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Kidney disease and risk of dementia: a cohort study

Short title: Kidney disease and dementia

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ABSTRACT

Objectives: It is unclear whether kidney disease is a risk factor for developing dementia. We examined the impact of kidney disease on risk of future dementia.

Design and setting: Nationwide cohort study in Denmark from January 1st 1995 until December 31st 2016.

Participants: Patients diagnosed with kidney disease and matched general population cohort without kidney disease (matched 1:5 on age, sex and year of kidney disease diagnosis).

Primary and secondary outcome measures: All-cause dementia and its subtypes: Alzheimer's disease, vascular dementia and other specified or unspecified dementia. We computed five-year cumulative incidences (risk) and hazard ratios (HRs) for outcomes using Cox regression analyses.

Results: The study cohort comprised of 82,690 patients with kidney disease and 413,405 individuals from the general population. Five- and ten-year mortality rates were twice as high in patients with kidney disease compared to the general population. The five-year risk for all-cause dementia was 2.90% (95% confidence intervals: 2.78%-3.08%) in patients with kidney disease and 2.98% (2.92%-3.04%) in the general population. Compared to the general population, the adjusted HRs for all-cause dementia in patients with kidney disease were 1.06 (1.00-1.12) for the five-year follow-up and 1.08 (1.03-1.12) for the entire study period. Risk estimates for dementia subtypes differed substantially and were lower for Alzheimer's disease and higher for vascular dementia.

Conclusions: Patients diagnosed with kidney disease have a modestly increased rate of dementia, mainly driven by vascular dementia. Moreover, patients with kidney disease may be underdiagnosed with dementia due to high mortality and other comorbidities of higher priority.

Article summary

Strengths and limitations of this study (5 bullet points on methods):

- This is the first European population-based study examining the impact of hospital-diagnosed kidney disease on risk of future dementia.
- Using a large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up largely eliminated selection bias.
- We did not have data on albuminuria or estimated glomerular filtration rate (eGFR).
- Not all individuals with kidney disease or dementia are hospital-diagnosed and captured in the Danish registries.
- Results pertaining to dementia subtypes should be interpreted cautiously due to potential differential misclassification of dementia subtypes, particularly among patients with kidney disease

Contributors

BRK and CFC had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. ADK and CFC are guarantors of the study.

Concept and design: ADK, BRJ, HTS, VWF and CFC. Statistical analysis: BRJ. Drafting of the manuscript: ADK. Supervision: CFC. Interpretation and critical revision of the manuscript for important intellectual content: ADK, BRJ, HTS, VWF and CFC.

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Competing interests

The authors have no conflicts. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University.

Patient consent for publication / Ethics approval

The study was registered at Aarhus University (record number 2016-051-000001/603) as mandated by the Danish Data Protection Agency. According to Danish legislation, registry-

based studies do not require ethical review board approval or informed consent from the participants

Data availability statement

Data was accessed at secure servers, and cannot be shared due to Danish legislation.

INTRODUCTION

Dementia is a common, progressive age-related neurological disorder diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning.[1] Although the incidence rates of dementia have decreased modestly over the last 30 years, the prevalence of dementia is increasing worldwide, likely due to increased life expectancy.[2] This has enormous costs for the individuals and families affected, as well as the health care and society.[3]

Kidney disease is another disorder with a high (close to 10%) and increasing prevalence, partly due to ageing population, and increased incidence rates of hypertension and diabetes mellitus.[4]

Kidney disease and dementia share risk factors such as increasing age, hypertension, diabetes mellitus and hyperlipidemia, and the pathophysiology of small vessel disease.[5, 6] One potential link between kidney disease and dementia could be common susceptibility of kidney and brain tissue to vascular injury.[7] Kidney disease is associated with oxidative stress, chronic inflammation and changes in coagulation, and it might also affect the brain or cerebral vasculature indirectly or directly through metabolic derangements and uremic toxins.[7]

A previous population-based study in Taiwan found a hazard ratio (HR) of 1.41 for all-cause dementia in patients with a diagnosis of kidney disease (N=37,049) compared to the general population (N=74,098).[8] However, these findings may not be applicable to European populations, and this study did not examine potential differences across dementia subtypes. Furthermore, previous studies, where kidney disease was defined as persistent albuminuria or estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, provided mixed results.[9-12] Thus, whether kidney disease has an impact on risk of

dementia is presently uncertain. We investigated this for all-cause dementia and dementia subtypes (Alzheimer's disease, vascular and other dementia) in a nationwide cohort study.

METHODS

We followed the STROBE guidelines for reporting of cohort studies in epidemiology.

Study cohort

We conducted a nationwide cohort study of all Danish patients with hospital-diagnosed kidney disease and a matched general population comparison cohort without kidney disease during a study period from January 1st 1995 until December 31st 2016.

A flow chart of the study cohort is shown in Figure 1. We identified 122,670 patients with a first-time kidney disease diagnosis recorded during the study period. Next, we excluded patients who died (N=32,196) or did not reside in Denmark (N=465) during the first year after kidney disease diagnosis. Further exclusion criteria were diagnosis of dementia (N=1,909) and prodromal signs of dementia, i.e., mild cognitive impairment and amnestic syndrome (N=303) before kidney disease diagnosis. Additionally, we excluded patients diagnosed with dementia (N=1,300) and prodromal signs of dementia (N=156) during first year after a kidney disease diagnosis, because dementia diagnosed in this period is unlikely to be a consequence of kidney disease. Finally, we limited the cohort to adult patients aged 18 and above. The remaining 82,690 patients comprised our kidney disease cohort. For each patient in the kidney disease cohort, up to five individuals from the general population without a kidney disease diagnosis prior to index date were randomly selected and matched on age (birth year), sex and calendar year of index date, i.e., date of kidney disease diagnosis. Matching was performed as individual matching with replacement. The general population comparison cohort comprised of 413,405 individuals,

who were alive and had no dementia, mild cognitive impairment, amnestic syndrome or kidney disease prior to study entry.

Diagnoses

Diagnoses of kidney disease (exposure), dementia (outcome), mild cognitive impairment, amnestic syndrome and potential confounders were based on diagnoses obtained from the Danish National Patient Registry and/or the Danish Psychiatric Central Research Registry. These registries, covering all Danish hospitals, have recorded hospital admissions since 1977 and 1969 respectively, as well as outpatient specialist clinic visits since 1995.[13-15] We used all primary and secondary discharge diagnoses for all hospitalizations and outpatient clinic visits, but not emergency room visits (as diagnoses in this setting may be tentative and thus less valid). Diagnoses were identified according to the World Health Organization (WHO) International Classification of Diseases 8th edition (ICD-8) until the end of 1993 and 10th edition (ICD-10) thereafter (Supp. Table 1). We used the date of hospital admission or start of outpatient clinic follow-up as the date for all diagnoses.

Kidney disease

In the main analysis, we used an extended definition of kidney disease including chronic kidney disease as well as several other persistent kidney diseases, dialysis treatment and kidney transplant (for ICD codes, see Supplemental Table 1). In a sensitivity analysis, we used chronic kidney disease (restricted to ICD-8 792 and ICD-10 N18) as the exposure for all-cause dementia only.

Dementia

The validity of all-cause dementia is high with a positive predictive value of 86% in the Danish registries.[16] Dementia subtypes were mutually exclusive, and we only used the first

ever coded dementia subtype: Alzheimer's disease, vascular dementia and other (specified or unspecified) dementia, the latter comprising the majority of dementia diagnoses (for ICD codes, see Supp. Table 1). Because about one third of cases with other dementia without specification may be attributable to Alzheimer's disease,[16] we also included a combined outcome of Alzheimer's disease and other dementia.

Covariates

We identified cardiovascular disease (CVD), CVD risk factors, (any) cancer and socioeconomic status as potential confounders due to their association with kidney disease and dementia.[5, 6, 17] All covariates were assessed prior to study entry. CVD covariates were angina pectoris, myocardial infarction, stroke, peripheral arterial disease, venous thromboembolism, heart failure, heart valve disease and atrial fibrillation. Covariates related to CVD risk factors were hypercholesterolemia, hypertension, obesity, diabetes mellitus, and chronic obstructive pulmonary disease as a proxy for smoking. CVD risk factors were based on diagnoses from the Danish National Patient Registry and additionally on prescriptions of lipid lowering and antihypertensive drugs (see Anatomical Therapeutic Chemical [ATC] codes in Supp. Table 1) from the Danish National Prescription Registry, containing detailed individual-level data on prescriber, patient, and products for all outpatient prescriptions dispensed since 1995.[18]

Covariates related to socioeconomic status were highest education achieved, personal gross income and employment status obtained from the Integrated Database for Labor Market Research, established in 1981.[19] Education was categorized as: low (elementary school only), medium (high school and/or academy profession degree) and high (bachelor's, master's or higher degree). Personal gross income was categorized in quartiles. Employment status was categorized as: employed, retired and unemployed. We

used employment status during the 12-24 months preceding the study entry, since employment status during the year prior to kidney disease diagnosis is likely to underestimate the peak employment status.

Patient and public involvement

No patient involved.

Statistical analysis

We compared cumulative incidence (risk) of death as well as all-cause dementia (taking the competing risk of death into account) for the kidney disease and comparison cohorts. Hazard ratios for all-cause dementia and dementia subtypes and their corresponding 95% confidence intervals (CIs) were calculated using Cox regression analyses with time-on-study as the time scale. Proportional hazards assumption was tested graphically by log-log plots, and no violations were detected. Age, sex and calendar year of index date were already controlled for in the unadjusted Cox model, as these were the matching criteria. However, due to the built-in selection bias (see Discussion), the matching could not be completely retained, and the adjusted Cox model therefore included adjustments for age (age groups listed in Table 1), sex and calendar year of index date, as well as other potential confounders. Participants with missing values (<1% of personal gross income and <11% of employment status and education level each) were excluded from the adjusted analyses. Participants were followed from one year after index date until December 31st 2016, diagnosis of dementia, emigration or death, whichever came first. Thus, the minimum follow-up time was one year and maximum 22 years. Because all diagnoses and vital and emigration status are registered in national registries, we had no losses to follow-up.

We performed predefined stratification analyses for age (18-49, 50-59, 60-74, 75-84 and >85 years), sex, calendar year of index date (1995-2003 or 2004-2016), CVD, CVD risk factors, socioeconomic factors and follow-up time (1-5 years, 1-10 years and 1-22 years). Finally, in order to assess whether the risk of all-cause dementia was linked to kidney disease severity, we stratified the kidney disease cohort by presence or absence of kidney failure (defined as receiving dialysis treatment and/or kidney transplant, for codes see Supp. Table 1).

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

The study was registered at Aarhus University (record number 2016-051-000001/603) as mandated by the Danish Data Protection Agency. According to Danish legislation, registry-based studies do not require ethical review board approval or informed consent from the participants.

RESULTS

The study cohort consisted of a kidney disease cohort of 82,690 patients with kidney disease and a comparison cohort of 413,405 matched individuals from the general population without kidney disease. The median age was 69 years (interquartile range: 56-78 years). Women comprised 41% of all participants, and 71% were enrolled during 2004-2016 and 29% during 1995-2003 (Table 1). Diagnoses of CVD and CVD risk factors were much more frequent in the kidney disease than in the comparison cohort (Table 1). Furthermore, the kidney disease cohort had lower income, more unemployment and lower education than the comparison cohort (Table 1). Finally, the follow-up time was shorter for

the kidney disease than for the comparison cohort, with a median of 3.68 and 5.24 years, respectively (Table 1). This difference reflects a higher mortality rate in the kidney disease than the comparison cohort: 5- and 10-year mortality was twice as high in patients with kidney disease compared to the general population (Figure 2). During the study period, 466,071 (94%) participants died, 78,555 (95%) from the kidney disease cohort and 387,516 (94%) from the comparison cohort.

Kidney disease and risk of developing dementia

During follow-up, 3,462 (4.19% of 82,690) patients with kidney disease and 21,879 (5.29% of 413,405) individuals from the comparison cohort developed dementia, the majority classified as other dementia (Table 2). Alzheimer's disease was more frequent in the comparison cohort, and vascular dementia in the kidney disease cohort (Table 2).

The 5-, 10-, and 22-year risks of all-cause dementia were lower in patients with kidney disease than in the general population: 2.90% (95% CIs: 2.78%-3.08%), 4.96% (4.79%-5.14%) and 7.05% (6.70%-7.41%) for the kidney disease cohort and 2.98% (2.92%-3.04%), 6.03% (5.94%-6.12%) and 10.39% (10.17%-10.60%) for the comparison cohort (Figure 2).

The estimates for dementia subtypes were lowest for Alzheimer's disease and highest for vascular dementia (Table 2).

