

A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands

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Abstract

Purpose Because most population-based studies on the epidemiology of chronic kidney disease (CKD) are cross-sectional, there is, except for end-stage renal disease, hardly any information on incidence rates.

Methods We conducted a retrospective cohort study in a dynamic population, using data of 784,563 adult participants retrieved from the Integrated Primary Care Information database, a primary care database containing the complete electronic longitudinal medical records. CKD (both incidence and prevalence) was based on (1) an increased urine albumin-to-creatinine ratio, (2) a decreased estimated glomerular filtration rate, or (3) explicit statement in the medical record. Results were stratified by age

according to the WHO standard population, sex, and diabetes mellitus.

Results Based on a single measurement only, the incidence rate of CKD in adults was 1,213 per 100,000 person-years, and 6.7 percent of the adult population had a prevalent diagnosis of CKD. The incidence rate increased by age and was the highest in participants with diabetes with an incidence of 25,000 per 100,000 person-years, affecting over 75 percent of participants with diabetes.

Conclusions This is the first study to report the incidence rates of all stages of CKD for the entire adult population, stratified by sex, 5-year age groups, and diabetes. Our data demonstrate that the incidence of CKD increases with age and is the highest in participants with diabetes mellitus.

The first author works for the Medicine Evaluation Board, the drug regulatory agency in the Netherlands.

The views expressed in this article are the personal view of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency.

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Introduction

Background

The prevalence of chronic kidney disease (CKD) has been widely studied in population-based, cross-sectional studies, with marked heterogeneity in prevalence data ranging from 19 to 71 percent for the highest age category [1–3], probably due to selection bias [4]. Limited information is available on (age-specific) incidence rates for CKD [2, 5–13].

Chronic kidney disease is associated with an increased risk of hospitalization, cardiovascular, and all-cause mortality and constitutes a major health problem with substantial healthcare costs [14–18]. A recent meta-analysis showed that the relative risk of mortality, stratified by estimated glomerular filtration rate (eGFR), is similar in those with and without diabetes [19]. This suggests that the underlying CKD is an important predictor for mortality. Another meta-analysis reported a similar pattern in participants with hypertension emphasizing the importance of CKD as a predictor of clinical outcomes [19–21].

Objective

The objective of this study was to investigate the epidemiology, in particular the incidence, of CKD using prospectively gathered electronic health care records from a community-dwelling adult population. We studied the incidence and prevalence of CKD in the adult population stratified by sex, 5-year age categories (WHO standard population) [22], and the presence of diabetes mellitus.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational, dynamic database which contains the electronic medical records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP plays a pivotal role and acts as a gatekeeper of medical care and information. Almost all inhabitants of the Netherlands are registered with a GP, independent of their health status. In the Dutch health care, the GP has a crucial role and functions as gatekeeper for care. This implies that only the GP can refer the patient to a specialist and that there is a strong communication between the GP and the specialist. With CKD, the GP is responsible for diagnosis, evaluation, treatment, and follow-up, unless the patient should be referred to a specialist, as documented in the national

interdisciplinary referral agreement [23]. Patients should be referred with macro-albuminuria, an eGFR < 45 ml/min/1.73 m² with age < 65 years, an eGFR < 30 ml/min/1.73 m² with age > 65 years, or when an underlying renal disease is suspected. Details of the IPCI database have been described elsewhere [24, 25]. Briefly, the database contains the complete electronic medical records of approximately 1,000,000 participants. These records contain anonymous longitudinal data on demographics, symptoms and diagnoses (coded and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and drug prescriptions (inclusive indication and dosage regimen). To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiologic studies [25]. The scientific and ethical advisory board of the IPCI project approved the study.

Study design

Retrospective cohort study in a dynamic population.

Participants

The source population comprised all adults (20 years or older) who were registered with their GP for at least 365 days. The study period started on January 1, 1996 and ended on March 1, 2011. Participants with (a history of) a renal transplant prior to study entry were excluded. Participants were followed until renal transplant, death, transfer out of practice, last data drawdown, or end of the study period, whichever came first.

