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Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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ABSTRACT (298/300 words)

Objectives: REVEAL-CKD aims to estimate the prevalence of, and factors associated with, undiagnosed stage 3 chronic kidney disease (CKD).

Design: Multinational, retrospective, observational study.

Setting: Data from six country-specific electronic medical records and/or insurance claims databases from five countries (France, Germany, Italy, Japan and the USA [two databases]).

Participants: Eligible participants (≥18 years old) had ≥2 consecutive estimated glomerular filtration rate (eGFR) measurements (calculated from serum creatinine values, sex and age) taken from 2015 onwards that were indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2). Undiagnosed cases lacked an International Classification of Diseases 9/10 diagnosis code for CKD (any stage) any time before, and up to 6 months after, the second qualifying eGFR measurement (study index).

Main outcome measures: The primary outcome was point prevalence of undiagnosed stage 3 CKD. Time to diagnosis was assessed using the Kaplan–Meier approach. Factors associated with lacking a CKD diagnosis and risk of diagnostic delay were assessed using logistic regression adjusted for baseline covariates.

Results: The prevalence of undiagnosed stage 3 CKD was 95.5% (19,120/20,012 patients) in France, 84.3% (22,557/26,767) in Germany, 77.0% (50,547/65,676) in Italy, 92.1% (83,693/90,902) in Japan, 61.6% (13,845/22,470) in the US Explorys LCED database and 64.3% (161,254/250,879) in the US TriNetX database. The prevalence of undiagnosed CKD tended to increase with age. Factors associated with increased likelihood of undiagnosed CKD were female sex (vs male, range of odds ratio across countries: 1.29–1.77), stage 3a CKD (vs 3b, 1.81–3.66), no medical history (vs a history) of diabetes (1.26–2.77) or hypertension (1.35–1.78).

Conclusions: There are substantial opportunities to improve stage 3 CKD diagnosis, particularly in female patients and older patients. The low diagnosis rates in patients with comorbidities that put them at risk of disease progression and complications is alarming.

Trial registration: NCT04847531

STRENGTHS AND LIMITATIONS OF THIS STUDY

- REVEAL-CKD uses large, contemporary, country-specific databases to provide robust estimates of the prevalence of undiagnosed stage 3 CKD.
- The study uses a strict, consistent and internationally recognised definition of stage 3 CKD to ensure accuracy when calculating the prevalence of diagnosed/undiagnosed CKD.
- Data from the countries and databases examined may not be representative of other countries with substantially different healthcare systems or CKD screening policies.
- There is a risk of misclassification of undiagnosed CKD if diagnoses were made in environments that did not contribute to the databases used or if diagnosing physicians did not use ICD-9/10 codes appropriately.

INTRODUCTION

Chronic kidney disease (CKD) is an established global public health concern.[1] CKD has a significant effect on patients, attributable to direct mortality and morbidity, as well as elevated risk of cardiovascular diseases.[2] The global prevalence of CKD is rising,[3] owing to aging populations and increased prevalence of CKD-associated risk factors including type 2 diabetes (T2D) and hypertension.[4]

Early intervention and appropriate management of CKD is recommended in the internationally recognised Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[5] to help delay disease progression and reduce the incidence of complications. Furthermore, in 2019, KDIGO held a controversies conference on the topic of early identification and intervention in CKD. The consensus statement from this conference urged action, including the implementation of screening programs and interventions for high-risk individuals.[6] Early-stage CKD is primarily asymptomatic,[7] therefore CKD is primarily diagnosed at later disease stages and the initiation of effective interventions is delayed or missed.[5] Previous studies have demonstrated low levels of diagnosis of early-stage CKD in Italy,[8] Sweden[9] and the USA.[10-15] However, these previous studies have been limited to single countries or databases, or at-risk groups such as patients with T2D, and did not assess the prevalence of CKD diagnosis across various subgroups (eg, patients with or without comorbidities). There is a need for contemporary information on the prevalence of, and factors associated with, undiagnosed stage 3 CKD, as well as a need to understand factors associated with diagnostic delay in these patients.

REVEAL-CKD (NCT04847531) is a multinational, observational study designed to fill this evidence gap. REVEAL-CKD aims to quantify the prevalence of, and factors associated with, undiagnosed stage 3 CKD in large populations across several countries.[16] Here, we present

data on the prevalence of, and factors associated with, undiagnosed stage 3 CKD in France, Germany, Italy, Japan and the USA.

METHODS

Study design

The study design for REVEAL-CKD has been reported in detail elsewhere,[16] and is summarised below.

Data were extracted from established, verified relevant databases containing electronic medical records and/or insurance claims in the countries of interest. Data for France were extracted from The Health Improvement Network, a large database of anonymised, non-extrapolated electronic medical records.[17] Data for Germany were extracted from the German Disease Analyzer, a database of anonymised longitudinal data on drug prescriptions, diagnoses and medical and demographic data from a representative sample of practices throughout Germany.[18] Data for Italy were extracted from the IQVIA Longitudinal Patient Database, a computerised network of over 900 family physicians, which includes anonymised data on patient consultations and treatments.[19] Data for Japan were extracted from Japan Real World Data, an integrated database of medical information including both electronic medical records and claims data.[20] Data for the USA were extracted from two separate databases: Explorys Linked Claims and Electronic Medical Records Data (LCED), a database of inpatient and outpatient medical records and claims data from commercially insured individuals,[21] and TriNetX, a database of integrated electronic medical records and claims data from 35 healthcare organisations, which provides clinical patient data from both inpatient and outpatient encounters.[22]

Patients aged ≥18 years were included in the analyses if they had at least two consecutive estimated glomerular filtration rate (eGFR) measurements that fell within the range indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2) and were recorded >90 and ≤730 days apart (per KDIGO guideline recommendations), taken on or after 1 January 2015. All patients had at least 12 months of continuous presence in the database before the first qualifying eGFR measurement. Full inclusion and exclusion criteria are shown in **Supplementary table 1**. eGFR was calculated from serum creatinine values, sex and age, using the CKD Epidemiology Collaboration (CKD-EPI) equation.[23] In line with current trends among physicians[24 25] and guidance from expert recommendations,[26] race modifiers were not used in the calculation of eGFR.

To account for potential delays in recording of diagnostic codes, undiagnosed CKD was defined as lacking an International Classification of Diseases (ICD) 9/10 diagnosis code corresponding to CKD (any stage), any time before and up to 6 months after index (date of second qualifying eGFR measurement). The ICD coding system varied by country depending on what was available in each database; the full list of ICD-9/10 codes used to determine diagnosed cases can be found in **Supplementary table 2**. A sensitivity analysis was performed to calculate the overall prevalence of undiagnosed stage 3 CKD using a broader definition of CKD adapted from Winkelmayer et al.[27] This sensitivity analysis included diagnostic codes for several additional manifestations of renal disease (**Supplementary table 3**).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

Overall prevalence of undiagnosed stage 3 CKD and patient demographic and clinical characteristics at index are presented descriptively. Odds ratios for factors associated with being undiagnosed any time before and up to 6 months after index were calculated using logistic regression analysis, adjusted for covariates at index. Hazard ratios for diagnostic delay among patients undiagnosed at index were calculated using Cox regression analysis, adjusted for covariates at index. The Kaplan–Meier method was used to estimate the time to diagnosis among patients undiagnosed at index.

RESULTS

This analysis of patients with stage 3 CKD included 20 012 patients from France, 90 902 patients from Germany, 65 676 patients from Italy, 26 767 patients from Japan, 22 470 patients from the LCED database in the USA, and 250 879 patients from the TriNetX database in the USA (**Figure 1**). Characteristics of these patients at index are shown in **Supplementary Table 4**. At index, median age was 71–80 years, median eGFR was 49–52 mL/min/1.73 m^2, 66.9%–77.7% of patients had CKD stage 3a (eGFR ≥45 and <60 mL/min/1.73 m^2) and 22.3%–33.1% of patients had CKD stage 3b (eGFR ≥30 and <45 mL/min/1.73 m^2). The overall prevalence of urinary albumin-creatinine ratio (UACR) testing was very low and ranged from 1.8% (US, TriNetX) to 5.5% (Japan).

Overall prevalence of undiagnosed stage 3 CKD

The proportion of patients with stage 3 CKD without a diagnosis at or within 6 months after index varied by database, and was 95.5% in France, 84.3% in Germany, 77.0% in Italy, 92.1% in Japan, 61.6% in the US LCED database and 64.3% in the US TriNetX database (**Figure 2**A). In the sensitivity analysis using a broader set of ICD-9/10 codes to identify

CKD diagnoses, the prevalence of undiagnosed CKD was 53.6%–89.9% (**Supplementary Table 5**). The proportion of patients with undiagnosed CKD per calendar year at index is shown in **Supplementary Figure 1**. Overall, there were no prevailing trends in the proportion of patients with undiagnosed CKD per calendar year, except in Italy, where the proportion of undiagnosed CKD tended to increase over time (68.2% undiagnosed in 2015 to 83.1% in 2020).

Demographics and clinical characteristics of patients with diagnosed and undiagnosed stage 3 CKD

Characteristics for patients with diagnosed and undiagnosed stage 3 CKD at index are presented in **Table 1**.

Table 1. Overall patient characteristics at study index according to country, by CKD diagnosis status 6 months after index

Country	France		Germany		Italy		Japan		USA			
Database	**THIN Cegedim**		**Disease Analyzer**		**LPD**		**Japan RWD**		**LCED**		**TriNetX**	
	Undiagnosed n=19 120	**Diagnosed* n=892**	**Undiagnosed n=22 557**	**Diagnosed* n=4210**	**Undiagnosed n=50 547**	**Diagnosed* n=15 129**	**Undiagnosed n=83 693**	**Diagnosed* n=7209**	**Undiagnosed n=13 845**	**Diagnosed* n=8625**	**Undiagnosed n=161 254**	**Diagnosed* n=89 625**
Age, y, median (IQR)	80 (72–86)	77 (69–84)	79 (72–84)	79 (71–84)	80 (74–85)	80 (73–85)	76 (69–83)	77 (68–83)	74 (64–82)	74 (64–82)	71 (64–79)	70 (62–78)
Age groups, y												
<45	58 (0.3)	9 (1.0)	46 (0.2)	20 (0.5)	95 (0.2)	93 (0.6)	652 (0.8)	139 (1.9)	109 (0.8)	134 (1.6)	2426 (1.5)	3097 (3.5)
45–64	1551 (8.1)	126 (14.1)	1957 (8.7)	474 (11.3)	2724 (5.4)	1056 (7.0)	12 260 (14.6)	1026 (14.2)	3754 (27.1)	2237 (25.9)	38 302 (23.8)	25 424 (28.4)
65–74	4421 (23.1)	220 (24.7)	5088 (22.6)	944 (22.4)	10 976 (21.7)	3288 (21.7)	23 696 (28.3)	1931 (26.8)	3415 (24.7)	2177 (25.2)	57 891 (35.9)	29 989 (33.5)
≥75	13 090 (68.5)	537 (60.2)	15 466 (68.6)	2772 (65.8)	36 752 (72.7)	10 692 (70.7)	47 085 (56.3)	4113 (57.1)	6567 (47.4)	4077 (47.3)	62 635 (38.8)	31 115 (34.7)
Male, n (%)	8599 (45.0)	492 (55.2)	9173 (40.7)	2043 (48.5)	19 820 (39.2)	7908 (52.3)	43 658 (52.2)	4465 (61.9)	5438 (39.3)	4613 (53.5)	57 989 (36.0)	47 123 (52.6)
eGFR, mL/min/1.73 m^2, median (IQR)	52 (46–56)	45 (38–52)	52 (45–56)	49 (40–55)	51 (44–55)	45 (38–52)	53 (47–56)	45 (37–53)	53 (47–57)	47 (40–53)	53 (47–57)	47 (40–53)
CKD stage, n (%)												
CKD stage 3a	14 661 (76.7)	440 (49.3)	16 871 (74.8)	2621 (62.3)	36 460 (72.1)	7477 (49.4)	66 955 (80.0)	3713 (51.5)	11 348 (82.0)	4972 (57.6)	131 385 (81.5)	52 233 (58.3)
CKD stage 3b	4459 (23.3)	452 (50.7)	5686 (25.2)	1589 (37.7)	14 087 (27.9)	7652 (50.6)	16 738 (20.0)	3496 (48.5)	2497 (18.0)	3653 (42.4)	29 869 (18.5)	37 392 (41.7)
Baseline UACR available, n (%)	424 (2.2)	26 (2.9)	0 (0.0)†	0 (0.0)†	4 (<0.1)‡	5 (<0.1)‡	3851 (4.6)	1141 (15.8)	474 (3.4)	425 (4.9)	2455 (1.5)	2149 (2.4)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.32 (1.08–1.65)	1.34 (1.11–1.63)	1.29 (1.06–1.55)	1.32 (1.11–1.59)	1.27 (1.06–1.53)	1.40 (1.16–1.71)	1.32 (1.09–1.62)	1.24 (1.03–1.53)	1.16 (0.96–1.45)	1.24 (1.03–1.55)	1.14 (0.93–1.42)
Missing, n	6172	342	6904	1328	13 379	4134	33 243	2062	5673	4349	88 031	50 767
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.81 (2.18–3.53)	2.87 (2.20–3.70)	2.70 (2.07–3.49)	2.74 (2.12–3.39)	2.53 (1.97–3.21)	2.77 (2.22–3.34)	2.53 (2.04–3.13)	2.46 (1.89–3.13)	2.25 (1.71–2.95)	2.43 (1.87–3.13)	2.22 (1.68–2.92)
Missing, n	6331	345	6026	1061	14 915	4560	31 643	1946	4988	3948	78 408	47 066
Comorbidities, n (%)												
Hypertension	11 737 (61.4)	675 (75.7)	10 969 (48.6)	2710 (64.4)	38 849 (76.9)	12 475 (82.5)	47 311 (56.5)	5711 (79.2)	11 863 (85.7)	8198 (95.0)	123 002 (76.3)	80 153 (89.4)
Type 2 diabetes	3311 (17.3)	221 (24.8)	5145 (22.8)	1790 (42.5)	15 785 (31.2)§	5515 (36.5)§	15 655 (18.7)	3334 (46.2)	4667 (33.7)	4621 (53.6)	49 299 (30.6)	46 142 (51.5)
Established CVD¶	1368 (7.2)	81 (9.1)	1467 (6.5)	437 (10.4)	5153 (10.2)	1784 (11.8)	23 248 (27.8)	2389 (33.1)	3337 (24.1)	2955 (34.3)	26 666 (16.5)	23 078 (25.7)
Heart failure	922 (4.8)	64 (7.2)	3318 (14.7)	1046 (24.8)	4248 (8.4)	2130 (14.1)	26 077 (31.2)	3986 (55.3)	2523 (18.2)	2791 (32.4)	22 422 (13.9)	24 580 (27.4)
Atrial fibrillation	2057 (10.8)	104 (11.7)	3351 (14.9)	866 (20.6)	8293 (16.4)	2812 (18.6)	10 765 (12.9)	1226 (17.0)	2409 (17.4)	2218 (25.7)	23 224 (14.4)	17 990 (20.1)
Medication use, n (%)												
ACE inhibitor	4363 (22.8)	271 (30.4)	8023 (35.6)	1612 (38.3)	19 141 (37.9)	5957 (39.4)	4027 (4.8)	474 (6.6)	5058 (36.5)	3725 (43.2)	33 532 (20.8)	24 274 (27.1)
ARB	6181 (32.3)	349 (39.1)	8855 (39.3)	1718 (40.8)	19 770 (39.1)	6428 (42.5)	18 959 (22.7)	2463 (34.2)	3605 (26.0)	2697 (31.3)	22 656 (14.0)	15 290 (17.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	287 (0.6)	66 (0.4)	1082 (1.3)	281 (3.9)	11 (0.1)	11 (0.1)	1171 (0.7)	978 (1.1)
GLD (any)	3300 (17.3)	189 (21.2)	6742 (29.9)	1577 (37.5)	13 108 (25.9)	4255 (28.1)	11 303 (13.5)	2128 (29.5)	5012 (36.2)	4388 (50.9)	29 690 (18.4)	30 569 (34.1)
Antiplatelets	5636 (29.5)	328 (36.8)	5451 (24.2)	1146 (27.2)	23 245 (46.0)	7906 (52.3)	16 690 (19.9)	2106 (29.2)	1274 (9.2)	1202 (13.9)	8256 (5.1)	8052 (9.0)
Loop diuretic	2747 (14.4)	177 (19.8)	8564 (38.0)	1944 (46.2)	15 719 (31.1)	6441 (42.6)	10 346 (12.4)	1633 (22.7)	2720 (19.6)	2843 (33.0)	21 136 (13.1)	22 334 (24.9)
Anticoagulants	2885 (15.1)	133 (14.9)	6838 (30.3)	1344 (31.9)	12 214 (24.2)	3983 (26.3)	12 886 (15.4)	1600 (22.2)	3434 (24.8)	2913 (33.8)	28 521 (17.7)	26 465 (29.5)

Percentages represent the proportion of diagnosed/undiagnosed patients in a specific group (eg, age) or with a specific variable (eg, medical history).

*Diagnosed cases include patients with a corresponding ICD-9/10 diagnosis code for CKD at or within 6 months of study index (date of second qualifying eGFR measurement).

†UACR testing data not available in the German Disease Analyzer database.

‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio

Patients with undiagnosed CKD tended to have slightly higher eGFR values than those with diagnosed CKD. A greater proportion of patients with stage 3a CKD were undiagnosed than patients with stage 3b CKD. There were fewer comorbidities such as hypertension, T2D and established cardiovascular disease in patients who were undiagnosed than in those who were diagnosed. Similarly, the proportion of patients taking medicines such as glucose-lowering drugs, loop diuretics, angiotensin-II converting enzyme inhibitors and angiotensin receptor blockers tended to be lower in undiagnosed patients than in those who were diagnosed. In all databases, a greater proportion of stage 3 CKD cases were undiagnosed in female patients than in male patients (**Figure 2**B). Additionally, in all databases, patients aged less than 45 years had the lowest proportion of undiagnosed CKD; the prevalence of undiagnosed CKD increased in older age groups in France, Germany, Italy and in the US TriNetX database (**Supplementary Figure 2**).

Factors associated with undiagnosed CKD

The proportion of undiagnosed CKD tended to be higher in those without comorbidities at study index versus those with such comorbidities (**Figure 3**). When adjusting for baseline covariates, female patients (vs male patients), patients with CKD stage 3a (vs 3b) and patients without a diagnosis of diabetes or hypertension (vs those with a diagnosis) were consistently more likely to lack a CKD diagnosis before and up to 6 months after index (**Supplementary Figure 3**).

Time to CKD diagnosis

Among patients who lacked a diagnosis for stage 3 CKD at or before study index, the median (interquartile range [IQR]) follow-up duration was 2.22 (1.18–3.64) years in France, 0.61 (0.27–1.03) years in Germany, 3.64 (2.08–4.88) years in Italy, 1.96 (0.84–3.41) years in Japan, 1.28 (0.53–2.34) years in the US LCED database and 1.19 (0.44–2.32) years in the US

TriNetX database. In patients undiagnosed at index, only a small proportion received a diagnosis during follow-up: 686/19 293 patients (3.6%) in France, 1157/23 302 patients (5.0%) in Germany, 8152/52 533 patients (15.5%) in Italy, 3855/84 603 patients (4.6%) in Japan, 3987/15 376 patients (25.9%) in the US LCED database and 44 007/178 410 patients (24.7%) in the US TriNetX database.

Among patients undiagnosed at index, diagnoses tended to accrue slowly over the whole duration of follow-up (**Figure 4**). The proportion of patients with initial eGFR values indicative of stage 3b CKD (≥30 and <45 mL/min/1.73 m^2) who received a diagnosis during follow-up was consistently higher than patients with initial eGFR values indicative of stage 3a CKD (≥45 and <60 mL/min/1.73 m^2; **Figure 4**).

Among all patients undiagnosed at index (regardless of whether they received a diagnosis during follow-up), median time to diagnosis was only calculable using the Kaplan–Meier method for the US TriNetX database, because more than half of the patients in the other databases remained undiagnosed at the end of the study period. In this database, the overall median (IQR) time to diagnosis was 4.75 (4.68–4.82) years.

After adjusting for baseline covariates, in all countries, female patients (vs male patients) and patients with stage 3a CKD at index (vs 3b) were more likely to be diagnosed later during follow-up (**Supplementary Figure 4**). Although less pronounced, patients without a history of comorbidities such as diabetes, heart failure or hypertension had a slightly elevated likelihood of delayed diagnosis (vs patients with a history of these conditions). Older patients also typically had a greater likelihood of delayed diagnosis than patients aged less than 45 years.

DISCUSSION

REVEAL-CKD is a large, multinational, observational study that uses a consistent, strict definition for undiagnosed CKD based on internationally recognised guidelines. By extracting data from contemporary, country-specific databases, the study provides a robust estimate of the prevalence of undiagnosed CKD in countries across the globe. The results from this analysis of six databases from five countries (France, Germany, Italy, Japan and the USA) demonstrate severe shortcomings in the diagnosis of stage 3 CKD. Although there was some variability among countries, the consistently high proportions of undiagnosed stage 3 CKD despite clinical evidence of the disease are highly concerning, as are the low levels of UACR testing. Of note, except in Japan, the prevalence of UACR testing did not appear to be substantially higher even in patients with a diagnosis of stage 3 CKD. UACR testing, however, is necessary for assessing the risk of future progression to kidney failure.[28] Missing opportunities for early diagnosis, prognostic assessment and management leaves patients at greater risk of further disease progression and complications, including end-stage renal disease and cardiovascular events.[6 29-31] Early interventions in CKD have been shown to improve outcomes by slowing CKD progression and reducing cardiovascular risk,[6 32] and healthcare costs associated with the disease increase substantially as CKD stage advances.[33] It is therefore vital for clinicians to seize the opportunity to diagnose and manage the condition as early as possible to minimise the impact of the disease, both in terms of financial burden and effects on health-related quality of life.

It is reassuring that the patients who have comorbidities that are established risk factors for CKD, such as hypertension and T2D, had higher rates of diagnosis and tended to be diagnosed sooner than patients without these conditions. However, even in patients with these comorbidities, the prevalence of undiagnosed CKD remained high. In the US databases,

which had the lowest rates of undiagnosed CKD, approximately 50% of patients with comorbidities in addition to CKD still lacked a CKD diagnosis. Alarmingly, this was the case for patients with hypertension, T2D and established cardiovascular disease: groups in which KDIGO recommends screening for CKD,[6] owing to their elevated risks of CKD progression and associated complications.[34-36] Without an appropriate CKD diagnosis, opportunities may also be missed to prescribe newer therapies such as sodium-glucose cotransporter-2 inhibitors which have been shown to improve cardiorenal outcomes in patients with CKD.[37 38]

We observed that the prevalence of undiagnosed CKD tended to rise with age, and older patients tended to have a higher risk of increased diagnostic delay than younger patients. In elderly patients, physicians may assume that eGFR values indicative of stage 3 CKD are caused by age-related decline of kidney function.[39 40] However, large population-based studies indicate that even in older adults at lower risk for kidney failure, stage 3 CKD is associated with an elevated risk of mortality, cardiovascular events and acute kidney injury.[41] Accordingly, KDIGO guidelines support the use of a single threshold value to define CKD across age subgroups consistent with criteria for other chronic non-communicable diseases.[5] In elderly patients, the effects of late-stage CKD are likely to have a substantial influence on physical and cognitive abilities, medication safety and cardiovascular prognosis.[2 6 41] It is therefore important that physicians do not underestimate the burden and effects of CKD in elderly patients and initiate guideline-appropriate management in a timely manner. Existing clinical tools (such as confirmatory cystatin C testing in suspected cases of CKD) can help mitigate the risk of overdiagnosis, although these remain underutilised.[6] CKD management in elderly patients should be adapted taking into consideration factors such as their age, frailty, comedications and comorbidities.

In line with previous studies that suggest CKD is more prevalent in women than in men,[42 43] the proportion of female patients with stage 3 CKD was higher than in male patients in all countries except Japan. Despite the higher prevalence of CKD in female patients, after adjusting for potential confounding factors, female patients had a higher likelihood of being undiagnosed than male patients in all countries. It has been suggested that the rate of progression of CKD is slower in women than in men,[44-47] and physicians may therefore be less likely to diagnose the condition at early stages in women. However, the inequality demonstrated in this study is substantial, and suggests a need for elevated awareness to minimise this gender disparity.

REVEAL-CKD used the internationally recognised CKD-EPI equation to calculate eGFR values from available serum creatinine measurements.[23] Race was not included as a modifier in line with recent trends among physicians[24 25] and guidance from expert recommendations.[26] In a sensitivity analysis performed on the US TriNetX database which included data on race, a substantial proportion of Black patients (46.1%, corresponding to 9.2% of the overall TriNetX cohort) were reclassified as having CKD stage 2 (**Supplementary Table 6**) when the race modifier was included in the calculation of eGFR. The inclusion of this modifier may therefore allow CKD to progress further in Black patients before they receive appropriate diagnosis and intervention. The decision to use the CKD-EPI equation without race was made in part to facilitate comparisons among countries and databases in which race was not available, and also to ensure that the eGFR levels seen in patients included in REVEAL-CKD were likely to be reflective of eGFR levels calculated when the measurements were taken.

Some limitations must be kept in mind when interpreting these data. Results from the included countries may not be generalisable to other countries, which could have

significantly different diagnostic coding practices, healthcare systems and screening policies; conclusions regarding the observed differences between countries cannot be drawn for similar reasons. The TriNetX and LCED databases contained a high proportion of commercially insured patients, and therefore may not be representative of the overall US population. Furthermore, data licensing issues prevented the pooling of data from multiple databases to provide an overall estimate of the prevalence of undiagnosed CKD. Although serum creatinine is typically included in standard laboratory blood tests, patients who did not require blood tests will be missing from this analysis. As such, there may be a degree of selection bias present in these results toward patients who are being routinely monitored for other conditions, or who are actively seeking healthcare. Confirmatory UACR testing was not necessary to meet the study definition of stage 3 CKD owing to the extremely low levels of UACR testing in most of the cohorts. The proportion of inpatient versus outpatient encounters was unavailable for many of the databases used, and therefore comparisons between diagnoses in these two settings could not be made. Because many of the databases used did not include data on race, variability in the prevalence of undiagnosed CKD according to race could not be assessed. It is important to note that this study focused on underdiagnosis for stage 3 CKD; low levels of UACR testing in all countries studied suggest that the prevalence of undiagnosed stage 1 and 2 CKD may be even higher. Lastly, there is a risk of misclassification if CKD diagnoses were made in clinical settings that do not contribute to the databases, or if patients had CKD that was recognised by their healthcare providers but was not recorded with an appropriate ICD-9/10 code in the databases. Although a lack of such codes may not always indicate that a patient's CKD is undiagnosed, this definition of CKD diagnosis has been validated by previous real-world studies,[8 11 12 27] and provides an appropriate surrogate measure for rates of diagnosis in large epidemiological studies such as REVEAL-CKD.