The adjusted HR (aHR) for all-cause dementia was stable over time, 1.06 (1.00-1.12) for up to 5 years of follow-up, 1.08 (1.03-1.13) for up to 10 years of follow-up and 1.08 (1.03-1.12) for up to 22 years of follow-up (Table 2). When we restricted the kidney disease

exposure to chronic kidney disease only, the aHR for all-cause dementia was 1.04 (0.98-1.10) for up to 22 years of follow-up, and very similar for shorter follow-up (Table 2).

In analyses stratified by age, there was a stepwise decrease in HRs of all-cause dementia with increasing age: the aHRs for 18-49, 50-59, 60-74, 75-84 and ≥85 years age groups were 1.14 (0.78-1.67), 1.32 (1.09-1.61), 1.16 (1.08-1.24), 1.01 (0.95-1.08) and 0.90 (0.77-1.04), respectively. The rate of all-cause dementia did not differ by sex, calendar year of index date, or socioeconomic factors. Kidney disease was also associated with increased HR for dementia in most CVD subgroups (myocardial infarction, stroke, peripheral arterial disease, venous thromboembolism, heart failure and heart valve disease) and CVD risk factors (atrial fibrillation, hypertension, obesity and diabetes mellitus), but estimates were imprecise (Figure 3). Results for dementia subtypes showed consistent results (Supp. Figure 1).

DISCUSSION

In this nationwide study of nearly 500,000 participants, we found that being diagnosed with kidney disease is associated with a modestly increased risk of future dementia. When we restricted the exposure to chronic kidney disease only, the association was similar.

We found substantially smaller estimates than the only previous population-based study, where investigators in Taiwan found an HR of 1.41 (1.32-1.50) for all-cause dementia in patients with kidney disease compared to the general population.[8] This may partly be explained by differences between these Asian and European populations, study design differences or both. Our study included more recent data, five times as many participants,

finer age matching and longer follow-up period. Furthermore, we included dialysis treatment, kidney transplantation and hypertensive nephropathy in our kidney disease definition, and we did not exclude participants based on other kidney-related diagnoses. In contrast, the Taiwanese study excluded patients with these and several other kidney-related diagnoses. Thus, our study likely included relatively more patients with severe kidney disease in the kidney disease cohort and mild kidney disease in the comparison cohort. Finally, while we excluded patients who were diagnosed with dementia within one year after kidney disease diagnosis, the Taiwanese study did not do this, and in this population the incidence rate ratio for less than two years of follow-up was substantially higher than the incidence rate ratio for two or more years of follow-up.[8] Previous studies have reported an association between severe kidney disease (eGFR<30 ml/min/1.73 m^2) and increased risk of cognitive impairment at baseline and cognitive decline over time.[20, 21] However, studies that mainly included eGFR measurements within the normal range showed a stronger association between albuminuria and dementia than between eGFR and dementia.[9-12, 22] This finding is compatible with the notion that albuminuria has a better sensitivity than eGFR to detect more advanced kidney disease. Unfortunately, we did not have data on albuminuria or eGFR.

The lack of a strong association between kidney disease and dementia may possibly be explained in part by survivor bias due to very high mortality among patients with kidney disease.[23] Because dementia increases with age, patients with kidney disease may not survive long enough to develop dementia. Indeed, the fraction of participants diagnosed with dementia was lower in patients with severe than mild kidney disease (3.3% of patients with dialysis treatment or kidney transplant versus 4.2% of patients without these interventions, data not shown). This finding may reflect survivor bias or might suggest that

clinicians are more likely to underdiagnose dementia in the presence of life-threatening illness and reduced life expectancy (detection bias). This inference is further supported by our stratification analyses, showing lower risk estimates in the presence of CVD, e.g., myocardial infarction, and CVD risk factors known to be associated with increased mortality.[24] In contrast, a previous Danish study of 314,911 patients with myocardial infarction matched with 1,573,193 individuals from the general population, reported that myocardial infarction was associated with higher risk of vascular dementia, but not with risk of all-cause dementia or other subtypes.[25] Taken together, these findings suggest a possible misclassification bias for dementia subtypes, as clinicians may be more likely to diagnose vascular dementia, and less likely Alzheimer's disease, in patients with dementia and kidney disease or myocardial infarction than in individuals without these diseases.

Since HRs may change over time, the observed modest association between kidney disease and dementia may be limited to the first few years after a kidney disease diagnosis. On the other hand, the period-specific HRs are prone to a built-in selection bias.[23] In our study, this translates to preferential censoring of patients, due to death, from the kidney disease cohort in the beginning of follow-up. With increasing follow-up time, this can lead to a relative increase in the proportion of individuals susceptible to dementia in the comparison cohort and thereby explain why the unadjusted HRs attenuated with increasing follow-up time. Due to the built-in selection bias, the matching could not be retained, and for this reason we included matching covariates in our adjusted analysis. This can possibly explain why the unadjusted HRs attenuated, while the aHRs did not attenuate with increasing follow-up time.

The major strength of our study is its design: large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up thus largely eliminating selection bias.

Limitations of our study include survival and surveillance bias. Further limitations are misclassification bias, unmeasured or residual confounding, quality of coding and validity of diagnoses. Positive predictive value of kidney disease coded in Danish registries is high, but incomplete, i.e., not all individuals with kidney disease are captured.[26, 27] While validity of all-cause dementia and Alzheimer's disease in Danish registries is high, it is lower for other dementia subtypes.[16] Thus, the results pertaining to dementia subtypes should be interpreted cautiously. This caveat is particularly important since our results are compatible with differential misclassification of dementia subtypes among patients with kidney disease, where vascular risk factors are especially common, and the general population, where vascular risk is lower. Furthermore, we used the date of hospital admission or start of outpatient clinic follow-up as the date for all diagnoses, since the exact day is not available. This may have introduced a bias, particularly in the beginning of the follow-up. Finally, since all diagnoses are recorded by hospital physicians, mild kidney disease and mild dementia treated only by a general practitioner would not be recorded unless they were also assessed in the hospital or an outpatient clinic setting.

In conclusion, patients diagnosed with kidney disease have a modestly increased risk of being diagnosed with future dementia. This association is mainly driven by diagnoses of vascular dementia, and it may be limited to the first few years after the kidney disease diagnosis. On the other hand, patients with kidney disease may be underdiagnosed with dementia due to high mortality and other comorbidities of higher priority, and the true risk of future dementia may be somewhat higher than our study suggests.

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LEGENDS

Figure 1. Study flow chart.

Cohort of patients with incident kidney disease and individuals of the matched general population comparison cohort during 1995-2016.

Figure 2. Cumulative incidences of A) death and B) all-cause dementia in patients with kidney disease (kidney disease cohort) and individuals in a matched population without kidney disease (comparison cohort).

Figure 3. Risk of all-cause dementia in patients with kidney disease compared with individuals in a matched population without kidney disease stratified by covariates listed in Table 1.

HR: hazard ratio. 95% CI: 95% confidence interval.

Table 1. Characteristics of study cohort at baseline.

	Kidney disease cohort	Comparison cohort
Number of participants, N	82,690	413,405
Age groups, years		
18-49, N (%)	14,718 (17.8)	73,530 (17.8)
50-59, N (%)	11,059 (13.4)	55,330 (13.4)
60-74, N (%)	29,021 (35.1)	145,116 (35.1)
75-84, N (%)	20,381 (24.6)	102,063 (24.7)
≥85, N (%)	7,511 (9.1)	37,366 (9.0)
Women, %	33,589 (40.6)	167,914 (40.6)
Calendar period of kidney disease diagnosis		
1995-2003, N (%)	24,410 (29.5)	122,013 (29.5)
2004-2016, N (%)	58,280 (70.5)	291,392 (70.5)
Any cancer, N (%)	10,813 (13.1)	36,216 (8.8)
Angina pectoris, N (%)	17,346 (21.0)	38,656 (9.4)
Myocardial infarction, N (%)	10,303 (12.5)	22,061 (5.3)
Stroke, N (%)	7,885 (9.5)	19,210 (4.6)
Peripheral artery disease, N (%)	9,673 (11.7)	16,109 (3.9)
Venous thromboembolism, N (%)	3,703 (4.5)	9,351 (2.3)
Heart failure, N (%)	12,154 (14.7)	14,370 (3.5)
Heart valve disease, N (%)	4,700 (5.7)	9,080 (2.2)
Atrial fibrillation, N (%)	10,723 (13.0)	24,431 (5.9)
Hypercholesterolemia, N (%)	32,780 (39.6)	85,679 (20.7)
Hypertension, N (%)	66,500 (80.4)	202,597 (49.0)
Obesity, N (%)	8,146 (9.9)	10,189 (2.5)
Diabetes mellitus, N (%)	23,271 (28.1)	19,159 (4.6)
Chronic obstructive pulmonary disease, N (%)	10,218 (12.4)	26,936 (6.5)
Personal gross income during the year preceding the index date		
First quartile, N (%)	21,347 (25.8)	91,250 (22.1)
Second quartile, N (%)	24,556 (29.7)	101,853 (24.6)
Third quartile, N (%)	20,786 (25.1)	105,992 (25.6)
Fourth quartile, N (%)	15,823 (19.1)	110,942 (26.8)
Missing, N (%)	178 (0.2)	3,368 (0.8)
Employment status during the 12-24 months preceding the index date		
Employed, N (%)	22,654 (27.4)	147,470 (35.7)
Unemployed, N (%)	3,234 (3.9)	13,049 (3.2)
Retired, N (%)	46,838 (56.6)	226,446 (54.8)
Missing, N (%)	9,964 (12.1)	26,440 (6.3)
Highest education achieved [a]		
Low, N (%)	34,928 (42.2)	149,632 (36.2)
Medium, N (%)	29,666 (35.9)	156,227 (37.8)
High, N (%)	9,276 (11.2)	64,942 (15.7)
Missing, N (%)	8,820 (10.7)	42,604 (10.3)

Follow-up period, years		
Total, years	425,894	2,746,040
Median (interquartile range), years	3.68 (1.54-7.34)	5.24 (2.39-9.98)

Values are expressed as numbers, frequencies, median and interquartile values.

[a] Education was categorized as: low (elementary school only), medium (high school and/or academy profession degree) and high (bachelor's, master's or higher degree).

Table 2. Risk of all-cause dementia and dementia subtypes in patients with kidney disease compared with individuals in a matched population without kidney disease.

		Kidney disease cohort		Comparison cohort		Hazard ratios (95 % CI)	
		Events/No. at risk	Crude rate/1,000 person-years (95% CI)	Events/No. at risk	Crude rate/ 1,000 person-years (95% CI)	Unadjusted	Adjusted
Kidney disease defined as persistent kidney disease, dialysis treatment or kidney transplant (codes listed in Supplemental Table 1).							
	All-cause dementia						
	1-5 years follow-up	2,092/82,690	9.00 (8.62-9.40)	10,638/413,405	8.11 (7.95-8.26)	1.11 (1-06-1.17)	1.06 (1.00-1.12)
	1-10 years follow-up	3,072/82,690	8.59 (8.28-8.89)	17,840/413,405	8.13 (8.01-8.25)	1.06 (1.02-1.10)	1.08 (1.03-1.13)
	1-22 years follow-up	3,462/82,690	8.13 (7.86 -8.40)	21,879/413,405	7.97 (7.86-8.07)	1.01 (0.98-1.05)	1.08 (1.03-1.12)
	Dementia subtypes, 1-22 years follow-up						
	Alzheimer's disease	863/82,690	2.03 (1.89-2.16)	7,662/413,405	2.79 (2.73-2.85)	0.73 (0.68-0.78)	0.85 (0.78-0.92)
	Vascular dementia	585/82,690	1.37 (1.26-1.49)	2,608/413,405	0.95 (0.91-0.99)	1.43 (1.31-1.56)	1.26 (1.14-1.40)
	Other dementia	2,014/82,690	4.73 (4.52-4.94)	11,609/413,405	4.23 (4.15-4.30)	1.11 (1.06-1.16)	1.18 (1.11-1.25)
	Alzheimer's disease and other dementia	2,877/82,690	6.76 (6.51-7.01)	19,271/413,405	7.02 (6.92-7.12)	0.96 (0.92-1.00)	1.04 (1.00-1.09)
Kidney disease restricted to chronic kidney disease diagnosis only, i.e., ICD-8 code 792 and ICD-10 code DN18.							
	All-cause dementia						
	1-5 years follow-up	1,232/48,243	10.0 (9.47-10.6)	6,689/241,203	9.23 (9.01-9.45)	1.09 (1.02-1.16)	1.03 (0.96-1.11)
	1-10 years follow-up	1,646/48,243	9.68 (9.22-10.2)	10,564/241,203	9.36 (9.18-9.54)	1.04 (0.98-1.09)	1.03 (0.97-1.10)
	1-22 years follow-up	1,739/48,243	9.38 (8.95-9.83)	12,172/241,203	9.25 (9.09-9.42)	1.01 (0.96-1.06)	1.04 (0.98-1.10)