Outcome

Chronic kidney disease was based on abnormalities in estimated glomerular filtration rate (eGFR), albuminuria as a marker of kidney damage, or an explicit statement in the medical record, and stratified by stages 1–5 [26]. The eGFR was obtained from the equation published by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration [27]:

$$\text{eGFR} = 141 * \min(\text{Scr}/\kappa, 1)^\alpha * \max(\text{Scr}/\kappa, 1)^{-1.209} \\ * 0.993\text{Age} * 1.018 [\text{if female}] * 1.159 [\text{if black}],$$

where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

For the urine albumin-to-creatinine ratio (ACR), we used a cutoff of 3.5 mg/mmol (~ 30 mg/g) for women and 2.5 mg/mmol (~ 22 mg/g) for men for (micro-) albuminuria as a marker for kidney damage to define stages 1 and 2 of CKD. The last eGFR before the ACR measurement was used to distinguish between stages 1 and 2 of CKD. If no SCR measurement was available, the eGFR was assumed to be >90 ml/min/1.73 m².

In addition, the complete electronic medical record was screened for an explicit statement indicating CKD, using an algorithm including “kidney/renal” in combination with “insufficiency/failure”, “renal replacement therapy”, “dialysis”, and “transplantation”.

A definite diagnosis of CKD was made according to KDIGO guidelines if there were two measurements, at least 90 days apart, indicating either (micro-) albuminuria or eGFR < 60 ml/min/1.73 m², or two explicit statements in the medical record (at least 90 days apart) indicating CKD. The first date was used as index date. A “possible diagnosis” was based on a single abnormal measurement or explicit statement indicating CKD in the medical record. Participants with a statement in the medical record indicating CKD before the start of follow-up that could not be confirmed by subsequent measurements were excluded from the stage-specific analysis. Participants with a statement in the medical record indicating CKD after start of follow-up that could not be confirmed by subsequent measurements were not accounted, and follow-up was censored from that date. The following stages were used: stage 1 “eGFR ≥ 90 ml/min/1.73 m² with kidney damage”, stage 2 “eGFR 60–89 ml/min/1.73 m² with kidney damage”, stage 3 “eGFR 30–59 ml/min/1.73 m²”, stage 4 “eGFR 15–29 ml/min/1.73 m²”, stage 5 “eGFR < 15 ml/min/1.73 m² or dialysis” [28].

Diabetes mellitus

Because diabetes is a risk factor for the development of end-stage renal disease (ESRD), we stratified our analyses by underlying diabetes [14–16]. The diagnosis of diabetes was based on a prescription of a drug within the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system “A10” (drugs used in diabetes) [29].

Statistical analysis

The incidence rate was determined by dividing the number of cases by the total number of person-years of follow-up. Participants were censored on the date of first diagnosis for the respective disease stage. Overall incidence rates were calculated for the adult study population. Incidence rates were expressed per 100,000 person-years. Ninety-five

percent confidence intervals were calculated based on a Poisson distribution [30].

Prevalence was determined by dividing the number of cases by the number of persons with follow-up in the study population on January 1 of each calendar year. Cases included participants with a prevalent diagnosis or an incident diagnosis of CKD prior to the 1st of January. As CKD is a progressive disease, participants were allowed to move between stage-specific categories of CKD. Results displayed were weighted for the calendar year-specific denominator. Ninety-five percent confidence intervals were calculated based on normal distribution.

The results on the incidence and prevalence of CKD were stratified for age according to the WHO standard population, sex, and presence of diabetes mellitus [31].

Results

The source population consisted of 784,856 adult participants with a valid history of at least 365 days in the IPCI database. A total of 293 participants were excluded because of a history of a renal transplant prior to start of follow-up, leaving 784,563 participants available for analysis.