In conclusion, this analysis of six large, secondary databases from five countries demonstrates that most cases of stage 3 CKD are not diagnosed in a timely manner despite clinical evidence of the disease. Furthermore, although patients with existing risk factors for, or complications from, CKD were typically more likely to receive a CKD diagnosis, the prevalence of undiagnosed CKD in these patients remained alarmingly high. Clear opportunities exist for improved diagnosis of stage 3 CKD, particularly in female patients, elderly patients and patients at high risk of CKD progression and complications. Future research will help to quantify the impact of early diagnosis and initiation of effective therapies on the risk of CKD progression, complications and long-term patient outcomes.

Contributors

EJP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MA, EJP and HC developed and conducted the statistical analysis plan. All authors agreed the general content of the manuscript and were involved in drafting and critical revision of the manuscript during its development. All authors approved the final version of the manuscript before its submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Data used in this study were obtained from a third party and may not be publicly available. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Competing interests

SB, EJP, HC, KJ and EW are employees of AstraZeneca and hold stock options. MA is an employee of AstraZeneca. NT has received grants from AstraZeneca, Boehringer Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd

and Tricida, Inc, has received honoraria from AstraZeneca, Boehringer Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd and Tricida, Inc and holds stock options from Mesentech, Inc, Rénibus Therapeutics, Inc, pulseData and Tricida, Inc. MPS has received advisory board fees and honoraria from AstraZeneca, Bayer AG, Vifor Pharma Group and Boehringer Ingelheim/Eli Lilly and Company. LDN has received fees for scientific consultation and/or lectures by Astellas Pharma Inc, AstraZeneca, Mundipharma GmbH and Vifor Pharma Group. PK has received speaker's bureau and advisory board fees from AstraZeneca, Eli Lilly and Company and Novo Nordisk A/S, speaker's fees from Bayer AG and honoraria from AstraZeneca and Eli Lilly and Company. TM and JBV have no conflicts of interest to disclose.

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Ethics Approval

This study does not involve human participants. REVEAL-CKD is an analysis of commercially available anonymized electronic medical records and claims data and did not require ethics committee approval.

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Figure Legends

Figure 1. Cohort selection

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Figure 2. Overall prevalence of undiagnosed stage 3 CKD according to country and database

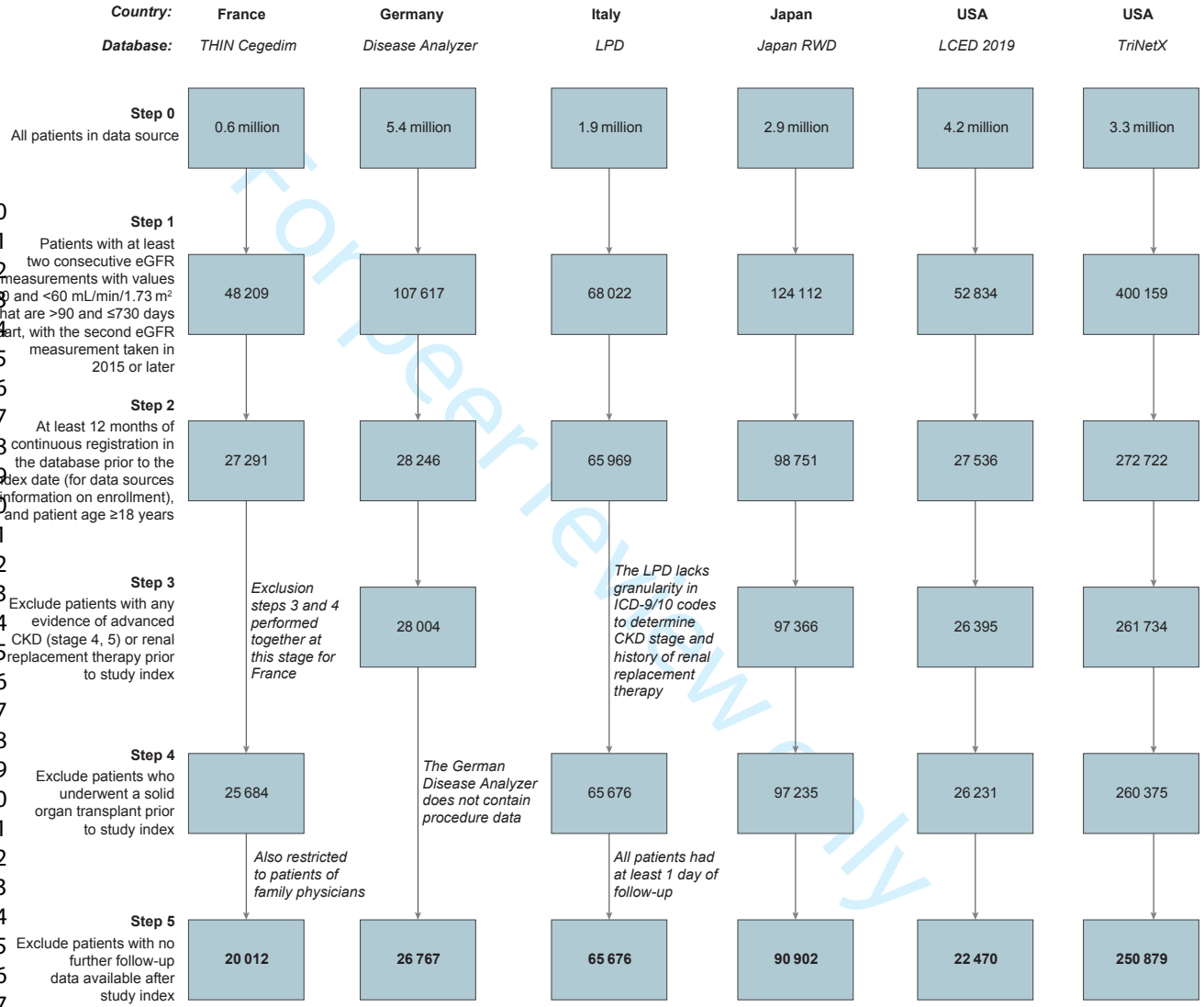
Undiagnosed cases are those which lack a diagnosis code for CKD (any stage), any time before and up to 6 months after study index.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

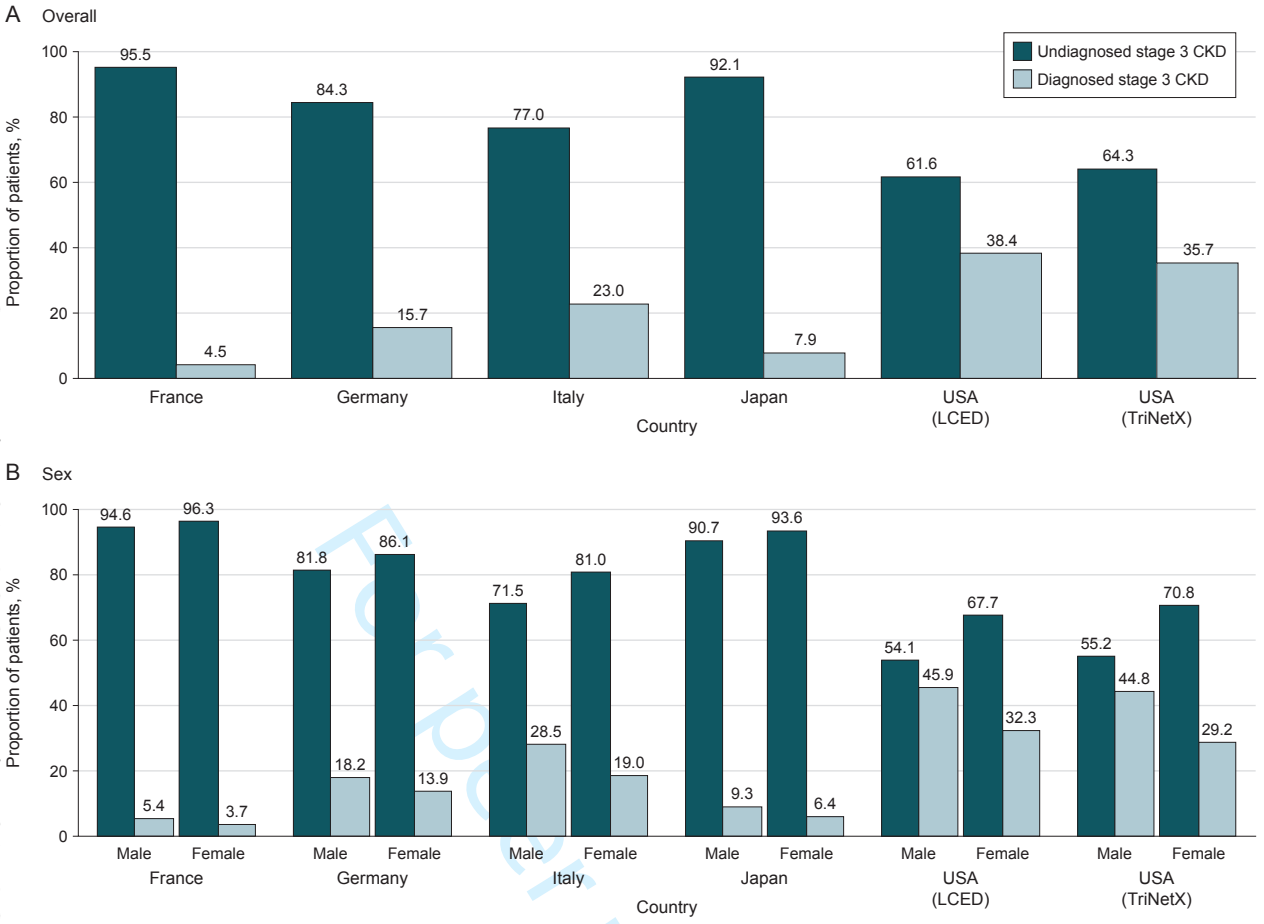
Figure 3. Prevalence of undiagnosed stage 3 CKD according to the presence of comorbidities at study index, by country and database

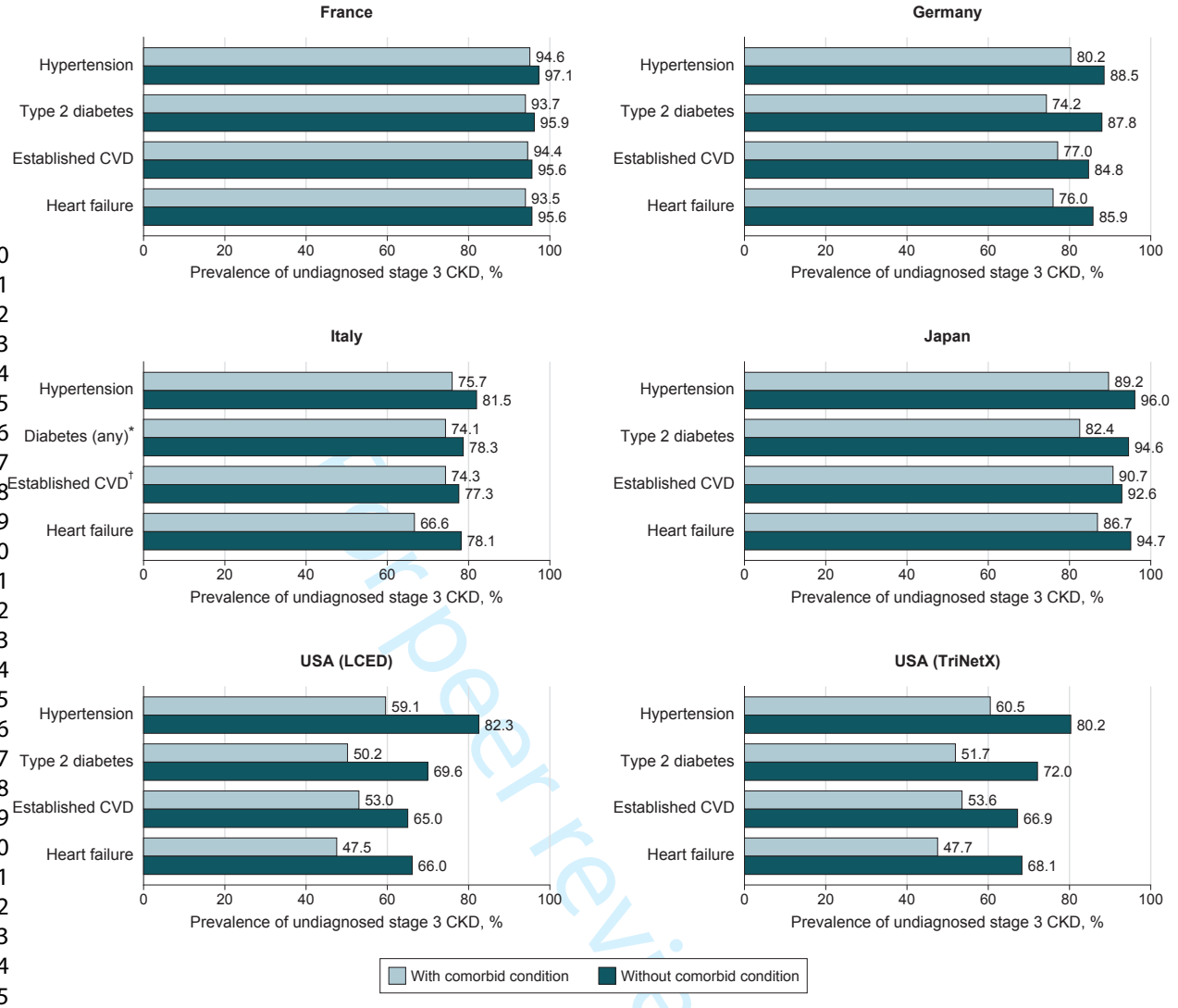
Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention. Study index is defined as the date of a patient's second qualifying eGFR measurement.
*Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
†Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data.

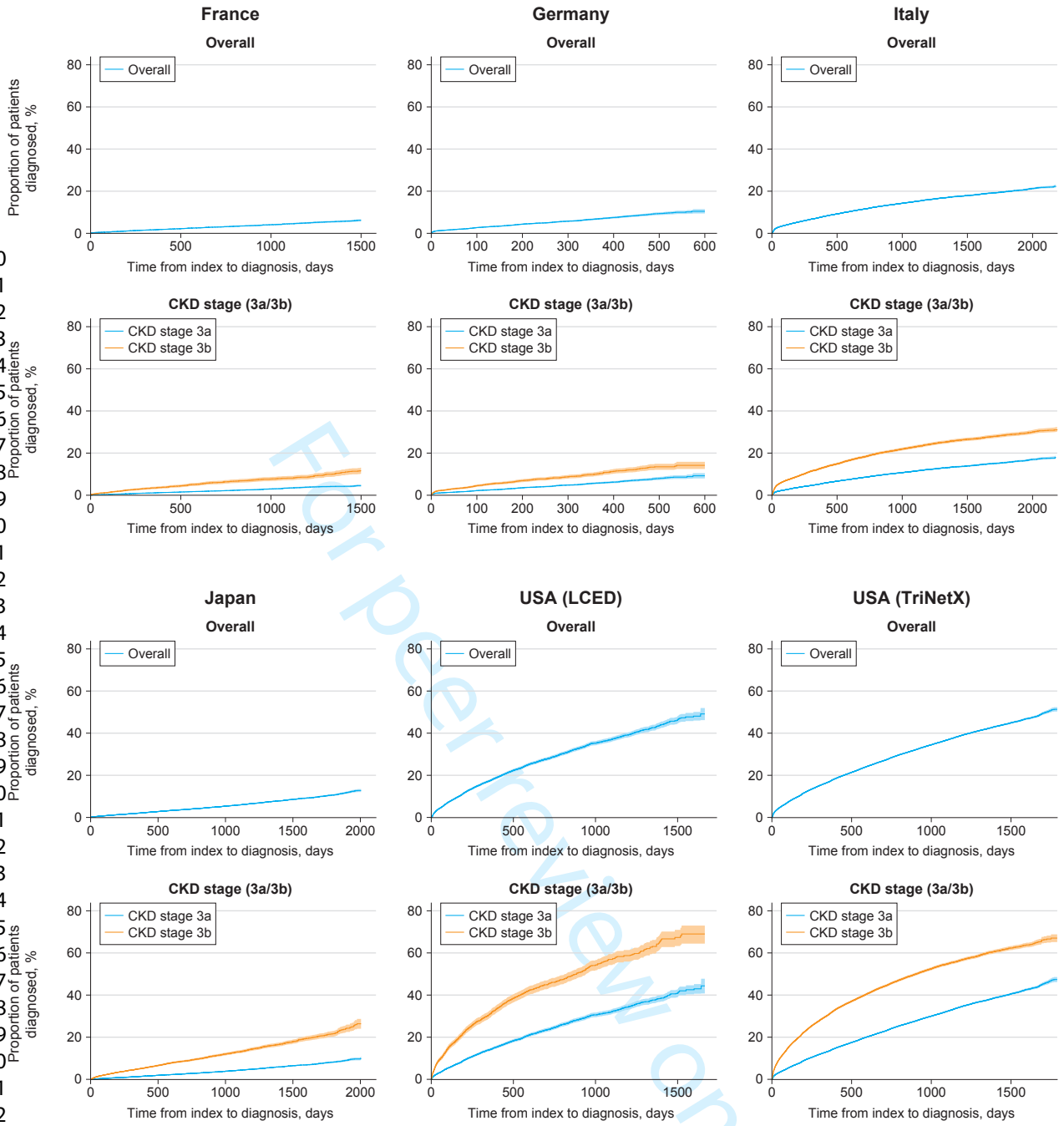
Figure 4. Kaplan–Meier estimates of time to CKD diagnosis according to country and database in patients undiagnosed at index, overall and by CKD stage (3a/3b)

Shaded areas represent 95% confidence intervals.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.









SUPPLEMENTAL MATERIALS

Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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Supplementary table 1. REVEAL-CKD study inclusion and exclusion criteria

Inclusion criteria:
• ≥2 consecutive eGFR laboratory measurements recorded in 2015 or later, with values ≥30 and <60 mL/min/1.73 m^2 (stage 3a/3b CKD using the CKD-EPI[1] equation) that are >90 and ≤730 days apart • ≥12 months of continuous presence in the database before the first qualifying eGFR measurement (look-back period) • Age ≥18 years at the index date (defined as the date of the second qualifying laboratory eGFR measurement indicative of stage 3a/3b CKD).
Exclusion criteria:
• Solid organ transplant recorded before the index date • Any evidence of advanced CKD (stages 4, 5, and end-stage renal disease) based on CKD diagnosis codes or renal replacement therapy before the index date.

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary table 2. ICD-9/10 codes used to identify patients with diagnosed stage 3 CKD

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD 10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 3. ICD-9/10 codes used to identify CKD in the sensitivity analysis using a broader definition for CKD adapted from Winkelmayer et al., 2005[2]

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Chronic renal insufficiency	582, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9	N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N19, N26.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359,

Description	ICD-9*	ICD-10†
		M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39
Acute renal failure	572.4, 580, 580.4, 580.81, 580.89, 580.9, 584.5, 584.6, 584.7, 584.8, 584.9, 791.2, 791.3	K76.7, N00.3, N00.8, N00.9, N01.3, N17.0, N17.1, N17.2, N17.8, N17.9, R82.1, R82.3
Miscellaneous	274.1, 440.1, 442.1, 453.3, 581, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 586, 587, 593, 593.1, 593.2, 593.3, 593.4, 593.5, 593.6, 593.7, 593.71, 593.72, 593.73, 593.81, 593.82, 593.89, 593.9, 753, 753.3, 866, 866.01, 866.1, 866.11, 866.12, 866.13	I70.1, I72.2, I82.3, N02.2, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N08, N13.4, N13.5, N13.70, N13.71, N13.721, N13.722, N13.729, N13.731, N13.732, N13.739, N13.8, N28.1, N28.81, N28.82, N28.83, N28.89, N28.9, Q60.2, Q60.5, Q63.0, Q63.1, Q63.2, Q63.3, Q63.8, Q63.9, R80.2, S31.001, S37.009, S37.019, S37.029, S37.039, S37.049, S37.059, S37.069

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD-10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 4. Overall patient characteristics at study index (date of second eGFR measurement) according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	THIN Cegedim	Disease Analyzer	LPD	Japan RWD	LCED	TriNetX
	n=20 012	n=26 767	n=65 676	n=90 902	n=22 470	n=250 879
CKD status*, n (%)						
Diagnosed	892 (4.5)	4210 (15.7)	15 129 (23.0)	7209 (7.9)	8625 (38.4)	89 625 (35.7)
Undiagnosed	19 120 (95.5)	22 557 (84.3)	50 547 (77.0)	83 693 (92.1)	13 845 (61.6)	161 254 (64.3)
Age, y, median (IQR)	80 (72–86)	79 (72–84)	80 (74–85)	76 (69–83)	74 (64–82)	71 (64–78)
Age groups, y						
<45	67 (0.3)	66 (0.2)	188 (0.3)	791 (0.9)	243 (1.1)	5523 (2.2)
45–64	1677 (8.4)	2431 (9.1)	3780 (5.8)	13 286 (14.6)	5991 (26.7)	63 726 (25.4)
65–74	4641 (23.2)	6032 (22.5)	14 264 (21.7)	25 627 (28.2)	5592 (24.9)	87 880 (35.0)
≥75	13 627 (68.1)	18 238 (68.1)	47 444 (72.2)	51 198 (56.3)	10 644 (47.4)	93 750 (37.4)
Male, n (%)	9091 (45.4)	11 216 (41.9)	27 728 (42.2)	48 123 (52.9)	10 051 (44.7)	105 112 (41.9)
eGFR, mL/min/1.73 m², median (IQR)	52 (45–56)	52 (44–56)	49 (42–55)	52 (46–56)	51 (44–56)	51 (44–56)
CKD stage, n (%)						
CKD stage 3a	15 101 (75.5)	19 492 (72.8)	43 937 (66.9)	70 668 (77.7)	16 320 (72.6)	183 618 (73.2)
CKD stage 3b	4911 (24.5)	7275 (27.2)	21 739 (33.1)	20 234 (22.3)	6150 (27.4)	67 261 (26.8)
Baseline UACR available, n (%)	450 (2.2)	0 (0.0)†	9 (<0.1)‡	4992 (5.5)	899 (4.0)	4604 (1.8)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.34 (1.10–1.63)	1.32 (1.09–1.58)	1.40 (1.14–1.71)	1.22 (0.98–1.50)	1.22 (0.98–1.50)
Missing, n	6514	8232	17 513	35 305	10 022	138 798
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.84 (2.17–3.65)	2.69 (2.07–3.36)	2.74 (2.30–3.31)	2.38 (1.84–3.05)	2.38 (1.81–3.05)
Missing, n	6676	7087	19 475	33 589	8936	125 474
Comorbidities, n (%)						
Hypertension	12 412 (62.0)	13 679 (51.1)	51 324 (78.1)	53 022 (58.3)	20 061 (89.3)	203 155 (81.0)
Type 2 diabetes	3532 (17.6)	6935 (25.9)	21 300 (32.4)§	18 989 (20.9)	9288 (41.3)	95 441 (38.0)
Established CVD¶	1449 (7.2)	1904 (7.1)	6937 (10.6)	25 637 (28.2)	6292 (28.0)	49 744 (19.8)
Heart failure	986 (4.9)	4364 (16.3)	6378 (9.7)	30 063 (33.1)	5314 (23.6)	47 002 (18.7)
Atrial fibrillation	2161 (10.8)	4217 (15.8)	11 105 (16.9)	11 991 (13.2)	4627 (20.6)	41 214 (16.4)
Medication use, n (%)						
ACE inhibitor	4634 (23.2)	9635 (36.0)	25 098 (38.2)	4501 (5.0)	8783 (39.1)	57 806 (23.0)
ARB	6530 (32.6)	10 573 (39.5)	26 198 (39.9)	21 422 (23.6)	6302 (28.0)	37 946 (15.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	353 (0.5)	1363 (1.5)	22 (0.1)	2149 (0.9)
GLD (any)	3489 (17.4)	8319 (31.1)	17 363 (26.4)	13 431 (14.8)	9400 (41.8)	60 259 (24.0)
Antiplatelets	5964 (29.8)	6597 (24.6)	31 151 (47.4)	18 796 (20.7)	2476 (11.0)	16 308 (6.5)
Loop diuretic	2924 (14.6)	10 508 (39.3)	22 160 (33.7)	11 979 (13.2)	5563 (24.8)	43 470 (17.3)
Anticoagulants	3018 (15.1)	8182 (30.6)	16 197 (24.7)	14 486 (15.9)	6347 (28.2)	54 986 (21.9)

Unless otherwise stated, percentages represent the proportion of patients in a specific group (eg, age) or with a specific variable (eg, medical history).
*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.
†UACR testing data not available in the German Disease Analyzer database.
‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio.

Supplementary table 5. Sensitivity analysis of undiagnosed stage 3 CKD using a broader CKD definition adapted from Winkelmayer et al., 2005 [2] according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	THIN Cegedim	Disease Analyzer	LPD	Japan RWD	LCED	TriNetX
	n=20 012	n=26 767	n=65 676	n=90 902	n=22 470	n=250 879
CKD status*, n (%)						
Diagnosed	2031 (10.1)	6165 (23.0)	21 146 (32.2)	12 113 (13.3)	10 421 (46.4)	109 735 (43.7)
Undiagnosed	17 981 (89.9)	20 602 (77.0)	44 530 (67.8)	78 789 (86.7)	12 049 (53.6)	141 144 (56.3)

*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.