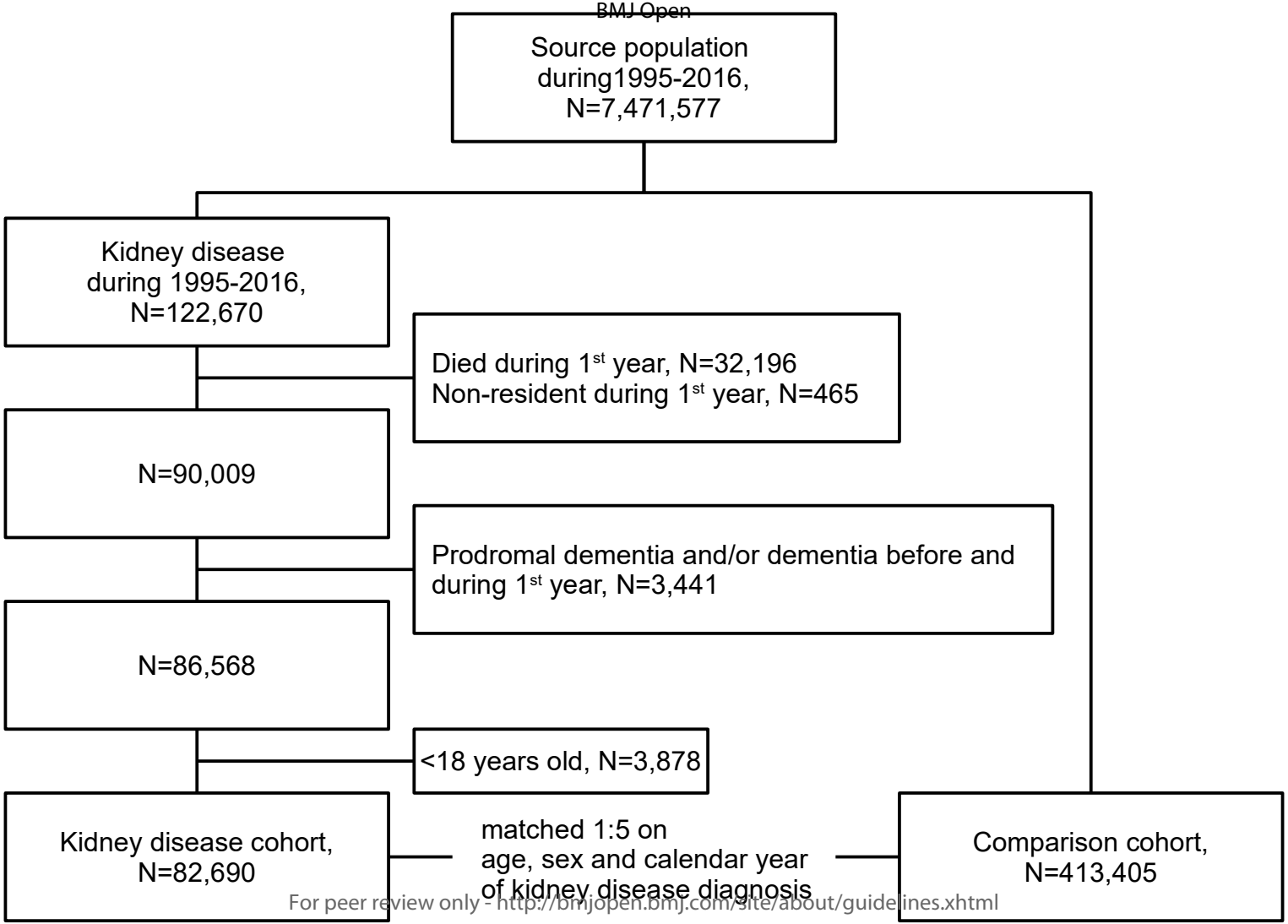
The subtypes of all-cause dementia are mutually exclusive, i.e., only the first diagnosis of any subtype of dementia is considered.

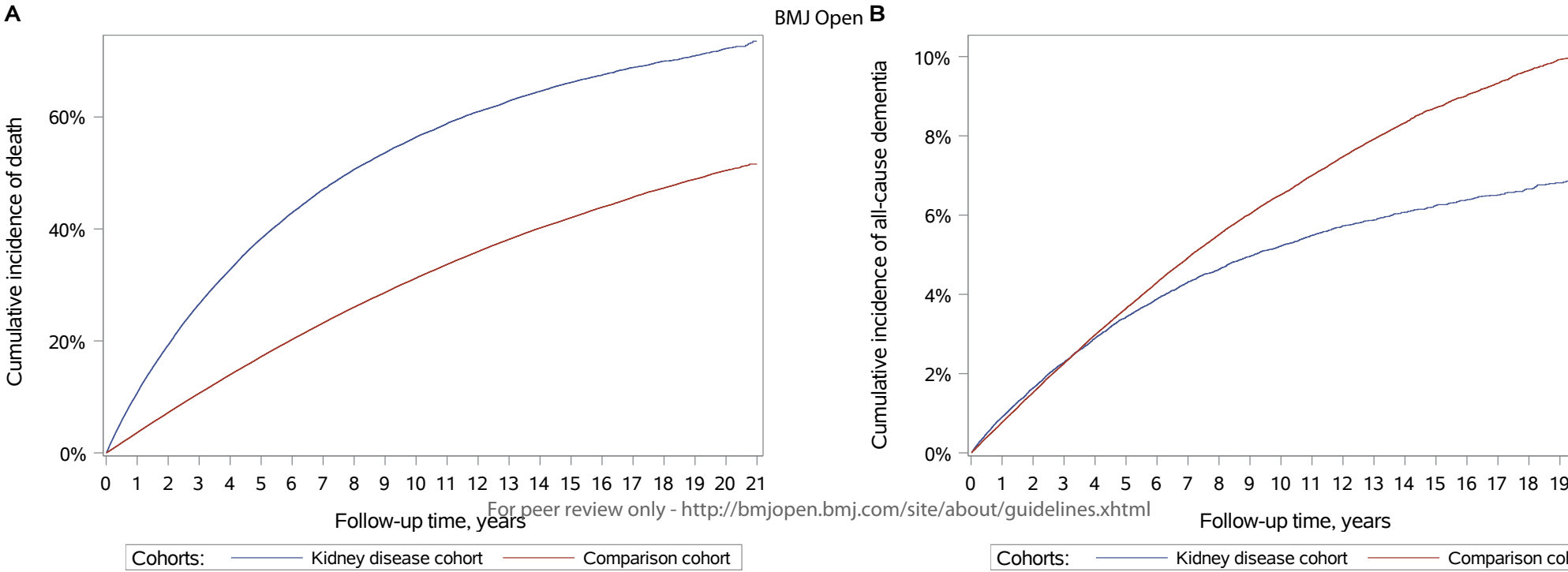
Kidney disease was defined as chronic kidney disease and several other persistent kidney diseases, as well as dialysis treatment or kidney transplant in the definition of kidney disease (Supplemental Table 1).

Chronic kidney disease was defined as International Classification of Diseases 8th edition (ICD-8) code 792 and 10th edition (ICD-10) code N18.

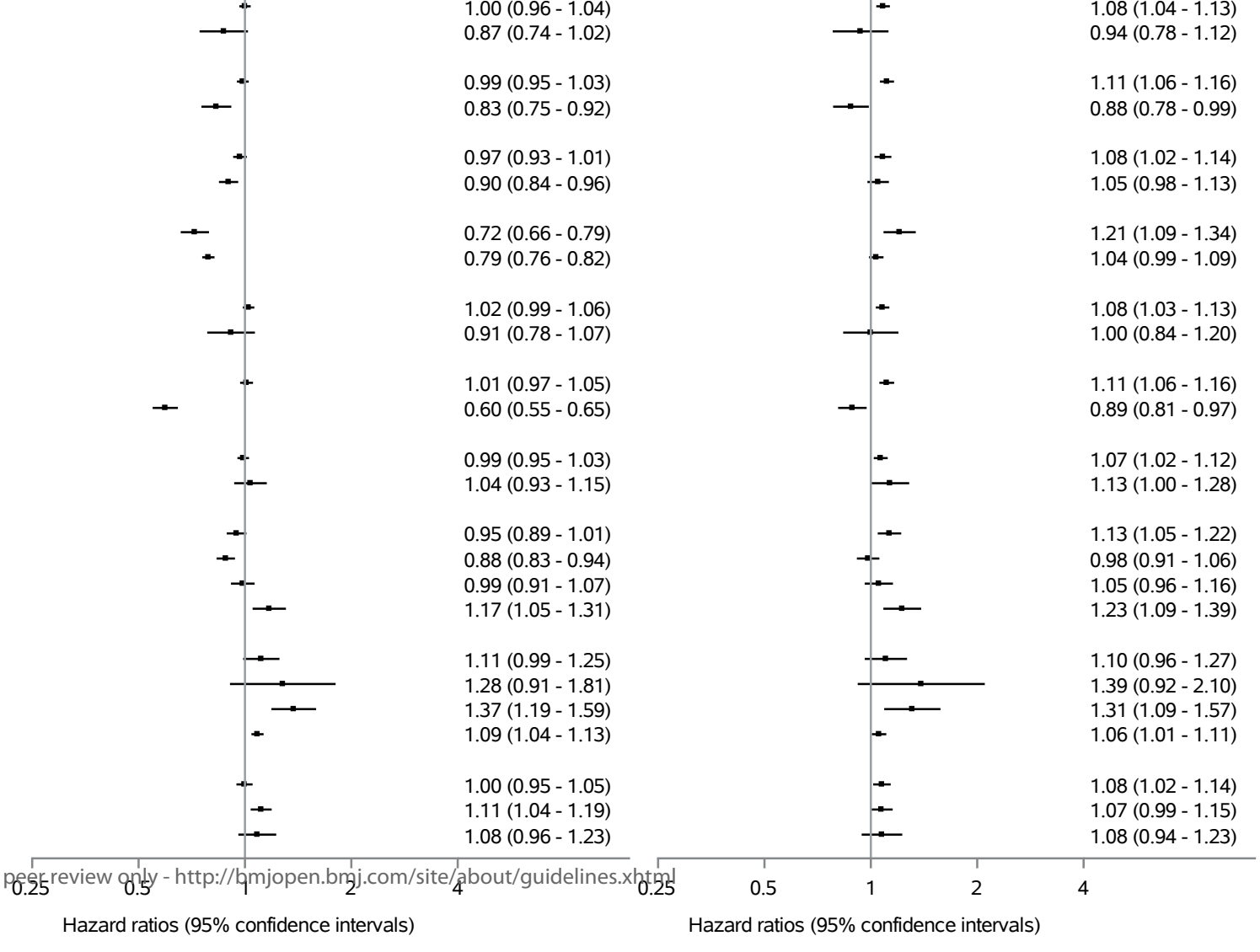
Multifactorially adjusted model included adjustments for covariates listed in Table 1.

95% CI: 95% confidence interval. No.: number.





