to ensure that donors were

considered healthy in parallel to kidney donors, who were also in contact with the health care system for some time before donating. We excluded blood donors who had diagnoses of the abovementioned cardiovascular diseases or redeemed prescriptions of antihypertensive drugs. Furthermore, we excluded patients <25 or >65 years.

For all cohorts the study period was divided into four calendar periods (see Figure 1 for illustration). Calendar period 1 was defined as the period of 1996-2002 for the kidney donors and general population cohort, and 1995-2001 for the blood donor cohort; calendar period 2 was defined as the period of 2003-2007 for the kidney donors and general population cohort, and 2002-2006 for the blood donor cohort; calendar period 3 was defined as the period of 2008-2012 for the kidney donors and general population cohort, and 2007-2011 for the blood donor cohort; calendar period 4 was defined as the period of 2013-2018 for the kidney donors and general population cohort, and 2012-2017 for the blood donor cohort.

Outcomes

We examined the following outcomes: 1) angina pectoris, 2) acute myocardial infarction, 3) ischemic stroke and 4) TIA both individually and combined as a composite endpoint, as well as 5) hypertension, 6) atrial fibrillation or flutter and 7) death. The diagnosis of hypertension was defined as redeemed prescriptions of minimum two classes of antihypertensive drugs within 180 days, vital status was ascertained trough CRS, while the other outcomes were based on inpatient and outpatient diagnosis codes. In the secondary analysis, we also included emergency room diagnosis codes given in the last four years of the study period because emergency room diagnoses could not be distinguished from inpatient and outpatient diagnoses among blood donors in the last four years of the study period.

Covariates

To address potential confounding, we examined the presence of COPD (only in the comparison with the blood donors) and alcohol related disorders in DNPR recorded at least two years before the index date. Furthermore, we examined the presence of prescriptions of lipid-lowering agents and antidepressants in DPR within one year before the index date (see Supplementary table 1 for codes). We did not include COPD or alcohol related disorders diagnosed within two years before index date to prevent including diagnoses detected during the donor evaluation process.

Statistical analysis

For each outcome, we followed all persons from index date until the first diagnosis of the specific outcome, death, emigration or end of study (December 2018 for the kidney donors and the general population cohort; December 2017 for the blood donors) whichever came first. All registry codes are provided in Supplementary table 1.

We conducted two separate analyses.

The primary analysis:

In the primary analysis we compared the risks of the outcomes in kidney donors with those in the general population cohort.

Patients' characteristics were presented as median with interquartile range (IQR) or proportion in percentage.

We calculated for each endpoint the incidence rates (IRs) among kidney donors and the general population cohort and the hazard ratio (HR) with 95% confidence intervals (CIs) using Cox proportional hazards regression analysis with the general population cohort as reference. Assumptions of proportional hazards were checked by log-minus-log plots and found acceptable. We calculated the cumulative 15-year risk of the composite endpoint, treating death as a competing risk. Furthermore, we

plotted the mortality as one minus Kaplan-Meier estimator and the cumulative incidence of the composite endpoint, atrial fibrillation or flutter and hypertension treating death as a competing risk.

The secondary analysis:

In the secondary analysis we compared the risks of the outcomes in kidney donors with those in the blood donor cohort.

Patients' characteristics were presented as median with IQR or proportion in percentage. In addition, we calculated weighted medians and weighted proportions for blood donors to estimate the expected proportions and medians had the blood donors had the same distribution of sex, age and calendar periods as the kidney donors. The weighting was based on the kidney donors' distribution of sex, age (25-39, 40-49, 50-59 and 60-65 years) and calendar periods.

We calculated for each endpoint the IRs among kidney donors and blood donors and the standardized incidence ratio (SIR) with 95% CIs as measures of the relative risk. SIRs were calculated as the number of observed cases among kidney donors divided by the number of cases that would be expected to occur if the kidney donors had the same incidence rates as the blood donors. The expected numbers were calculated as the time at risk multiplied by the blood donors' incidence rates according to sex, age (25-39, 40-49, 50-59 and 60-65 years) and calendar periods and summing the products. The 95% CIs were calculated under the assumption that the events followed a Poisson distribution.

All statistical analyses were performed with STATA version 15.1 (Stata Corp, College Station, Texas, USA)

Results

Patients' characteristics

The primary analysis:

We identified 1,325 kidney donors. After excluding kidney donors with cardiovascular disease, chronic liver disease, diabetes, cancer, COPD or autoimmune disease prior to index date or prescriptions of antihypertensive or antidiabetic drugs within one year prior to index, 1,103 (83.2%) kidney donors remained. Among the 222 excluded kidney donors, 19 had a previous diagnosis of cancer, 14 had a previous diagnosis of angina pectoris, 15 had a previous diagnosis of COPD, 18 had a previous diagnosis of autoimmune disease, while 152 had a redeemed prescription of an antihypertensive drug. The 1,103 kidney donors were matched to 11,030 sex- and age-matched individuals from the general population.

In both groups 56.0% were women and the median age was 52 years (IQR, 43-59). The median follow-up time was 7.8 years (IQR, 3.9-12.1) in kidney donors and 7.6 (IQR, 3.7-11.8) in the general population cohort. Kidney donors had fewer diagnoses of alcohol related disorders and fewer filled prescriptions for lipid modifying agents and antidepressants compared with the comparisons from the general population (Table 1a).