The median age of the study population was 44.4 years at the start of follow-up [interquartile range (IQR) 31.7–59.2 years]; 48.1 % were males and 4.3 % of participants had a diagnosis of diabetes. A total of 2.1 million person-years of follow-up were available for the study population, the maximal duration of follow-up being 10.7 years, with a median of 2.3 years (IQR 1.3–3.4 years). Detailed population characteristics are available (online table 1 and 2).

For the study population, 1,379,097 eGFR measurements and 178,425 ACR measurements were available. A total of 42,780 participants had evidence of CKD prior to the start of follow-up; of these, 41,343 participants had an

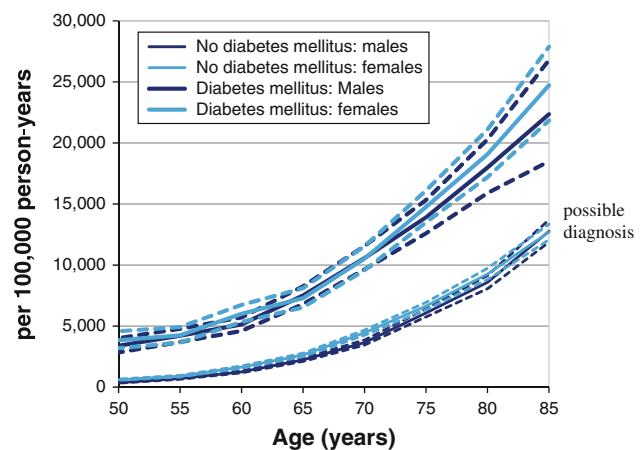


Fig. 1 Incidence of chronic kidney disease—all stages

Table 1 Overall incidence of chronic kidney disease

Age (years)	No diabetes						Diabetes					
	Males			Females			Males			Females		
	Cases	IR*	95 % CI	Cases	IR*	95 % CI	Cases	IR*	95 % CI	Cases	IR*	95 % CI
20–24	20	24	(15–37)	24	29	(19–43)	0	–	(–)	2	823	(164–2,637)
25–29	18	21	(13–33)	50	57	(43–75)	1	329	(30–1,534)	9	2,680	(1,323–4,891)
30–34	23	25	(16–37)	58	63	(48–81)	15	2,542	(1,485–4,087)	11	1,749	(928–3,026)
35–39	70	67	(53–84)	99	93	(76–113)	25	2,511	(1,665–3,646)	20	1,990	(1,254–3,013)
40–44	124	114	(95–135)	214	193	(169–221)	36	2,096	(1,492–2,868)	42	2,822	(2,062–3,777)
45–49	200	193	(167–221)	344	326	(293–361)	84	3,031	(2,433–3,732)	66	3,036	(2,368–3,837)
50–54	334	359	(322–399)	570	608	(560–660)	129	3,391	(2,843–4,015)	118	3,839	(3,193–4,580)
55–59	562	704	(648–764)	718	899	(835–966)	232	4,209	(3,693–4,777)	171	4,250	(3,649–4,924)
60–64	846	1,247	(1,165–1,334)	1,117	1,636	(1,542–1,734)	330	5,134	(4,602–5,711)	287	6,006	(5,341–6,731)
65–69	1,048	2,235	(2,103–2,374)	1,280	2,628	(2,487–2,775)	408	7,503	(6,801–8,258)	332	7,287	(6,535–8,103)
70–74	1,225	3,651	(3,451–3,860)	1,649	4,461	(4,249–4,680)	466	10,567	(9,640–11,559)	439	10,525	(9,574–11,544)
75–79	1,319	6,072	(5,751–6,406)	1,823	6,640	(6,341–6,950)	400	13,912	(12,598–15,326)	490	14,758	(13,495–16,109)
80–84	973	8,586	(8,059–9,138)	1,561	9,263	(8,812–9,731)	258	17,989	(15,894–20,287)	369	19,073	(17,201–21,095)
85+	746	12,764	(11,873–13,705)	1,518	12,697	(12,071–13,348)	112	22,355	(18,497–26,790)	258	24,722	(21,842–27,879)

* IR Incidence rate per 100,000 person-years. Chronic kidney disease was determined from a single abnormal measurement (possible diagnosis)

abnormal measurement, and in an additional 1,437 participants, the presence of CKD was explicitly stated in the medical record with no measurement available prior to the start of follow-up. There were 23,643 incident cases of CKD; of these, 22,722 were based on abnormal measurements, and an additional 921 cases were based on explicit statements in the medical record.