	Unadjusted	Adjusted
	HR (95% CI)	HR (95% CI)
Age groups, years		
18-49	2.34 (1.76 - 3.11)	1.14 (0.78 - 1.67)
50-59	1.95 (1.66 - 2.30)	1.32 (1.08 - 1.61)
60-74	1.48 (1.39 - 1.57)	1.16 (1.08 - 1.24)
75-84	1.10 (1.04 - 1.16)	1.01 (0.95 - 1.08)
85+	0.93 (0.84 - 1.02)	0.90 (0.77 - 1.04)
Sex		
Male	1.03 (0.98 - 1.08)	1.07 (1.01 - 1.13)
Female	1.00 (0.94 - 1.05)	1.09 (1.02 - 1.16)
Calender period of match date		
1995-2003	0.95 (0.90 - 1.00)	1.11 (1.03 - 1.19)
2004-2016	1.07 (1.02 - 1.12)	1.05 (1.00 - 1.11)
Any cancer		
No	1.02 (0.98 - 1.06)	1.10 (1.05 - 1.15)
Yes	0.84 (0.76 - 0.93)	0.90 (0.80 - 1.02)
Angina pectoris		
No	0.94 (0.91 - 0.98)	1.08 (1.03 - 1.14)
Yes	0.98 (0.91 - 1.06)	1.05 (0.96 - 1.15)
Myocardial infarction		
No	0.99 (0.95 - 1.03)	1.08 (1.03 - 1.13)
Yes	0.94 (0.85 - 1.04)	1.03 (0.92 - 1.17)
Stroke		
No	0.98 (0.95 - 1.02)	1.08 (1.03 - 1.13)
Yes	0.85 (0.76 - 0.94)	1.04 (0.93 - 1.17)
Peripheral artery disease		
No	0.98 (0.95 - 1.02)	1.08 (1.03 - 1.13)
Yes	0.87 (0.78 - 0.97)	1.03 (0.90 - 1.17)
Venous thromboembolism		
No	1.02 (0.98 - 1.05)	1.08 (1.04 - 1.13)
Yes	0.78 (0.66 - 0.94)	0.90 (0.72 - 1.11)
Heart failure		
No	0.96 (0.92 - 1.00)	1.09 (1.04 - 1.14)
Yes	0.79 (0.72 - 0.88)	0.94 (0.83 - 1.07)
Heart valve disease		
No	1.00 (0.96 - 1.04)	1.08 (1.04 - 1.13)
Yes	0.87 (0.74 - 1.02)	0.94 (0.78 - 1.12)
Atrial fibrillation		
No	0.99 (0.95 - 1.03)	1.11 (1.06 - 1.16)
Yes	0.83 (0.75 - 0.92)	0.88 (0.78 - 0.99)
Hypercholesterolemia		
No	0.97 (0.93 - 1.01)	1.08 (1.02 - 1.14)
Yes	0.90 (0.84 - 0.96)	1.05 (0.98 - 1.13)
Hypertension		
No	0.72 (0.66 - 0.79)	1.21 (1.09 - 1.34)
Yes	0.79 (0.76 - 0.82)	1.04 (0.99 - 1.09)
Obesity		
No	1.02 (0.99 - 1.06)	1.08 (1.03 - 1.13)
Yes	0.91 (0.78 - 1.07)	1.00 (0.84 - 1.20)
Diabetes mellitus		
No	1.01 (0.97 - 1.05)	1.11 (1.06 - 1.16)
Yes	0.60 (0.55 - 0.65)	0.89 (0.81 - 0.97)
Chronic obstructive pulmonary disease		
No	0.99 (0.95 - 1.03)	1.07 (1.02 - 1.12)
Yes	1.04 (0.93 - 1.15)	1.13 (1.00 - 1.28)
Personal gross income during the		
0%-25%	0.95 (0.89 - 1.01)	1.13 (1.05 - 1.22)
26%-50%	0.88 (0.83 - 0.94)	0.98 (0.91 - 1.06)
51%-75%	0.99 (0.91 - 1.07)	1.05 (0.96 - 1.16)
76%-100%	1.17 (1.05 - 1.31)	1.23 (1.09 - 1.39)
Employment status during the year preceeding the index date		
Employed	1.11 (0.99 - 1.25)	1.10 (0.96 - 1.27)
Unemployed	1.28 (0.91 - 1.81)	1.39 (0.92 - 2.10)
Not available	1.37 (1.19 - 1.59)	1.31 (1.09 - 1.57)
Retired	1.09 (1.04 - 1.13)	1.06 (1.01 - 1.11)
Highest education achieved		
Low	1.00 (0.95 - 1.05)	1.08 (1.02 - 1.14)
Medium	1.11 (1.04 - 1.19)	1.07 (0.99 - 1.15)
High	1.08 (0.96 - 1.23)	1.08 (0.94 - 1.23)

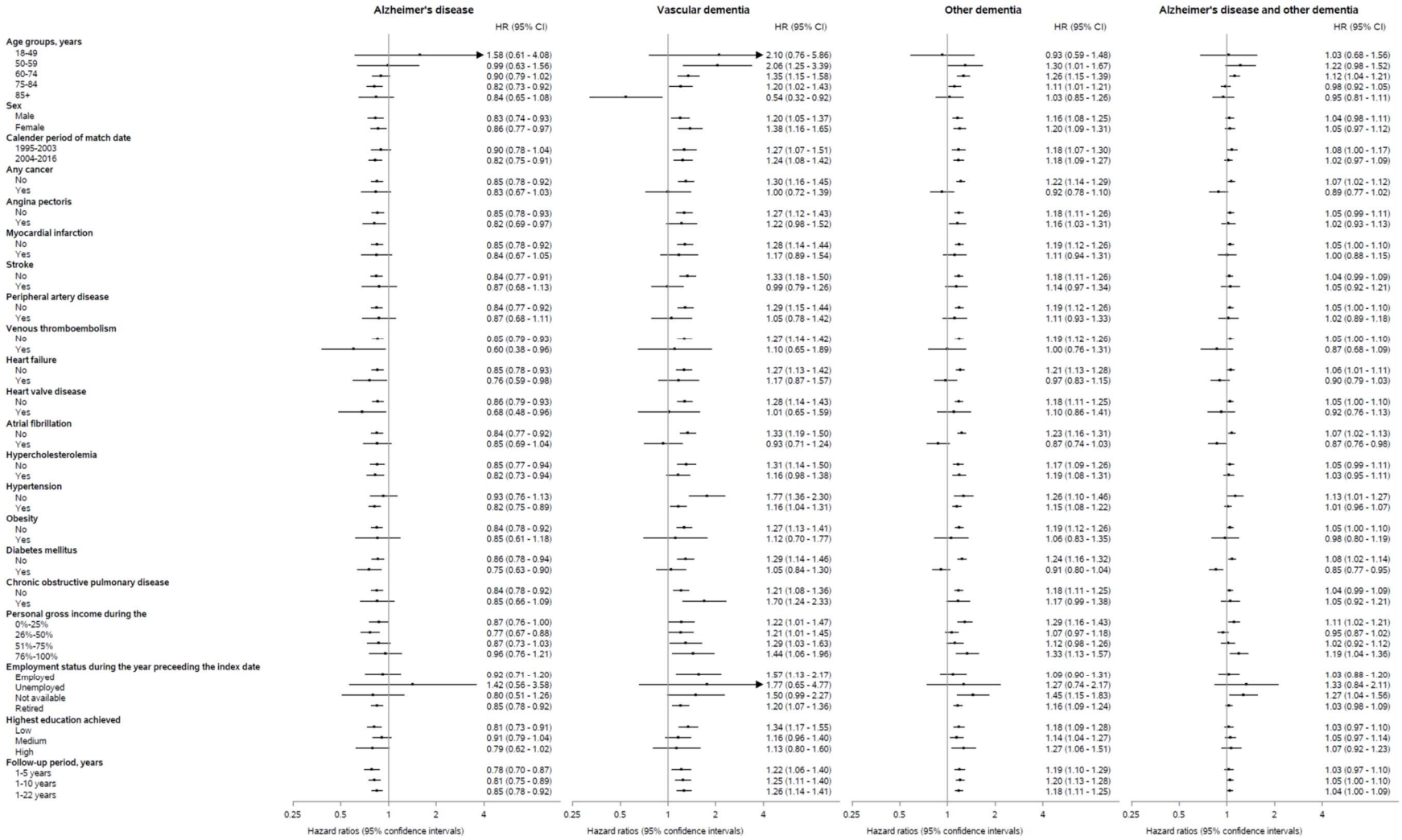


Supplemental Table 1. List of codes for diagnoses, procedures and prescriptions on which definitions of exposure, outcomes and covariates were based.

Diagnoses and procedures			Cases, first time	Cases, ever	ICD-8 codes	ICD-10 codes	Procedure codes	ATC codes
Kidney disease								
		Chronic kidney disease	41,925	58,025	**792**	**N18**		
	Subtypes of kidney disease	Diabetic nephropathy	19,462	24,852	249.02, 250.02	E102, E112, E132, E142, N08.3		
		Glomerulonephritis (without nephrotic syndrome)	2,240	3,719	582	N03		
		Hereditary nephropathy, not elsewhere classified	169	256	756.0, 753.3	N07		
		Chronic tubulo-interstitial nephritis	2,195	2,934	590.09, 593.20, 760.4	N11		
		Glomerular disorders in diseases classified elsewhere	338	1,613		N08		
		Unspecified kidney failure	15,234	26,641		N19		
		Hypertensive nephropathy	4,407	7,858	403, 404	I12, I13		
		Albuminuria/proteinuria	1,967	2,291	789.0	N39.1		
		Recurrent and persistent haematuria	3,371	3,593		N02		
		Renal agenesis and other reductional defects of kidney	379	437		Q60		
		Polycystic kidney disease	2,328	2,837	753.10-753.19	Q61.1-Q61.4		
	Dialysis		1,918	13,872		Z99.2		
		April1 1973-December 31 1995					94300, 94340	
		<1996					94350	
		>=1996						
	Kidney transplant		245	2,560	Y95.09	Z94.0		
		1973-1995					57480, 57490	
		>=1996					KKAS	
Diagnoses related to dementia (mild cognitive impairment and amnestic syndromes)					291.19	F04, F05.1, F06.7, F10.6, F18.6, F19.6		
Outcomes								
	All-cause dementia				290.09, 290.10, 293.09, 293.19, 094.19, 292.09,	F00, G30, G30.0, G30.1, G30.8, G30.9), F01.0x, F01.1x, F01.2x, F01.3x, F01.8X, F01.9x), F02, F03, F1x.73 (F10.73-F19.73); G23.1;		

				290.11, 290.18, 290.19	G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85		
		Alzheimer's disease		290.09, 290.10	F00, G30, G30.0, G30.1, G30.8, G30.9		
		Vascular dementia		293.09, 293.19	F01.0x, F01.1x, F01.2x, F01.3x, F01.8X, F01.9x		
		Other dementia		094.19, 292.09, 290.11, 290.18, 290.19	F02, F03, F10.73-F19.73; G23.1; G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85		
Covariates							
	Angina pectoris			413	I20 (except I20.0), I25.1, I25.9		
	Myocardial infarction			410	I21, I22, I23		
	Stroke			431, 433-434	I61, I63-I64		
	Peripheral artery disease			440-445	I70, I71, I72, I73, I74, I77		
	Venous thromboembolism			451.00, 451.08-09, 451.90, 451.92, 671.01-03, 671.08-09, 450.99, 973.99	I80.1-I80.3, O22.3, O87.1, I26.0, I26.9, O88.2		
	Heart failure			42709, 42710, 42711, 42719, 42899, 78249	I50, I11.0, I13.0, I13.2		
	Heart valve disease			394-398	I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22		
	Atrial fibrillation			42793, 42794	I48		
	Hypercholesterolemia			27200	E780		C10
	Hypertension			400-404	DI10-DI15, I67.4		C02-C03 C07-C09
	Obesity			277	E65-E68		
	Diabetes mellitus			249, 250 (excluding 249.02, 250.02)	E10 (excluding E10.2), E11 (excluding E11.2), H36.0		
	Chronic obstructive pulmonary disease			490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3		
	Cancer			140-172, 174-194, 200-207	C00-26, C30-34, C37-41, C43, C45-58, C60-76, C80-85, C88, C90-97		

Supplemental Figure 1. Risk of dementia subtypes in patients with kidney disease compared with individuals in a matched population without kidney disease stratified by covariates listed in Table 1.



HR: hazard ratio. 95% CI: 95% confidence interval.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	7-11
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13 Figures and Tables
		(*b*) Report category boundaries when continuous variables were categorized	Figures and Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

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

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

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Kidney disease and risk of dementia: a Danish nationwide cohort study

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Kidney disease and risk of dementia: a Danish nationwide cohort study

Short title: Kidney disease and dementia

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Word count (Introduction-Discussion): 3,191; Abstract: 256

Tables: 2; Figures: 3; Supplemental tables: 1; Supplemental figures: 2

ABSTRACT

Objectives: It is unclear whether kidney disease is a risk factor for developing dementia. We examined the association between kidney disease and risk of future dementia.

Design and setting: Nationwide historical registry-based cohort study in Denmark based on data from January 1, 1995 until December 31, 2016.

Participants: All patients diagnosed with kidney disease and matched general population cohort without kidney disease (matched 1:5 on age, sex and year of kidney disease diagnosis).

Primary and secondary outcome measures: All-cause dementia and its subtypes: Alzheimer's disease, vascular dementia and other specified or unspecified dementia. We computed five-year cumulative incidences (risk) and hazard ratios (HRs) for outcomes using Cox regression analyses.

Results: The study cohort comprised 82,690 patients with kidney disease and 413,405 individuals from the general population. Five- and ten-year mortality rates were twice as high in patients with kidney disease compared to the general population. The five-year risk for all-cause dementia was 2.90% (95% confidence interval: 2.78%-3.08%) in patients with kidney disease and 2.98% (2.92%-3.04%) in the general population. Compared to the general population, the adjusted HRs for all-cause dementia in patients with kidney disease were 1.06 (1.00-1.12) for the five-year follow-up and 1.08 (1.03-1.12) for the entire study period. Risk estimates for dementia subtypes differed substantially and were lower for Alzheimer's disease and higher for vascular dementia.

Conclusions: Patients diagnosed with kidney disease have a modestly increased rate of dementia, mainly driven by vascular dementia. Moreover, patients with kidney disease may be underdiagnosed with dementia due to high mortality and other comorbidities of higher priority.