The secondary analysis:

We identified 1,325 kidney donors and 448,549 blood donors. After excluding individuals <25 or >65 years and individuals with cardiovascular disease prior to index date or antihypertensive drugs within one year prior to index, 1,047 kidney donors and 263,063 blood donors remained and were eligible for analysis.

The proportion of women was 56.0% among kidney donors and 49.0% among blood donors. The weighted proportion of women among blood donors was 56.0%. The median age was 51 years (IQR, 42-57) among kidney donors and 39 years (IQR, 31-47) among blood donors, while the weighted median age was 50 years (IQR, 42-

56) among blood donors. The median follow-up time was 7.9 years (IQR, 4.0-12.2) among kidney donors and 14.7 (9.3-18.2) among blood donors, while the weighted median follow-up time was 7.9 years (4.3-12.8) among blood donors. The proportions and weighted proportions of COPD, alcohol related disorders, and use of lipid modifying agents and antidepressants were lower in blood donors compared with kidney donors (Table 1b).

Study outcomes

The primary analysis:

Table 2a presents the IRs and HRs of the specific outcomes for kidney donors and the general population cohort. Figure 2 presents the cumulative incidence curves for the composite endpoint, atrial fibrillation or flutter, death and hypertension for the kidney donors and the general population cohort. The cumulative 15-year risk for composite endpoint among the kidney donors was 9.1% and 10.0% among the general population cohort (Figure 2). In the first 20 years of follow-up the cumulative incidence of death was higher in the general population cohort compared with kidney donors; however, after 20 years of follow-up the cumulative incidence for death increased more in kidney donors compared with the general population cohort (Figure 2). Compared with the general population cohort, kidney donors had a virtually similar risk of the composite endpoint (5.9 events v 6.9 per 1000 person years; HR = 0.85 (95% CI, 0.64-1.12)) and a decreased risk of atrial fibrillation or flutter (2.1 events v 3.4 per 1000 person years; HR = 0.59 (95% CI, 0.38-0.94) and death (3.7 events v 6.3 per 1000 person years; HR = 0.58 (95% CI, 0.41-0.81), while the risk of hypertension was virtually similar (17.4 events v 16.0 per 1000 person years; HR = 1.11 (95% CI, 0.93-1.32)) (Table 2a).

The secondary analysis:

Table 2b presents the IRs and SIRs of the specific outcomes in the kidney donors compared with the blood donors. The SIR for composite endpoint was 1.12 (95% CI, 0.85-1.47; Observed events/expected events (O/E) = 53/47.3). The SIR for atrial fibrillation or flutter was 0.84 (95% CI, 0.52-1.33; O/E = 18/21.4), the SIR for hypertension was 1.40 (95% CI, 1.18-1.67; O/E = 135/96.4), while the SIR for death was 1.11 (95% CI, 0.77-1.61; O/E = 29/26.1). In summary, kidney donors and blood donors had similar risks of cardiovascular disease and death; while kidney donors had an increased risk of being treated for hypertension.

Discussion

In this nationwide population-based cohort study, we did not identify a higher risk of ischemic cerebrovascular disease, ischemic heart disease, atrial fibrillation or flutter or death after living kidney donation neither when comparing kidney donors with the general population nor in the comparison with blood donors. Our findings suggested a higher risk of being treated for hypertension after living kidney donation when compared with blood donors.

The selection process of kidney donors in clinical practice aims to minimize the risk of intra- and post-operative complications as well as the long-term risk of reduced nephron mass. It involves a thorough medical evaluation to ensure that only healthy persons are allowed to donate their kidney. Despite the inclusion criteria in the primary analysis, comparisons from the general population cohort had more comorbidities and used more medication before index date than the kidney donors, which may explain the observed general lower risk of cardiovascular disease and death in kidney donors. The health requirements for blood donation are similar to the requirements for kidney donation in respect to hypertension, cardiovascular disease, chronic disease, etc. (Supplementary table 2), although the pre-donation medical

workup for blood donors is less extensive. Thus, blood donors may constitute a more similar comparison cohort than the general population, especially with respect to cardiovascular risk factors such as hypertension and diabetes. Although blood donors had fewer comorbidities and used less medication, they had risks of the outcomes similar to kidney donors except for being treated for hypertension which was higher in kidney donors.

To our knowledge, no studies have specifically investigated the association between living kidney donation and atrial fibrillation or flutter and our finding of no increased risk of atrial fibrillation or flutter thus adds to the existing literature. Results from studies investigating the risk of cardiovascular disease after living kidney donation are conflicting [7-12]. A study by Garg et al. based on regional health care databases and using the general population as a comparison cohort showed a hazard ratio of major cardiovascular events and death of 0.66 (95% CI, 0.48-0.90) between groups [7]. This result is in line with the results from our primary analysis; however, like in our primary analysis, Garg et al. attributed this association to confounding by a better health among kidney donors. Contrary to Garg et al., Mjøen et al. identified a 40% increased risk of cardiovascular death among kidney donors [12] when compared with a cohort consisting of self-proclaimed healthy individuals. In this study all-cause mortality started to increase 15 years after kidney donation i.e. after most of our follow-up ended. Multiple studies have investigated the risk of hypertension after kidney donation. A meta-analysis found an association between living kidney donation and increased diastolic blood pressure but found no clear association with hypertension [3], while two recently published studies by Holscher et al. and Haugen et al. found increased risk of hypertension among kidney donors (HR = 1.19 (95% CI, 1.01-1.41) and odds ratio = 1.25 (95% CI, 1.12-1.39) respectively) [18, 19].