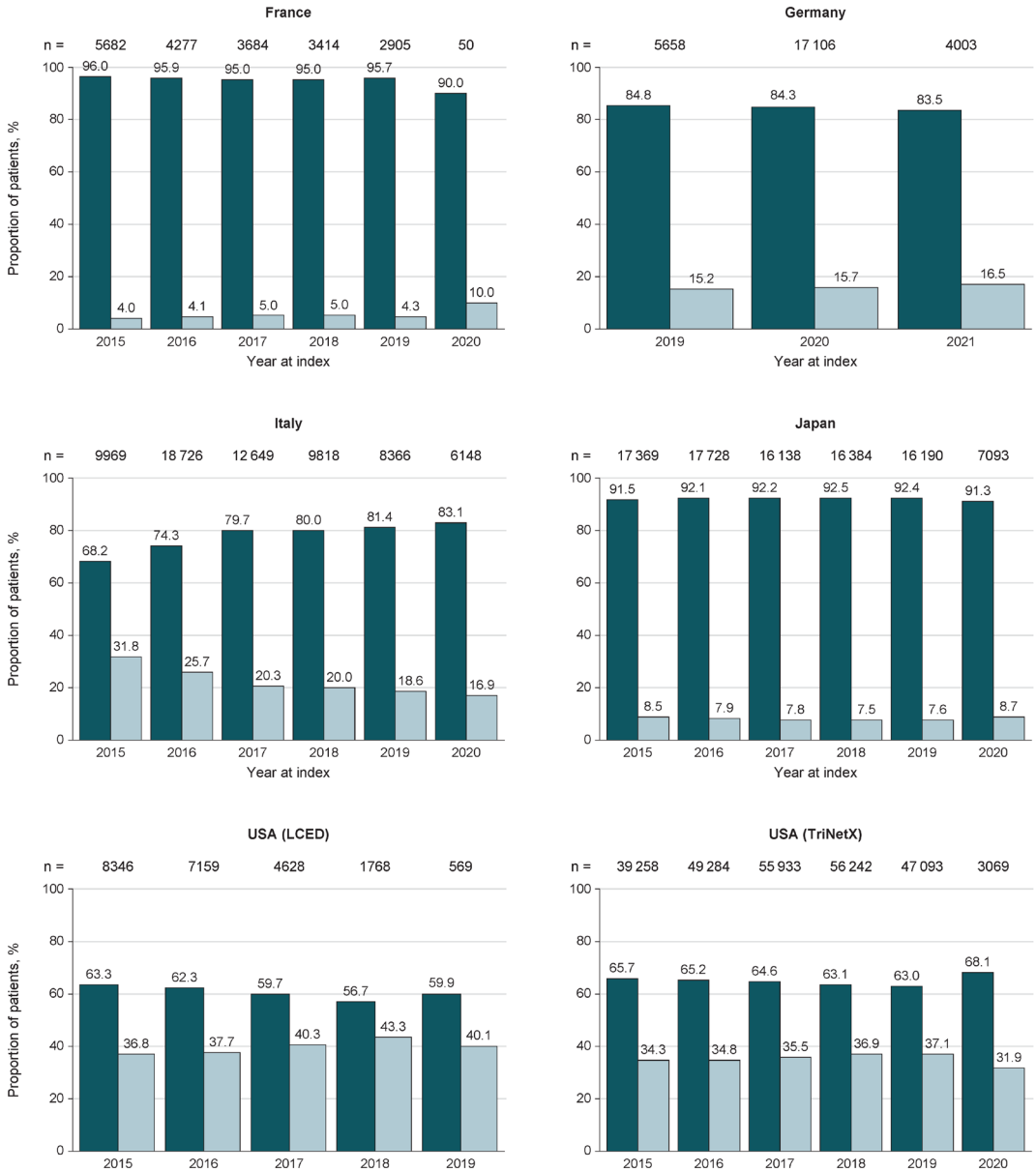
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Supplementary table 6. Comparison of CKD stages in Black and non-Black patients from the US TriNetX database when calculating eGFR using two different equations: CKD-EPI (without adjusting for race) and CKD-EPI (with race modifier)[1]

	CKD-EPI, no race modifier	CKD-EPI, with race modifier
Black (n=50 283)		
CKD stage 2, n (%)	0 (0.0)	23 156 (46.1)
CKD stage 3a, n (%)	36 005 (71.6)	20 455 (40.7)
CKD stage 3b, n (%)	14 278 (28.4)	6672 (13.3)
Non-Black (n=200 596)		
CKD stage 2, n (%)	0 (0.0)	0 (0.0)
CKD stage 3a, n (%)	147 613 (73.6)	147 613 (73.6)
CKD stage 3b, n (%)	52 983 (26.4)	52 983 (26.4)

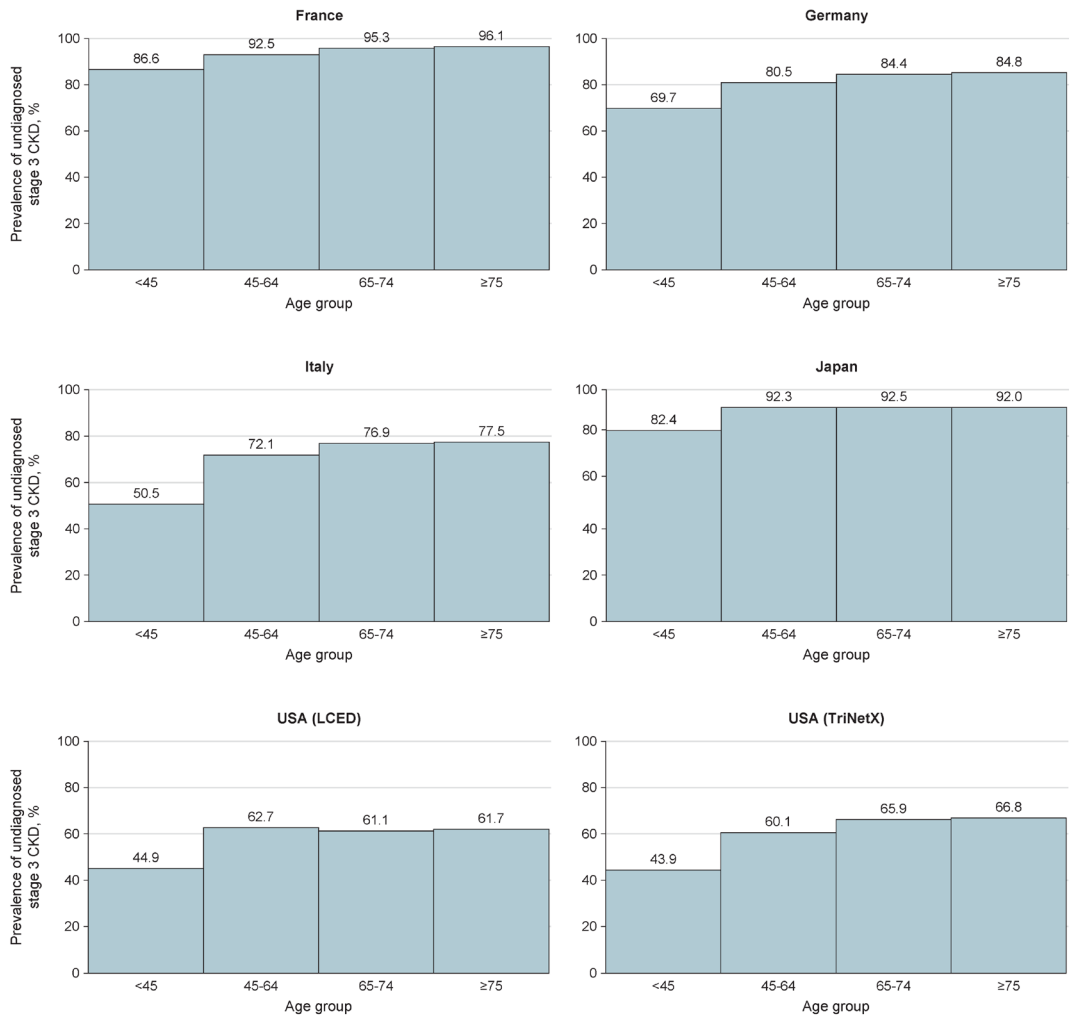
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary figure 1. Prevalence of undiagnosed stage 3 CKD according to calendar year of study index according to country and database



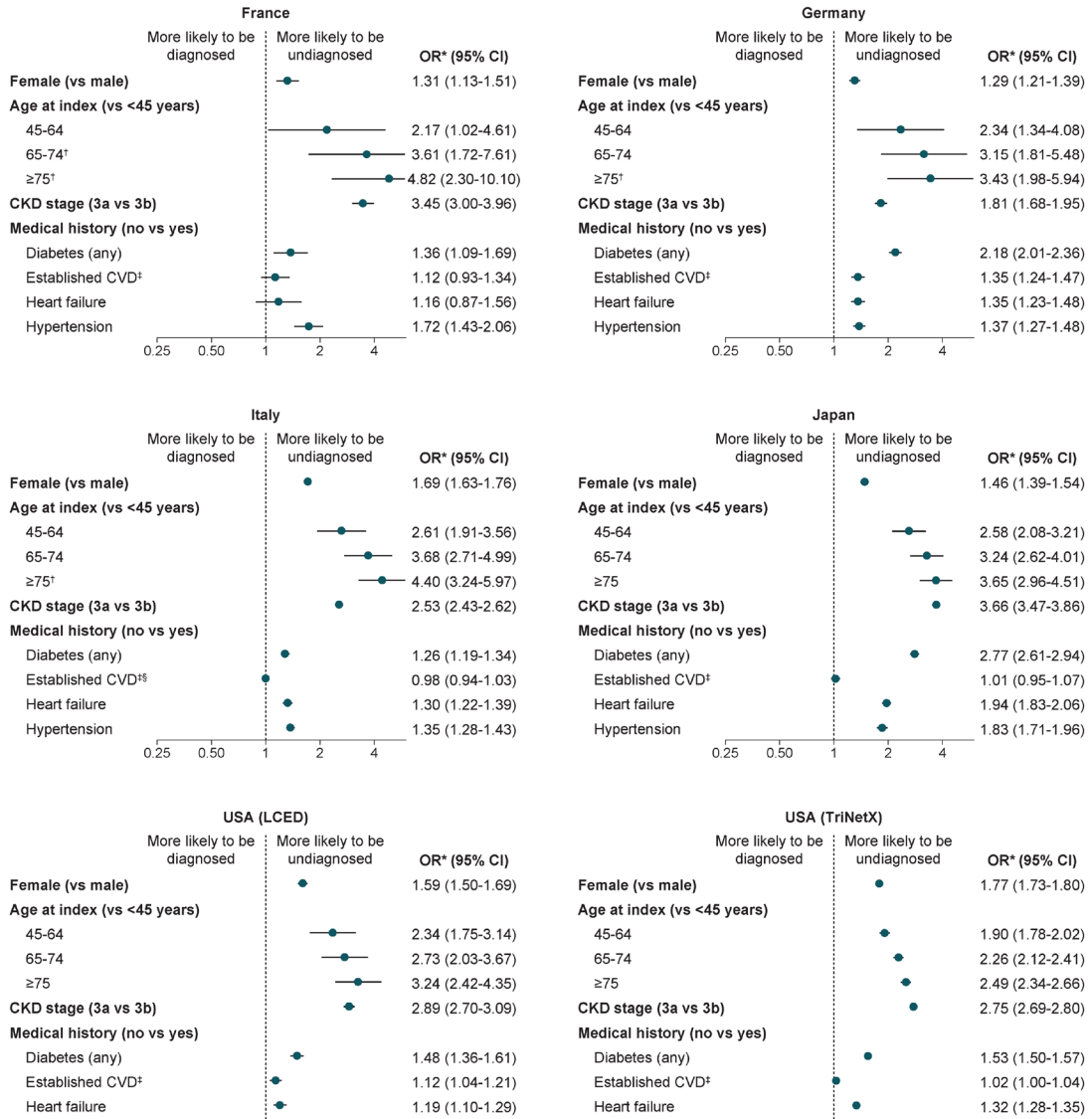
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 2. Prevalence of undiagnosed stage 3 CKD according to age group at study index according to country and database



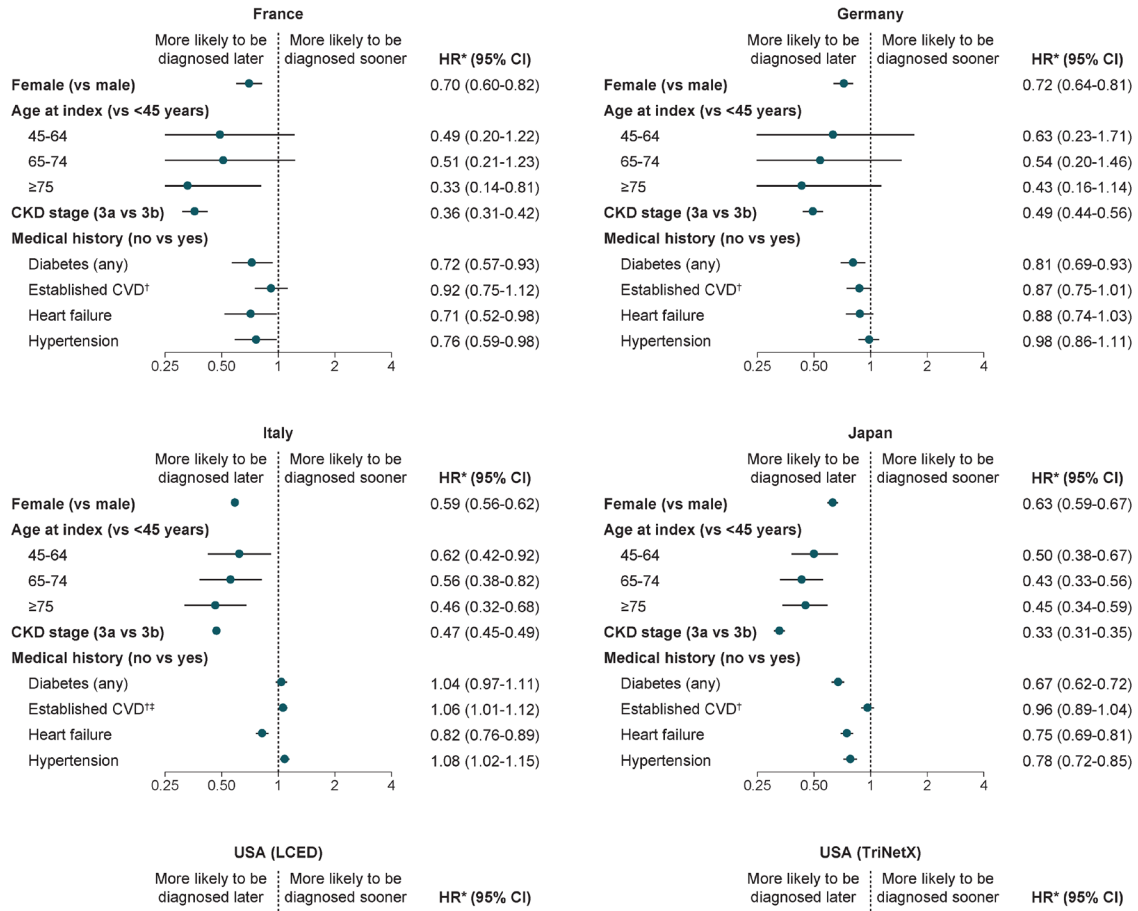
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 3. Factors associated with a lack of CKD diagnosis any time before or up to 6 months after index date according to country and database



Whiskers represent 95% confidence intervals.
*Odds ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors, and other glucose-lowering drugs).
†Upper 95% confidence interval extends beyond the boundary of the graph.
‡Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
§Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
CKD, chronic kidney disease; CVD, cardiovascular disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 4. Factors associated with time to CKD diagnosis in patients undiagnosed at index according to country and database



Whiskers represent 95% confidence intervals.

[a]Hazard ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors and other glucose-lowering drugs).

[b]Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.

[c]Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.

CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; LCED, Explorys Linked Claims and Electronic Medical Records Data.

References

1. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12. doi: 10.7326/0003-4819-150-9-200905050-00006
2. Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis.* 2005;46(2):225–32. doi: 10.1053/j.ajkd.2005.04.029

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Title, page 1, and abstract, page 3 [Design section] b) Abstract, page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) Abstract, page 3 (Setting section) 1.2) Abstract, page 3 (Setting and Participants sections) 1.3) N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Materials and Methods, page 6 (Study Design)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Materials and Methods, page 6 (Study Design)		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	A) Eligibility criteria, follow-up duration and data sources described in Materials and Methods, page 6 and 7 (Study Design)	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1) Materials and Methods, page 7 (Study Design) with full lists of ICD9/10 codes used to identify diagnosed/undiagnosed cases given in Supplementary Materials 6.2) N/A (eligible patients were identified based on eGFR which was calculated from serum creatinine as described in Materials and Methods and according to internationally-recognized equations for eGFR calculations) 6.3) N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Materials and Methods, page 7 (Study Design section)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1) Full list of ICD9/10 codes used in Supplementary Tables 2 and 3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Materials and Methods, page 6 (Study Design section)		

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	Materials and Methods, page 7 (Study Design section); potential bias addressed in Discussion, pages 16 and 17		
Study size	10	Explain how the study size was arrived at	N/A (all eligible patients within specified time frame were included)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	N/A (quantitative variables collected from existing EMR/claims databases; CKD stage groupings based on existing KDIGO guidelines referenced in the manuscript)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how	Materials and Methods, pages 7 and 8 (Study Design and Statistical Analysis sections)		

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) Author Contributions section, page 19 12.2) N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3) N/A
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a) Results, page 8 b) N/A c) Figure 1 (cohort selection)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1) Figure 1 (cohort selection); Results, page 8
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic,	a) Results, pages 9 and 12		

		clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(Demographics and Clinical Characteristics of Patients with Diagnosed and Undiagnosed CKD section); Table 1 b) Table 1 c) Results, page 12 (Time to CKD Diagnosis section)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Results, pages 8 and 9		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	a) Results, page 13; confounders for multivariate analyses given in footnotes of supplementary Figure 3 and 4 b) N/A c) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and	Results, pages 12 and 13		

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion, page 14		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pages 16 and 17 (Strengths and Limitations)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion, page 17 (Strengths and Limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, page 18 (Conclusions)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, page 17 (Strengths and Limitations)		
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	Funding, page 20		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data Availability Statement, page 19; Supplementary Appendix

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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Primary Subject Heading:	Renal medicine
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Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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ABSTRACT (298/300 words)

Objectives: REVEAL-CKD aims to estimate the prevalence of, and factors associated with, undiagnosed stage 3 chronic kidney disease (CKD).

Design: Multinational, observational study.

Setting: Data from six country-specific electronic medical records and/or insurance claims databases from five countries (France, Germany, Italy, Japan and the USA [two databases]).

Participants: Eligible participants (≥18 years old) had ≥2 consecutive estimated glomerular filtration rate (eGFR) measurements (calculated from serum creatinine values, sex and age) taken from 2015 onwards that were indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2). Undiagnosed cases lacked an International Classification of Diseases 9/10 diagnosis code for CKD (any stage) any time before, and up to 6 months after, the second qualifying eGFR measurement (study index).

Main outcome measures: The primary outcome was point prevalence of undiagnosed stage 3 CKD. Time to diagnosis was assessed using the Kaplan–Meier approach. Factors associated with lacking a CKD diagnosis and risk of diagnostic delay were assessed using logistic regression adjusted for baseline covariates.

Results: The prevalence of undiagnosed stage 3 CKD was 95.5% (19,120/20,012 patients) in France, 84.3% (22,557/26,767) in Germany, 77.0% (50,547/65,676) in Italy, 92.1% (83,693/90,902) in Japan, 61.6% (13,845/22,470) in the US Explorys LCED database and 64.3% (161,254/250,879) in the US TriNetX database. The prevalence of undiagnosed CKD increased with age. Factors associated with undiagnosed CKD were female sex (vs male, range of odds ratio across countries: 1.29–1.77), stage 3a CKD (vs 3b, 1.81–3.66), no medical history (vs a history) of diabetes (1.26–2.77) or hypertension (1.35–1.78).

Conclusions: There are substantial opportunities to improve stage 3 CKD diagnosis, particularly in female patients and older patients. The low diagnosis rates in patients with

comorbidities that put them at risk of disease progression and complications requires attention.

Trial registration: NCT04847531

STRENGTHS AND LIMITATIONS OF THIS STUDY

- REVEAL-CKD uses large, contemporary, country-specific databases to provide robust estimates of the prevalence of undiagnosed stage 3 CKD.
- The study uses a strict, consistent and internationally recognised definition of stage 3 CKD to ensure accuracy when calculating the prevalence of diagnosed/undiagnosed CKD.
- Data from the countries and databases examined may not be representative of other countries with substantially different healthcare systems or CKD screening policies.
- There is a risk of misclassification of undiagnosed CKD if diagnoses were made in environments that did not contribute to the databases used or if diagnosing physicians did not use ICD-9/10 codes appropriately.

INTRODUCTION

Chronic kidney disease (CKD) is an established global public health concern.[1] CKD has a significant effect on patients, attributable to direct mortality and morbidity, as well as elevated risk of cardiovascular diseases.[2] The global prevalence of CKD is rising,[3] owing to aging populations and increased prevalence of CKD-associated risk factors including type 2 diabetes (T2D) and hypertension.[4]

Early intervention and appropriate management of CKD is recommended in the internationally recognised Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[5] to help delay disease progression and reduce the incidence of complications. Furthermore, in 2019, KDIGO held a controversies conference on the topic of early identification and intervention in CKD. The consensus statement from this conference urged action, including the implementation of screening programs and interventions for high-risk individuals.[6] Early-stage CKD is primarily asymptomatic,[7] therefore CKD is primarily diagnosed at later disease stages and the initiation of effective interventions is delayed or missed.[5] Previous studies have demonstrated low levels of diagnosis of early-stage CKD in Italy,[8] Sweden[9] and the USA.[10-15] However, these previous studies have been limited to single countries or databases, or at-risk groups such as patients with T2D, and did not assess the prevalence of CKD diagnosis across various subgroups (eg, patients with or without comorbidities). There is a need for contemporary information on the prevalence of, and factors associated with, undiagnosed stage 3 CKD, as well as a need to understand factors associated with diagnostic delay in these patients.

REVEAL-CKD (NCT04847531) is a multinational, observational study designed to fill this evidence gap. REVEAL-CKD aims to quantify the prevalence of, and factors associated with, undiagnosed stage 3 CKD in large populations across several countries.[16] Here, we present

data on the prevalence of, and factors associated with, undiagnosed stage 3 CKD in France, Germany, Italy, Japan and the USA.

METHODS

Study design

The study design for REVEAL-CKD has been reported in detail elsewhere,[16] and is summarised below.

Existing secondary data were extracted from established, verified relevant databases containing electronic medical records and/or insurance claims in the countries of interest. Data for France were extracted from The Health Improvement Network, a large database of anonymised electronic medical records.[17] Data for Germany were extracted from the German Disease Analyzer, a database of anonymised longitudinal data on drug prescriptions, diagnoses and medical and demographic data contributed by a panel of more than 2500 physicians in Germany.[18] Data for Italy were extracted from the IQVIA Longitudinal Patient Database, a computerised network of over 900 family physicians, which includes anonymised data on patient consultations and treatments.[19] Data for Japan were extracted from Japan Real World Data, an integrated database of medical information including both electronic medical records and claims data.[20] Data for the USA were extracted from two separate databases: Explorys Linked Claims and Electronic Medical Records Data (LCED), a database of inpatient and outpatient medical records and claims data from commercially insured individuals,[21] and TriNetX, a database of integrated electronic medical records and claims data from 35 healthcare organisations, which provides clinical patient data from both inpatient and outpatient encounters.[22] The coverage of each database used is described in **Supplementary table 1**.

Patients aged ≥18 years were included in the analyses if they had at least two consecutive estimated glomerular filtration rate (eGFR) measurements that fell within the range indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2) and were recorded >90 and ≤730 days apart, taken on or after 1 January 2015. The decision to require at least two eGFR measurements with a gap of at least 90 days between each measurement was made to ensure that patients met the KDIGO definition for CKD,[5] and to avoid potential misclassification of patients based on single spurious eGFR measurements <60 mL/min/1.73 m^2. All patients had at least 12 months of continuous presence in the database before the first qualifying eGFR measurement. Full inclusion and exclusion criteria are shown in **Supplementary table 2**. eGFR was calculated from serum creatinine values, sex and age, using the CKD Epidemiology Collaboration (CKD-EPI) equation.[23] In line with current trends among physicians[24 25] and guidance from expert recommendations,[26] race modifiers were not used in the calculation of eGFR.

To account for potential delays in recording of diagnostic codes, undiagnosed CKD was defined as lacking an International Classification of Diseases (ICD) 9/10 diagnosis code corresponding to CKD (any stage), any time before and up to 6 months after index (date of second qualifying eGFR measurement). The ICD coding system varied by country depending on what was available in each database; the full list of ICD-9/10 codes used to determine diagnosed cases can be found in **Supplementary table 3**. A sensitivity analysis was performed to calculate the overall prevalence of undiagnosed stage 3 CKD using a broader definition of CKD adapted from Winkelmayer et al.[27] This sensitivity analysis included diagnostic codes for several additional manifestations of renal disease (**Supplementary table 4**).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

Overall prevalence of undiagnosed stage 3 CKD and patient demographic and clinical characteristics at index are presented descriptively. Odds ratios for factors associated with being undiagnosed any time before and up to 6 months after index were calculated using logistic regression analysis, adjusted for covariates at index. Hazard ratios for diagnostic delay among patients undiagnosed at index were calculated using Cox regression analysis, adjusted for covariates at index. The Kaplan–Meier method was used to estimate the time to diagnosis among patients undiagnosed at index. Statistical analysis was performed using Python 3.7 and R 4.0.2.

RESULTS

This analysis of patients with stage 3 CKD included 20 012 patients from France, 90 902 patients from Germany, 65 676 patients from Italy, 26 767 patients from Japan, 22 470 patients from the LCED database in the USA, and 250 879 patients from the TriNetX database in the USA (**Figure 1**). Characteristics of these patients at index are shown in **Supplementary Table 5**. At index, median age was 71–80 years, median eGFR was 49–52 mL/min/1.73 m^2, 66.9%–77.7% of patients had CKD stage 3a (eGFR ≥45 and <60 mL/min/1.73 m^2) and 22.3%–33.1% of patients had CKD stage 3b (eGFR ≥30 and <45 mL/min/1.73 m^2). The overall prevalence of urinary albumin-creatinine ratio (UACR) testing was very low and ranged from 1.8% (US, TriNetX) to 5.5% (Japan).

Overall prevalence of undiagnosed stage 3 CKD

The proportion of patients with stage 3 CKD without a diagnosis at or within 6 months after index varied by database, and was 95.5% in France, 84.3% in Germany, 77.0% in Italy, 92.1% in Japan, 61.6% in the US LCED database and 64.3% in the US TriNetX database (**Figure 2**A). In the sensitivity analysis using a broader set of ICD-9/10 codes to identify CKD diagnoses, the prevalence of undiagnosed CKD was 53.6%–89.9% (**Supplementary Table 6**). The proportion of patients with undiagnosed CKD per calendar year at index is shown in **Supplementary Figure 1**. Overall, there were no prevailing trends in the proportion of patients with undiagnosed CKD per calendar year, except in Italy, where the proportion of undiagnosed CKD tended to increase over time (68.2% undiagnosed in 2015 to 83.1% in 2020).

Demographics and clinical characteristics of patients with diagnosed and undiagnosed stage 3 CKD

Characteristics for patients with diagnosed and undiagnosed stage 3 CKD at index are presented in **Table 1**.