Article summary

Strengths and limitations of this study (5 bullet points on methods):

- This is the first European population-based study examining the association between hospital-diagnosed kidney disease and risk of future dementia.
- We conducted a nationwide registry-based cohort study of all Danish residents with kidney disease and a 1:5 matched general population comparison cohort without kidney disease during a study period from 1995-2016.
- We did not have data on albuminuria or estimated glomerular filtration rate.
- Not all individuals with kidney disease or dementia are hospital-diagnosed and thus captured in the Danish registries.
- Results pertaining to dementia subtypes should be interpreted cautiously due to potential differential misclassification of dementia subtypes, particularly among patients with kidney disease

Contributors

BRJ and CFC had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. ADK and CFC are guarantors of the study.

Concept and design: ADK, BRJ, HTS, VWF and CFC. Statistical analysis: BRJ. Drafting of the manuscript: ADK. Supervision: CFC. Interpretation and critical revision of the manuscript for important intellectual content: ADK, BRJ, HTS, VWF and CFC.

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The funding sources had no role in the design, conduct, analysis or reporting of this study.

Competing interests

The authors have no conflicts of interest to declare. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University.

Patient consent for publication/Ethics approval

The study was registered at Aarhus University (record number 2016-051-000001/603) as mandated by the Danish Data Protection Agency. According to Danish legislation, registry-based studies do not require ethical review board approval or informed consent from the participants

Data availability statement

Data was accessed at secure servers, and cannot be shared due to Danish legislation.

INTRODUCTION

Dementia is a common, progressive age-related neurological disorder diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning.[1] Although the incidence rates of dementia have decreased modestly over the last 30 years, the prevalence of dementia is increasing worldwide, likely due to increased life expectancy.[2] This has enormous costs for the individuals and families affected, as well as the health care and society.[3]

Kidney disease is another disorder with a high (close to 10%) and increasing prevalence, partly due to ageing population, and increased incidence rates of hypertension and diabetes mellitus.[4]

Kidney disease and dementia share risk factors such as increasing age, hypertension, diabetes mellitus, hyperlipidemia, and the pathophysiology of small vessel disease.[5, 6] One potential link between kidney disease and dementia could be common susceptibility of kidney and brain tissue to vascular injury.[7] Kidney disease is associated with oxidative stress, chronic inflammation and changes in coagulation, and it might also affect the brain or cerebral vasculature indirectly or directly through metabolic derangements and uremic toxins.[7]

A previous population-based study in Taiwan found a hazard ratio (HR) of 1.41 for all-cause dementia in patients with a diagnosis of kidney disease (N=37,049) compared to the general population (N=74,098).[8] However, these findings may not be applicable to European populations, and the Taiwanese study did not examine potential differences across dementia subtypes. Furthermore, previous studies, where kidney disease was defined as persistent albuminuria or estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, reported mixed results.[9-13] Thus, whether kidney disease is associated

with risk of dementia is presently uncertain. We investigated this for all-cause dementia and dementia subtypes (Alzheimer's disease, vascular dementia and other dementia) in a nationwide cohort study.

METHODS

We followed the STROBE guidelines for reporting of cohort studies in epidemiology.

Study cohort

We conducted a nationwide cohort study of all Danish patients with hospital-diagnosed kidney disease and a matched general population comparison cohort without kidney disease during a study period from January 1, 1995 until December 31, 2016.

A flow chart of the study cohort is shown in figure 1. We identified 122,670 patients with a first-time kidney disease diagnosis recorded during the study period. Next, we excluded patients who died (N=32,196) or did not reside in Denmark (N=465) during the first year after kidney disease diagnosis. Further exclusion criteria were diagnosis of dementia (N=1,909) and prodromal signs of dementia, i.e., mild cognitive impairment and amnestic syndrome (N=303) before kidney disease diagnosis. Additionally, we excluded patients diagnosed with dementia (N=1,300) and prodromal signs of dementia (N=156) during first year after a kidney disease diagnosis, because dementia diagnosed in this period is unlikely to be a consequence of kidney disease. Finally, we limited the cohort to adult patients aged 18 and above. The remaining 82,690 patients comprised our kidney disease cohort. For each patient in the kidney disease cohort, up to five individuals from the general population without a kidney disease diagnosis prior to index date were randomly selected and matched on age (birth year), sex and calendar year of index date, i.e., date of kidney disease diagnosis. Matching was performed as individual matching with

replacement. [14] The general population comparison cohort comprised 413,405 individuals, who were alive and had no dementia, mild cognitive impairment, amnestic syndrome or kidney disease prior to study entry.

Diagnoses

Diagnoses of kidney disease (exposure), dementia (outcome), mild cognitive impairment, amnestic syndrome and covariateswere based on diagnoses obtained from the Danish National Patient Registry and/or the Danish Psychiatric Central Research Registry. These registries, covering all Danish hospitals, have recorded hospital admissions since 1977 and 1969 respectively, as well as outpatient specialist clinic visits since 1995.[15-17] We used all primary and secondary discharge diagnoses for all hospitalizations and outpatient clinic visits, but not emergency room visits (as diagnoses in this setting may be tentative and thus less valid). Diagnoses were identified according to the World Health Organization's International Classification of Diseases 8th edition (ICD-8) until the end of 1993 and 10th edition (ICD-10) thereafter (suppemental table 1). We used the date of hospital admission or start of outpatient clinic follow-up as the date for all diagnoses.

Kidney disease

In the main analysis, we used an extended definition of kidney disease including chronic kidney disease as well as several other persistent kidney diseases, dialysis treatment and kidney transplant (for ICD codes, see supplemental table 1). Importantly, this extended kidney disease definition did not include acute and/or potentially reversible kidney injury. In a sensitivity analysis, we used chronic kidney disease (restricted to ICD-8 792 and ICD-10 N18) as the exposure for all-cause dementia only. KDIGO (Kidney Disease Improving Global Outcomes) defines chronic kidney as persistent (>3 months) eGFR <60 ml/min/1.73 m2 or kidney damage, often ascertained by the presence of albuminuria. [18]

Dementia

The validity of all-cause dementia is high with a positive predictive value of 86% in the Danish registries.[19] Dementia subtypes were mutually exclusive, and we only used the first coded dementia subtype: Alzheimer's disease, vascular dementia and other (specified or unspecified) dementia, the latter comprising the majority of dementia diagnoses (for ICD codes, see supplemental table 1). As about one third of cases with other dementia without specification may be attributable to Alzheimer's disease,[19] we also included a combined outcome of Alzheimer's disease and other dementia.

Covariates

We identified cardiovascular disease (CVD), CVD risk factors, (any) cancer and socioeconomic status as potential confounders due to their reported associations with kidney disease and dementia (listed in table 1).[5, 6, 20] All covariates were assessed prior to study entry. CVD covariates were angina pectoris, myocardial infarction, stroke, peripheral arterial disease, venous thromboembolism, heart failure, heart valve disease and atrial fibrillation. Covariates related to CVD risk factors were hypercholesterolemia, hypertension, obesity, diabetes mellitus, and chronic obstructive pulmonary disease as a proxy for smoking. CVD risk factors were based on diagnoses from the Danish National Patient Registry and additionally on prescriptions of lipid lowering and antihypertensive drugs (see Anatomical Therapeutic Chemical codes in supplemental table 1) from the Danish National Prescription Registry, containing detailed individual-level data on prescriber, patient and products for all outpatient prescriptions dispensed since 1995.[21] Covariates related to socioeconomic status were highest education achieved, personal gross income and employment status obtained from the Integrated Database for Labor Market Research, established in 1981.[22] Education was categorized as: low (elementary

school only), medium (high school and/or academy profession degree) and high (bachelor's, master's or higher degree). Personal gross income was categorized in quartiles. Employment status was categorized as: employed, retired and unemployed. We used employment status during the 12-24 months preceding the study entry, since employment status during the year prior to kidney disease diagnosis is likely to underestimate the peak employment status.

Patient and public involvement

No patients involved.

Statistical analysis

We compared cumulative incidence (risk) of death as well as all-cause dementia (taking the competing risk of death into account) for the kidney disease and comparison cohorts. Hazard ratios for all-cause dementia and dementia subtypes and their corresponding 95% confidence intervals (CIs) were calculated using Cox regression analyses with time-on-study as the time scale. Proportional hazards assumption was tested graphically by log-log plots, and no violations were detected (supplemental figure 1). Age, sex and calendar year of index date were already controlled for in the unadjusted Cox model, as these were the matching criteria. However, to account for the matching methodology and due to the built-in selection bias (see Discussion) as the matching could not be completely retained, the adjusted Cox model therefore included adjustments for age (age groups listed in table 1), sex and calendar year of index date, as well as other potential confounders (as listed in table 1). Participants with missing values (<1% of personal gross income and <11% of employment status and education level each) were excluded from the adjusted analyses. Participants were followed from one year after index date until a diagnosis of dementia or censoring at December 31, 2016, emigration or death, whichever came first. Thus, the

minimum follow-up time was one year and maximum 22 years. Because all diagnoses and vital and emigration status are registered in national registries, we had no losses to follow-up.

We performed predefined stratification analyses for age (18-49, 50-59, 60-74, 75-84 and >85 years), sex, calendar year of index date (1995-2003 or 2004-2016), CVD, CVD risk factors, socioeconomic factors and follow-up time (1-5 years, 1-10 years and 1-22 years). Finally, in order to assess whether the risk of all-cause dementia was linked to kidney disease severity, we stratified the kidney disease cohort by presence or absence of kidney failure (defined as receiving dialysis treatment and/or kidney transplant, for codes see supplemental table 1).

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

The study was registered at Aarhus University (record number 2016-051-000001/603) as mandated by the Danish Data Protection Agency. According to Danish legislation, registry-based studies do not require ethical review board approval or informed consent from the participants.

RESULTS

The study cohort consisted of a kidney disease cohort of 82,690 patients with kidney disease and a comparison cohort of 413,405 matched individuals from the general population without kidney disease. The median age was 69 years (interquartile range: 56-78 years). Women comprised 41% of all participants, and 71% were enrolled during 2004-2016 and the remaining 29% during 1995-2003 (table 1). Diagnoses of CVD and CVD risk

factors were much more frequent in the kidney disease cohort than in the comparison cohort (table 1). Furthermore, the kidney disease cohort had lower income, higher unemployment rate and lower education than the comparison cohort (table 1). Finally, the follow-up time was shorter for the kidney disease cohort than for the comparison cohort, with a median of 3.7 and 5.2 years, respectively (table 1). This difference reflects a higher mortality rate in the kidney disease than the comparison cohort: 5- and 10-year mortality was twice as high in patients with kidney disease compared to the general population (figure 2). During the study period, 466,071 (94%) participants died, 78,555 (95%) from the kidney disease cohort and 387,516 (94%) from the comparison cohort.

Kidney disease and risk of developing dementia

During follow-up, 3,462 (4.19% of 82,690) patients with kidney disease and 21,879 (5.29% of 413,405) individuals from the comparison cohort developed dementia, the majority classified as other dementia (table 2). Alzheimer's disease was more frequent in the comparison cohort, and vascular dementia in the kidney disease cohort (table 2).

The 5-, 10-, and 22-year risks of all-cause dementia were lower in patients with kidney disease than in the general population: 2.90% (95% CI: 2.78%-3.08%), 4.96% (4.79%-5.14%) and 7.05% (6.70%-7.41%) for the kidney disease cohort and 2.98% (2.92%-3.04%), 6.03% (5.94%-6.12%) and 10.39% (10.17%-10.60%) for the comparison cohort (figure 2).

The estimates for dementia subtypes were lowest for Alzheimer's disease and highest for vascular dementia (table 2).

The adjusted HR (aHR) for all-cause dementia was stable over time. 1.06 (1.00-1.12) for up to 5 years of follow-up, 1.08 (1.03-1.13) for up to 10 years of follow-up and 1.08 (1.03-1.12) for up to 22 years of follow-up (table 2). When we restricted the kidney disease exposure to chronic kidney disease only, the aHR for all-cause dementia was 1.04 (0.98-1.10) for up to 22 years of follow-up and very similar for shorter follow-up (table 2).

In analyses stratified by age, there was a stepwise decrease in HRs of all-cause dementia with increasing age: the aHRs for 18-49, 50-59, 60-74, 75-84 and ≥85 years age groups were 1.14 (0.78-1.67), 1.32 (1.09-1.61), 1.16 (1.08-1.24), 1.01 (0.95-1.08) and 0.90 (0.77-1.04), respectively. The rate of all-cause dementia did not differ by sex, calendar year of index date or socioeconomic factors. Kidney disease was also associated with increased HR for dementia in most CVD subgroups (myocardial infarction, stroke, peripheral arterial disease, venous thromboembolism, heart failure and heart valve disease) and CVD risk factors (atrial fibrillation, hypertension, obesity and diabetes mellitus), but estimates were imprecise (figure 3). Results for dementia subtypes showed consistent results (supplemental figure 2).