Several biological mechanisms may explain a potential increased risk of hypertension in living kidney donors. The reduced renal function observed after

donor nephrectomy may lead to elevated sympathetic and renin-angiotensin-aldosterone system (RAAS) activity as well as hypervolemia, salt retention and endothelial dysfunction which are linked to increased risk of hypertension[20-22].

Several limitations should be considered when interpreting our results. First, although we have included virtually all living kidney donors in Denmark in the period 1996-2018, the total number of kidney donors was still small. This affects the precision of our estimates and may have masked small adverse effects of kidney donation. Second, the exclusion of marginal kidney donors implies that the results are not necessarily valid for potential kidney donors with coexisting diseases. Third, Mjøen et al. [12] found that the all-cause mortality started to increase 15 years after kidney donation. Thus, the limited time of follow-up (median = 8 years) may have been insufficient to detect adverse effects of kidney donation. The mortality curves from our primary study (Figure 2) suggest an adverse effect of kidney donation 20 years after donation; however, due to the few numbers of kidney donors with more than 20 years of follow up it is uncertain whether this is a true effect. Fourth, we lacked baseline information on some significant potential confounders including actual values of blood pressure, glomerular filtration rate and body mass index. Fifth, hypertension and diabetes are known to be considerably underdiagnosed in the Danish population [23, 24]; thus, despite we set up inclusion criteria about no hypertension and no diabetes some of the included comparisons from the general population and blood donors may still have suffered from hypertension and diabetes. Sixth, since kidney donors are offered regular follow-up visits at renal departments after donation, kidney donors are more likely than non-donors to be identified with hypertension and may have a lower threshold for treatment due to their previous donation. This may have led to an overestimation of the relative risk of hypertension among the kidney donors. Seventh, emergency room diagnoses were included in the last four years of follow-up in the secondary study. No validation studies have investigated these diagnoses. However, the majority of the cardiovascular events in

the kidney donors were ascertained through inpatient and outpatient diagnoses. Validation studies have shown that inpatient and outpatient diagnoses of acute myocardial infarction, angina pectoris, atrial fibrillation or flutter and ischemic stroke are recorded accurately in DNPR, while the recording of TIA has limited predictive values [25-27]. Thus, we believe that the impact of misclassification of these outcomes was minor. Finally, no validation study has investigated the procedure codes for living donor nephrectomy; however, we think, by adding requirements of examination or contact concerning donation before the nephrectomy date, we have ensured that virtually all included living kidney donors are true living kidney donors.

In conclusion, this study did not identify a clearly increased risk of cardiovascular disease after living kidney donation, although there may be a slightly increased risk of being treated for hypertension. Whether this reflects a greater risk of high blood pressure or may represent surveillance bias, misclassification and/or differences in the threshold for treatment remains to be clarified. The lack of associations between living kidney donation and cardiovascular disease supports the safety of living kidney donation based on current principles involving rigorous medical examination and strict requirements for living kidney donation. Most likely the safety of living kidney donation relies on this. The potential increased risk of hypertension found in this study; however, also emphasizes the importance of subsequent regular follow-up care of kidney donors.

Supplementary

Background

In the following section, I will give a short description of the living kidney donor evaluation process and the blood donation selection process based on the Danish guidelines.

Living kidney donation evaluation process

Before living kidney donation is allowed, the potential donor has to go through an evaluation process. The purpose of the evaluation process is to assess whether the donor is eligible as a donor both physically and mentally. The evaluation process consists of interviews and medical examinations. Beside testing whether the potential donor is immunologically compatible to the recipient, the medical examinations includes biochemical screening for diabetes and dyslipidemia, radiographic and nuclear medicine examinations of the kidneys and urinary system, ECG and blood pressure measurements [28]. Some of the requirements for kidney donation that are both related to cardiovascular risk and leads to preclusion in the evaluation process are listed in Supplementary table 2.

Blood donation selection process

Before every blood donation, the donor has to answer a questionnaire containing various questions about the donor's health and risk behavior. Based on the answers, it is evaluated whether the donor is allowed to donate[29]. Some of the requirements that are related to cardiovascular risk and leads to deferral in the selection process are listed in the Supplementary table 2. Blood pressure measurement is not a requirement before donation; although, it is measured regularly before donation to screen for hypertension.

Methodological considerations

Study design

We designed this study as a nation-wide cohort study based on prospectively collected data. Cohort studies are studies that measure the occurrence of events within one or more cohorts over time, usually comparing the occurrence in an exposed group with that in an unexposed group. In this study, we had one exposed group – the kidney donors, and two unexposed groups – the general population cohort and the blood donor cohort. We chose a cohort study design, because cohort studies are efficient when the exposure is rare. Furthermore, the design was suitable to investigate our multiple outcomes. The nationwide Danish registries enabled us to identify virtually all kidney donors in Denmark in the period of 1996-2018. Because the data is prospectively collected it is highly unlikely that the outcome status would have affected the classification of exposure.