Incidence of CKD

The overall incidence of a possible diagnosis of CKD in adults was 1,213 per 100,000 person-years (95 % CI

1,198–1,283 per 100,000 person-years). The overall incidence rates for stages 1–5 CKD were 205, 11, 859, 41, and 24 per 100,000 person-years. The overall incidence of a definite diagnosis of CKD was 479 per 100,000 person-years (95 % CI 470–489 per 100,000 person-years). The overall incidence rates for stages 1–5 CKD were 60, 5, 370, 25, and 18 per 100,000 person-years. Confirmation of the first incident abnormal SCR or ACR measurement by a subsequent abnormal measurement (as required for definite diagnosis of CKD) was obtained after a median of 301 days (interquartile range 148–444 days).

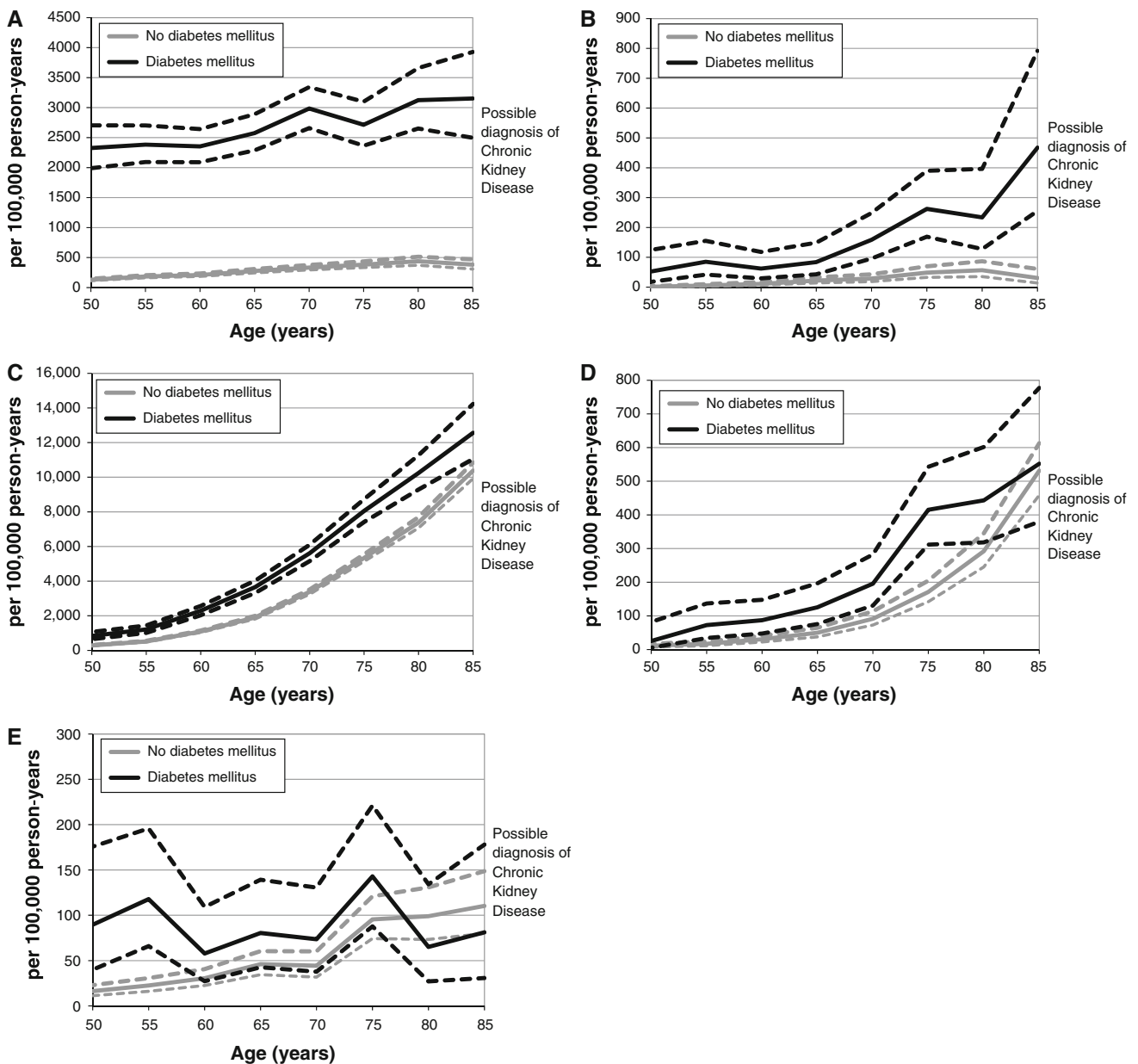


Fig. 2 a Incidence of chronic kidney disease—stage 1. b Incidence of chronic kidney disease—stage 2. c Incidence of chronic kidney disease—stage 3. d Incidence of chronic kidney disease—stage 4. e Incidence of chronic kidney disease—stage 5

Table 2 Overall prevalence of chronic kidney disease

Age (years)	No diabetes						Diabetes					
	Males			Females			Males			Females		
	Cases*	%	95 %CI	Cases*	%	95 %CI	Cases*	%	95 %CI	Cases*	%	95 %CI