Kidney disease severity and risk of developing dementia

In the kidney disease cohort, fewer patients with end-stage kidney disease developed dementia during follow-up compared with other patients with kidney disease: 3.3% (61 out of 1,866) of patients with dialysis treatment or kidney transplant and 4.2% (3,401 out of 80,982) of patients without these interventions.

DISCUSSION

In this nationwide study of nearly 500,000 participants, we found that being diagnosed with kidney disease is associated with a modestly increased risk of future dementia. When we restricted the exposure to chronic kidney disease only, the association was similar.

We found substantially smaller estimates than the only previous population-based study, where investigators in Taiwan found an HR of 1.41 (1.32-1.50) for all-cause dementia in patients with kidney disease compared to the general population.[8] This may partly be explained by differences between these Asian and European populations, study design differences or both. Our study included more recent data, five times as many participants, finer age matching and a longer follow-up period. Furthermore, we included dialysis treatment, kidney transplantation and hypertensive nephropathy in our kidney disease definition, and we did not exclude participants based on other kidney-related diagnoses. In contrast, the Taiwanese study excluded patients with these and several other kidney-related diagnoses. Thus, our study likely included relatively more patients with severe kidney disease in the kidney disease cohort and mild kidney disease in the comparison cohort. Finally, while we excluded patients who were diagnosed with dementia within one year after kidney disease diagnosis, the Taiwanese study did not do this, and in this population, the incidence rate ratio for less than two years of follow-up was substantially higher than the incidence rate ratio for two or more years of follow-up.[8]

A meta-analysis of cross-sectional and cohort studies including more than 50,000 participants showed an association between kidney disease (eGFR<60 ml/min/1.73 m^2) and cognitive impairment. [13] The cognitive domains that were predominantly affected (i.e., orientation, attention, concept formation and reasoning) differed from those affected by dementia, suggesting that kidney disease may be more closely linked with other cognitive

impairment than with dementia. Unfortunately, we did not have data on cognitive performance. [21, 22]

Interestingly, studies that mainly included eGFR measurements within the normal range showed a stronger association between albuminuria and dementia than between eGFR and dementia.[9-12, 23] This finding suggests that albuminuria may be a better marker than eGFR of more advanced kidney disease. Unfortunately, we did not have data on albuminuria or eGFR.

The lack of a strong association between kidney disease and dementia may possibly be explained in part by survivor bias due to very high mortality among patients with kidney disease.[24] As dementia increases with age, patients with kidney disease may not survive long enough to develop dementia. Indeed, the fraction of participants diagnosed with dementia was lower in patients with severe than mild kidney disease (3.3% of patients with dialysis treatment or kidney transplant versus 4.2% of patients without these interventions). This finding may reflect survivor bias or might suggest that clinicians are more likely to underdiagnose dementia in the presence of life-threatening illness and reduced life expectancy (detection bias). This inference is further supported by our stratification analyses, that show lower risk estimates in the presence of CVD, e.g., myocardial infarction, and CVD risk factors known to be associated with increased mortality.[25] In contrast, a previous Danish study of 314,911 patients with myocardial infarction matched with 1,573,193 individuals from the general population reported that myocardial infarction was associated with higher risk of vascular dementia but not with risk of all-cause dementia or other subtypes.[26] Taken together, these findings suggest a possible misclassification bias for dementia subtypes as clinicians may be more likely to

diagnose vascular dementia, and less likely Alzheimer's disease, in patients with dementia and kidney disease or myocardial infarction than in individuals without these diseases.

Since HRs may change over time, the observed modest association between kidney disease and dementia may be limited to the first few years after a kidney disease diagnosis. On the other hand, the period-specific HRs are prone to a built-in selection bias.[24] In our study, this translates to preferential censoring of patients, due to death, from the kidney disease cohort in the beginning of follow-up. With increasing follow-up time, this can lead to a relative increase in the proportion of individuals susceptible to dementia in the comparison cohort and thereby explain why the unadjusted HRs attenuated with increasing follow-up time. Due to this built-in selection bias, the matching could not be retained, and for this reason we included matching covariates in our adjusted analysis. This can possibly explain why the unadjusted HRs attenuated, while the aHRs did not attenuate with increasing follow-up time. The major strength of our study is its design: large nationwide registry-based cohort study with individual-level data and a complete follow-up on all Danish patients with hospital-diagnosed kidney disease and a matched general population comparison cohort without kidney disease during a study period from 1995-2016.

Limitations of our study include selection, survival and surveillance bias. As we did not perform multiple imputations for income, employment status and education level, the exclusion of participants with missing values may have biased our estimates. However, this would only bias the estimates if the missing values were not random. The unbiased estimates may be even larger if the missing values are linked to lower levels of income, employment and education. Further limitations are misclassification bias (of kidney disease, dementia and covariates), unmeasured or residual confounding, quality of coding

and validity of diagnoses. The positive predictive value of kidney disease coded in the Danish National Patient Registry has been reported to be 100%, whereas completeness may only be 37%; i.e., not all individuals with kidney disease are captured.[27-29] While the positive predictive value of all-cause dementia and Alzheimer's disease in the Danish National Patient Registry is 86% and 81%, respectively, it is lower for other dementia subtypes.[19] Thus, the results pertaining to dementia subtypes should be interpreted cautiously. This caveat is particularly important since our results are compatible with differential misclassification of dementia subtypes among patients with kidney disease, where vascular risk factors are especially common, and the general population, where vascular risk is lower. Furthermore, we used the date of hospital admission or start of outpatient clinic follow-up as the date for all diagnoses since the exact day is not available. This may have introduced a bias, particularly in the beginning of the follow-up. Additionally, there is a variable lag time between dementia onset and the date of diagnosis. Finally, since all diagnoses are recorded by hospital physicians, mild kidney disease and mild dementia treated only by a general practitioner would not be recorded unless they were also assessed in the hospital or an outpatient clinic setting.

In conclusion, patients diagnosed with kidney disease have a modestly increased risk of being diagnosed with future dementia. This association is mainly driven by diagnoses of vascular dementia, and it may be limited to the first few years after the kidney disease diagnosis. On the other hand, patients with kidney disease may be underdiagnosed with dementia due to high mortality and other comorbidities of higher priority, and the true risk of future dementia may be somewhat higher than our study suggests.

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LEGENDS

Figure 1. Study flow chart.

Cohort of patients with incident kidney disease and individuals of the matched general population comparison cohort during 1995-2016.

Figure 2. Cumulative incidences of A) death and B) all-cause dementia in patients with kidney disease (kidney disease cohort) and individuals in a matched population without kidney disease (comparison cohort).

Figure 3. Risk of all-cause dementia in patients with kidney disease compared with individuals in a matched population without kidney disease stratified by covariates listed in table 1.

HR: hazard ratio. CI: confidence interval.

Table 1. Characteristics of study cohort at baseline.

	Kidney disease cohort	Comparison cohort
Number of participants, N	82,690	413,405
Age groups, years		
18-49, N (%)	14,718 (17.8)	73,530 (17.8)
50-59, N (%)	11,059 (13.4)	55,330 (13.4)
60-74, N (%)	29,021 (35.1)	145,116 (35.1)
75-84, N (%)	20,381 (24.6)	102,063 (24.7)
≥85, N (%)	7,511 (9.1)	37,366 (9.0)
Women, %	33,589 (40.6)	167,914 (40.6)
Calendar period of kidney disease diagnosis		
1995-2003, N (%)	24,410 (29.5)	122,013 (29.5)
2004-2016, N (%)	58,280 (70.5)	291,392 (70.5)
Any cancer, N (%)	10,813 (13.1)	36,216 (8.8)
Angina pectoris, N (%)	17,346 (21.0)	38,656 (9.4)
Myocardial infarction, N (%)	10,303 (12.5)	22,061 (5.3)
Stroke, N (%)	7,885 (9.5)	19,210 (4.6)
Peripheral artery disease, N (%)	9,673 (11.7)	16,109 (3.9)
Venous thromboembolism, N (%)	3,703 (4.5)	9,351 (2.3)
Heart failure, N (%)	12,154 (14.7)	14,370 (3.5)
Heart valve disease, N (%)	4,700 (5.7)	9,080 (2.2)
Atrial fibrillation, N (%)	10,723 (13.0)	24,431 (5.9)
Hypercholesterolemia, N (%)	32,780 (39.6)	85,679 (20.7)
Hypertension, N (%)	66,500 (80.4)	202,597 (49.0)
Obesity, N (%)	8,146 (9.9)	10,189 (2.5)
Diabetes mellitus, N (%)	23,271 (28.1)	19,159 (4.6)
Chronic obstructive pulmonary disease, N (%)	10,218 (12.4)	26,936 (6.5)
Personal gross income during the year preceding the index date		
First quartile, N (%)	21,347 (25.8)	91,250 (22.1)
Second quartile, N (%)	24,556 (29.7)	101,853 (24.6)
Third quartile, N (%)	20,786 (25.1)	105,992 (25.6)
Fourth quartile, N (%)	15,823 (19.1)	110,942 (26.8)
Missing, N (%)	178 (0.2)	3,368 (0.8)
Employment status during the 12-24 months preceding the index date		
Employed, N (%)	22,654 (27.4)	147,470 (35.7)
Unemployed, N (%)	3,234 (3.9)	13,049 (3.2)
Retired, N (%)	46,838 (56.6)	226,446 (54.8)
Missing, N (%)	9,964 (12.1)	26,440 (6.3)
Highest education achieved[a]		
Low, N (%)	34,928 (42.2)	149,632 (36.2)
Medium, N (%)	29,666 (35.9)	156,227 (37.8)
High, N (%)	9,276 (11.2)	64,942 (15.7)
Missing, N (%)	8,820 (10.7)	42,604 (10.3)

Follow-up period, years		
Total, years	425,894	2,746,040
Median (interquartile range), years	3.68 (1.54-7.34)	5.24 (2.39-9.98)

Values are expressed as numbers, frequencies, median and interquartile values.

[a]Education was categorized as: low (elementary school only), medium (high school and/or academy profession degree) and high (bachelor's, master's or higher degree).

Table 2. Risk of all-cause dementia and dementia subtypes in patients with kidney disease compared with individuals in a matched population without kidney disease.

		Kidney disease cohort		Comparison cohort		Hazard ratios (95 % CI)	
		Events/No. at risk	Crude rate/1,000 person-years (95% CI)	Events/No. at risk	Crude rate/ 1,000 person-years (95% CI)	Unadjusted	Adjusted
Kidney disease defined as persistent kidney disease, dialysis treatment or kidney transplant (codes listed in supplemental table 1).							
	All-cause dementia						
	1-5 years follow-up	2,092/82,690	9.00 (8.62-9.40)	10,638/413,405	8.11 (7.95-8.26)	1.11 (1-06-1.17)	1.06 (1.00-1.12)
	1-10 years follow-up	3,072/82,690	8.59 (8.28-8.89)	17,840/413,405	8.13 (8.01-8.25)	1.06 (1.02-1.10)	1.08 (1.03-1.13)
	1-22 years follow-up	3,462/82,690	8.13 (7.86 -8.40)	21,879/413,405	7.97 (7.86-8.07)	1.01 (0.98-1.05)	1.08 (1.03-1.12)
	Dementia subtypes, 1-22 years follow-up						
	Alzheimer's disease	863/82,690	2.03 (1.89-2.16)	7,662/413,405	2.79 (2.73-2.85)	0.73 (0.68-0.78)	0.85 (0.78-0.92)
	Vascular dementia	585/82,690	1.37 (1.26-1.49)	2,608/413,405	0.95 (0.91-0.99)	1.43 (1.31-1.56)	1.26 (1.14-1.40)
	Other dementia	2,014/82,690	4.73 (4.52-4.94)	11,609/413,405	4.23 (4.15-4.30)	1.11 (1.06-1.16)	1.18 (1.11-1.25)
	Alzheimer's disease and other dementia	2,877/82,690	6.76 (6.51-7.01)	19,271/413,405	7.02 (6.92-7.12)	0.96 (0.92-1.00)	1.04 (1.00-1.09)
Kidney disease restricted to chronic kidney disease diagnosis only, i.e., ICD-8 code 792 and ICD-10 code DN18.							
	All-cause dementia						
	1-5 years follow-up	1,232/48,243	10.0 (9.47-10.6)	6,689/241,203	9.23 (9.01-9.45)	1.09 (1.02-1.16)	1.03 (0.96-1.11)
	1-10 years follow-up	1,646/48,243	9.68 (9.22-10.2)	10,564/241,203	9.36 (9.18-9.54)	1.04 (0.98-1.09)	1.03 (0.97-1.10)
	1-22 years follow-up	1,739/48,243	9.38 (8.95-9.83)	12,172/241,203	9.25 (9.09-9.42)	1.01 (0.96-1.06)	1.04 (0.98-1.10)