We could have studied the research question with a case-control design; however, because the exposure was rare, we would have had to include large groups of cases and controls, to catch an acceptable amount of kidney donors. Furthermore, if we conducted at case-control study we would not have been able to obtain absolute risk estimates.

Exposure and outcome

The exposure in this study was living kidney donation. At first, we defined living kidney donors as all individuals with a procedure code for removal of a kidney from a living donor between 1996 and 2018 in DNPR. Among these individuals, we observed that around 1% died at the same date as the nephrectomy code was given. We knew from the literature that the post-operative mortality after living donor nephrectomy was around 0.03% [30]. Based on that, we concluded that these donors

had to be deceased donors wrongly coded as living kidney donors. We attempted to increase the specificity of the definition of living kidney donation by adding an additional requirement of a diagnosis code indicating a contact related to the donation of a kidney or a code representing the examination of a potential organ or tissue donor before the recorded date of nephrectomy. After application of the additional requirement, all individuals who died on the date of donation were excluded from the cohort. We therefore defined kidney donors as individuals who had a procedure code for removal of kidney from a living donor, and at the same time had either a diagnosis code indicating a contact related to the donation of a kidney or a code representing the examination of a potential organ or tissue donor registered between 1994 and the recorded date of nephrectomy. We think by adding the additional requirements that we have increased the positive predictive value of the definition of living kidney donation significantly.

For the cardiovascular outcomes, we used the admission date as the date of diagnosis because we assumed that most patient who got a diagnosis of a cardiovascular disease would have the disease at the first date of the admission/visit because of the often acute onset of cardiovascular diseases.

The hypertension outcome was based on redeemed prescriptions of antihypertensive drugs. We used redeemed prescriptions in order to capture individuals diagnosed with hypertension by the general practitioner. We did not include hospital diagnosis of hypertension in this definition because of the high risk of detection bias due to the fact that most kidney donors are followed regularly at renal departments after donation.

To increase the power of the study we decided to combine the ischemic cardiovascular outcomes into a composite endpoint. To prevent mixture of effects pointing in different directions we only included outcomes which we expected would be equally affected by kidney donation.

Statistics

In the primary analysis we calculated the cumulative 15-year risk of the composite endpoint for the kidney donors and the general population treating death as a competing risk. The cumulative 15-year risk were calculated to estimate the absolute risk of composite endpoint in the first 15 years of follow-up in the kidney donors and the general population cohort. We treated death as a competing risk instead of treating death as a censoring event to prevent overestimation of the cumulative 15-year risk.

In the primary analysis we compared the risk in the kidney donors with that in the blood donors using Cox proportional hazards regression analysis. The hazard ratio is a relative risk measure and represents the ratio of the hazard function of an event in the kidney donors to that in the general population cohort under the assumption that the hazard functions are proportional. Where the hazard function is the probability of occurrence of an event per unit time at risk, at a point in time, *t*. The assumption of proportional hazards might be violated for the death outcome; however, due to the low number of deaths after 20 years of follow-up, we did not split up the follow-up time.

In the secondary analysis we calculated standardized incidence ratios (SIRs) as a measure of relative risk. We did not calculate hazard ratios because individual matching between kidney donors and blood donors was not feasible.

The SIR was used to estimate the incidence rate ratio between the kidney and blood donors if the blood donors had the same sex, age and calendar period distribution as the kidney donors. In that way, we could adjust for differences between the kidney and blood donors regarding sex, age, and calendar period. The SIR was calculated as the incidence rate among kidney donors divided by the weighted average of the sex-, age- and calendar period-specific incidence rates in blood donors. Where the weighting was based on the distribution of risk time in kidney donors according to sex, age and calendar periods.

We calculated the SIRs based on our self-defined calendar periods instead of calendar time because the study periods in the kidney donors and blood donors were different. If we had calculated the SIRs based on calendar time, the SIRs might have been erroneous because the weights of kidney donors would have been applied to blood donors with shorter follow-up time.

We reported weighted estimates in blood donors in the secondary analysis to illustrate how much sex, age, and covariates had been balanced in the use of SIRs. The weighting was based on the distribution of age, sex and calendar periods among kidney donors.

The 95% CIs of the SIRs were calculated under the assumption that the events followed a Poisson distribution. It is well-known that the incidences of cardiovascular disease, hypertension and death increase with age. This tendency is also observable at the cumulative incidence curves especially at the mortality curves (Figure 2). This increment in incidence rates violates with the assumption that the events follow a Poisson distribution. A way to solve this problem would be to split up the follow-up time, and calculate multiple SIRs; however, due to the low number of events this method caused too imprecise estimates to be useful.

Systematic and random error

Epidemiological studies are prone to two kinds of errors – random error and systematic error. Random error affects the precision of the study and arises due to statistical fluctuations. The size of random error decreases with sample size – the larger the study population, the smaller random error. Systematic errors can be divided into categories – confounding, selection bias and information bias. Systematic errors are systematically deviations from the true values that do not decrease with sample size. In the following section, I will explain how the different sources of errors might have affected the study's reliability and validity.