Table 1. Overall patient characteristics at study index according to country, by CKD diagnosis status 6 months after index

Country	France		Germany		Italy		Japan		USA			
Database	**THIN Cegedim**		**Disease Analyzer**		**LPD**		**Japan RWD**		**LCED**		**TriNetX**	
	Undiagnosed n=19 120	**Diagnosed* n=892**	**Undiagnosed n=22 557**	**Diagnosed* n=4210**	**Undiagnosed n=50 547**	**Diagnosed* n=15 129**	**Undiagnosed n=83 693**	**Diagnosed* n=7209**	**Undiagnosed n=13 845**	**Diagnosed* n=8625**	**Undiagnosed n=161 254**	**Diagnosed* n=89 625**
Age, y, median (IQR)	80 (72–86)	77 (69–84)	79 (72–84)	79 (71–84)	80 (74–85)	80 (73–85)	76 (69–83)	77 (68–83)	74 (64–82)	74 (64–82)	71 (64–79)	70 (62–78)
Age groups, y												
<45	58 (0.3)	9 (1.0)	46 (0.2)	20 (0.5)	95 (0.2)	93 (0.6)	652 (0.8)	139 (1.9)	109 (0.8)	134 (1.6)	2426 (1.5)	3097 (3.5)
45–64	1551 (8.1)	126 (14.1)	1957 (8.7)	474 (11.3)	2724 (5.4)	1056 (7.0)	12 260 (14.6)	1026 (14.2)	3754 (27.1)	2237 (25.9)	38 302 (23.8)	25 424 (28.4)
65–74	4421 (23.1)	220 (24.7)	5088 (22.6)	944 (22.4)	10 976 (21.7)	3288 (21.7)	23 696 (28.3)	1931 (26.8)	3415 (24.7)	2177 (25.2)	57 891 (35.9)	29 989 (33.5)
≥75	13 090 (68.5)	537 (60.2)	15 466 (68.6)	2772 (65.8)	36 752 (72.7)	10 692 (70.7)	47 085 (56.3)	4113 (57.1)	6567 (47.4)	4077 (47.3)	62 635 (38.8)	31 115 (34.7)
Male, n (%)	8599 (45.0)	492 (55.2)	9173 (40.7)	2043 (48.5)	19 820 (39.2)	7908 (52.3)	43 658 (52.2)	4465 (61.9)	5438 (39.3)	4613 (53.5)	57 989 (36.0)	47 123 (52.6)
eGFR, mL/min/1.73 m^2, median (IQR)	52 (46–56)	45 (38–52)	52 (45–56)	49 (40–55)	51 (44–55)	45 (38–52)	53 (47–56)	45 (37–53)	53 (47–57)	47 (40–53)	53 (47–57)	47 (40–53)
CKD stage, n (%)												
CKD stage 3a	14 661 (76.7)	440 (49.3)	16 871 (74.8)	2621 (62.3)	36 460 (72.1)	7477 (49.4)	66 955 (80.0)	3713 (51.5)	11 348 (82.0)	4972 (57.6)	131 385 (81.5)	52 233 (58.3)
CKD stage 3b	4459 (23.3)	452 (50.7)	5686 (25.2)	1589 (37.7)	14 087 (27.9)	7652 (50.6)	16 738 (20.0)	3496 (48.5)	2497 (18.0)	3653 (42.4)	29 869 (18.5)	37 392 (41.7)
Baseline UACR available, n (%)	424 (2.2)	26 (2.9)	0 (0.0)†	0 (0.0)†	4 (<0.1)‡	5 (<0.1)‡	3851 (4.6)	1141 (15.8)	474 (3.4)	425 (4.9)	2455 (1.5)	2149 (2.4)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.32 (1.08–1.65)	1.34 (1.11–1.63)	1.29 (1.06–1.55)	1.32 (1.11–1.59)	1.27 (1.06–1.53)	1.40 (1.16–1.71)	1.32 (1.09–1.63)	1.24 (1.03–1.53)	1.16 (0.96–1.45)	1.24 (1.03–1.55)	1.14 (0.93–1.42)
Missing, n	6172	342	6904	1328	13 379	4134	33 243	2062	5673	4349	88 031	50 767
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.81 (2.18–3.53)	2.87 (2.20–3.70)	2.70 (2.07–3.49)	2.74 (2.12–3.39)	2.53 (1.97–3.21)	2.77 (2.22–3.34)	2.53 (2.04–3.13)	2.46 (1.89–3.13)	2.25 (1.71–2.95)	2.43 (1.87–3.13)	2.22 (1.68–2.92)
Missing, n	6331	345	6026	1061	14 915	4560	31 643	1946	4988	3948	78 408	47 066
Comorbidities, n (%)												
Hypertension	11 737 (61.4)	675 (75.7)	10 969 (48.6)	2710 (64.4)	38 849 (76.9)	12 475 (82.5)	47 311 (56.5)	5711 (79.2)	11 863 (85.7)	8198 (95.0)	123 002 (76.3)	80 153 (89.4)
Type 2 diabetes	3311 (17.3)	221 (24.8)	5145 (22.8)	1790 (42.5)	15 785 (31.2)§	5515 (36.5)§	15 655 (18.7)	3334 (46.2)	4667 (33.7)	4621 (53.6)	49 299 (30.6)	46 142 (51.5)
Established CVD¶	1368 (7.2)	81 (9.1)	1467 (6.5)	437 (10.4)	5153 (10.2)	1784 (11.8)	23 248 (27.8)	2389 (33.1)	3337 (24.1)	2955 (34.3)	26 666 (16.5)	23 078 (25.7)
Heart failure	922 (4.8)	64 (7.2)	3318 (14.7)	1046 (24.8)	4248 (8.4)	2130 (14.1)	26 077 (31.2)	3986 (55.3)	2523 (18.2)	2791 (32.4)	22 422 (13.9)	24 580 (27.4)
Atrial fibrillation	2057 (10.8)	104 (11.7)	3351 (14.9)	866 (20.6)	8293 (16.4)	2812 (18.6)	10 765 (12.9)	1226 (17.0)	2409 (17.4)	2218 (25.7)	23 224 (14.4)	17 990 (20.1)
Medication use, n (%)												
ACE inhibitor	4363 (22.8)	271 (30.4)	8023 (35.6)	1612 (38.3)	19 141 (37.9)	5957 (39.4)	4027 (4.8)	474 (6.6)	5058 (36.5)	3725 (43.2)	33 532 (20.8)	24 274 (27.1)
ARB	6181 (32.3)	349 (39.1)	8855 (39.3)	1718 (40.8)	19 770 (39.1)	6428 (42.5)	18 959 (22.7)	2463 (34.2)	3605 (26.0)	2697 (31.3)	22 656 (14.0)	15 290 (17.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	287 (0.6)	66 (0.4)	1082 (1.3)	281 (3.9)	11 (0.1)	11 (0.1)	1171 (0.7)	978 (1.1)
GLD (any)	3300 (17.3)	189 (21.2)	6742 (29.9)	1577 (37.5)	13 108 (25.9)	4255 (28.1)	11 303 (13.5)	2128 (29.5)	5012 (36.2)	4388 (50.9)	29 690 (18.4)	30 569 (34.1)
Antiplatelets	5636 (29.5)	328 (36.8)	5451 (24.2)	1146 (27.2)	23 245 (46.0)	7906 (52.3)	16 690 (19.9)	2106 (29.2)	1274 (9.2)	1202 (13.9)	8256 (5.1)	8052 (9.0)
Loop diuretic	2747 (14.4)	177 (19.8)	8564 (38.0)	1944 (46.2)	15 719 (31.1)	6441 (42.6)	10 346 (12.4)	1633 (22.7)	2720 (19.6)	2843 (33.0)	21 136 (13.1)	22 334 (24.9)
Anticoagulants	2885 (15.1)	133 (14.9)	6838 (30.3)	1344 (31.9)	12 214 (24.2)	3983 (26.3)	12 886 (15.4)	1600 (22.2)	3434 (24.8)	2913 (33.8)	28 521 (17.7)	26 465 (29.5)

Percentages represent the proportion of diagnosed/undiagnosed patients in a specific group (eg, age) or with a specific variable (eg, medical history).

*Diagnosed cases include patients with a corresponding ICD-9/10 diagnosis code for CKD at or within 6 months of study index (date of second qualifying eGFR measurement).

†UACR testing data not available in the German Disease Analyzer database.

‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio

Patients with undiagnosed CKD tended to have slightly higher eGFR values than those with diagnosed CKD. A greater proportion of patients with stage 3a CKD were undiagnosed than patients with stage 3b CKD. There were fewer comorbidities such as hypertension, T2D and established cardiovascular disease in patients who were undiagnosed than in those who were diagnosed. Similarly, the proportion of patients taking medicines such as glucose-lowering drugs, loop diuretics, angiotensin-II converting enzyme inhibitors and angiotensin receptor blockers tended to be lower in undiagnosed patients than in those who were diagnosed. In all databases, a greater proportion of stage 3 CKD cases were undiagnosed in female patients than in male patients (**Figure 2**B). Additionally, in all databases, patients aged less than 45 years had the lowest proportion of undiagnosed CKD; the prevalence of undiagnosed CKD increased in older age groups in France, Germany, Italy and in the US TriNetX database (**Supplementary Figure 2**).

Factors associated with undiagnosed CKD

The proportion of undiagnosed CKD tended to be higher in those without comorbidities at study index versus those with such comorbidities (**Figure 3**). When adjusting for baseline covariates, female patients (vs male patients), patients with CKD stage 3a (vs 3b) and patients without a diagnosis of diabetes or hypertension (vs those with a diagnosis) were consistently more likely to lack a CKD diagnosis before and up to 6 months after index (**Supplementary Figure 3**).

Time to CKD diagnosis

Among patients who lacked a diagnosis for stage 3 CKD at or before study index, the median (interquartile range [IQR]) follow-up duration was 2.22 (1.18–3.64) years in France, 0.61 (0.27–1.03) years in Germany, 3.64 (2.08–4.88) years in Italy, 1.96 (0.84–3.41) years in Japan, 1.28 (0.53–2.34) years in the US LCED database and 1.19 (0.44–2.32) years in the US

TriNetX database. In patients undiagnosed at index, only a small proportion received a diagnosis during follow-up: 686/19 293 patients (3.6%) in France, 1157/23 302 patients (5.0%) in Germany, 8152/52 533 patients (15.5%) in Italy, 3855/84 603 patients (4.6%) in Japan, 3987/15 376 patients (25.9%) in the US LCED database and 44 007/178 410 patients (24.7%) in the US TriNetX database.

Among patients undiagnosed at index, diagnoses tended to accrue slowly over the whole duration of follow-up (**Figure 4**). The proportion of patients with initial eGFR values indicative of stage 3b CKD (≥30 and <45 mL/min/1.73 m^2) who received a diagnosis during follow-up was consistently higher than patients with initial eGFR values indicative of stage 3a CKD (≥45 and <60 mL/min/1.73 m^2; **Figure 4**).

Among all patients undiagnosed at index (regardless of whether they received a diagnosis during follow-up), median time to diagnosis was only calculable using the Kaplan–Meier method for the US TriNetX database, because more than half of the patients in the other databases remained undiagnosed at the end of the study period. In this database, the overall median (IQR) time to diagnosis was 4.75 (4.68–4.82) years.

After adjusting for selected baseline covariates, in all countries, female patients (vs male patients) and patients with stage 3a CKD at index (vs 3b) were more likely to be diagnosed later during follow-up (**Supplementary Figure 4**). Although less pronounced, patients without a history of comorbidities such as diabetes, heart failure or hypertension had a slightly elevated likelihood of delayed diagnosis (vs patients with a history of these conditions). Older patients also typically had a greater likelihood of delayed diagnosis than patients aged less than 45 years.

DISCUSSION

REVEAL-CKD is a large, multinational, observational study that uses a consistent, strict definition for undiagnosed CKD based on internationally recognised guidelines. By extracting data from contemporary, country-specific databases, the study provides a robust estimate of the prevalence of undiagnosed CKD in countries across the globe. The results from this analysis of six databases from five countries (France, Germany, Italy, Japan and the USA) demonstrate severe shortcomings in the diagnosis of stage 3 CKD. Although there was some variability among countries, the consistently high proportions of undiagnosed stage 3 CKD despite clinical evidence of the disease are highly concerning, as are the low levels of UACR testing. Of note, except in Japan, the prevalence of UACR testing did not appear to be substantially higher even in patients with a diagnosis of stage 3 CKD. UACR testing, however, is necessary for assessing the risk of future progression to kidney failure.[28] Missing opportunities for early diagnosis, prognostic assessment and management leaves patients at greater risk of further disease progression and complications, including end-stage renal disease and cardiovascular events.[6 29-31] Early interventions in CKD have been shown to improve outcomes by slowing CKD progression and reducing cardiovascular risk,[6 32] and healthcare costs associated with the disease increase substantially as CKD stage advances.[33] It is therefore vital for clinicians to seize the opportunity to diagnose and manage the condition as early as possible to minimise the impact of the disease, both in terms of financial burden and effects on health-related quality of life.

It is reassuring that the patients who have comorbidities that are established risk factors for CKD, such as hypertension and T2D, had higher rates of diagnosis and tended to be diagnosed sooner than patients without these conditions. However, even in patients with these comorbidities, the prevalence of undiagnosed CKD remained high. In the US databases,

which had the lowest rates of undiagnosed CKD, approximately 50% of patients with comorbidities in addition to CKD still lacked a CKD diagnosis. Alarmingly, this was the case for patients with hypertension, T2D and established cardiovascular disease: groups in which KDIGO recommends screening for CKD,[6] owing to their elevated risks of CKD progression and associated complications.[34-36] Without an appropriate CKD diagnosis, opportunities may also be missed to prescribe newer therapies such as sodium-glucose cotransporter-2 inhibitors which have been shown to improve cardiorenal outcomes in patients with CKD.[37 38]

We observed that the prevalence of undiagnosed CKD tended to rise with age, and older patients tended to have a higher risk of increased diagnostic delay than younger patients. In elderly patients, physicians may assume that eGFR values indicative of stage 3 CKD are caused by age-related decline of kidney function.[39 40] However, large population-based studies indicate that even in older adults at lower risk for kidney failure, stage 3 CKD is associated with an elevated risk of mortality, cardiovascular events and acute kidney injury.[41] Accordingly, KDIGO guidelines support the use of a single threshold value to define CKD across age subgroups consistent with criteria for other chronic non-communicable diseases.[5] In elderly patients, the effects of late-stage CKD are likely to have a substantial influence on physical and cognitive abilities, medication safety and cardiovascular prognosis.[2 6 41] It is therefore important that physicians do not underestimate the burden and effects of CKD in elderly patients and initiate guideline-appropriate management in a timely manner. Existing clinical tools (such as confirmatory cystatin C testing in suspected cases of CKD) can help mitigate the risk of overdiagnosis, although these remain underutilised.[6] CKD management in elderly patients should be adapted taking into consideration factors such as their age, frailty, comedications and comorbidities.

In line with previous studies that suggest CKD is more prevalent in women than in men,[42 43] the proportion of female patients with stage 3 CKD was higher than in male patients in all countries except Japan. Despite the higher prevalence of CKD in female patients, after adjusting for potential confounding factors, female patients had a higher likelihood of being undiagnosed than male patients in all countries. It has been suggested that the rate of progression of CKD is slower in women than in men,[44-47] and physicians may therefore be less likely to diagnose the condition at early stages in women. However, the inequality demonstrated in this study is substantial, and suggests a need for elevated awareness to minimise this gender disparity.

REVEAL-CKD used the internationally recognised CKD-EPI equation to calculate eGFR values from available serum creatinine measurements.[23] Multiple consecutive eGFR measurements indicative of stage 3 CKD were required to confirm the presence of chronic kidney disease, in line with KDIGO recommendations suggesting a threshold of >90 days to consider the condition to be chronic.[5] Estimates of the prevalence of undiagnosed stage 3 CKD based on a single measurement are likely to be higher, owing to the potential for the inclusion of patients with isolated eGFR measurements within the threshold for stage 3 CKD (as a result of, for example, transient dehydration or acute kidney injury). When calculating eGFR, race was not included as a modifier in line with recent trends among physicians[24 25] and guidance from expert recommendations.[26] Inclusion of the race modifier may have been expected to inflate eGFR in Black patients. Indeed, in a sensitivity analysis performed on the US TriNetX database which included data on race (**Supplementary Table 7**), we saw that a substantial proportion of Black patients (46.1%, corresponding to 9.2% of the overall TriNetX cohort) were reclassified as having stage 2 CKD (eGFR between 60–89 mL/min/1.73 m^2) when the race modifier was included in the calculation of eGFR. The inclusion of this modifier may therefore allow CKD to progress further in Black patients

before they receive appropriate diagnosis and intervention. The decision to use the CKD-EPI equation without race was made in part to facilitate comparisons among countries and databases in which race was not available, and also to provide a consistent method of calculating eGFR for measurements taken across a time period where the inclusion of the race modifier was being actively debated.[48-52]

Some limitations must be kept in mind when interpreting these data. Results from the included countries may not be generalisable to other countries, which could have significantly different diagnostic coding practices, healthcare systems and screening policies; conclusions regarding the observed differences between countries cannot be drawn for similar reasons. The TriNetX and LCED databases contained a high proportion of commercially insured patients, and therefore may not be representative of the overall US population. Furthermore, data licensing issues prevented the pooling of data from multiple databases to provide an overall estimate of the prevalence of undiagnosed CKD. Although serum creatinine is typically included in standard laboratory blood tests, patients who did not require blood tests will be missing from this analysis. As such, there may be a degree of selection bias present in these results toward patients who are being routinely monitored for other conditions, or who are actively seeking healthcare. Confirmatory UACR testing was not necessary to meet the study definition of stage 3 CKD owing to the extremely low levels of UACR testing in most of the cohorts. For the same reason, UACR testing was not included in the multivariate analyses which assessed factors associated with a lack of CKD diagnosis and factors associated with time to CKD diagnosis. The proportion of inpatient versus outpatient encounters was unavailable for many of the databases used, and therefore comparisons between diagnoses in these two settings could not be made. Because many of the databases used did not include data on race, variability in the prevalence of undiagnosed CKD according to race could not be assessed. Because data were collected from between 2015 and

2020, physicians may have still been using the race modifier for Black patients. Therefore, some Black patients may have been classified as having stage 2 CKD and have been less likely to receive a diagnosis as a result. It is important to note that this study focused on underdiagnosis for stage 3 CKD; low levels of UACR testing in all countries studied suggest that the prevalence of undiagnosed stage 1 and 2 CKD may be even higher. Lastly, there is a risk of misclassification if CKD diagnoses were made in clinical settings that do not contribute to the databases, or if patients had CKD that was recognised by their healthcare providers but was not recorded with an appropriate ICD-9/10 code in the databases. Although a lack of such codes may not always indicate that a patient's CKD is undiagnosed, this definition of CKD diagnosis has been validated by previous real-world studies,[8 11 12 27] and provides an appropriate surrogate measure for rates of diagnosis in large epidemiological studies such as REVEAL-CKD.

In conclusion, this analysis of six large, secondary databases from five countries demonstrates that most cases of stage 3 CKD are not diagnosed in a timely manner despite clinical evidence of the disease. Furthermore, although patients with existing risk factors for, or complications from, CKD were typically more likely to receive a CKD diagnosis, the prevalence of undiagnosed CKD in these patients remained alarmingly high. Clear opportunities exist for improved diagnosis of stage 3 CKD, particularly in female patients, elderly patients and patients at high risk of CKD progression and complications. Future research will help to quantify the impact of early diagnosis and initiation of effective therapies on the risk of CKD progression, complications and long-term patient outcomes.

Contributors

NT, SB, EJP, EW, HC, KJ and PK were responsible for the study concept and design. EJP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MA, EJP and HC developed and conducted the statistical analysis plan. NT, TM, MPS, JBJV, LDN, MA, SB, EJP, EW, HC, KJ and PK were involved in review and editing of manuscript drafts, as well as critical revision of the content during its development. All authors approved the final version of the manuscript before its submission. The corresponding author (NT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Data used in this study were obtained from a third party and may not be publicly available. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Competing interests

SB, EJP, HC, KJ and EW are employees of AstraZeneca and hold stock options. MA is an employee of AstraZeneca. NT has received grants from AstraZeneca, Boehringer

Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd and Tricida, Inc, has received honoraria from AstraZeneca, Boehringer Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd and Tricida, Inc and holds stock options from Mesentech, Inc, Rénibus Therapeutics, Inc, pulseData and Tricida, Inc. MPS has received advisory board fees and honoraria from AstraZeneca, Bayer AG, Vifor Pharma Group and Boehringer Ingelheim/Eli Lilly and Company. LDN has received fees for scientific consultation and/or lectures by Astellas Pharma Inc, AstraZeneca, Mundipharma GmbH and Vifor Pharma Group. PK has received speaker's bureau and advisory board fees from AstraZeneca, Eli Lilly and Company and Novo Nordisk A/S, speaker's fees from Bayer AG and honoraria from AstraZeneca and Eli Lilly and Company. TM and JBV have no conflicts of interest to disclose.

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REVEAL-CKD is funded by AstraZeneca (grant number N/A). It is a non-interventional observational study, and as such, no drugs are supplied or funded. AstraZeneca designed the REVEAL-CKD study with input and guidance from the external authors. AstraZeneca provided funding for data collection, management and analysis. An AstraZeneca team reviewed this manuscript for scientific accuracy during its development and was allowed to make suggestions. However, the final content, analysis and interpretation of the data was determined by the authors. The decision to submit the data for publication was determined by the authors.

Ethics Approval

REVEAL-CKD used de-identified data from existing databases and did not require data collection beyond that of routine clinical care. No identifiable information was collected or examined as part of the study. All externally conducted analyses were completed in line with

local ethics regulations/legislation. De-identified, internally licensed databases were shared with AstraZeneca by the licensee; therefore, ethics review and approval was not required for the use of these databases for this study.

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Figure Legends

Figure 1. Cohort selection

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Figure 2. Overall prevalence of undiagnosed stage 3 CKD according to country and database

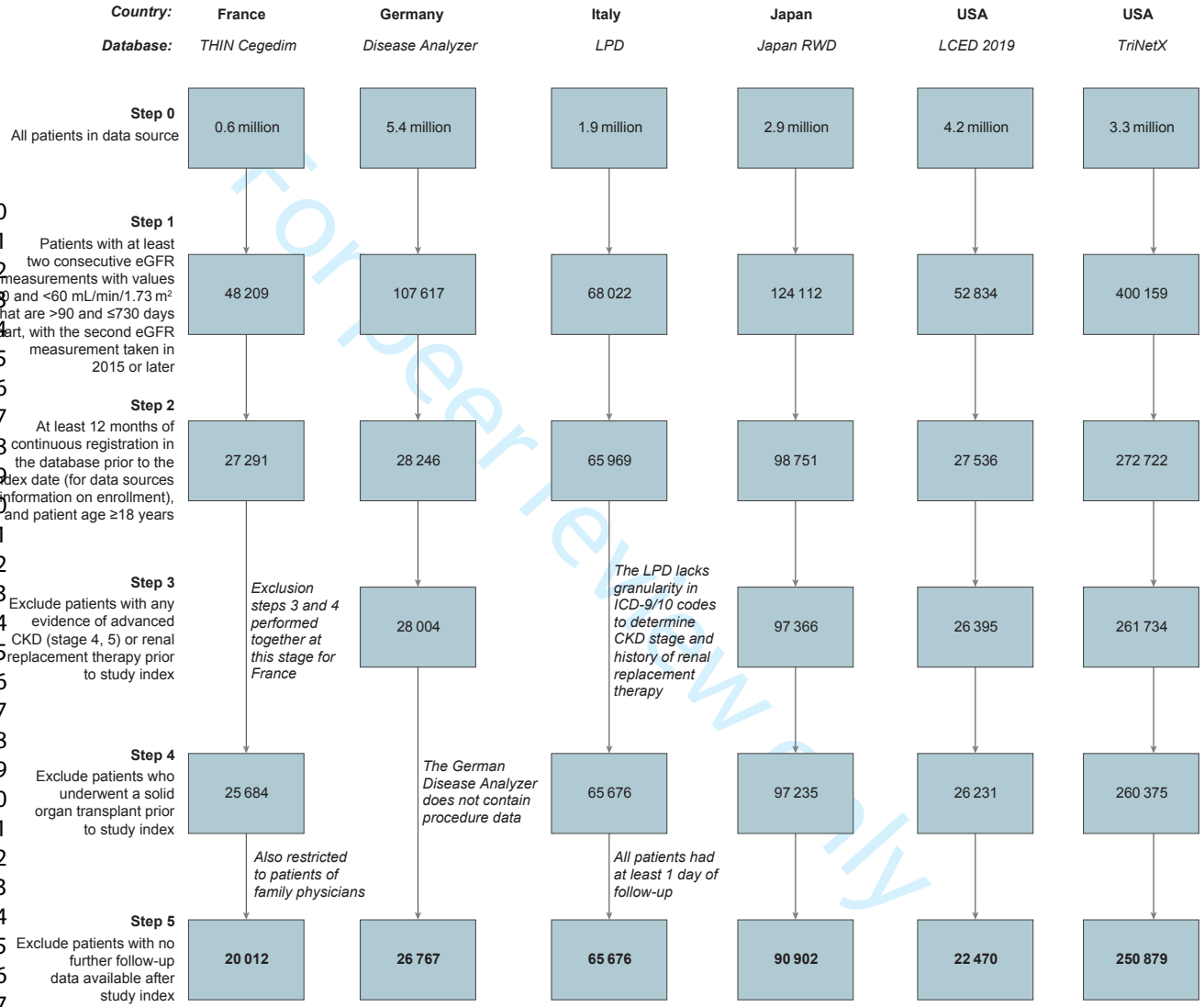
Undiagnosed cases are those which lack a diagnosis code for CKD (any stage), any time before and up to 6 months after study index.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

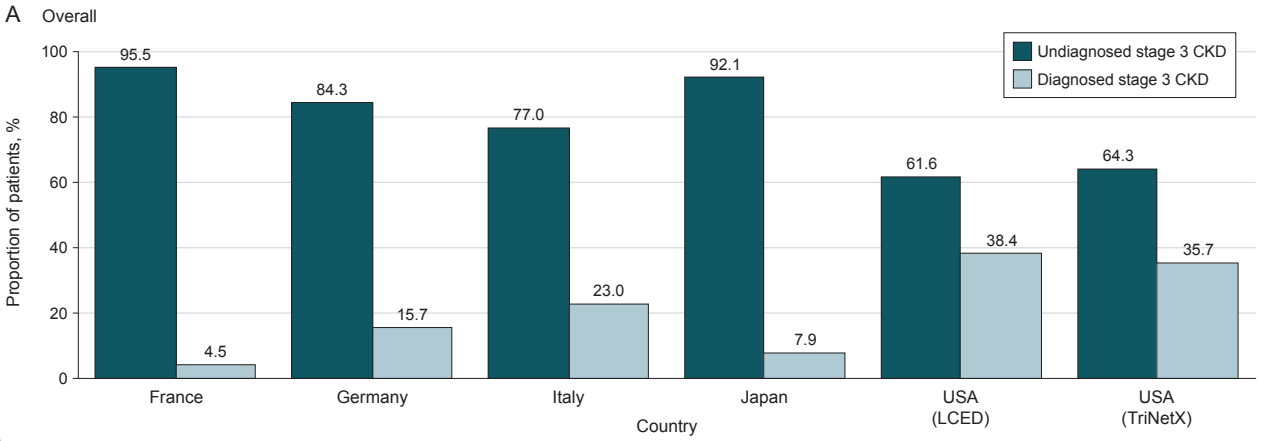
Figure 3. Prevalence of undiagnosed stage 3 CKD according to the presence of comorbidities at study index, by country and database

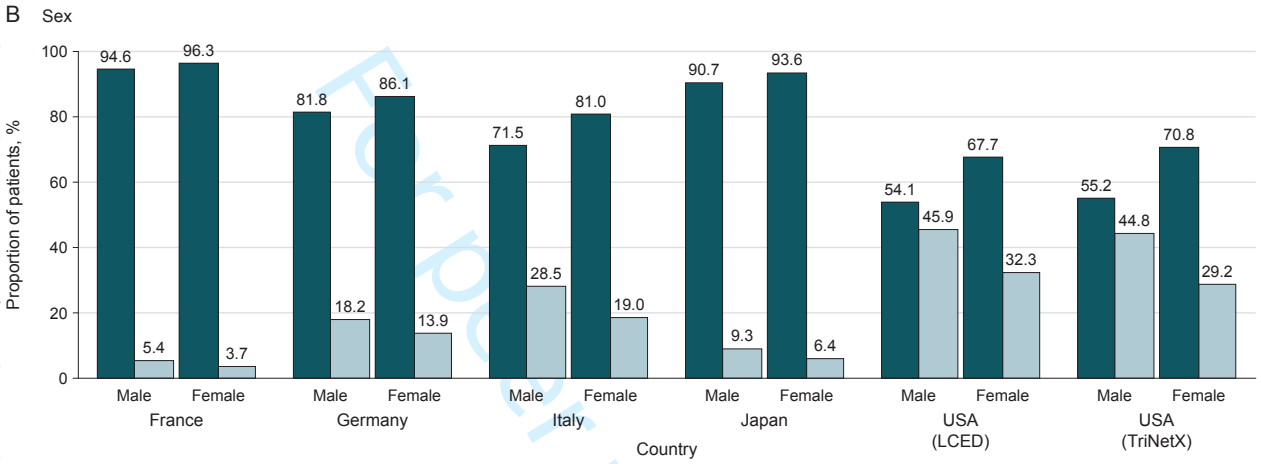
Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention. Study index is defined as the date of a patient's second qualifying eGFR measurement.
*Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
†Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data.