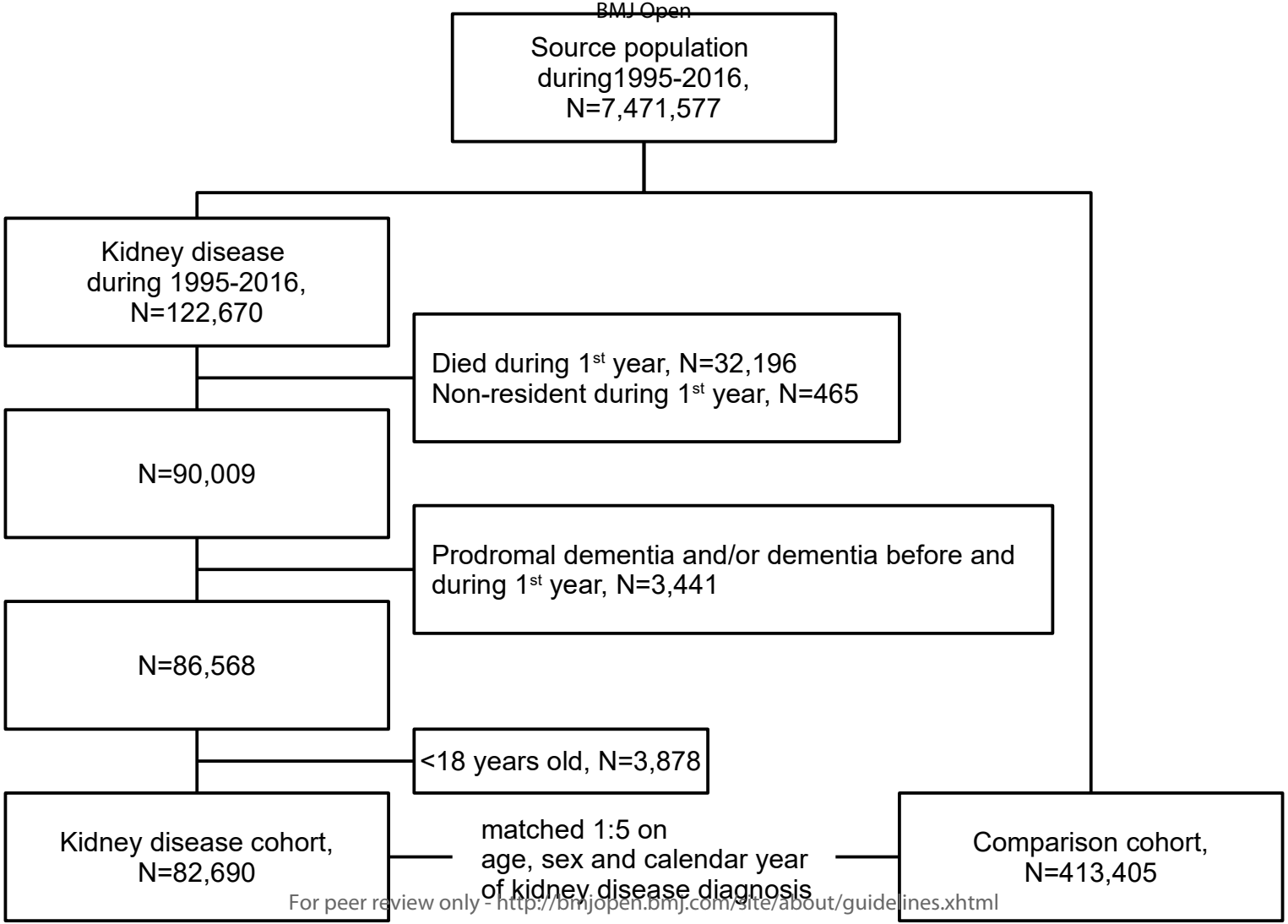
The subtypes of all-cause dementia are mutually exclusive, i.e., only the first diagnosis of any subtype of dementia is considered.

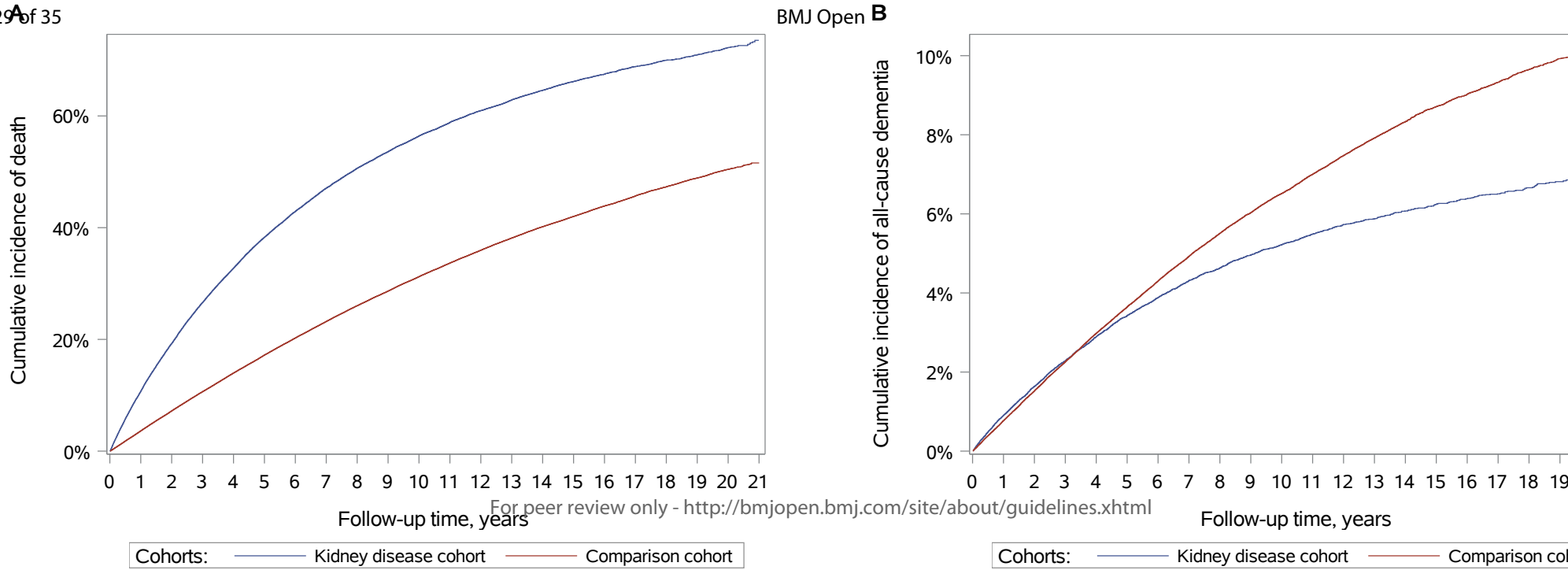
Kidney disease was defined as chronic kidney disease and several other persistent kidney diseases as well as dialysis treatment or kidney transplant in the definition of kidney disease (supplemental table 1).

Chronic kidney disease was defined as ICD-8 code 792 and ICD-10 code N18.

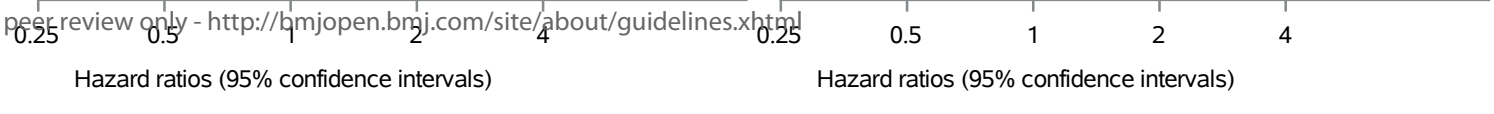
Multifactorially adjusted model included adjustments for covariates listed in table 1.

CI: confidence interval. No.: number.





	Unadjusted	Adjusted
	HR (95% CI)	HR (95% CI)
Age groups, years		
18-49	2.34 (1.76 - 3.11)	1.14 (0.78 - 1.67)
50-59	1.95 (1.66 - 2.30)	1.32 (1.08 - 1.61)
60-74	1.48 (1.39 - 1.57)	1.16 (1.08 - 1.24)
75-84	1.10 (1.04 - 1.16)	1.01 (0.95 - 1.08)
85+	0.93 (0.84 - 1.02)	0.90 (0.77 - 1.04)
Sex		
Male	1.03 (0.98 - 1.08)	1.07 (1.01 - 1.13)
Female	1.00 (0.94 - 1.05)	1.09 (1.02 - 1.16)
Calender period of match date		
1995-2003	0.95 (0.90 - 1.00)	1.11 (1.03 - 1.19)
2004-2016	1.07 (1.02 - 1.12)	1.05 (1.00 - 1.11)
Any cancer		
No	1.02 (0.98 - 1.06)	1.10 (1.05 - 1.15)
Yes	0.84 (0.76 - 0.93)	0.90 (0.80 - 1.02)
Angina pectoris		
No	0.94 (0.91 - 0.98)	1.08 (1.03 - 1.14)
Yes	0.98 (0.91 - 1.06)	1.05 (0.96 - 1.15)
Myocardial infarction		
No	0.99 (0.95 - 1.03)	1.08 (1.03 - 1.13)
Yes	0.94 (0.85 - 1.04)	1.03 (0.92 - 1.17)
Stroke		
No	0.98 (0.95 - 1.02)	1.08 (1.03 - 1.13)
Yes	0.85 (0.76 - 0.94)	1.04 (0.93 - 1.17)
Peripheral artery disease		
No	0.98 (0.95 - 1.02)	1.08 (1.03 - 1.13)
Yes	0.87 (0.78 - 0.97)	1.03 (0.90 - 1.17)
Venous thromboembolism		
No	1.02 (0.98 - 1.05)	1.08 (1.04 - 1.13)
Yes	0.78 (0.66 - 0.94)	0.90 (0.72 - 1.11)
Heart failure		
No	0.96 (0.92 - 1.00)	1.09 (1.04 - 1.14)
Yes	0.79 (0.72 - 0.88)	0.94 (0.83 - 1.07)
Heart valve disease		
No	1.00 (0.96 - 1.04)	1.08 (1.04 - 1.13)
Yes	0.87 (0.74 - 1.02)	0.94 (0.78 - 1.12)
Atrial fibrillation		
No	0.99 (0.95 - 1.03)	1.11 (1.06 - 1.16)
Yes	0.83 (0.75 - 0.92)	0.88 (0.78 - 0.99)
Hypercholesterolemia		
No	0.97 (0.93 - 1.01)	1.08 (1.02 - 1.14)
Yes	0.90 (0.84 - 0.96)	1.05 (0.98 - 1.13)
Hypertension		
No	0.72 (0.66 - 0.79)	1.21 (1.09 - 1.34)
Yes	0.79 (0.76 - 0.82)	1.04 (0.99 - 1.09)
Obesity		
No	1.02 (0.99 - 1.06)	1.08 (1.03 - 1.13)
Yes	0.91 (0.78 - 1.07)	1.00 (0.84 - 1.20)
Diabetes mellitus		
No	1.01 (0.97 - 1.05)	1.11 (1.06 - 1.16)
Yes	0.60 (0.55 - 0.65)	0.89 (0.81 - 0.97)
Chronic obstructive pulmonary disease		
No	0.99 (0.95 - 1.03)	1.07 (1.02 - 1.12)
Yes	1.04 (0.93 - 1.15)	1.13 (1.00 - 1.28)
Personal gross income during the		
0%-25%	0.95 (0.89 - 1.01)	1.13 (1.05 - 1.22)
26%-50%	0.88 (0.83 - 0.94)	0.98 (0.91 - 1.06)
51%-75%	0.99 (0.91 - 1.07)	1.05 (0.96 - 1.16)
76%-100%	1.17 (1.05 - 1.31)	1.23 (1.09 - 1.39)
Employment status during the year preceeding the index date		
Employed	1.11 (0.99 - 1.25)	1.10 (0.96 - 1.27)
Unemployed	1.28 (0.91 - 1.81)	1.39 (0.92 - 2.10)
Not available	1.37 (1.19 - 1.59)	1.31 (1.09 - 1.57)
Retired	1.09 (1.04 - 1.13)	1.06 (1.01 - 1.11)
Highest education achieved		
Low	1.00 (0.95 - 1.05)	1.08 (1.02 - 1.14)
Medium	1.11 (1.04 - 1.19)	1.07 (0.99 - 1.15)
High	1.08 (0.96 - 1.23)	1.08 (0.94 - 1.23)



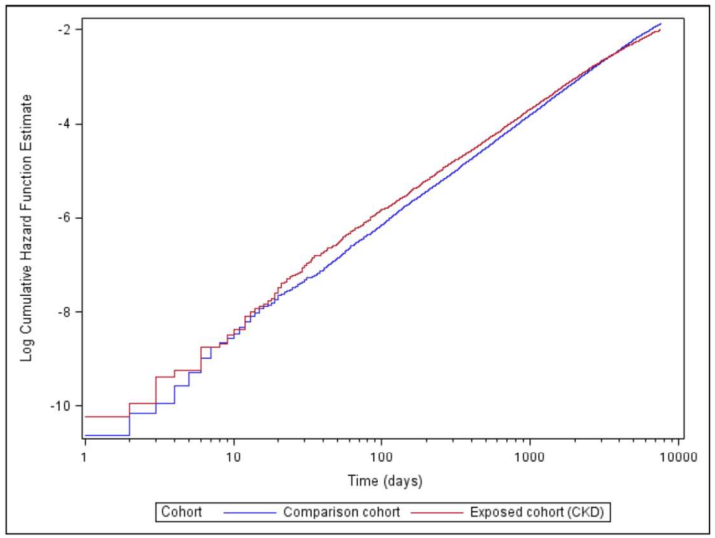
Supplemental table 1. List of codes for diagnoses, procedures and prescriptions on which definitions of exposure, outcomes and covariates were based.