Random error

In this study, the precision of the estimates for cardiovascular disease and death were limited by the small number of events, reflected by the wide 95% CIs. While, the estimates for hypertension were more precise due to the larger number of events. The imprecision of estimates for cardiovascular disease and death makes the estimates less certain and thereby makes the conclusion less clear. As mentioned in the discussion, this imprecision might have masked small adverse effects of kidney donation.

Confounding

A confounder is a variable that leads to distorted associations between exposure and outcome. A confounder is characterized by three things: 1) it is associated with the exposure, 2) it is a risk factor for the outcome and 3) it is not an intermediate step in the causal pathway between exposure and outcome. Several methods can be used to limit confounding; in the design phase it can be limited by randomization, matching and restriction, in the analysis phase it can be limited by stratification and adjustment including standardization.

Studies investigating the long-term cardiovascular risks in living kidney donors are prone to confounding because the kidney donors are a highly selected segment of the general population with an inherently lower baseline cardiovascular risk compared with the general population.

We aimed to limit the effect of potential confounding mainly by three methods. First, differences in sex and age were handle by sex- and age-matching in the primary analysis and sex- and age-standardization in the secondary analysis. Second, in the general population cohort we sought to mimic the requirements for kidney donation by restricting to individuals without significant preexisting comorbidity. Third, we included blood donors as a comparison cohort for the secondary analysis. As

explained earlier the requirements for blood donation are similar to the requirements for living kidney donation; hence, we *a priori* expected the blood donors to be comparable in respect to preexisting comorbidities. In the secondary analysis we did not exclude individuals with preexisting comorbidities other than cardiovascular diseases and hypertension because the proportions of individuals with significant preexisting comorbidities were low in both kidney and blood donors.

Despite our efforts to limit the effect of confounding in the two analysis, the associations may still have been distorted by unmeasured and residual confounding. First, hypertension and diabetes are known to be considerably underdiagnosed in the general population [23, 24]; thus, despite we set up inclusion criteria about no hypertension and no diabetes some of the included comparisons from the general population may still have suffered from hypertension and diabetes. Since hypertension and diabetes are risks factors of cardiovascular disease, this may have biased and decreased the relative estimates away from unity in the primary analysis. Second, in the secondary analysis we exploited the official requirements of no hypertension and no diabetes before blood donation to limit confounding from hypertension and diabetes. However, since hypertension and diabetes were assessed by a questionnaire, and not through a thorough medical examination, diabetes and hypertension may also have been underdiagnosed among blood donors, which may have biased and decreased the relative estimates away from unity in the secondary analysis. Third, in both analysis, data on lifestyle factors including smoking, physical exercise, alcohol use and diet were unavailable. Lifestyle factors greatly affects the cardiovascular risk. Accordingly, lifestyle factors may have confounded the associations. We used diagnosis of COPD as a proxy for smoking habits and alcohol related disorders as a proxy for alcohol consumption. Based on these variables, the general population cohort seemed to have a higher alcohol consumption than the kidney donors, while the blood donors seemed to smoke less and have a lower alcohol consumption than the kidney donors. Fourth, despite the similarities in the

requirements of living kidney and blood donation the requirements for blood donation seemed to be more rigorous than the requirements for blood donation (Supplementary table 2), which may have decreased the blood donors baseline cardiovascular risk and thereby biased and increased the relative estimates away from unity in the secondary analysis. Fifth, despite the adjustment for age in the secondary analysis by standardization, the wide age intervals might have resulted in insufficient adjustment for age in the secondary study. However, when we looked at the baseline characteristics, the age seemed to be balanced appropriately in the use of SIR.

Selection bias

Selection bias arises when the association between exposure and outcome in those who are enrolled in the study is different from those who are not enrolled in the study. Loss of follow-up may also introduce selection bias if the loss of follow-up is associated to both the exposure and outcome.

Since all living kidney and blood donations are carried out at public hospitals, and thus should be recorded in the DNPR and SCANDAT respectively, we have identified virtually all kidney and blood donors during the study period, which minimizes the selection bias. Furthermore, because the CRS encompass the entire Danish population, every resident in Denmark can act as a comparison in the general population cohort, if they meet the inclusion criteria. This also reduces the selection bias. Moreover, the virtually complete follow-up in Danish registries also diminish the selection bias. In the general population cohort, we excluded individuals who were also in the kidney donor cohort. This could potentially lead to bias. However, due to the rarity of living kidney donation, we think this had a negligible impact on the estimates.

Information bias

Information bias can occur if the classification of exposure, covariates or outcome variables is erroneous. Erroneous classification that is dependent on other study variables is referred to as differential misclassification. While erroneous classification that is independent on other study variables is referred to as non-differential misclassification. Bias from differential misclassification can go in either directions. While bias from non-differential misclassification goes towards unity if the variable is dichotomous. In the following section, I will describe the potential misclassification of exposure and outcome. Misclassification of comorbidities is described under residual confounding in the confounding section.

Misclassification of exposure

As explained under the exposure section, we think we have increased the specificity of the definition of living kidney donation by adding the additional requirement, and thereby reduced the risk of misclassification.

In the blood donor cohort, we did not exclude individuals who had undergone living kidney donation before index date. However, due to the rarity of living kidney donation, we think this had a negligible impact on the estimates.