20–24	112	0.1	(0.1–0.1)	113	0.1	(0.1–0.1)	3	1.0	(0.0–2.1)	4	1.4	(0.0–2.7)
25–29	89	0.1	(0.1–0.1)	172	0.2	(0.1–0.2)	7	2.0	(0.5–3.5)	29	7.3	(4.7–9.8)
30–34	119	0.1	(0.1–0.1)	239	0.2	(0.2–0.3)	55	7.9	(5.9–9.9)	45	6	(4.4–7.8)
35–39	261	0.2	(0.2–0.3)	430	0.4	(0.3–0.4)	108	8.8	(7.2–10.4)	100	8.2	(6.6–9.7)
40–44	400	0.3	(0.3–0.4)	803	0.6	(0.6–0.7)	194	9.0	(7.8–10.2)	189	10.0	(8.6–11.3)
45–49	746	0.6	(0.6–0.7)	1,345	1.1	(1.1–1.2)	324	9.4	(8.4–10.4)	301	11.0	(9.8–12.1)
50–54	1,088	1.0	(1.0–1.1)	2,346	2.2	(2.1–2.3)	565	11.8	(10.9–12.7)	583	14.4	(13.3–15.5)
55–59	1,925	2.1	(2.0–2.2)	3,651	3.9	(3.8–4.1)	962	13.4	(12.6–14.2)	877	16.4	(15.4–17.3)
60–64	3,471	4.3	(4.1–4.4)	6,121	7.3	(7.1–7.4)	1,723	18.9	(18.0–19.7)	1,562	21.9	(21.0–22.9)
65–69	4,779	8.4	(8.2–8.6)	7,777	12.5	(12.3–12.8)	2,189	26.3	(25.4–27.3)	2,254	30.7	(29.7–31.8)
70–74	6,720	15.2	(14.9–15.5)	11,026	21.2	(20.8–21.5)	2,815	36.1	(35.1–37.2)	3,169	40.5	(39.4–41.6)
75–79	8,376	25.7	(25.2–26.1)	13,549	30.8	(30.3–31.2)	3,161	49.5	(48.3–50.7)	4,347	53.9	(52.9–55.0)
80–84	7,465	36.8	(36.1–37.4)	14,318	42.9	(42.4–43.5)	2,574	61.3	(59.8–62.7)	4,475	67.1	(66.0–68.3)
85+	6,033	48.2	(47.3–49.0)	5,818	54.3	(53.8–54.9)	1,528	72.9	(71.0–74.8)	3,973	77.1	(76.0–78.3)