Diagnoses and procedures			Cases, first time	Cases, ever	ICD-8 codes	ICD-10 codes	Procedure codes	ATC codes
Kidney disease								
		Chronic kidney disease	41,925	58,025	**792**	**N18**		
	Subtypes of kidney disease	Diabetic nephropathy	19,462	24,852	249.02, 250.02	E102, E112, E132, E142, N08.3		
		Glomerulonephritis (without nephrotic syndrome)	2,240	3,719	582	N03		
		Hereditary nephropathy, not elsewhere classified	169	256	756.0, 753.3	N07		
		Chronic tubulo-interstitial nephritis	2,195	2,934	590.09, 593.20, 760.4	N11		
		Glomerular disorders in diseases classified elsewhere	338	1,613		N08		
		Unspecified kidney failure	15,234	26,641		N19		
		Hypertensive nephropathy	4,407	7,858	403, 404	I12, I13		
		Albuminuria/proteinuria	1,967	2,291	789.0	N39.1		
		Recurrent and persistent haematuria	3,371	3,593		N02		
		Renal agenesis and other reductional defects of kidney	379	437		Q60		
		Polycystic kidney disease	2,328	2,837	753.10-753.19	Q61.1-Q61.4		
	Dialysis		1,918	13,872		Z99.2		
		April 1, 1973 - December 31, 1995					94300, 94340	
		<1996					94350	
		>=1996						
	Kidney transplant		245	2,560	Y95.09	Z94.0		
		1973-1995					57480, 57490	
		>=1996					KKAS	
Diagnoses related to dementia (mild cognitive impairment and amnestic syndromes)					291.19	F04, F05.1, F06.7, F10.6, F18.6, F19.6		
Outcomes								
	All-cause dementia				290.09, 290.10, 293.09, 293.19, 094.19, 292.09,	F00, G30, G30.0, G30.1, G30.8, G30.9), F01.0x, F01.1x, F01.2x, F01.3x, F01.8X, F01.9x), F02, F03, F1x.73 (F10.73-F19.73); G23.1;		

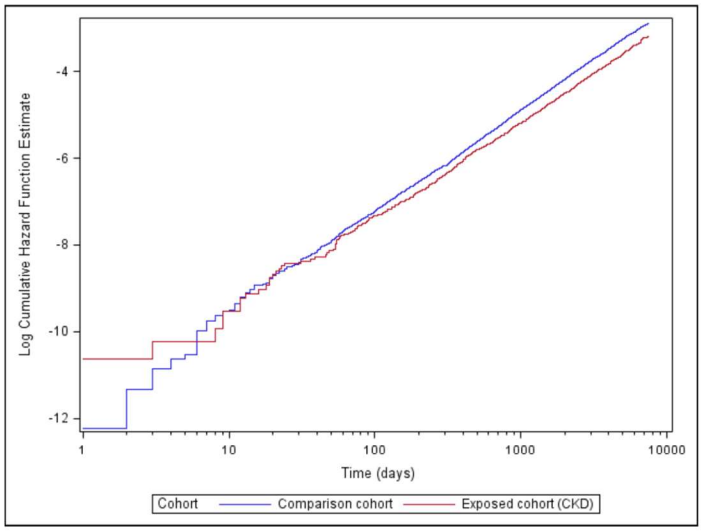
				290.11, 290.18, 290.19	G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85		
		Alzheimer's disease		290.09, 290.10	F00, G30, G30.0, G30.1, G30.8, G30.9		
		Vascular dementia		293.09, 293.19	F01.0x, F01.1x, F01.2x, F01.3x, F01.8X, F01.9x		
		Other dementia		094.19, 292.09, 290.11, 290.18, 290.19	F02, F03, F10.73-F19.73; G23.1; G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85		
Covariates							
	Angina pectoris			413	I20 (except I20.0), I25.1, I25.9		
	Myocardial infarction			410	I21, I22, I23		
	Stroke			431, 433-434	I61, I63-I64		
	Peripheral artery disease			440-445	I70, I71, I72, I73, I74, I77		
	Venous thromboembolism			451.00, 451.08-09, 451.90, 451.92, 671.01-03, 671.08-09, 450.99, 973.99	I80.1-I80.3, O22.3, O87.1, I26.0, I26.9, O88.2		
	Heart failure			42709, 42710, 42711, 42719, 42899, 78249	I50, I11.0, I13.0, I13.2		
	Heart valve disease			394-398	I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22		
	Atrial fibrillation			42793, 42794	I48		
	Hypercholesterolemia			27200	E780		C10
	Hypertension			400-404	DI10-DI15, I67.4		C02-C03 C07-C09
	Obesity			277	E65-E68		
	Diabetes mellitus			249, 250 (excluding 249.02, 250.02)	E10 (excluding E10.2), E11 (excluding E11.2), H36.0		
	Chronic obstructive pulmonary disease			490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3		
	Cancer			140-172, 174-194, 200-207	C00-26, C30-34, C37-41, C43, C45-58, C60-76, C80-85, C88, C90-97		

Supplemental figure 1. Proportional hazards for A) all-cause dementia, B) Alzheimer's disease, C) vascular dementia and D) other dementia.

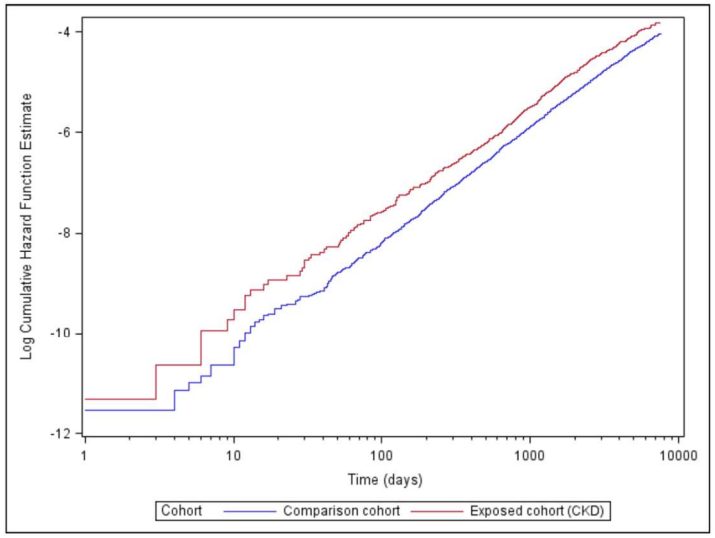
A



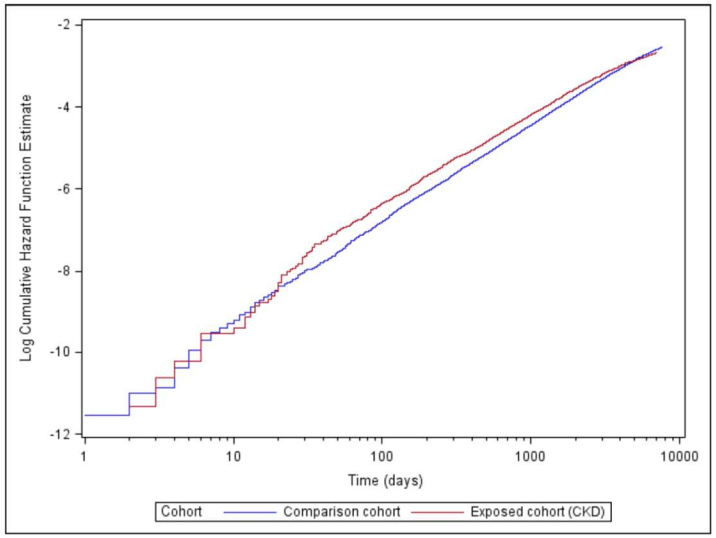
B



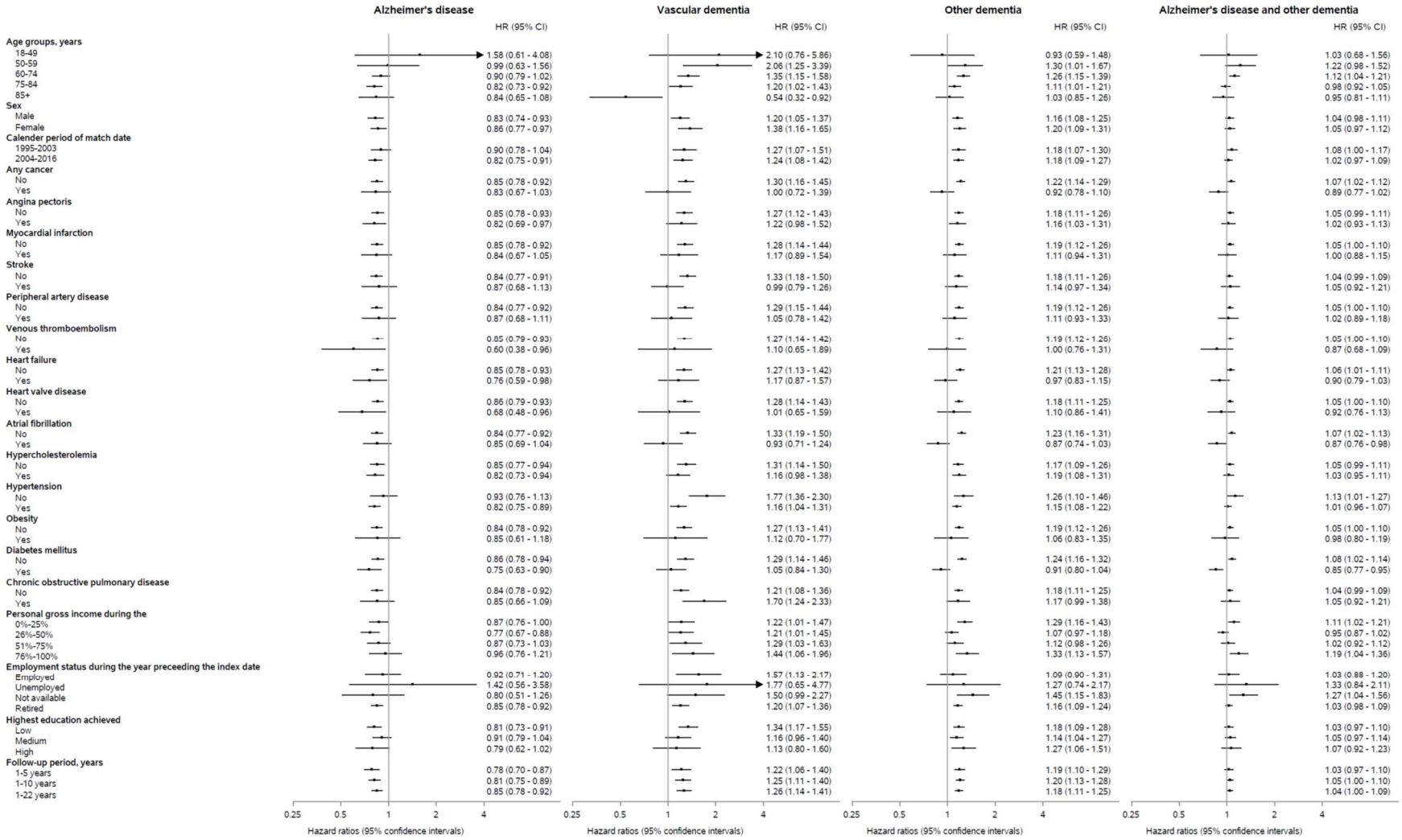
C



D



Supplemental figure 2. Risk of dementia subtypes in patients with kidney disease compared with individuals in a matched population without kidney disease stratified by covariates listed in Table 1.



HR: hazard ratio. 95% CI: 95% confidence interval.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	7-11
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13 Figures and Tables
		(*b*) Report category boundaries when continuous variables were categorized	Figures and Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

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

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