Misclassification of outcome

After the kidney donation living kidney donors are offered regular follow-up visits at renal departments. At every visit the blood pressure is measured. This increases the chance of detection of hypertension in kidney donors, which may lead to an overestimation of the relative estimates of the associations between living kidney donation and hypertension. The chance of detection of atrial fibrillation or flutter might also be increased at the follow-up visits; however, we did not observe increased risks of atrial fibrillation or flutter among kidney donors.

If a blood donor continues to donate blood after inclusion in the comparison cohort, there is a chance that the blood pressure will be measured at the blood bank. This would increase the chance for detection of hypertension and would counteract the effect of the aforementioned bias.

The threshold for treatment of hypertension might be lower in kidney donors compared with their comparisons, because physicians are more concerned of hypertension in people with reduced kidney function. This will lead to an overestimation of the risk of hypertension among donors, and thereby lead to an overestimation of the association between living kidney donation and hypertension.

We chose to define hypertension as the redemption of prescriptions of minimum two classes of antihypertensive drugs. We chose this definition because it has a high specificity [31]. However, the sensitivity might be low, because individuals with hypertension only treated with one antihypertensive drug are not caught. Accordingly, the absolute estimates might be underestimated.

The vital status was ascertained through CRS. Data on death is accurately recorded in CRS and is unlikely to cause misclassification.

As explained in the discussion section, the cardiovascular outcomes are recorded accurately in DNPR with high positive predictive values, except for TIA. A misclassification of TIA is probably independent of the exposure, leading to bias towards unity of the relative estimates.

In conclusion, information bias may have led to overestimations of the relative estimates for hypertension, while it is unlikely that misclassification had a major impact on death and cardiovascular disease.

Generalizability

Denmark has a rather homogenous population in respect to ethnicity with a majority of Caucasians and small minority of people of African descent. African Americans have a higher risk of kidney failure than European Americans [32, 33]. Variants of

the apolipoprotein 1 (APOL1) gene that are frequent in African Americans have been associated to kidney failure [34]. Hence, donors of African descent might be more vulnerable to the nephrectomy than donors of European descent, and thereby have an increased risk of cardiovascular disease. Accordingly, the result from our study might not be generalizable to people of African descent.

Kidney donors are a highly selected cohort without significant preexisting comorbidity, and with a characteristic age-distribution. Thus, the estimates might not be applicable to people with significant comorbidities or with age outside the range of the kidney donors in the study; and therefore, the estimates cannot be used as an argument to relax the rigorous requirements of living kidney donation.

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Tables and figures

Table 1a, Baseline characteristics of the kidney donors and the sex- and age-matched general population cohort in the primary analysis:

	Kidney donors (N=1,103)	General population (N=11,030)
Female gender, %	56.0	56.0
Age, median years (IQR*)	52 (43-59)	52 (43-59)
Lipid modifying drugs, %	2.8	3.5
Alcohol related disorders, %	1.1	1.5
Antidepressants, %	5.9	7.0

*Interquartile range

Table 1b, Baseline characteristics of the kidney donors and the blood donors in the secondary analysis:

	Kidney donors (N=1,047)	Blood donors (N=263,063)	Blood donors, weighted estimates (N=263,063)
Female gender, %	56.0	49.0	56.0
Age, median years (IQR*)	51 (42-57)	39 (31-47)	50 (42-56)
Lipid modifying drugs, %	2.7	0.1	0.7
Alcohol related disorders, %	1.4	0.9	0.9
COPD, %	1.0	0.1	0.2
Antidepressants, %	6.2	1.0	1.2

*Interquartile range

Table 2a, Incidence rates (IRs) and hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for outcomes in the primary analysis:

	IRs among kidney donors (per 1,000 person-years)	IRs among the general population cohort (per 1,000 person-years)	HRs (95% CI)
Composite endpoint*	5.9	6.9	0.85 (0.64-1.12)
Hypertension	17.4	16.0	1.11 (0.93-1.32)
Atrial fibrillation or flutter	2.1	3.4	0.59 (0.38-0.94)
Angina pectoris	3.3	3.8	0.87 (0.60-1.25)
Acute myocardial infarction	1.4	1.6	0.86 (0.49-1.53)
Ischemic stroke	1.3	1.7	0.71 (0.39-1.27)
TIA (transient ischemic attack)	1.1	1.0	1.10 (0.57-2.11)
Death	3.7	6.3	0.58 (0.41-0.81)

* Composite endpoint includes angina pectoris, acute myocardial infarction, ischemic stroke and TIA

Table 2b, Incidence rates (IRs) and standardized incidence ratios (SIRs) and corresponding 95% confidence interval (CI) in the secondary analysis:

	IRs among kidney donors (per 1,000 person-years)	IRs among blood donors (per 1,000 person-years)	Observed events/expected events	SIRs (95% CI)
Composite endpoint*	6.0	4.2	53/47.3	1.12 (0.85-1.47)
Atrial fibrillation or flutter	2.0	1.8	18/21.4	0.84 (0.52-1.33)
Angina pectoris	3.6	2.5	32/27.6	1.16 (0.81-1.64)
Acute myocardial infarction	1.4	1.1	13/10.7	1.22 (0.71-2.13)
Ischemic stroke	1.3	0.9	12/11.4	1.05 (0.59-1.87)
TIA (transient ischemic attack)	0.9	0.7	8/8.5	0.94 (0.47-1.91)
Hypertension	16.7	10.1	135/96.4	1.40 (1.18-1.67)
Death	3.2	2.5	29/26.1	1.11 (0.77-1.61)