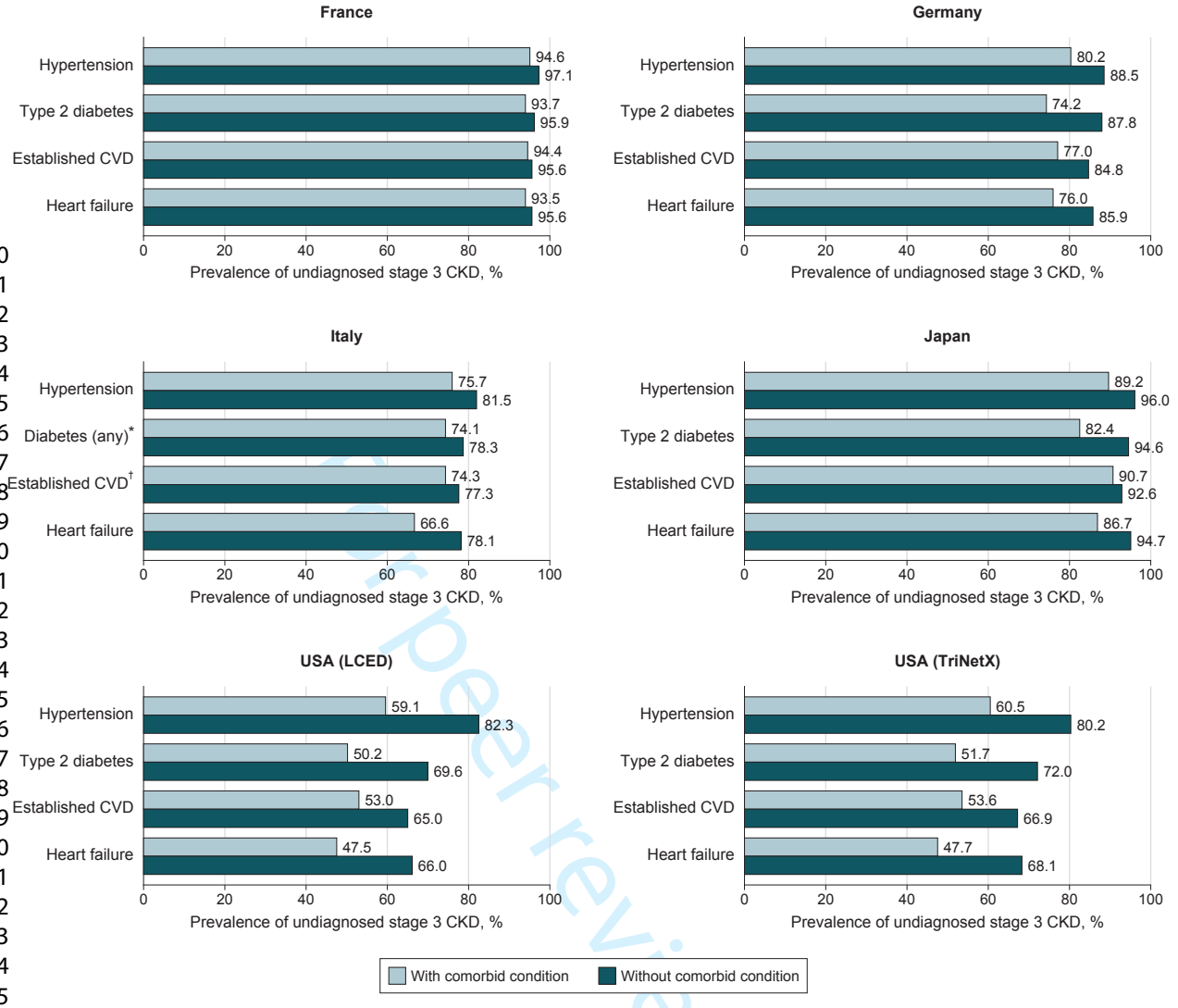
Figure 4. Kaplan–Meier estimates of time to CKD diagnosis according to country and database in patients undiagnosed at index, overall and by CKD stage (3a/3b)

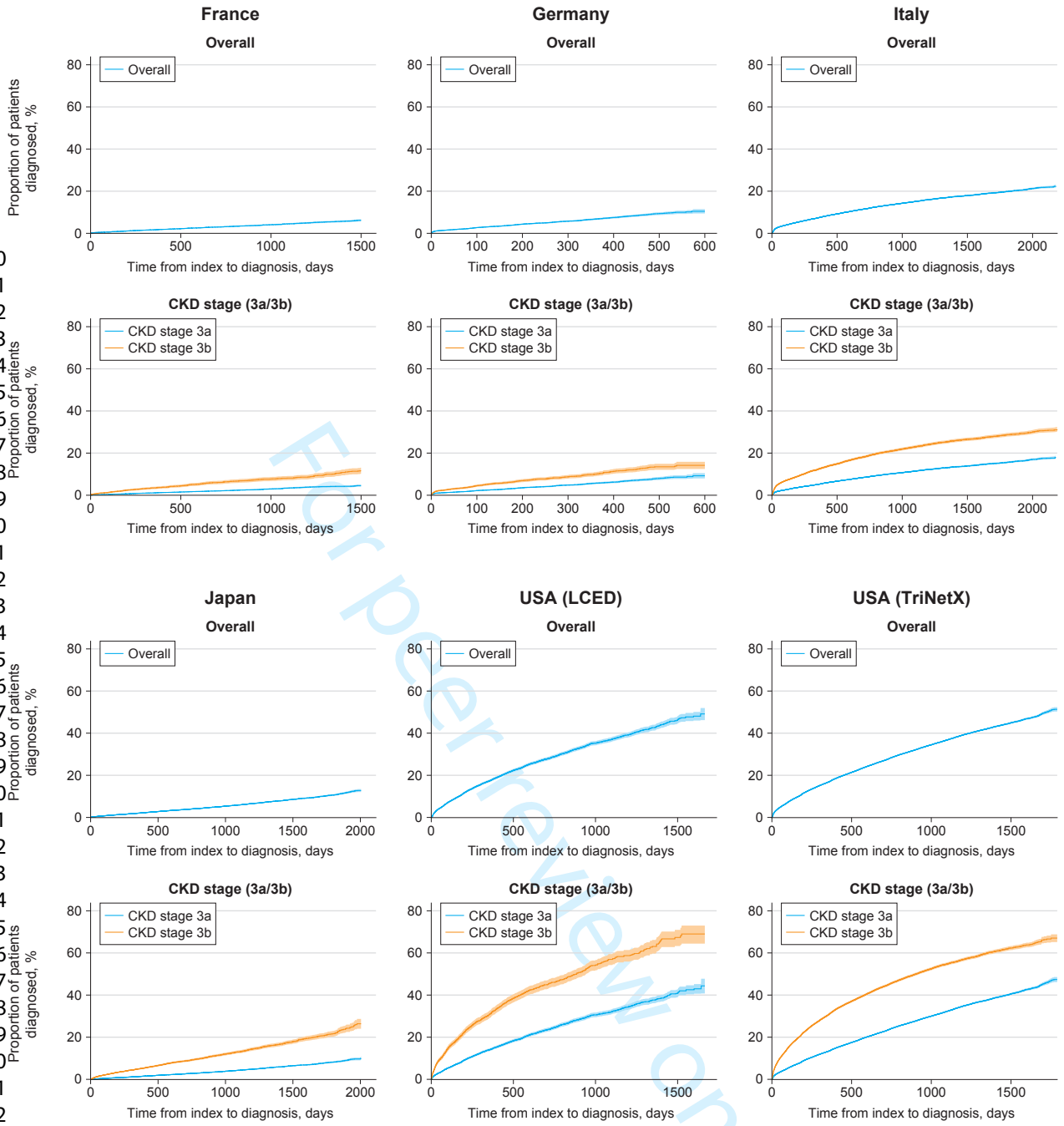
Shaded areas represent 95% confidence intervals.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.











SUPPLEMENTARY MATERIALS

Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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Supplementary Table 1. Data sources used in the REVEAL-CKD study.

Country	Data source(s)	Database type (EMR/claims)	Coverage
France	THIN: The Health Improvement Network/Cegedim Health Data	EMR	Primary care
Germany	IQVIA Disease Analyzer	EMR	Primary care/endocrinology
Japan	Japan RWD	EMR and claims	Inpatient/outpatient
USA	TriNetX	EMR and claims	Inpatient/outpatient
	LCED	EMR and claims	Inpatient/outpatient
Italy	The Health Search Database/IQVIA Health Solutions Italy	EMR	Primary care

EMR, electronic medical records; LCED, Explorys Linked Claims and Electronic Medical Records Data; RWD, Real World Data.

Supplementary table 2. REVEAL-CKD study inclusion and exclusion criteria

Inclusion criteria:
• ≥2 consecutive eGFR laboratory measurements recorded in 2015 or later, with values ≥30 and <60 mL/min/1.73 m^2 (stage 3a/3b CKD using the CKD-EPI[1] equation) that are >90 and ≤730 days apart • ≥12 months of continuous presence in the database before the first qualifying eGFR measurement (look-back period) • Age ≥18 years at the index date (defined as the date of the second qualifying laboratory eGFR measurement indicative of stage 3a/3b CKD).
Exclusion criteria:
• Solid organ transplant recorded before the index date • Any evidence of advanced CKD (stages 4, 5, and end-stage renal disease) based on CKD diagnosis codes or renal replacement therapy before the index date.

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary table 3. ICD-9/10 codes used to identify patients with diagnosed stage 3 CKD

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD 10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 4. ICD-9/10 codes used to identify CKD in the sensitivity analysis using a broader definition for CKD adapted from Winkelmayer et al., 2005[2]

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Chronic renal insufficiency	582, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9	N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N19, N26.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359,

Description	ICD-9*	ICD-10†
		M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39
Acute renal failure	572.4, 580, 580.4, 580.81, 580.89, 580.9, 584.5, 584.6, 584.7, 584.8, 584.9, 791.2, 791.3	K76.7, N00.3, N00.8, N00.9, N01.3, N17.0, N17.1, N17.2, N17.8, N17.9, R82.1, R82.3
Miscellaneous	274.1, 440.1, 442.1, 453.3, 581, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 586, 587, 593, 593.1, 593.2, 593.3, 593.4, 593.5, 593.6, 593.7, 593.71, 593.72, 593.73, 593.81, 593.82, 593.89, 593.9, 753, 753.3, 866, 866.01, 866.1, 866.11, 866.12, 866.13	I70.1, I72.2, I82.3, N02.2, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N08, N13.4, N13.5, N13.70, N13.71, N13.721, N13.722, N13.729, N13.731, N13.732, N13.739, N13.8, N28.1, N28.81, N28.82, N28.83, N28.89, N28.9, Q60.2, Q60.5, Q63.0, Q63.1, Q63.2, Q63.3, Q63.8, Q63.9, R80.2, S31.001, S37.009, S37.019, S37.029, S37.039, S37.049, S37.059, S37.069

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD-10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 5. Overall patient characteristics at study index (date of second eGFR measurement) according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
CKD status*, n (%)						
Diagnosed	892 (4.5)	4210 (15.7)	15 129 (23.0)	7209 (7.9)	8625 (38.4)	89 625 (35.7)
Undiagnosed	19 120 (95.5)	22 557 (84.3)	50 547 (77.0)	83 693 (92.1)	13 845 (61.6)	161 254 (64.3)
Age, y, median (IQR)	80 (72–86)	79 (72–84)	80 (74–85)	76 (69–83)	74 (64–82)	71 (64–78)
Age groups, y						
<45	67 (0.3)	66 (0.2)	188 (0.3)	791 (0.9)	243 (1.1)	5523 (2.2)
45–64	1677 (8.4)	2431 (9.1)	3780 (5.8)	13 286 (14.6)	5991 (26.7)	63 726 (25.4)
65–74	4641 (23.2)	6032 (22.5)	14 264 (21.7)	25 627 (28.2)	5592 (24.9)	87 880 (35.0)
≥75	13 627 (68.1)	18 238 (68.1)	47 444 (72.2)	51 198 (56.3)	10 644 (47.4)	93 750 (37.4)
Male, n (%)	9091 (45.4)	11 216 (41.9)	27 728 (42.2)	48 123 (52.9)	10 051 (44.7)	105 112 (41.9)
eGFR, mL/min/1.73 m², median (IQR)	52 (45–56)	52 (44–56)	49 (42–55)	52 (46–56)	51 (44–56)	51 (44–56)
CKD stage, n (%)						
CKD stage 3a	15 101 (75.5)	19 492 (72.8)	43 937 (66.9)	70 668 (77.7)	16 320 (72.6)	183 618 (73.2)
CKD stage 3b	4911 (24.5)	7275 (27.2)	21 739 (33.1)	20 234 (22.3)	6150 (27.4)	67 261 (26.8)
Baseline UACR available, n (%)	450 (2.2)	0 (0.0)†	9 (<0.1)‡	4992 (5.5)	899 (4.0)	4604 (1.8)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.34 (1.10–1.63)	1.32 (1.09–1.58)	1.40 (1.14–1.71)	1.22 (0.98–1.50)	1.22 (0.98–1.50)
Missing, n	6514	8232	17 513	35 305	10 022	138 798
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.84 (2.17–3.65)	2.69 (2.07–3.36)	2.74 (2.30–3.31)	2.38 (1.84–3.05)	2.38 (1.81–3.05)
Missing, n	6676	7087	19 475	33 589	8936	125 474
Comorbidities, n (%)						
Hypertension	12 412 (62.0)	13 679 (51.1)	51 324 (78.1)	53 022 (58.3)	20 061 (89.3)	203 155 (81.0)
Type 2 diabetes	3532 (17.6)	6935 (25.9)	21 300 (32.4)§	18 989 (20.9)	9288 (41.3)	95 441 (38.0)
Established CVD¶	1449 (7.2)	1904 (7.1)	6937 (10.6)	25 637 (28.2)	6292 (28.0)	49 744 (19.8)
Heart failure	986 (4.9)	4364 (16.3)	6378 (9.7)	30 063 (33.1)	5314 (23.6)	47 002 (18.7)
Atrial fibrillation	2161 (10.8)	4217 (15.8)	11 105 (16.9)	11 991 (13.2)	4627 (20.6)	41 214 (16.4)
Medication use, n (%)						
ACE inhibitor	4634 (23.2)	9635 (36.0)	25 098 (38.2)	4501 (5.0)	8783 (39.1)	57 806 (23.0)
ARB	6530 (32.6)	10 573 (39.5)	26 198 (39.9)	21 422 (23.6)	6302 (28.0)	37 946 (15.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	353 (0.5)	1363 (1.5)	22 (0.1)	2149 (0.9)
GLD (any)	3489 (17.4)	8319 (31.1)	17 363 (26.4)	13 431 (14.8)	9400 (41.8)	60 259 (24.0)
Antiplatelets	5964 (29.8)	6597 (24.6)	31 151 (47.4)	18 796 (20.7)	2476 (11.0)	16 308 (6.5)
Loop diuretic	2924 (14.6)	10 508 (39.3)	22 160 (33.7)	11 979 (13.2)	5563 (24.8)	43 470 (17.3)

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
Anticoagulants	3018 (15.1)	8182 (30.6)	16 197 (24.7)	14 486 (15.9)	6347 (28.2)	54 986 (21.9)

Unless otherwise stated, percentages represent the proportion of patients in a specific group (eg, age) or with a specific variable (eg, medical history).
*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.
†UACR testing data not available in the German Disease Analyzer database.
‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio.

Supplementary table 6. Sensitivity analysis of undiagnosed stage 3 CKD using a broader CKD definition adapted from Winkelmayer et al., 2005 [2] according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
CKD status*, n (%)						
Diagnosed	2031 (10.1)	6165 (23.0)	21 146 (32.2)	12 113 (13.3)	10 421 (46.4)	109 735 (43.7)
Undiagnosed	17 981 (89.9)	20 602 (77.0)	44 530 (67.8)	78 789 (86.7)	12 049 (53.6)	141 144 (56.3)

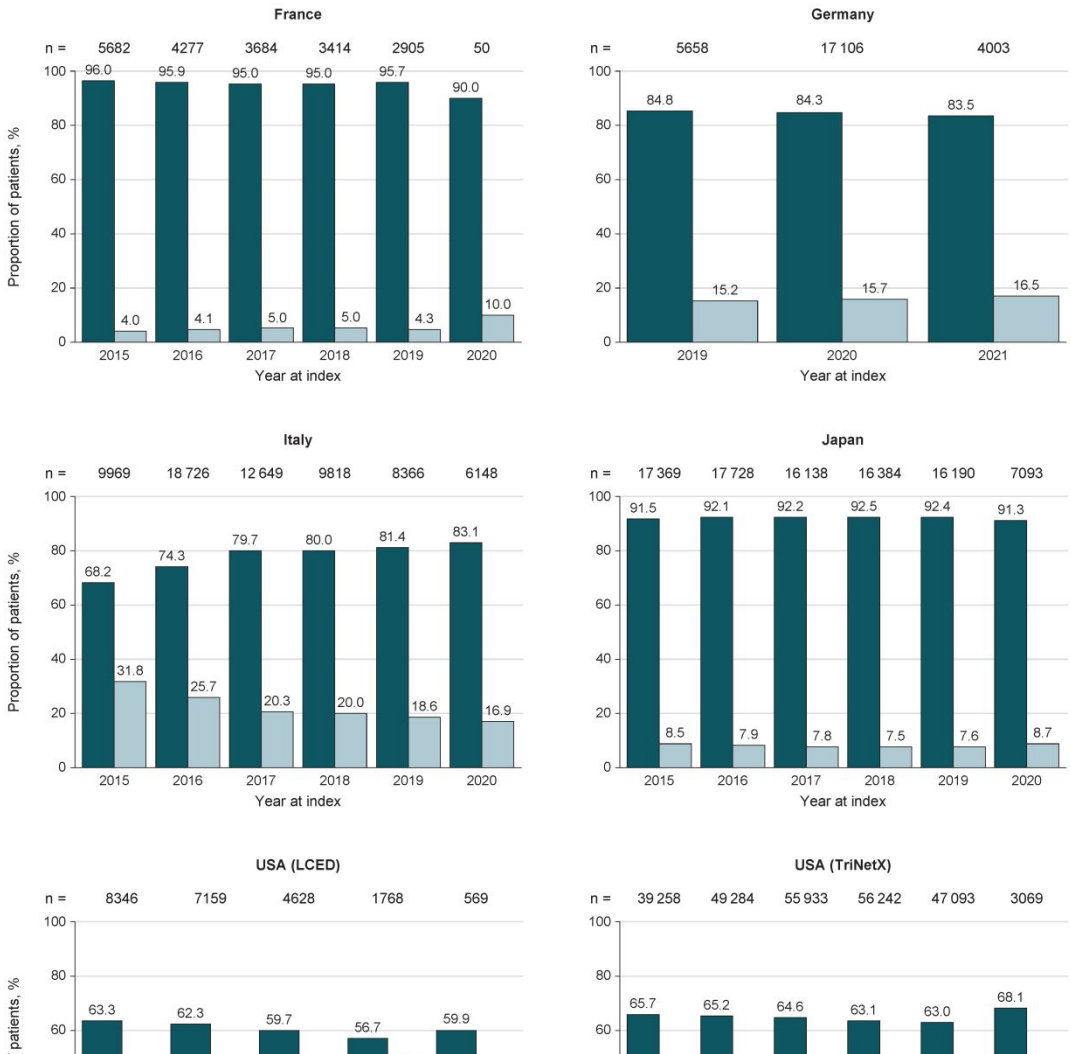
*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Supplementary table 7. Comparison of CKD stages in Black and non-Black patients from the US TriNetX database when calculating eGFR using two different equations: CKD-EPI (without adjusting for race) and CKD-EPI (with race modifier)[1]

	CKD-EPI, no race modifier	CKD-EPI, with race modifier
Black (n=50 283)		
Stage 2 CKD, n (%)	0 (0.0)	23 156 (46.1)
Stage 3a CKD, n (%)	36 005 (71.6)	20 455 (40.7)
Stage 3b CKD, n (%)	14 278 (28.4)	6672 (13.3)
Non-Black (n=200 596)		
Stage 2 CKD, n (%)	0 (0.0)	0 (0.0)
Stage 3a CKD, n (%)	147 613 (73.6)	147 613 (73.6)
Stage 3b CKD, n (%)	52 983 (26.4)	52 983 (26.4)

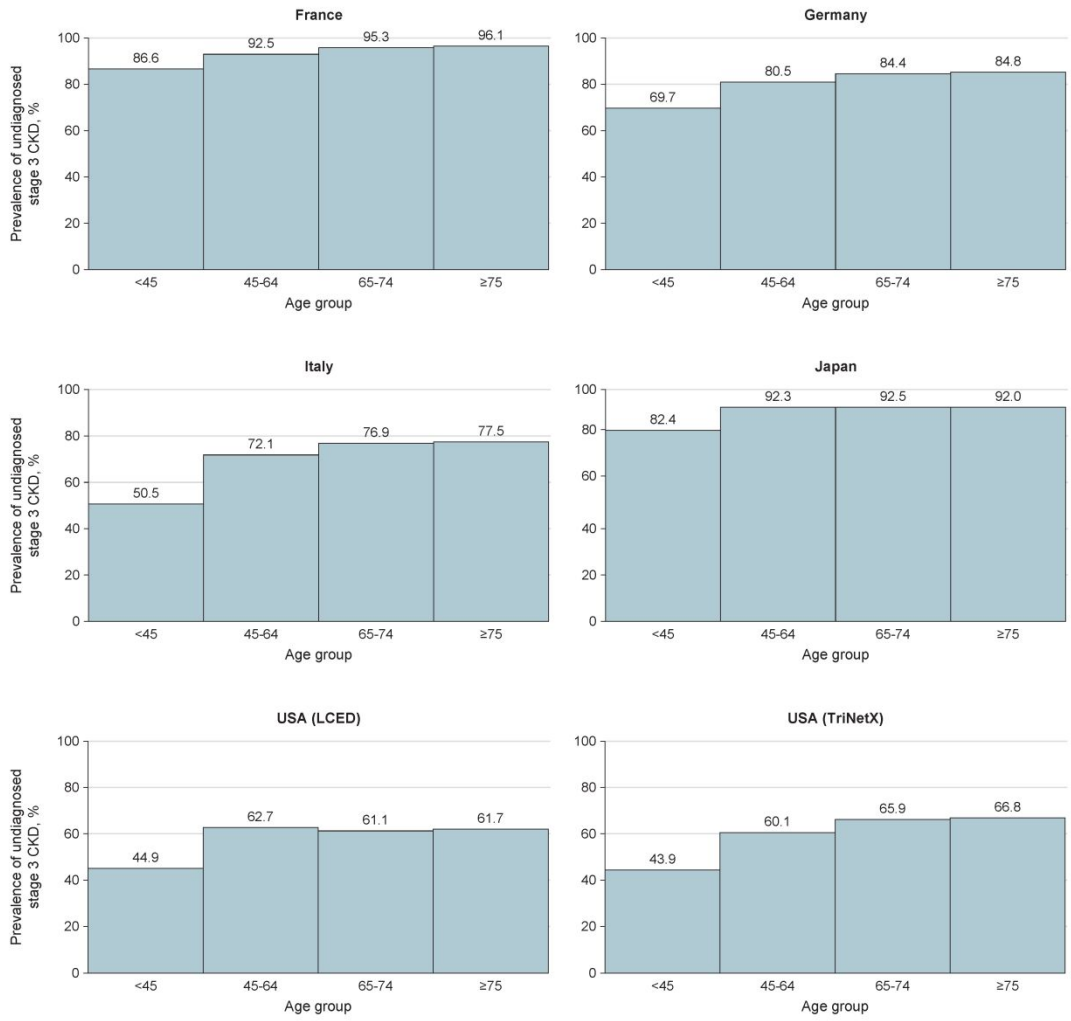
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary figure 1. Prevalence of undiagnosed stage 3 CKD according to calendar year of study index according to country and database



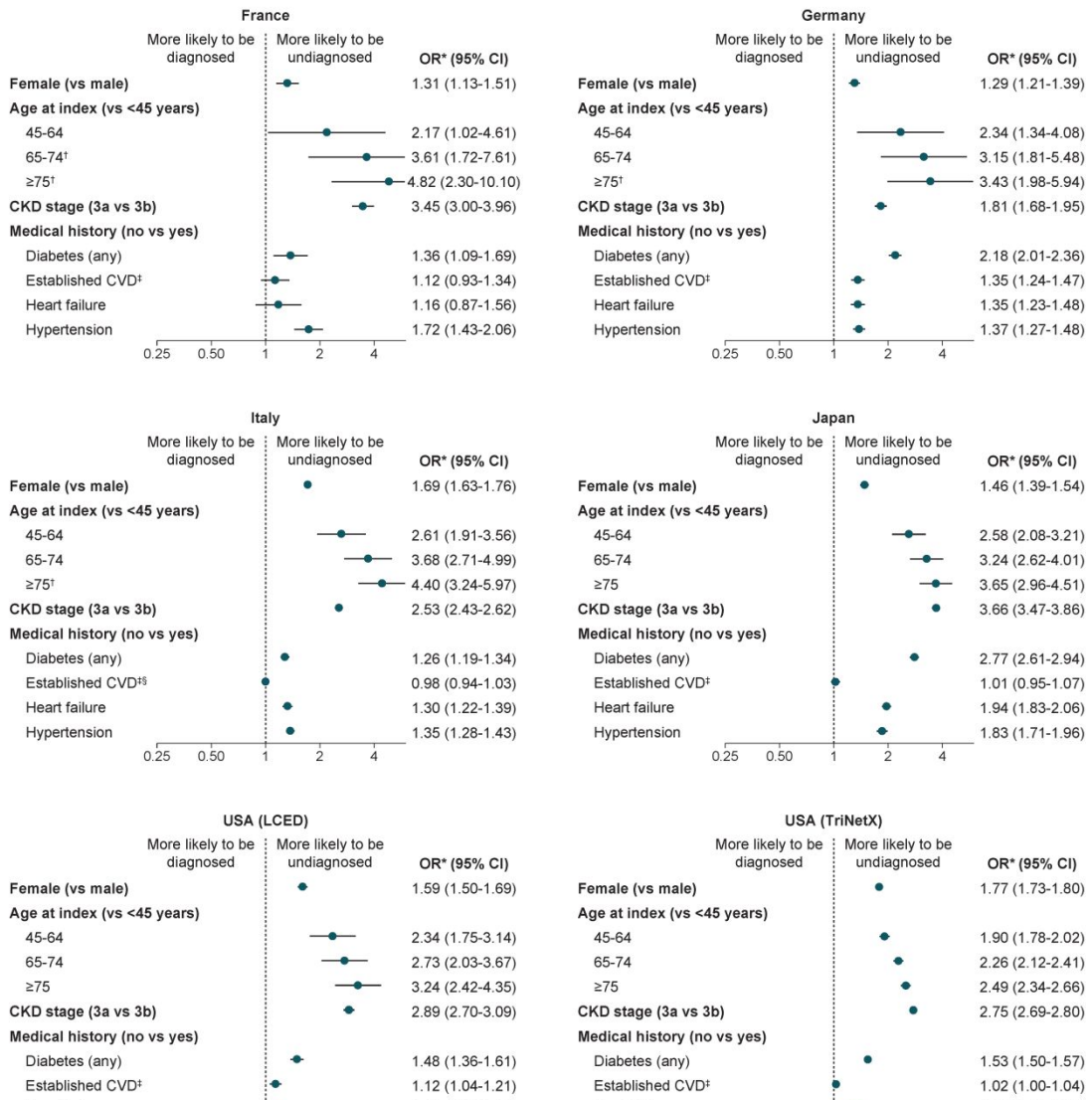
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 2. Prevalence of undiagnosed stage 3 CKD according to age group at study index according to country and database



CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 3. Factors associated with a lack of CKD diagnosis any time before or up to 6 months after index date according to country and database



Whiskers represent 95% confidence intervals.