* Chronic kidney disease was determined from a single abnormal measurement (possible diagnosis)

For a possible diagnosis, the incidence rate was higher in females (1,362 per 100,000 person-years) than in males (1,029 per 100,000 person-years), $p < 0.001$. The incidence rates were higher in participants with diabetes (7,120 per 100,000 person-years) than in those without (973 per 100,000 person-years; $p < 0.001$). The highest incidence rate of CKD was reached in women with diabetes, aged ≥ 85 years (25,000 per 100,000 person-years). Results stratified by age, sex, and diabetes are shown in Fig. 1 and Table 1. There was a marked increase in the incidence rate for stages 3 and 4 CKD as of the age of 50 years and older, both in participants with and without diabetes, whereas the incidence rate of stage 2 CKD only increased with age in participants with diabetes. (Figures 2a–e) Comprehensive stage-specific tables are available (online tables 3A–E).

Prevalence of CKD

The overall prevalence of CKD (possible diagnosis) was 6.7 % (95 CI % 6.6–6.7 %) and 0.55, 0.03, 5.38, 0.41, 0.16 % for stages 1–5. The overall prevalence of CKD (definite diagnosis) was 5.1 % (5.1–5.1 %) and 0.32, 0.03, 4.17, 0.38, 0.15 % for stages 1–5. In line with the incidence data, the prevalence of CKD increased with age, female sex, and diabetes to more than 75 % in diabetic female participants aged ≥ 85 years as shown in Table 2 and Fig. 3. Prevalence of all stages of CKD, except for stage 1, increased with age (Fig. 4a–e). In participants with diabetes, the prevalence of stages 1 and 2 CKD was higher in

males. In participants without diabetes, stage 5 CKD was significantly more prevalent in males than in females from the age of 75 onward (Fig. 4e). Irrespective of the presence of diabetes, the prevalence of stage 3 CKD was higher in females than in males for all age groups. Comprehensive stage-specific tables are available (online tables 4A–E).

Discussion

This is the first study to report incidence rates of CKD for the entire community-dwelling adult population for stages 1–5 of CKD, stratified by sex, 5-year age groups, and diabetes. The overall incidence of CKD in adults in our