* Composite endpoint includes angina pectoris, acute myocardial infarction, ischemic stroke and TIA

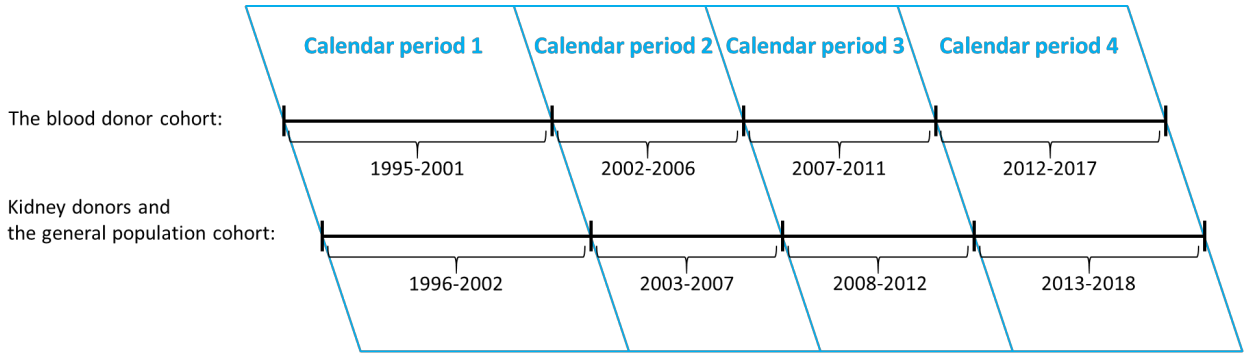

Figure 1. Definition of calendar periods used in the study.