*Odds ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors, and other glucose-lowering drugs).

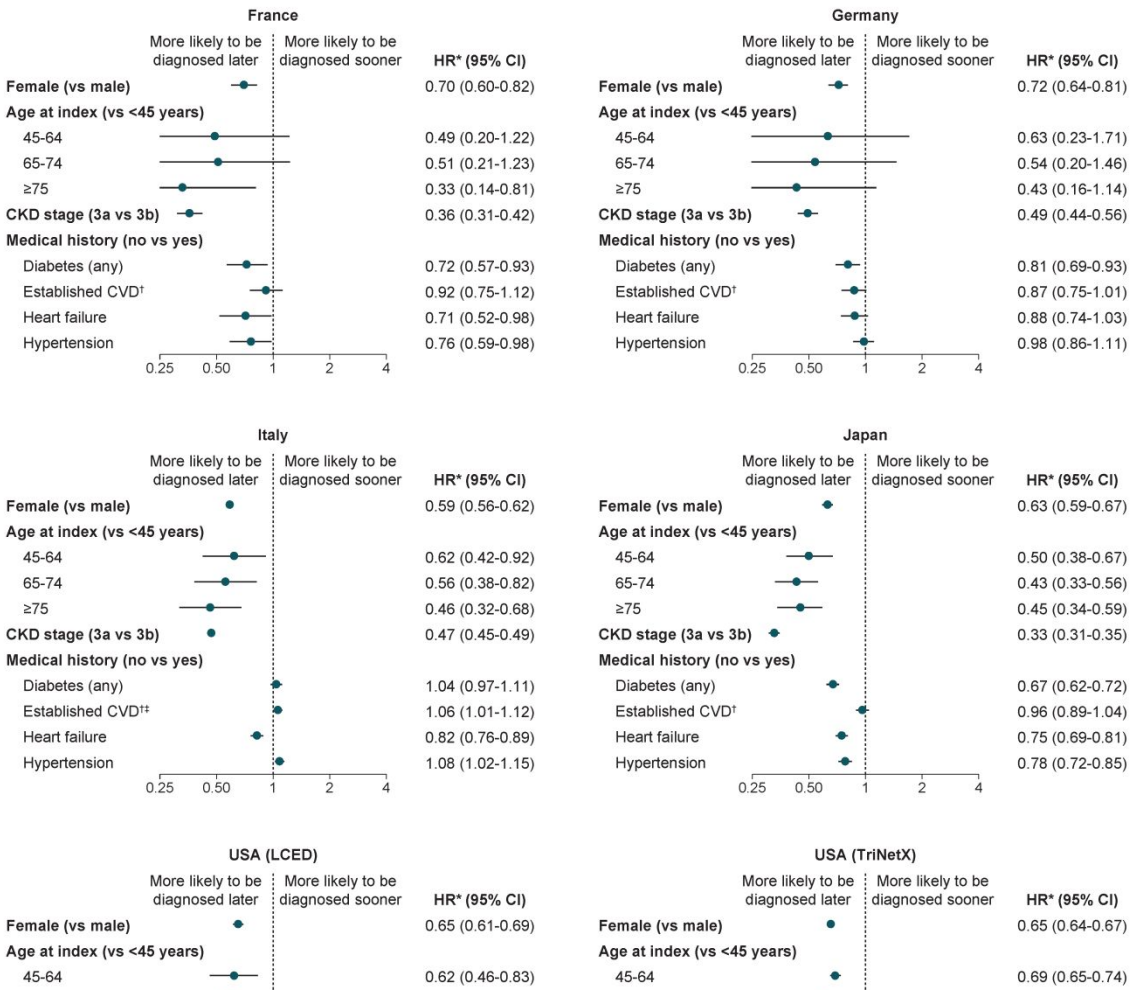
†Upper 95% confidence interval extends beyond the boundary of the graph.

‡Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.

§Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.

CKD, chronic kidney disease; CVD, cardiovascular disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 4. Factors associated with time to CKD diagnosis in patients undiagnosed at index according to country and database



Whiskers represent 95% confidence intervals.

[a]Hazard ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors and other glucose-lowering drugs).

[b]Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.

[c]Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.

CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; LCED, Explorys Linked Claims and Electronic Medical Records Data.

References

1. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12. doi: 10.7326/0003-4819-150-9-200905050-00006
2. Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis.* 2005;46(2):225–32. doi: 10.1053/j.ajkd.2005.04.029

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Title, page 1, and abstract, page 3 [Design section] b) Abstract, page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) Abstract, page 3 (Setting section) 1.2) Abstract, page 3 (Setting and Participants sections) 1.3) N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Materials and Methods, page 6 (Study Design)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Materials and Methods, page 6 (Study Design)		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	A) Eligibility criteria, follow-up duration and data sources described in Materials and Methods, page 6 and 7 (Study Design)	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1) Materials and Methods, page 7 (Study Design) with full lists of ICD9/10 codes used to identify diagnosed/undiagnosed cases given in Supplementary Materials 6.2) N/A (eligible patients were identified based on eGFR which was calculated from serum creatinine as described in Materials and Methods and according to internationally-recognized equations for eGFR calculations) 6.3) N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Materials and Methods, page 7 (Study Design section)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1) Full list of ICD9/10 codes used in Supplementary Tables 2 and 3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Materials and Methods, page 6 (Study Design section)		

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	Materials and Methods, page 7 (Study Design section); potential bias addressed in Discussion, pages 16 and 17		
Study size	10	Explain how the study size was arrived at	N/A (all eligible patients within specified time frame were included)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	N/A (quantitative variables collected from existing EMR/claims databases; CKD stage groupings based on existing KDIGO guidelines referenced in the manuscript)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how	Materials and Methods, pages 7 and 8 (Study Design and Statistical Analysis sections)		

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) Author Contributions section, page 19 12.2) N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3) N/A
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a) Results, page 8 b) N/A c) Figure 1 (cohort selection)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1) Figure 1 (cohort selection); Results, page 8
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic,	a) Results, pages 9 and 12		

		clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(Demographics and Clinical Characteristics of Patients with Diagnosed and Undiagnosed CKD section); Table 1 b) Table 1 c) Results, page 12 (Time to CKD Diagnosis section)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Results, pages 8 and 9		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	a) Results, page 13; confounders for multivariate analyses given in footnotes of supplementary Figure 3 and 4 b) N/A c) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and	Results, pages 12 and 13		

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion, page 14		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pages 16 and 17 (Strengths and Limitations)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion, page 17 (Strengths and Limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, page 18 (Conclusions)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, page 17 (Strengths and Limitations)		
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	Funding, page 20		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data Availability Statement, page 19; Supplementary Appendix

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Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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ABSTRACT (298/300 words)

Objectives: REVEAL-CKD aims to estimate the prevalence of, and factors associated with, undiagnosed stage 3 chronic kidney disease (CKD).

Design: Multinational, observational study.

Setting: Data from six country-specific electronic medical records and/or insurance claims databases from five countries (France, Germany, Italy, Japan and the USA [two databases]).

Participants: Eligible participants (≥18 years old) had ≥2 consecutive estimated glomerular filtration rate (eGFR) measurements (calculated from serum creatinine values, sex and age) taken from 2015 onwards that were indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2). Undiagnosed cases lacked an International Classification of Diseases 9/10 diagnosis code for CKD (any stage) any time before, and up to 6 months after, the second qualifying eGFR measurement (study index).

Main outcome measures: The primary outcome was point prevalence of undiagnosed stage 3 CKD. Time to diagnosis was assessed using the Kaplan–Meier approach. Factors associated with lacking a CKD diagnosis and risk of diagnostic delay were assessed using logistic regression adjusted for baseline covariates.

Results: The prevalence of undiagnosed stage 3 CKD was 95.5% (19,120/20,012 patients) in France, 84.3% (22,557/26,767) in Germany, 77.0% (50,547/65,676) in Italy, 92.1% (83,693/90,902) in Japan, 61.6% (13,845/22,470) in the US Explorys LCED database and 64.3% (161,254/250,879) in the US TriNetX database. The prevalence of undiagnosed CKD increased with age. Factors associated with undiagnosed CKD were female sex (vs male, range of odds ratio across countries: 1.29–1.77), stage 3a CKD (vs 3b, 1.81–3.66), no medical history (vs a history) of diabetes (1.26–2.77) or hypertension (1.35–1.78).

Conclusions: There are substantial opportunities to improve stage 3 CKD diagnosis, particularly in female patients and older patients. The low diagnosis rates in patients with

comorbidities that put them at risk of disease progression and complications requires attention.

Trial registration: NCT04847531

STRENGTHS AND LIMITATIONS OF THIS STUDY

- REVEAL-CKD uses large, contemporary, country-specific databases to provide robust estimates of the prevalence of undiagnosed stage 3 CKD.
- The study uses a strict, consistent and internationally recognised definition of stage 3 CKD to ensure accuracy when calculating the prevalence of diagnosed/undiagnosed CKD.
- Data from the countries and databases examined may not be representative of other countries with substantially different healthcare systems or CKD screening policies.
- There is a risk of misclassification of undiagnosed CKD if diagnoses were made in environments that did not contribute to the databases used or if diagnosing physicians did not use ICD-9/10 codes appropriately.

INTRODUCTION

Chronic kidney disease (CKD) is an established global public health concern.[1] CKD has a significant effect on patients, attributable to direct mortality and morbidity, as well as elevated risk of cardiovascular diseases.[2] The global prevalence of CKD is rising,[3] owing to aging populations and increased prevalence of CKD-associated risk factors including type 2 diabetes (T2D) and hypertension.[4]

Early intervention and appropriate management of CKD is recommended in the internationally recognised Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[5] to help delay disease progression and reduce the incidence of complications. Furthermore, in 2019, KDIGO held a controversies conference on the topic of early identification and intervention in CKD. The consensus statement from this conference urged action, including the implementation of screening programs and interventions for high-risk individuals.[6] Early-stage CKD is primarily asymptomatic,[7] therefore CKD is primarily diagnosed at later disease stages and the initiation of effective interventions is delayed or missed.[5] Previous studies have demonstrated low levels of diagnosis of early-stage CKD in Italy,[8] Sweden[9] and the USA.[10-15] However, these previous studies have been limited to single countries or databases, or at-risk groups such as patients with T2D, and did not assess the prevalence of CKD diagnosis across various subgroups (eg, patients with or without comorbidities). There is a need for contemporary information on the prevalence of, and factors associated with, undiagnosed stage 3 CKD, as well as a need to understand factors associated with diagnostic delay in these patients.

REVEAL-CKD (NCT04847531) is a multinational, observational study designed to fill this evidence gap. REVEAL-CKD aims to quantify the prevalence of, and factors associated with, undiagnosed stage 3 CKD in large populations across several countries.[16] Here, we present

data on the prevalence of, and factors associated with, undiagnosed stage 3 CKD in France, Germany, Italy, Japan and the USA.

METHODS

Study design

The study design for REVEAL-CKD has been reported in detail elsewhere,[16] and is summarised below.

Existing secondary data were extracted from established, verified relevant databases containing electronic medical records and/or insurance claims in the countries of interest. Data for France were extracted from The Health Improvement Network, a large database of anonymised electronic medical records.[17] Data for Germany were extracted from the German Disease Analyzer, a database of anonymised longitudinal data on drug prescriptions, diagnoses and medical and demographic data contributed by a panel of more than 2500 physicians in Germany.[18] Data for Italy were extracted from the IQVIA Longitudinal Patient Database, a computerised network of over 900 family physicians, which includes anonymised data on patient consultations and treatments.[19] Data for Japan were extracted from Japan Real World Data, an integrated database of medical information including both electronic medical records and claims data.[20] Data for the USA were extracted from two separate databases: Explorys Linked Claims and Electronic Medical Records Data (LCED), a database of inpatient and outpatient medical records and claims data from commercially insured individuals,[21] and TriNetX, a database of integrated electronic medical records and claims data from 35 healthcare organisations, which provides clinical patient data from both inpatient and outpatient encounters.[22] The coverage of each database used is described in **Supplementary table 1**.

Patients aged ≥18 years were included in the analyses if they had at least two consecutive estimated glomerular filtration rate (eGFR) measurements that fell within the range indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2) and were recorded >90 and ≤730 days apart, taken on or after 1 January 2015. The decision to require at least two eGFR measurements with a gap of at least 90 days between each measurement was made to ensure that patients met the requirements for the KDIGO definition of CKD.[5] In order to investigate the potential impact of requiring two eGFR measurements to classify patients, a sensitivity analysis was performed on data from the TriNetX database that included all patients with at least one eGFR measurement within the range of stage 3 CKD, taken within the same date range used for the main analysis. All patients had at least 12 months of continuous presence in the database before the first qualifying eGFR measurement. Full inclusion and exclusion criteria are shown in **Supplementary table 2**. eGFR was calculated from serum creatinine values, sex and age, using the CKD Epidemiology Collaboration (CKD-EPI) equation.[23] In line with current trends among physicians[24 25] and guidance from expert recommendations,[26] race modifiers were not used in the calculation of eGFR.

To account for potential delays in recording of diagnostic codes, undiagnosed CKD was defined as lacking an International Classification of Diseases (ICD) 9/10 diagnosis code corresponding to CKD (any stage), any time before and up to 6 months after index (date of second qualifying eGFR measurement). The ICD coding system varied by country depending on what was available in each database; the full list of ICD-9/10 codes used to determine diagnosed cases can be found in **Supplementary table 3**. A sensitivity analysis was performed to calculate the overall prevalence of undiagnosed stage 3 CKD using a broader definition of CKD adapted from Winkelmayer et al.[27] This sensitivity analysis included diagnostic codes for several additional manifestations of renal disease (**Supplementary table 4**).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

Overall prevalence of undiagnosed stage 3 CKD and patient demographic and clinical characteristics at index are presented descriptively. Comorbidities at index were identified using ICD-9/10 codes. Medication use at index was identified by the presence of at least one prescription for a given medication at or in the 12 months before index. Odds ratios for factors associated with being undiagnosed any time before and up to 6 months after index were calculated using logistic regression analysis, adjusted for covariates at index. Hazard ratios for diagnostic delay among patients undiagnosed at index were calculated using Cox regression analysis, adjusted for covariates at index. The Kaplan–Meier method was used to estimate the time to diagnosis among patients undiagnosed at index. Statistical analysis was performed using Python 3.7 and R 4.0.2.

RESULTS

This analysis of patients with stage 3 CKD included 20 012 patients from France, 90 902 patients from Germany, 65 676 patients from Italy, 26 767 patients from Japan, 22 470 patients from the LCED database in the USA, and 250 879 patients from the TriNetX database in the USA (**Figure 1**). Characteristics of these patients at index are shown in **Table 1**.

Table 1. Overall patient characteristics at study index (date of second eGFR measurement) according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
CKD status*, n (%)						
Diagnosed	892 (4.5)	4210 (15.7)	15 129 (23.0)	7209 (7.9)	8625 (38.4)	89 625 (35.7)
Undiagnosed	19 120 (95.5)	22 557 (84.3)	50 547 (77.0)	83 693 (92.1)	13 845 (61.6)	161 254 (64.3)
Age, y, median (IQR)	80 (72–86)	79 (72–84)	80 (74–85)	76 (69–83)	74 (64–82)	71 (64–78)
Age groups, y						
<45	67 (0.3)	66 (0.2)	188 (0.3)	791 (0.9)	243 (1.1)	5523 (2.2)
45–64	1677 (8.4)	2431 (9.1)	3780 (5.8)	13 286 (14.6)	5991 (26.7)	63 726 (25.4)
65–74	4641 (23.2)	6032 (22.5)	14 264 (21.7)	25 627 (28.2)	5592 (24.9)	87 880 (35.0)
≥75	13 627 (68.1)	18 238 (68.1)	47 444 (72.2)	51 198 (56.3)	10 644 (47.4)	93 750 (37.4)
Male, n (%)	9091 (45.4)	11 216 (41.9)	27 728 (42.2)	48 123 (52.9)	10 051 (44.7)	105 112 (41.9)
eGFR, mL/min/1.73 m², median (IQR)	52 (45–56)	52 (44–56)	49 (42–55)	52 (46–56)	51 (44–56)	51 (44–56)
CKD stage, n (%)						
CKD stage 3a	15 101 (75.5)	19 492 (72.8)	43 937 (66.9)	70 668 (77.7)	16 320 (72.6)	183 618 (73.2)
CKD stage 3b	4911 (24.5)	7275 (27.2)	21 739 (33.1)	20 234 (22.3)	6150 (27.4)	67 261 (26.8)
Baseline UACR available, n (%)	450 (2.2)	0 (0.0)†	9 (<0.1)‡	4992 (5.5)	899 (4.0)	4604 (1.8)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.34 (1.10–1.63)	1.32 (1.09–1.58)	1.40 (1.14–1.71)	1.22 (0.98–1.50)	1.22 (0.98–1.50)
Missing, n	6514	8232	17 513	35 305	10 022	138 798
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.84 (2.17–3.65)	2.69 (2.07–3.36)	2.74 (2.30–3.31)	2.38 (1.84–3.05)	2.38 (1.81–3.05)
Missing, n	6676	7087	19 475	33 589	8936	125 474
Comorbidities, n (%)						
Hypertension	12 412 (62.0)	13 679 (51.1)	51 324 (78.1)	53 022 (58.3)	20 061 (89.3)	203 155 (81.0)
Type 2 diabetes	3532 (17.6)	6935 (25.9)	21 300 (32.4)§	18 989 (20.9)	9288 (41.3)	95 441 (38.0)
Established CVD¶	1449 (7.2)	1904 (7.1)	6937 (10.6)	25 637 (28.2)	6292 (28.0)	49 744 (19.8)
Heart failure	986 (4.9)	4364 (16.3)	6378 (9.7)	30 063 (33.1)	5314 (23.6)	47 002 (18.7)
Atrial fibrillation	2161 (10.8)	4217 (15.8)	11 105 (16.9)	11 991 (13.2)	4627 (20.6)	41 214 (16.4)
Medication use, n (%)						
ACE inhibitor	4634 (23.2)	9635 (36.0)	25 098 (38.2)	4501 (5.0)	8783 (39.1)	57 806 (23.0)
ARB	6530 (32.6)	10 573 (39.5)	26 198 (39.9)	21 422 (23.6)	6302 (28.0)	37 946 (15.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	353 (0.5)	1363 (1.5)	22 (0.1)	2149 (0.9)
GLD (any)	3489 (17.4)	8319 (31.1)	17 363 (26.4)	13 431 (14.8)	9400 (41.8)	60 259 (24.0)
Antiplatelets	5964 (29.8)	6597 (24.6)	31 151 (47.4)	18 796 (20.7)	2476 (11.0)	16 308 (6.5)
Loop diuretic	2924 (14.6)	10 508 (39.3)	22 160 (33.7)	11 979 (13.2)	5563 (24.8)	43 470 (17.3)

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
Anticoagulants	3018 (15.1)	8182 (30.6)	16 197 (24.7)	14 486 (15.9)	6347 (28.2)	54 986 (21.9)

Unless otherwise stated, percentages represent the proportion of patients in a specific group (eg, age) or with a specific variable (eg, medical history).
*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.
†UACR testing data not available in the German Disease Analyzer database.
‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio.

At index, median age was 71–80 years, median eGFR was 49–52 mL/min/1.73 m^2, 66.9%–77.7% of patients had CKD stage 3a (eGFR ≥45 and <60 mL/min/1.73 m^2) and 22.3%–33.1% of patients had CKD stage 3b (eGFR ≥30 and <45 mL/min/1.73 m^2). The overall prevalence of urinary albumin-creatinine ratio (UACR) testing was very low and ranged from 1.8% (US, TriNetX) to 5.5% (Japan).

Overall prevalence of undiagnosed stage 3 CKD

The proportion of patients with stage 3 CKD without a diagnosis at or within 6 months after index varied by database, and was 95.5% in France, 84.3% in Germany, 77.0% in Italy, 92.1% in Japan, 61.6% in the US LCED database and 64.3% in the US TriNetX database (**Figure 2**A). In the sensitivity analysis using a broader set of ICD-9/10 codes to identify CKD diagnoses, the prevalence of undiagnosed CKD was 53.6%–89.9% (**Supplementary table 5**). In the sensitivity analysis of 532 921 patients in the TriNetX database who had at least one qualifying eGFR measurement, the prevalence of undiagnosed stage 3 CKD was 82.2% (**Supplementary table 6**).

The proportion of patients with undiagnosed CKD per calendar year at index is shown in **Supplementary Figure 1**. Overall, there were no prevailing trends in the proportion of patients with undiagnosed CKD per calendar year, except in Italy, where the proportion of undiagnosed CKD tended to increase over time (68.2% undiagnosed in 2015 to 83.1% in 2020).

Demographics and clinical characteristics of patients with diagnosed and undiagnosed stage 3 CKD

Characteristics for patients with diagnosed and undiagnosed stage 3 CKD at index are presented in **Supplementary Table 7**.

Patients with undiagnosed CKD tended to have slightly higher eGFR values than those with diagnosed CKD. A greater proportion of patients with stage 3a CKD were undiagnosed than patients with stage 3b CKD. There were fewer comorbidities such as hypertension, T2D and established cardiovascular disease in patients who were undiagnosed than in those who were diagnosed. Similarly, the proportion of patients taking medicines such as glucose-lowering drugs, loop diuretics, angiotensin-II converting enzyme inhibitors and angiotensin receptor blockers tended to be lower in undiagnosed patients than in those who were diagnosed. In the sensitivity analysis of 532 921 patients in the US TriNetX database who had at least one qualifying eGFR measurement, the prevalence of comorbidities was lower than in the main cohort (**Supplementary table 6**). In all databases, a greater proportion of stage 3 CKD cases were undiagnosed in female patients than in male patients (**Figure 2**B). Additionally, in all databases, patients aged less than 45 years had the lowest proportion of undiagnosed CKD; the prevalence of undiagnosed CKD increased in older age groups in France, Germany, Italy and in the US TriNetX database (**Supplementary Figure 2**).

Factors associated with undiagnosed CKD

The proportion of undiagnosed CKD tended to be higher in those without comorbidities at study index versus those with such comorbidities (**Figure 3**). When adjusting for baseline covariates, female patients (vs male patients), patients with CKD stage 3a (vs 3b) and patients without a diagnosis of diabetes or hypertension (vs those with a diagnosis) were consistently more likely to lack a CKD diagnosis before and up to 6 months after index (**Supplementary Figure 3**).

Time to CKD diagnosis

Among patients who lacked a diagnosis for stage 3 CKD at or before study index, the median (interquartile range [IQR]) follow-up duration was 2.22 (1.18–3.64) years in France, 0.61

(0.27–1.03) years in Germany, 3.64 (2.08–4.88) years in Italy, 1.96 (0.84–3.41) years in Japan, 1.28 (0.53–2.34) years in the US LCED database and 1.19 (0.44–2.32) years in the US TriNetX database. In patients undiagnosed at index, only a small proportion received a diagnosis during follow-up: 686/19 293 patients (3.6%) in France, 1157/23 302 patients (5.0%) in Germany, 8152/52 533 patients (15.5%) in Italy, 3855/84 603 patients (4.6%) in Japan, 3987/15 376 patients (25.9%) in the US LCED database and 44 007/178 410 patients (24.7%) in the US TriNetX database.

Among patients undiagnosed at index, diagnoses tended to accrue slowly over the whole duration of follow-up (**Figure 4**). The proportion of patients with initial eGFR values indicative of stage 3b CKD (≥30 and <45 mL/min/1.73 m^2) who received a diagnosis during follow-up was consistently higher than patients with initial eGFR values indicative of stage 3a CKD (≥45 and <60 mL/min/1.73 m^2; **Figure 4**).

Among all patients undiagnosed at index (regardless of whether they received a diagnosis during follow-up), median time to diagnosis was only calculable using the Kaplan–Meier method for the US TriNetX database, because more than half of the patients in the other databases remained undiagnosed at the end of the study period. In this database, the overall median (IQR) time to diagnosis was 4.75 (4.68–4.82) years.

After adjusting for selected baseline covariates, in all countries, female patients (vs male patients) and patients with stage 3a CKD at index (vs 3b) were more likely to be diagnosed later during follow-up (**Supplementary Figure 4**). Although less pronounced, patients without a history of comorbidities such as diabetes, heart failure or hypertension had a slightly elevated likelihood of delayed diagnosis (vs patients with a history of these conditions). Older patients also typically had a greater likelihood of delayed diagnosis than patients aged less than 45 years.