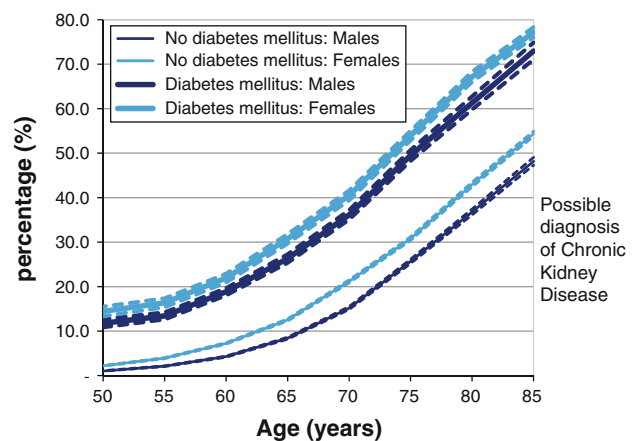


Fig. 3 Prevalence of chronic kidney disease—all stages

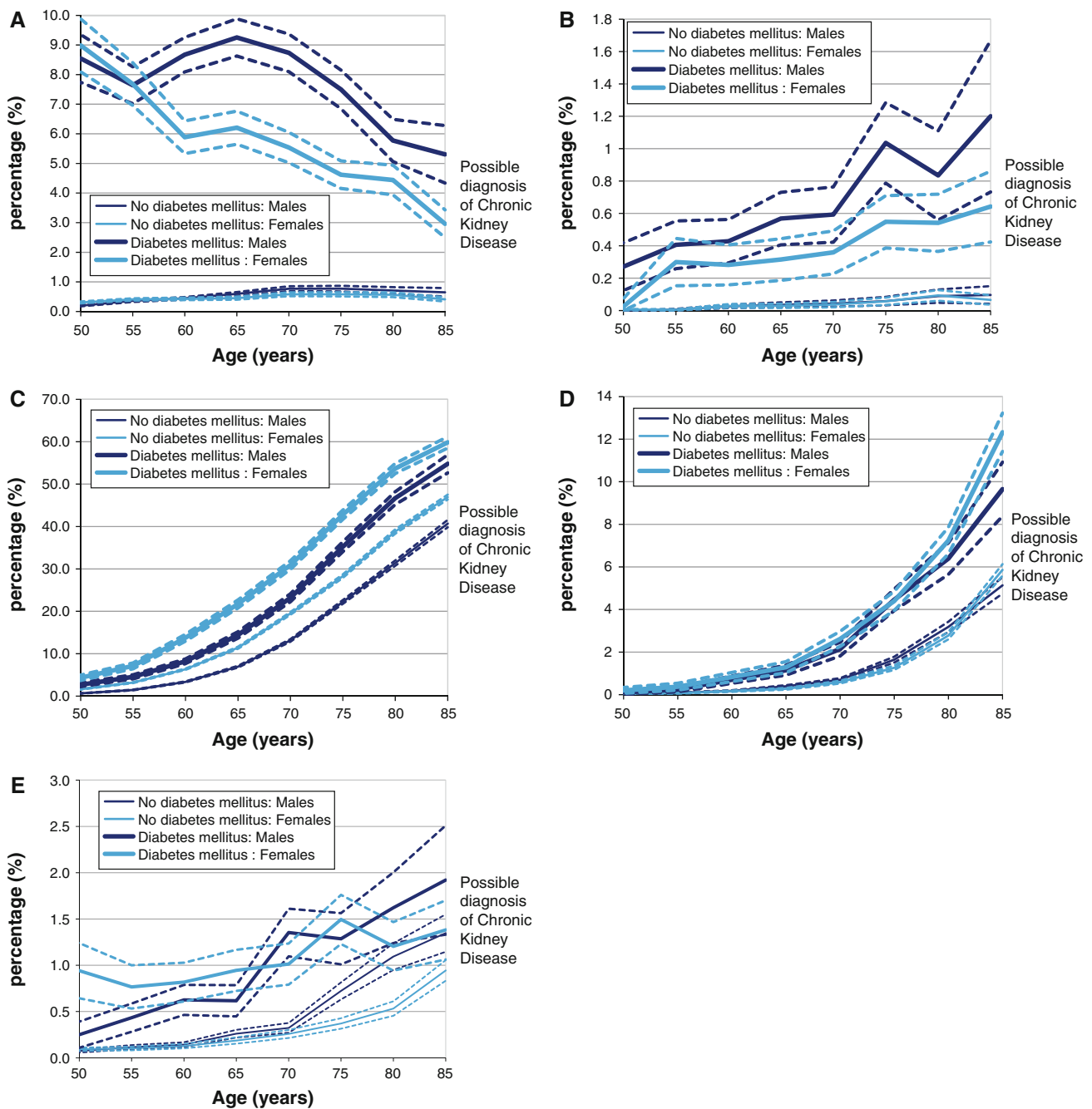


Fig. 4 **a** Prevalence of chronic kidney disease—stage 1. **b** Prevalence of chronic kidney disease—stage 2. **c** Prevalence of chronic kidney disease—stage 3. **d** Prevalence of chronic kidney disease—stage 4. **e** Prevalence of chronic kidney disease—stage 5

study was 1,213 per 100,000 person-years. The incidence rate increased with age and was the highest in females and in participants with diabetes mellitus. Indeed, in female diabetic participants, the incidence rate was close to 25,000 per 100,000 person-years. For stage 1 of CKD—especially in participants with diabetes—the prevalence decreased with advancing age, despite an increase in incidence rate, possibly due to a more rapid decline in eGFR with reclassification to prevalent stage 3 of CKD or excess

mortality. Strengths of our data are the population-based setting, large sample size, and the use of laboratory data to define CKD. In addition, the risk of selection bias is unlikely as almost all inhabitants of the Netherlands are registered with a GP, and data are collected as part of routine patient care, irrespective of any research questions.