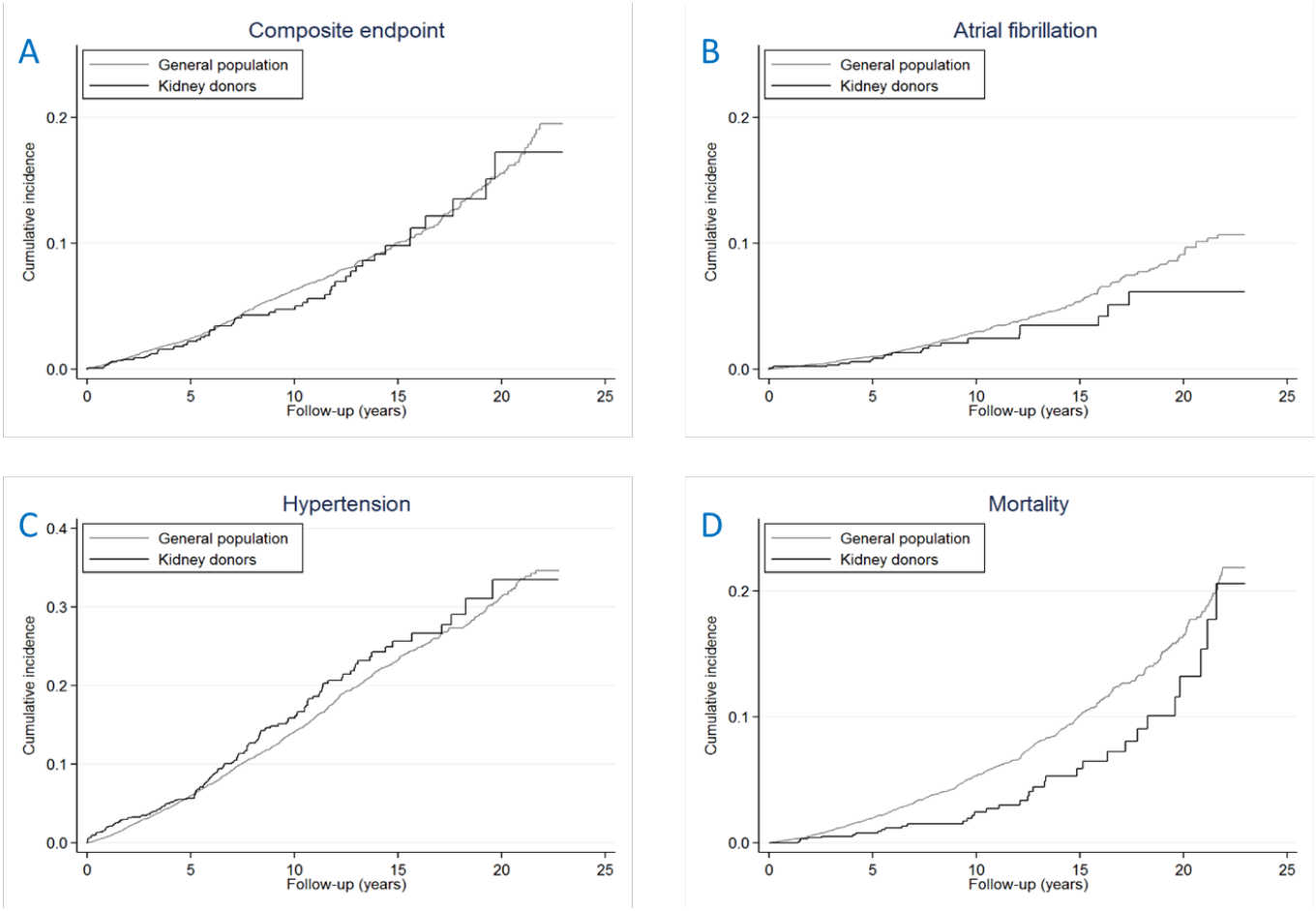

Figure 2. Cumulative risk of outcomes. (A) Cumulative risk of composite endpoint (angina pectoris, acute myocardial infarction, ischemic stroke and TIA) in kidney donors compared with the risk in the general population cohort. (B) Cumulative risk of atrial fibrillation or flutter in kidney donors compared with the risk in the general population cohort. (C) Cumulative risk of hypertension in kidney donors compared with the risk in the general population cohort. (D) Cumulative mortality risk in kidney donors compared with the risk in the general population cohort.

Supplementary table 1, ICD (International Classification of Diseases), ATC (Anatomical Therapeutic Chemical Classification System) and NCSP (NOMESCO Classification of Surgical Procedures) codes

Variable	Codes
Living kidney donation	KYKA00 (NCSP) or KYKA01 (NCSP), combined with Z00.5 (ICD-10) or Z52.4 (ICD-10)
Cardiovascular disease	
1. Atrial fibrillation or flutter	ICD-8: 42793, 42794; ICD-10: I48
2. Heart failure	ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
3. Angina pectoris	ICD-8: 411, 413; ICD-10: I20, I25.1, I25.9
4. Myocardial infarction	ICD-8: 410; ICD-10: I21
5. Ischemic stroke	ICD-8: 433, 434; ICD-10: 163
6. Intracranial hemorrhage	ICD-8: 430, 431; ICD-10: I60, I61, I62
7. Transient ischemic attack	ICD-8: 435; ICD-10: G45.9
Diabetes	ICD-8: 249, 250; ICD-10: E10, E11, E14; ATC: A10B, A10A
Hypertension	ATC: Combination of ≥2 of the following classes within 180 days: Alpha adrenic blockers(C02A, C02B, C02C), non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52), vasodilators (C02DB, C02DD, C02DG, C04), beta blockers (C07), Calcium channel blockers (C07F, C08, C09BB, C09DB), RAAS inhibitor (C09)
Chronic kidney disease	ICD-8: 249.02, 250.02, 582, 583, 584, 590.09, 593.20, 753.10-753.19, 792; ICD-10: E10.2, E11.2, E14.2, N03, N05, N11.0, N14; N16, N18-N19, N26, Q61.1-Q61.4.
Chronic obstructive pulmonary disease	ICD-8: 491, 492; ICD-10: J44
Chronic liver disease	ICD-8: 571 (except 571.10, 571.11, 571.19), 070.00, 070.02, 070.04, 070.06, 070.08, 571, 573.00, 573.04; ICD-10: B150, B162, B190, K70.2, K70.3, K70.4, K71, K72, K73, K74, K76.6
Alcohol related disorder	ICD-8: 291, 303, 571.10, 577.10, 577.90, 456; ICD-10: G31.2, G62.1, G72.1, I42.6, K29.2, Z72.1, K70, K86.0
Cancer	ICD-8: 140-207 (except 177); ICD-10: C00-C96 (except C44)
Autoimmune disease	ICD-8: 712, 734; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, D86
Lipid modifying agents	ATC: M01
Antidepressants	ATC: N06A

Supplementary table 2, Requirements related to the cardiovascular risk for living kidney donation and blood donation. The requirements are based on the requirements that were valid during the study periods[28, 29].

Condition/medication	Living kidney donation	Blood donation
Age	No official limits	1995-2007: 18-64 years 2008-2017: 17-66 years
Hypertension	Only allowed if well-treated	Not allowed
Obesity	BMI have to be under 30 kg/m^2	No upper limit
Diabetes	Not allowed	Not allowed
Cardiovascular disease	Not allowed	Not allowed
Kidney disease	Not allowed	Not allowed
Cancer	Not allowed	Not allowed
Dyslipidemia	Only allowed if well-treated	Not allowed

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28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

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37. Use of medical databases in clinical epidemiology. *2008*.

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39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

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    Sandra Kruchov Thygesen. Atrial fibrillation in patients with ischemic stroke: A population-based study. Research year report. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. PhD thesis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. PhD thesis. *2009*.

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78. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

79. Kirurgisk fjernelse af milten og risikoen for efterfølgende infektioner, blodpropper og død. Danmark 1996-2005. (Online publication only). *2013*.

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117. Clara Reece Medici: Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation. Research year report. *2016*.

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142. Frederikke Schønfeldt Troelsen: Risk and prognosis of primary liver, gallbladder, bile duct, and pancreatic cancer a negative CT scan of the abdomen: A Danish population-based cohort study. Research year report. *2019*.

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148. Jeppe Damgren Vesterager: Hospital variation in the risk of infection after hip fracture surgery: A population-based cohort study. Research year report. *2020*.