DISCUSSION

REVEAL-CKD is a large, multinational, observational study that uses a consistent, strict definition for undiagnosed CKD based on internationally recognised guidelines. By extracting data from contemporary, country-specific databases, the study provides a robust estimate of the prevalence of undiagnosed CKD in countries across the globe. The results from this analysis of six databases from five countries (France, Germany, Italy, Japan and the USA) demonstrate severe shortcomings in the diagnosis of stage 3 CKD. Although there was some variability among countries, the consistently high proportions of undiagnosed stage 3 CKD despite clinical evidence of the disease are highly concerning, as are the low levels of UACR testing. Of note, except in Japan, the prevalence of UACR testing did not appear to be substantially higher even in patients with a diagnosis of stage 3 CKD. UACR testing, however, is necessary for assessing the risk of future progression to kidney failure.[28] Missing opportunities for early diagnosis, prognostic assessment and management leaves patients at greater risk of further disease progression and complications, including end-stage renal disease and cardiovascular events.[6 29-31] Early interventions in CKD have been shown to improve outcomes by slowing CKD progression and reducing cardiovascular risk,[6 32] and healthcare costs associated with the disease increase substantially as CKD stage advances.[33] It is therefore vital for clinicians to seize the opportunity to diagnose and manage the condition as early as possible to minimise the impact of the disease, both in terms of financial burden and effects on health-related quality of life.

It is reassuring that the patients who have comorbidities that are established risk factors for CKD, such as hypertension and T2D, had higher rates of diagnosis and tended to be diagnosed sooner than patients without these conditions. However, even in patients with these comorbidities, the prevalence of undiagnosed CKD remained high. In the US databases,

which had the lowest rates of undiagnosed CKD, approximately 50% of patients with comorbidities in addition to CKD still lacked a CKD diagnosis. Alarmingly, this was the case for patients with hypertension, T2D and established cardiovascular disease: groups in which KDIGO recommends screening for CKD,[6] owing to their elevated risks of CKD progression and associated complications.[34-36] Without an appropriate CKD diagnosis, opportunities may also be missed to prescribe newer therapies such as sodium-glucose cotransporter-2 inhibitors which have been shown to improve cardiorenal outcomes in patients with CKD.[37 38]

We observed that the prevalence of undiagnosed CKD tended to rise with age, and older patients tended to have a higher risk of increased diagnostic delay than younger patients. In elderly patients, physicians may assume that eGFR values indicative of stage 3 CKD are caused by age-related decline of kidney function.[39 40] However, large population-based studies indicate that even in older adults at lower risk for kidney failure, stage 3 CKD is associated with an elevated risk of mortality, cardiovascular events and acute kidney injury.[41] Accordingly, KDIGO guidelines support the use of a single threshold value to define CKD across age subgroups consistent with criteria for other chronic non-communicable diseases.[5] In elderly patients, the effects of late-stage CKD are likely to have a substantial influence on physical and cognitive abilities, medication safety and cardiovascular prognosis.[2 6 41] It is therefore important that physicians do not underestimate the burden and effects of CKD in elderly patients and initiate guideline-appropriate management in a timely manner. Existing clinical tools (such as confirmatory cystatin C testing in suspected cases of CKD) can help mitigate the risk of overdiagnosis, although these remain underutilised.[6] CKD management in elderly patients should be adapted taking into consideration factors such as their age, frailty, comedications and comorbidities.

In line with previous studies that suggest CKD is more prevalent in women than in men,[42 43] the proportion of female patients with stage 3 CKD was higher than in male patients in all countries except Japan. Despite the higher prevalence of CKD in female patients, after adjusting for potential confounding factors, female patients had a higher likelihood of being undiagnosed than male patients in all countries. It has been suggested that the rate of progression of CKD is slower in women than in men,[44-47] and physicians may therefore be less likely to diagnose the condition at early stages in women. However, the inequality demonstrated in this study is substantial, and suggests a need for elevated awareness to minimise this gender disparity.

REVEAL-CKD used the internationally recognised CKD-EPI equation to calculate eGFR values from available serum creatinine measurements.[23] Multiple consecutive eGFR measurements indicative of stage 3 CKD were required to confirm the presence of CKD, in line with KDIGO recommendations suggesting a threshold of >90 days to consider the condition to be chronic.[5] This decision was made to conform to these widely used guidelines, and to avoid overestimating the prevalence of undiagnosed stage 3 CKD by including patients who had isolated eGFR measurements within the threshold of inclusion for stage 3 CKD (as a result of, for example, transient dehydration or acute kidney injury). To investigate the potential impact of requiring two qualifying eGFR measurements for inclusion in REVEAL-CKD, a sensitivity analysis was performed using the TriNetX database that included patients with at least one eGFR measurement indicative of stage 3 CKD. Among these patients, the prevalence of undiagnosed stage 3 CKD was higher than in the main REVEAL-CKD cohort (82.2% versus 64.3%, respectively), whereas the prevalence of comorbidities was lower. This suggests that the requirement of multiple eGFR measurements may have biased the sample to select for patients with inherently poorer health status, because they may have been receiving more frequent healthcare visits than those with a

single measurement, and therefore may have had more eGFR measurements taken. Although it is difficult to confirm which patients in this sensitivity analysis truly had stage 3 CKD and who were included as a result of transient eGFR dips, it should be noted that these findings suggest that the true prevalence of undiagnosed stage 3 CKD may be even higher than identified in the present study.

When calculating eGFR, race was not included as a modifier in line with recent trends among physicians[24 25] and guidance from expert recommendations.[26] Inclusion of the race modifier may have been expected to inflate eGFR in Black patients. Indeed, in a sensitivity analysis performed on the US TriNetX database which included data on race (**Supplementary Table 8**), we saw that a substantial proportion of Black patients (46.1%, corresponding to 9.2% of the overall TriNetX cohort) were reclassified as having stage 2 CKD (eGFR between 60–89 mL/min/1.73 m^2) when the race modifier was included in the calculation of eGFR. The inclusion of this modifier may therefore allow CKD to progress further in Black patients before they receive appropriate diagnosis and intervention. The decision to use the CKD-EPI equation without race was made in part to facilitate comparisons among countries and databases in which race was not available, and also to provide a consistent method of calculating eGFR for measurements taken across a time period where the inclusion of the race modifier was being actively debated.[48-52]

Some limitations must be kept in mind when interpreting these data. Results from the included countries may not be generalisable to other countries, which could have significantly different diagnostic coding practices, healthcare systems and screening policies; conclusions regarding the observed differences between countries cannot be drawn for similar reasons. The TriNetX and LCED databases contained a high proportion of commercially insured patients, and therefore may not be representative of the overall US

population. Furthermore, data licensing issues prevented the pooling of data from multiple databases to provide an overall estimate of the prevalence of undiagnosed CKD. Confirmatory UACR testing was not necessary to meet the study definition of stage 3 CKD owing to the extremely low levels of UACR testing in most of the cohorts. For the same reason, UACR testing was not included in the multivariate analyses which assessed factors associated with a lack of CKD diagnosis and factors associated with time to CKD diagnosis. The proportion of inpatient versus outpatient encounters was unavailable for many of the databases used, and therefore comparisons between diagnoses in these two settings could not be made. Because many of the databases used did not include data on race, variability in the prevalence of undiagnosed CKD according to race could not be assessed. Because data were collected from between 2015 and 2020, physicians may have still been using the race modifier for Black patients. Therefore, some Black patients may have been classified as having stage 2 CKD and have been less likely to receive a diagnosis as a result. It is important to note that this study focused on underdiagnosis for stage 3 CKD; low levels of UACR testing in all countries studied suggest that the prevalence of undiagnosed stage 1 and 2 CKD may be even higher. Lastly, there is a risk of misclassification if CKD diagnoses were made in clinical settings that do not contribute to the databases, or if patients had CKD that was recognised by their healthcare providers but was not recorded with an appropriate ICD-9/10 code in the databases. Although a lack of such codes may not always indicate that a patient's CKD is undiagnosed, this definition of CKD diagnosis has been validated by previous real-world studies,[8 11 12 27] and provides an appropriate surrogate measure for rates of diagnosis in large epidemiological studies such as REVEAL-CKD.

In conclusion, this analysis of six large, secondary databases from five countries demonstrates that most cases of stage 3 CKD are not diagnosed in a timely manner despite clinical evidence of the disease. Furthermore, although patients with existing risk factors for,

or complications from, CKD were typically more likely to receive a CKD diagnosis, the prevalence of undiagnosed CKD in these patients remained alarmingly high. Clear opportunities exist for improved diagnosis of stage 3 CKD, particularly in female patients, elderly patients and patients at high risk of CKD progression and complications. Future research will help to quantify the impact of early diagnosis and initiation of effective therapies on the risk of CKD progression, complications and long-term patient outcomes.

Contributors

NT, SB, EJP, EW, HC, KJ and PK were responsible for the study concept and design. EJP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MA, EJP and HC developed and conducted the statistical analysis plan. NT, TM, MPS, JBJV, LDN, MA, SB, EJP, EW, HC, KJ and PK were involved in review and editing of manuscript drafts, as well as critical revision of the content during its development. All authors approved the final version of the manuscript before its submission. The corresponding author (NT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Data used in this study were obtained from a third party and may not be publicly available. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Competing interests

SB, EJP, HC, KJ and EW are employees of AstraZeneca and hold stock options. MA is an employee of AstraZeneca. NT has received grants from AstraZeneca, Boehringer

Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd and Tricida, Inc, has received honoraria from AstraZeneca, Boehringer Ingelheim/Eli Lilly and Company, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Ltd and Tricida, Inc and holds stock options from Mesentech, Inc, Rénibus Therapeutics, Inc, pulseData and Tricida, Inc. MPS has received advisory board fees and honoraria from AstraZeneca, Bayer AG, Vifor Pharma Group and Boehringer Ingelheim/Eli Lilly and Company. LDN has received fees for scientific consultation and/or lectures by Astellas Pharma Inc, AstraZeneca, Mundipharma GmbH and Vifor Pharma Group. PK has received speaker's bureau and advisory board fees from AstraZeneca, Eli Lilly and Company and Novo Nordisk A/S, speaker's fees from Bayer AG and honoraria from AstraZeneca and Eli Lilly and Company. TM and JBV have no conflicts of interest to disclose.

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Ethics Approval

REVEAL-CKD used de-identified data from existing databases and did not require data collection beyond that of routine clinical care. No identifiable information was collected or examined as part of the study. All externally conducted analyses were completed in line with

local ethics regulations/legislation. De-identified, internally licensed databases were shared with AstraZeneca by the licensee; therefore, ethics review and approval was not required for the use of these databases for this study.

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Figure Legends

Figure 1. Cohort selection

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Figure 2. Prevalence of undiagnosed stage 3 CKD according to country and database (**A**) overall and (**B**) by sex

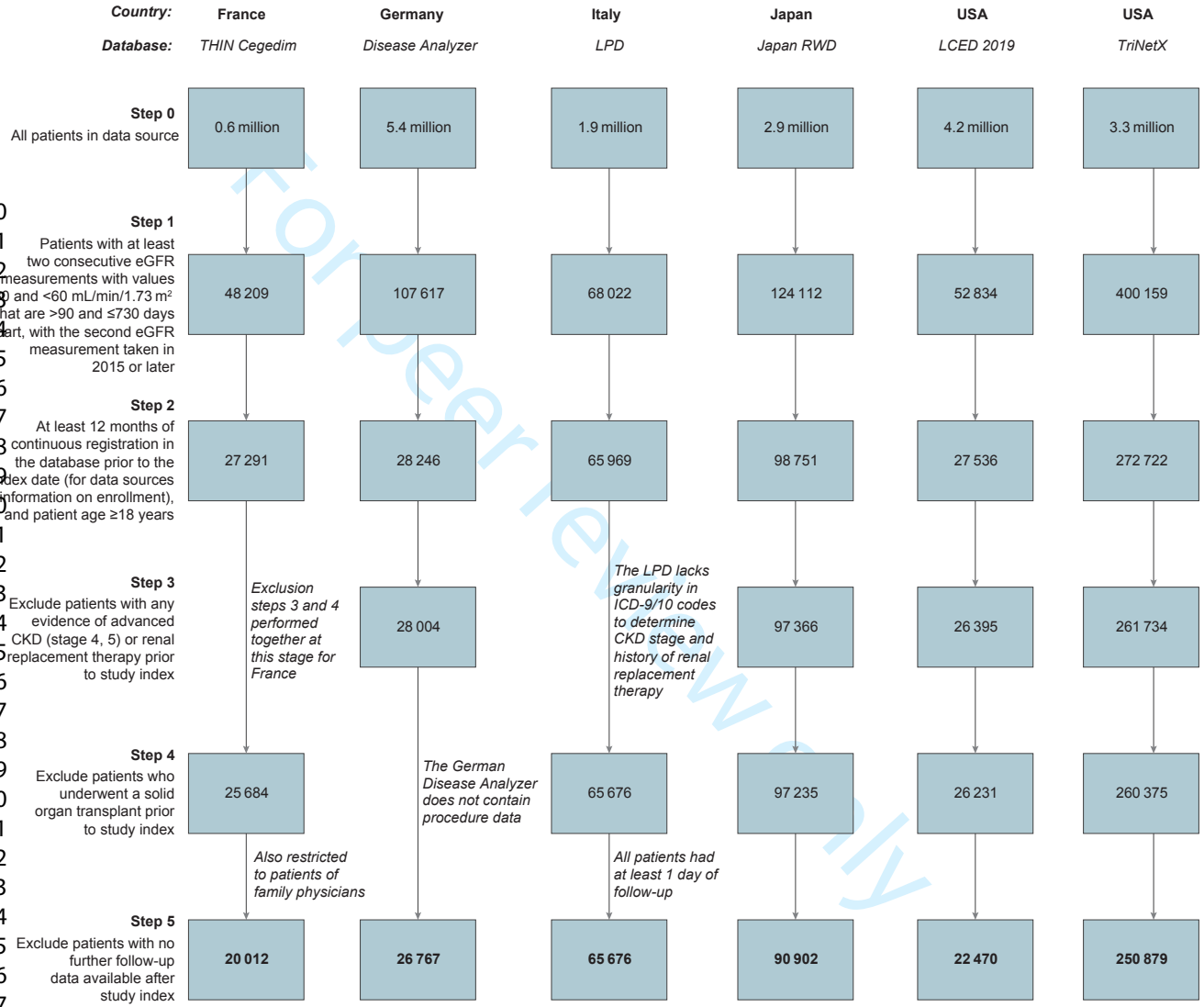
Undiagnosed cases are those which lack a diagnosis code for CKD (any stage), any time before and up to 6 months after study index.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

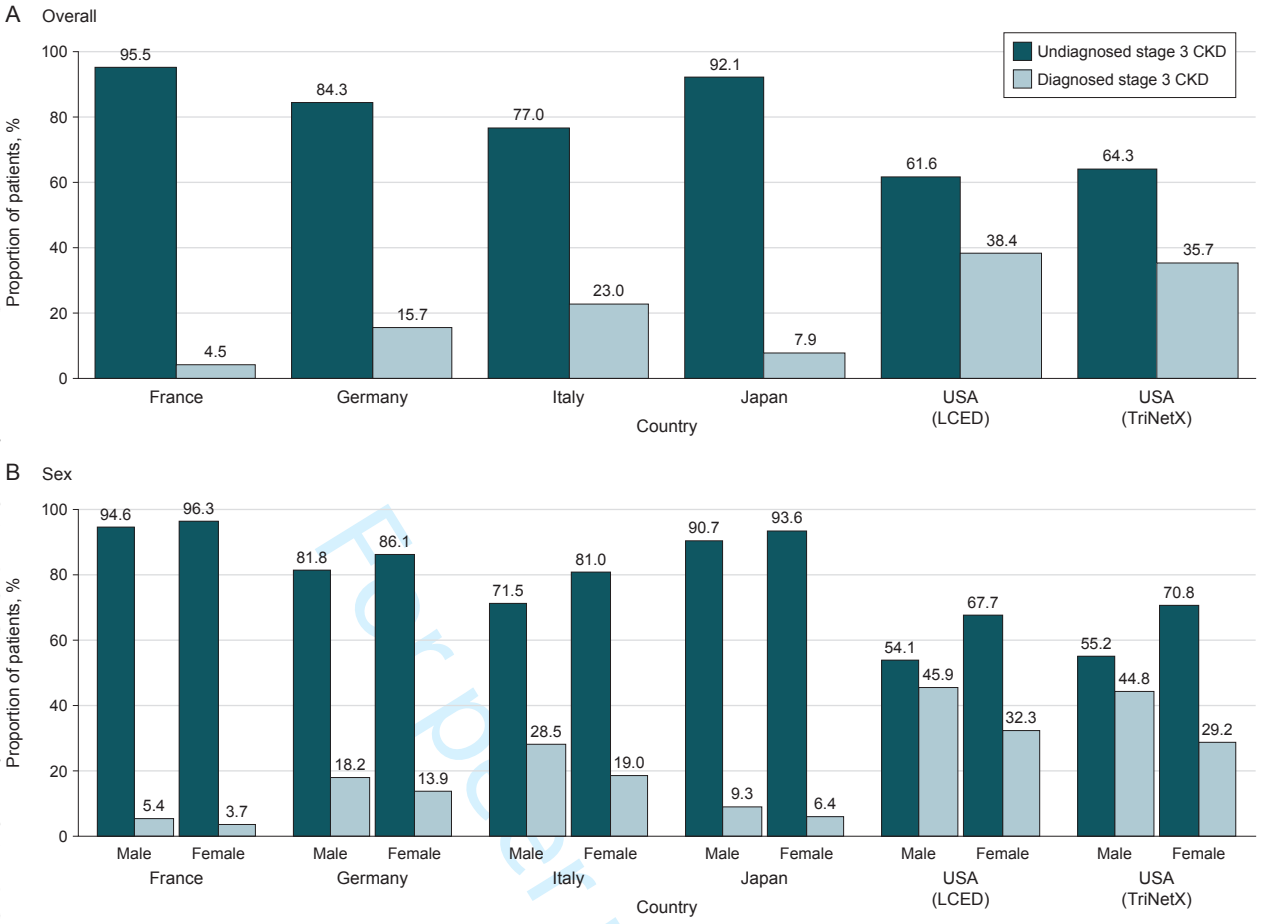
Figure 3. Prevalence of undiagnosed stage 3 CKD according to the presence of comorbidities at study index, by country and database

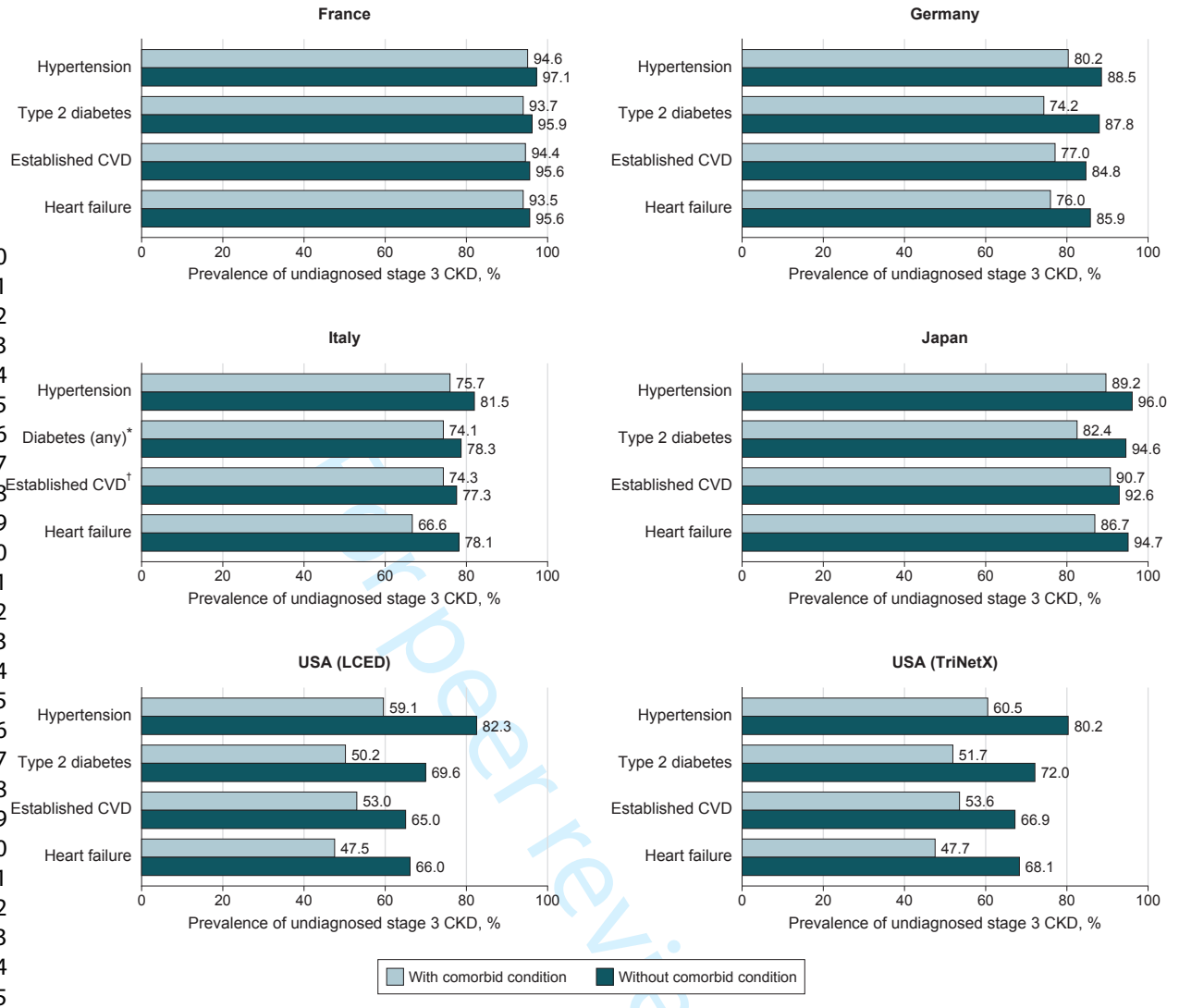
Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention. Study index is defined as the date of a patient's second qualifying eGFR measurement.
*Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
†Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LCED, Explorys Linked Claims and Electronic Medical Records Data.

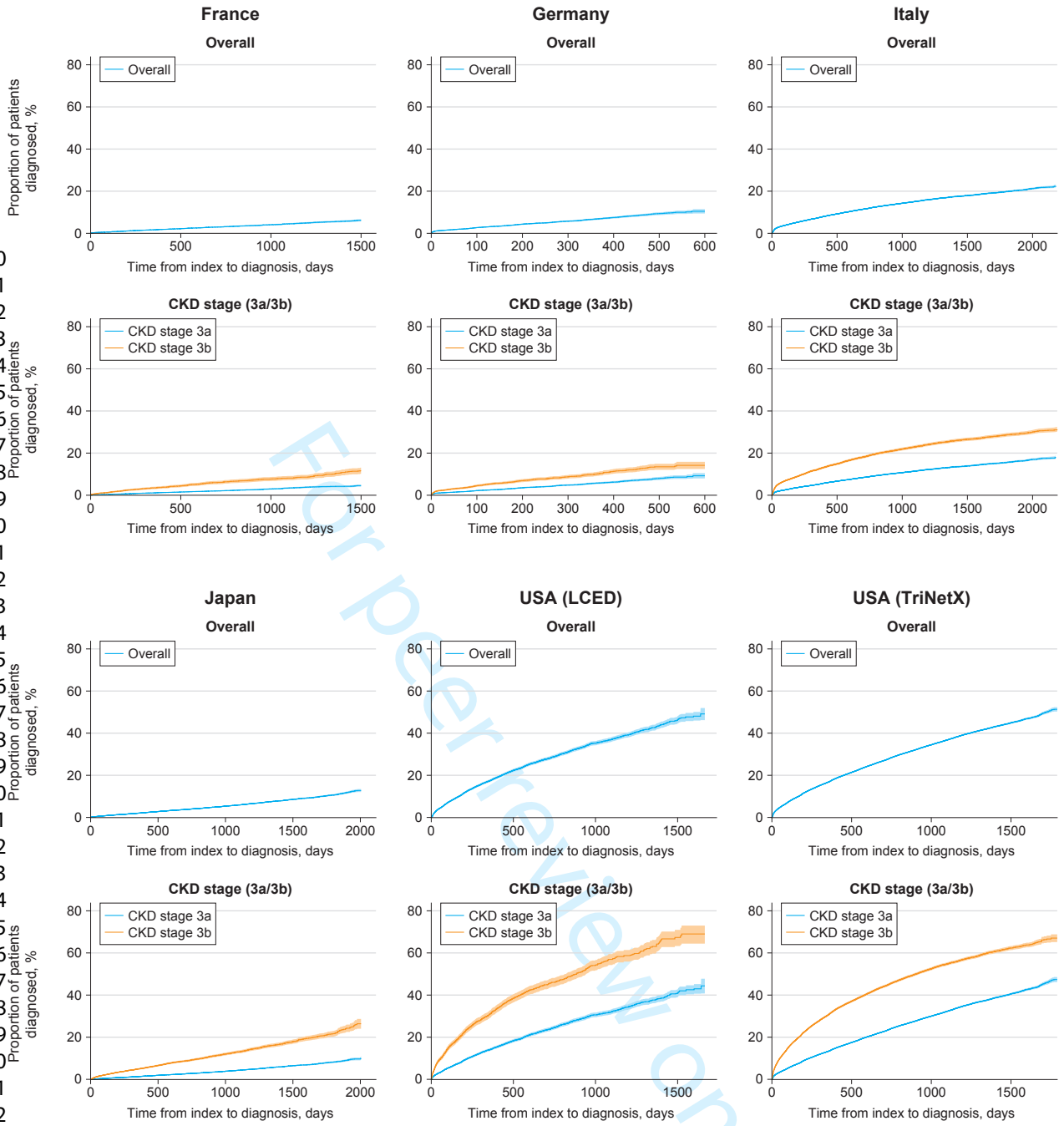
Figure 4. Kaplan–Meier estimates of time to CKD diagnosis according to country and database in patients undiagnosed at index, overall and by CKD stage (3a/3b)

Shaded areas represent 95% confidence intervals.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.









SUPPLEMENTARY MATERIALS

Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study

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Supplementary table 1. Data sources used in the REVEAL-CKD study.

Country	Data source(s)	Database type (EMR/claims)	Coverage
France	THIN: The Health Improvement Network/Cegedim Health Data	EMR	Primary care
Germany	IQVIA Disease Analyzer	EMR	Primary care/endocrinology
Japan	Japan RWD	EMR and claims	Inpatient/outpatient
USA	TriNetX	EMR and claims	Inpatient/outpatient
	LCED	EMR and claims	Inpatient/outpatient
Italy	The Health Search Database/IQVIA Health Solutions Italy	EMR	Primary care

EMR, electronic medical records; LCED, Explorys Linked Claims and Electronic Medical Records Data; RWD, Real World Data.

Supplementary table 2. REVEAL-CKD study inclusion and exclusion criteria

Inclusion criteria:
• ≥2 consecutive eGFR laboratory measurements recorded in 2015 or later, with values ≥30 and <60 mL/min/1.73 m^2 (stage 3a/3b CKD using the CKD-EPI[1] equation) that are >90 and ≤730 days apart • ≥12 months of continuous presence in the database before the first qualifying eGFR measurement (look-back period) • Age ≥18 years at the index date (defined as the date of the second qualifying laboratory eGFR measurement indicative of stage 3a/3b CKD).
Exclusion criteria:
• Solid organ transplant recorded before the index date • Any evidence of advanced CKD (stages 4, 5, and end-stage renal disease) based on CKD diagnosis codes or renal replacement therapy before the index date.