As for all observational research, our study has potential limitations as well. Diagnostic bias might be a concern as laboratory results were taken in the process of day-to-day

Table 3 Prevalence of reduced estimated glomerular filtration rate (<60 ml/min/1.73 m²)

Age (years)	IPCI: (Current Study) participants	IPCI (Current Study)‡	Viktorsdot tir et al. 2005[40]	Coresh et al. 2005 [41] *,**	Nitsch et al. 2006[42]	Cirillo et al. 2006 [43]	Hallan et al. 2006 [3]*	Brown et al. 2005 [44]	McClellan et al. 2006 [1]
20 to 24	98,712	0.0	NA			†0.2		†2.5	NA
25 to 29	73,241	0.1	NA						NA
30 to 34	72,520	0.1	NA	0.2		0.3	0.2		NA
35 to 39	79,139	0.2	1.5		†4.6	0.4		5.7	NA
40 to 44	78,280	0.3	1.9						NA
45 to 49	73,208	0.7	2.9						
50 to 54	64,338	1.4	4.2	1.8		1.9	1.4	10.3	19.3
55 to 59	58,002	2.8	5.3						
60 to 64	53,439	5.8	8.8		15.2	6.2			31.6
65 to 69	39,505	11.0	26.4	7.2			6.3	26.7	
70 to 74	32,973	19.3	28.5			12.8			51.3
75 to 79	26,934	30.4	28.6		25.3				
80 to 84	19,286	43.0		24.9		32.7	18.6	43.1	62.7
85+	14,986	54.7	43.8						71.0

* Categories 15–29 and 30–59 ml/min/1.73 m² combined

** 1988–1994 data

† Age 18 and above

‡ Prevalent chronic kidney disease, stages 3, 4, and 5 (possible diagnosis)

patient care—in asymptomatic participants, this could imply that the incidence and prevalence of CKD are underestimated as no laboratory results were available. Individual laboratory data on analysis technique and calibration were not available. Estimated GFR might not adequately reflect actual GFR, especially in those with diabetes [32–39]. In that respect, our data reflect clinical practice because there is no general accepted formula to estimate GFR from serum creatinine with adjustment for diabetes at this point in time. In addition, potential misclassification is reported to be limited for GFR < 90 ml/min/1.73 m² [32]. Finally, participants with stages 4 and 5 CKD are detected; however, for those referred to the specialist, limited data on disease progression, with the exception of dialysis and transplant, are available after initial diagnosis. Therefore, it is not possible to confirm whether all patients indeed progressed to end-stage renal disease.

Few studies have reported incidence rates for CKD in the general population [5–13]. Comparison of incidence rates in our study with results of these studies is difficult, because these used a different case definition of CKD. The overall prevalence of our study is in line with the findings from previous cross-sectional studies, although there is substantial heterogeneity among these studies as well, with reported prevalence rates of 19–71 percent in the older age categories (Table 3) [2]. In prospective studies, where data are progressively collected during the study period, it is possible to confirm a first abnormal measurement (indicating CKD), with a second abnormal measurement

(“definite diagnosis”) within a reasonable time. In our study population that reflects day-to-day clinical practice, a first abnormal measurement is followed by a second measurement only after a median 301 days (IQR 148–444 days), and it might be missing completely as a result of referral to a specialist. Therefore, the use of a definite diagnosis of CKD likely underestimates the real values in a population-based study.

In conclusion, this study is the first to report incidence rates for stages 1–5 of CKD stratified by age, sex, and diabetes. Our results are expected to be generalizable to a western, predominantly Caucasian population, although differences in nationally implemented clinical guidelines, health care policy, and reimbursement might contribute to divergent findings in other countries. It shows that CKD is a major health problem, which affects the majority of the population at older age, especially in those with diabetes.

Conflict of interest None.

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