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary table 3. ICD-9/10 codes used to identify patients with diagnosed stage 3 CKD

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD 10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 4. ICD-9/10 codes used to identify CKD in the sensitivity analysis using a broader definition for CKD adapted from Winkelmayer et al., 2005[2]

Description	ICD-9*	ICD-10†
CKD, stage I	585.1‡	N18.1§
CKD, stage II	585.2	N18.2
CKD, stage III	585.3	N18.3
CKD, stage IV (severe)	585.4	N18.4
CKD, stage V	585.5	N18.5
End-stage renal disease	585.6	N18.6
CKD, unspecified	585.9	N18.9
Chronic renal insufficiency	582, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9	N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N19, N26.9
Hypertensive CKD	403, 403.01, 403.1, 403.11, 403.9, 403.91, 404, 404.01, 404.02, 404.03, 404.1, 404.11, 404.12, 404.13, 404.9, 404.91, 404.92, 404.93	I12.0, I12.9, I13.0, I13.10, I13.11, I13.2
Diabetes with renal manifestation	250.4, 250.41, 250.42, 250.43	E10.2, E11.2, E11.21, E11.22, E11.29
Disorders from impaired renal function	588, 588.1, 588.81, 588.89, 588.9	N25.0, N25.1, N25.81, N25.89, N25.9, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359,

Description	ICD-9*	ICD-10†
		M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39
Acute renal failure	572.4, 580, 580.4, 580.81, 580.89, 580.9, 584.5, 584.6, 584.7, 584.8, 584.9, 791.2, 791.3	K76.7, N00.3, N00.8, N00.9, N01.3, N17.0, N17.1, N17.2, N17.8, N17.9, R82.1, R82.3
Miscellaneous	274.1, 440.1, 442.1, 453.3, 581, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 586, 587, 593, 593.1, 593.2, 593.3, 593.4, 593.5, 593.6, 593.7, 593.71, 593.72, 593.73, 593.81, 593.82, 593.89, 593.9, 753, 753.3, 866, 866.01, 866.1, 866.11, 866.12, 866.13	I70.1, I72.2, I82.3, N02.2, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N08, N13.4, N13.5, N13.70, N13.71, N13.721, N13.722, N13.729, N13.731, N13.732, N13.739, N13.8, N28.1, N28.81, N28.82, N28.83, N28.89, N28.9, Q60.2, Q60.5, Q63.0, Q63.1, Q63.2, Q63.3, Q63.8, Q63.9, R80.2, S31.001, S37.009, S37.019, S37.029, S37.039, S37.049, S37.059, S37.069

*ICD-9 codes were used to identify CKD in Italy and in the US LCED and TriNetX databases.
†ICD-10 codes were used to identify CKD in France, Germany, Japan and the US LCED and TriNetX databases.
‡The ICD-9 code 585 (CKD, unspecified) was included in the code list for Italy owing to the large proportion of non-specific CKD reporting in this database.
§The ICD-10 codes N18 and N18.0 (CKD, unspecified) were included in the code list for France owing to the large proportion of non-specific CKD reporting in this database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; ICD, International Classification of Diseases.

Supplementary table 5. Sensitivity analysis of undiagnosed stage 3 CKD using a broader CKD definition adapted from Winkelmayer et al., 2005[2] according to country and database

Country	France	Germany	Italy	Japan	USA	
Database	**THIN Cegedim n=20 012**	**Disease Analyzer n=26 767**	**LPD n=65 676**	**Japan RWD n=90 902**	**LCED n=22 470**	**TriNetX n=250 879**
CKD status*, n (%)						
Diagnosed	2031 (10.1)	6165 (23.0)	21 146 (32.2)	12 113 (13.3)	10 421 (46.4)	109 735 (43.7)
Undiagnosed	17 981 (89.9)	20 602 (77.0)	44 530 (67.8)	78 789 (86.7)	12 049 (53.6)	141 144 (56.3)

*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort for each country/database.
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data; LPD, Longitudinal Patient Database; RWD, Real World Data; THIN, The Health Improvement Network.

Supplementary table 6. Sensitivity analysis of undiagnosed CKD in patients in the TriNetX database with one eGFR measurement indicative of stage 3 CKD

Country	**USA**
Database	**TriNetX n=532 921**
CKD status*, n (%)	
Diagnosed	94 780 (17.8)
Undiagnosed	438 141 (82.2)
Age, y, median (IQR)	67 (59–75)
Age groups, y	
<45	28 888 (5.4)
45–64	187 109 (35.1)
65–74	174 126 (32.7)
≥75	142 798 (26.8)
Male, n (%)	232 069 (43.5)
eGFR, mL/min/1.73 m^2, median (IQR)	54 (48–58)
CKD stage, n (%)	
CKD stage 3a	439 183 (82.4)
CKD stage 3b	93 738 (17.6)
Baseline UACR available, n (%)	5495 (1.0)
HDL, mmol/L, median (IQR)	1.24 (1.01–1.53)
Missing, n	349 531
LDL, mmol/L, median (IQR)	2.51 (1.91–3.21)
Missing, n	322 358
Comorbidities, n (%)	
Hypertension	371 933 (69.8)
Type 2 diabetes	160 129 (30.0)
Established CVD†	81 883 (15.4)
Heart failure	66 522 (12.5)
Atrial fibrillation	64 232 (12.1)
Medication use, n (%)	
ACE inhibitor	100 723 (18.9)
ARB	58 812 (11.0)
SGLT2 inhibitor	3777 (0.7)
GLD (any)	100 714 (18.9)
Antiplatelets	25 371 (4.8)
Loop diuretic	64 161 (12.0)
Anticoagulants	107 616 (20.2)

Unless otherwise stated, percentages represent the proportion of patients in a specific group (eg, age) or with a specific variable (eg, medical history).
*Percentages represent the proportion of diagnosed/undiagnosed cases in the overall cohort.
†Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter-2; UACR, urinary albumin-creatinine ratio.

Supplementary table 7. Overall patient characteristics at study index according to country, by CKD diagnosis status 6 months after index

Country	France		Germany		Italy		Japan		USA			
Database	**THIN Cegedim**		**Disease Analyzer**		**LPD**		**Japan RWD**		**LCED**		**TriNetX**	
	Undiagnosed n=19 120	**Diagnosed* n=892**	**Undiagnosed n=22 557**	**Diagnosed* n=4210**	**Undiagnosed n=50 547**	**Diagnosed* n=15 129**	**Undiagnosed n=83 693**	**Diagnosed* n=7209**	**Undiagnosed n=13 845**	**Diagnosed* n=8625**	**Undiagnosed n=161 254**	**Diagnosed* n=89 625**
Age, y, median (IQR)	80 (72–86)	77 (69–84)	79 (72–84)	79 (71–84)	80 (74–85)	80 (73–85)	76 (69–83)	77 (68–83)	74 (64–82)	74 (64–82)	71 (64–79)	70 (62–78)
Age groups, y												
<45	58 (0.3)	9 (1.0)	46 (0.2)	20 (0.5)	95 (0.2)	93 (0.6)	652 (0.8)	139 (1.9)	109 (0.8)	134 (1.6)	2426 (1.5)	3097 (3.5)
45–64	1551 (8.1)	126 (14.1)	1957 (8.7)	474 (11.3)	2724 (5.4)	1056 (7.0)	12 260 (14.6)	1026 (14.2)	3754 (27.1)	2237 (25.9)	38 302 (23.8)	25 424 (28.4)
65–74	4421 (23.1)	220 (24.7)	5088 (22.6)	944 (22.4)	10 976 (21.7)	3288 (21.7)	23 696 (28.3)	1931 (26.8)	3415 (24.7)	2177 (25.2)	57 891 (35.9)	29 989 (33.5)
≥75	13 090 (68.5)	537 (60.2)	15 466 (68.6)	2772 (65.8)	36 752 (72.7)	10 692 (70.7)	47 085 (56.3)	4113 (57.1)	6567 (47.4)	4077 (47.3)	62 635 (38.8)	31 115 (34.7)
Male, n (%)	8599 (45.0)	492 (55.2)	9173 (40.7)	2043 (48.5)	19 820 (39.2)	7908 (52.3)	43 658 (52.2)	4465 (61.9)	5438 (39.3)	4613 (53.5)	57 989 (36.0)	47 123 (52.6)
eGFR, mL/min/1.73 m², median (IQR)	52 (46–56)	45 (38–52)	52 (45–56)	49 (40–55)	51 (44–55)	45 (38–52)	53 (47–56)	45 (37–53)	53 (47–57)	47 (40–53)	53 (47–57)	47 (40–53)
CKD stage, n (%)												
CKD stage 3a	14 661 (76.7)	440 (49.3)	16 871 (74.8)	2621 (62.3)	36 460 (72.1)	7477 (49.4)	66 955 (80.0)	3713 (51.5)	11 348 (82.0)	4972 (57.6)	131 385 (81.5)	52 233 (58.3)
CKD stage 3b	4459 (23.3)	452 (50.7)	5686 (25.2)	1589 (37.7)	14 087 (27.9)	7652 (50.6)	16 738 (20.0)	3496 (48.5)	2497 (18.0)	3653 (42.4)	29 869 (18.5)	37 392 (41.7)
Baseline UACR available, n (%)	424 (2.2)	26 (2.9)	0 (0.0)†	0 (0.0)†	4 (<0.1)‡	5 (<0.1)‡	3851 (4.6)	1141 (15.8)	474 (3.4)	425 (4.9)	2455 (1.5)	2149 (2.4)
HDL, mmol/L, median (IQR)	1.37 (1.11–1.65)	1.32 (1.08–1.65)	1.34 (1.11–1.63)	1.29 (1.06–1.55)	1.32 (1.11–1.59)	1.27 (1.06–1.53)	1.40 (1.16–1.71)	1.32 (1.09–1.6	1.24 (1.03–1.53)	1.16 (0.96–1.45)	1.24 (1.03–1.55)	1.14 (0.93–1.42)
Missing, n	6172	342	6904	1328	13 379	4134	33 243	2062	5673	4349	88 031	50 767
LDL, mmol/L, median (IQR)	2.89 (2.24–3.61)	2.81 (2.18–3.53)	2.87 (2.20–3.70)	2.70 (2.07–3.49)	2.74 (2.12–3.39)	2.53 (1.97–3.21)	2.77 (2.22–3.34)	2.53 (2.04–3.1	2.46 (1.89–3.13)	2.25 (1.71–2.95)	2.43 (1.87–3.13)	2.22 (1.68–2.92)
Missing, n	6331	345	6026	1061	14 915	4560	31 643	1946	4988	3948	78 408	47 066
Comorbidities, n (%)												
Hypertension	11 737 (61.4)	675 (75.7)	10 969 (48.6)	2710 (64.4)	38 849 (76.9)	12 475 (82.5)	47 311 (56.5)	5711 (79.2)	11 863 (85.7)	8198 (95.0)	123 002 (76.3)	80 153 (89.4)
Type 2 diabetes	3311 (17.3)	221 (24.8)	5145 (22.8)	1790 (42.5)	15 785 (31.2)§	5515 (36.5)§	15 655 (18.7)	3334 (46.2)	4667 (33.7)	4621 (53.6)	49 299 (30.6)	46 142 (51.5)
Established CVD¶	1368 (7.2)	81 (9.1)	1467 (6.5)	437 (10.4)	5153 (10.2)	1784 (11.8)	23 248 (27.8)	2389 (33.1)	3337 (24.1)	2955 (34.3)	26 666 (16.5)	23 078 (25.7)
Heart failure	922 (4.8)	64 (7.2)	3318 (14.7)	1046 (24.8)	4248 (8.4)	2130 (14.1)	26 077 (31.2)	3986 (55.3)	2523 (18.2)	2791 (32.4)	22 422 (13.9)	24 580 (27.4)
Atrial fibrillation	2057 (10.8)	104 (11.7)	3351 (14.9)	866 (20.6)	8293 (16.4)	2812 (18.6)	10 765 (12.9)	1226 (17.0)	2409 (17.4)	2218 (25.7)	23 224 (14.4)	17 990 (20.1)
Medication use, n (%)												
ACE inhibitor	4363 (22.8)	271 (30.4)	8023 (35.6)	1612 (38.3)	19 141 (37.9)	5957 (39.4)	4027 (4.8)	474 (6.6)	5058 (36.5)	3725 (43.2)	33 532 (20.8)	24 274 (27.1)
ARB	6181 (32.3)	349 (39.1)	8855 (39.3)	1718 (40.8)	19 770 (39.1)	6428 (42.5)	18 959 (22.7)	2463 (34.2)	3605 (26.0)	2697 (31.3)	22 656 (14.0)	15 290 (17.1)
SGLT2 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	287 (0.6)	66 (0.4)	1082 (1.3)	281 (3.9)	11 (0.1)	11 (0.1)	1171 (0.7)	978 (1.1)
GLD (any)	3300 (17.3)	189 (21.2)	6742 (29.9)	1577 (37.5)	13 108 (25.9)	4255 (28.1)	11 303 (13.5)	2128 (29.5)	5012 (36.2)	4388 (50.9)	29 690 (18.4)	30 569 (34.1)
Antiplatelets	5636 (29.5)	328 (36.8)	5451 (24.2)	1146 (27.2)	23 245 (46.0)	7906 (52.3)	16 690 (19.9)	2106 (29.2)	1274 (9.2)	1202 (13.9)	8256 (5.1)	8052 (9.0)
Loop diuretic	2747 (14.4)	177 (19.8)	8564 (38.0)	1944 (46.2)	15 719 (31.1)	6441 (42.6)	10 346 (12.4)	1633 (22.7)	2720 (19.6)	2843 (33.0)	21 136 (13.1)	22 334 (24.9)
Anticoagulants	2885 (15.1)	133 (14.9)	6838 (30.3)	1344 (31.9)	12 214 (24.2)	3983 (26.3)	12 886 (15.4)	1600 (22.2)	3434 (24.8)	2913 (33.8)	28 521 (17.7)	26 465 (29.5)

Percentages represent the proportion of diagnosed/undiagnosed patients in a specific group (eg, age) or with a specific variable (eg, medical history).

*Diagnosed cases include patients with a corresponding ICD-9/10 diagnosis code for CKD at or within 6 months of study index (date of second qualifying eGFR measurement).

†UACR testing data not available in the German Disease Analyzer database.

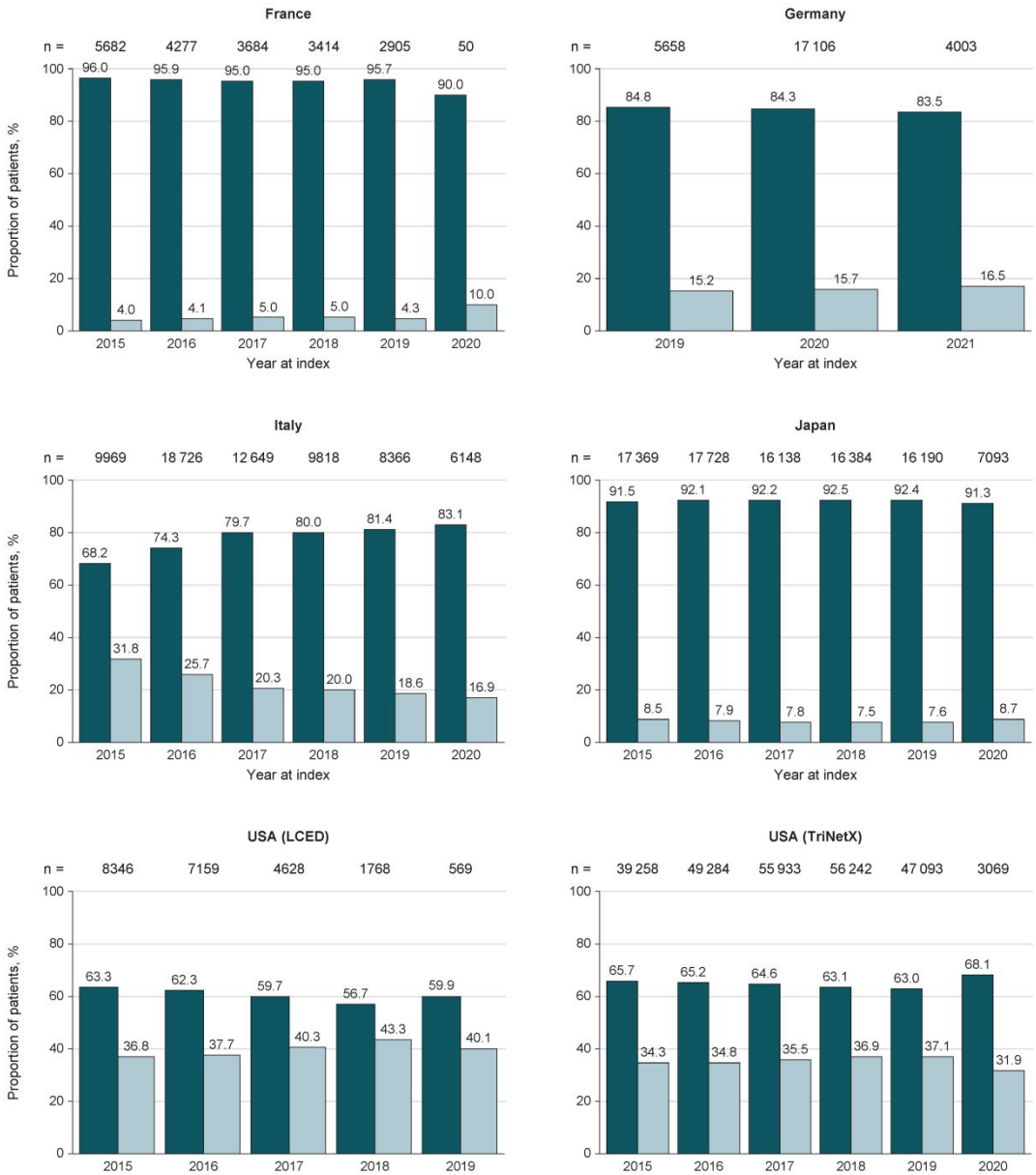
‡Direct measurements of UACR were not available in the IQVIA Longitudinal Patient Database in Italy, however, UACR was calculated as urine albumin (mg/dL) divided by urine creatinine (g/dL) if patients had records for both of these variables on the same day.
§Owing to a lack of granularity for ICD-9 diagnostic codes in the database used, type of diabetes could not be determined in patients from Italy.
‖Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischaemic attack, coronary artery bypass graft and percutaneous coronary intervention.
¶Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile range; LCED, Explorys Linked Claims and Electronic Medical Records Data; LDL, low-density lipoprotein; LPD, Longitudinal Patient Database; RWD, Real World Data; SGLT2, sodium-glucose cotransporter-2; THIN, The Health Improvement Network; UACR, urinary albumin-creatinine ratio

Supplementary table 8. Comparison of CKD stages in Black and non-Black patients from the US TriNetX database when calculating eGFR using two different equations: CKD-EPI (without adjusting for race) and CKD-EPI (with race modifier)[1]

	CKD-EPI, no race modifier	**CKD-EPI, with race modifier**
Black (n=50 283)		
Stage 2 CKD, n (%)	0 (0.0)	23 156 (46.1)
Stage 3a CKD, n (%)	36 005 (71.6)	20 455 (40.7)
Stage 3b CKD, n (%)	14 278 (28.4)	6672 (13.3)
Non-Black (n=200 596)		
Stage 2 CKD, n (%)	0 (0.0)	0 (0.0)
Stage 3a CKD, n (%)	147 613 (73.6)	147 613 (73.6)
Stage 3b CKD, n (%)	52 983 (26.4)	52 983 (26.4)

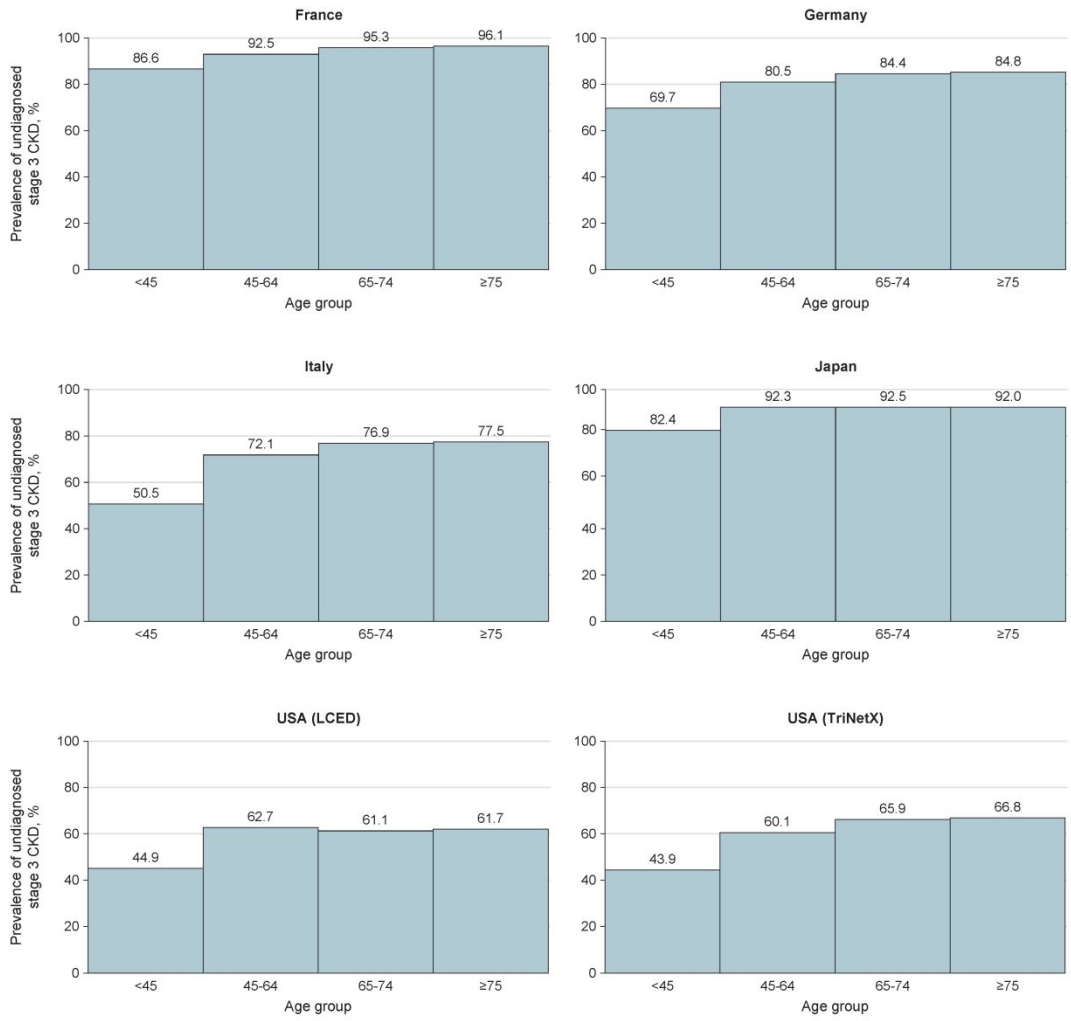
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Supplementary figure 1. Prevalence of undiagnosed stage 3 CKD according to calendar year of study index according to country and database



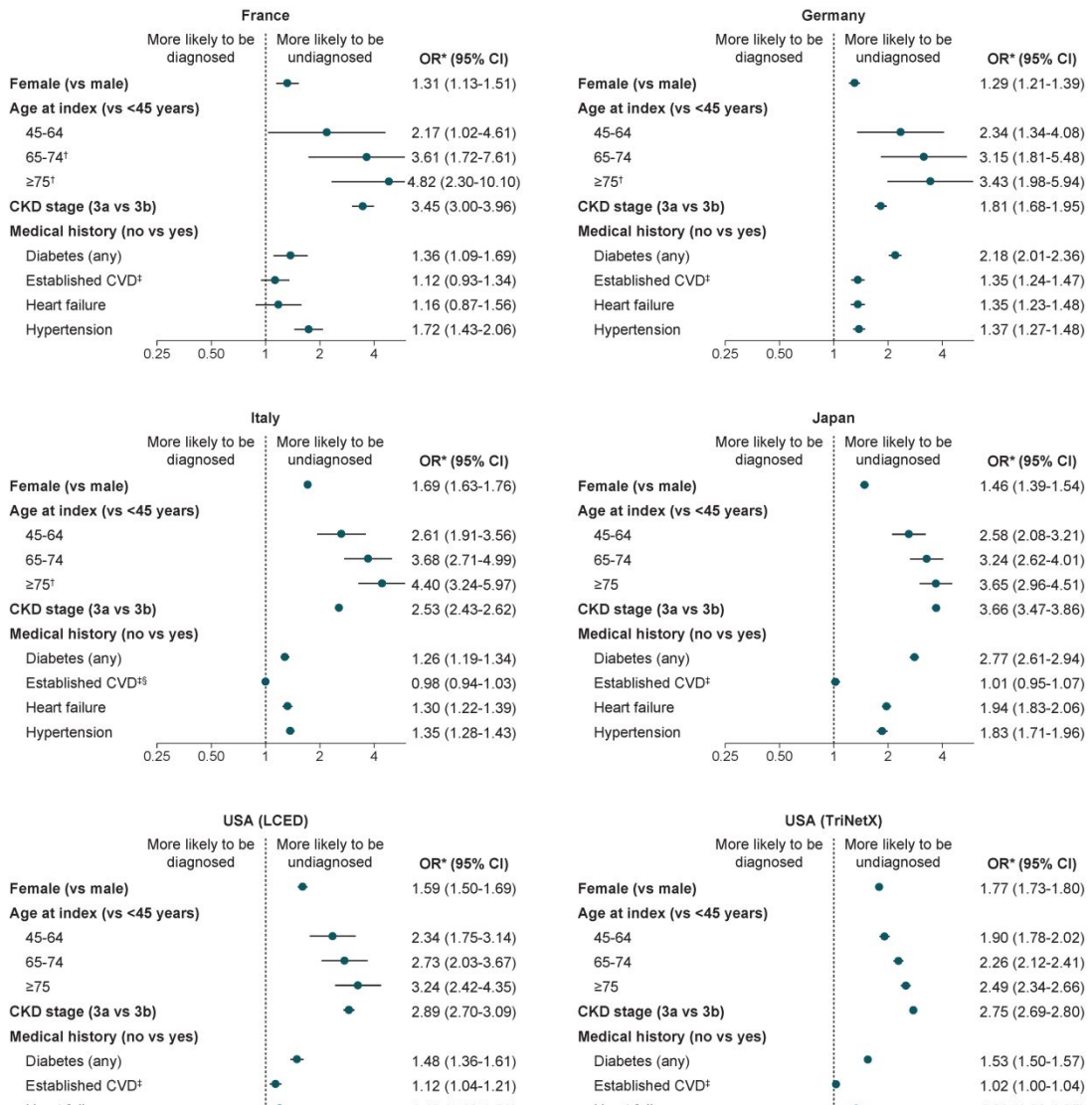
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 2. Prevalence of undiagnosed stage 3 CKD according to age group at study index according to country and database



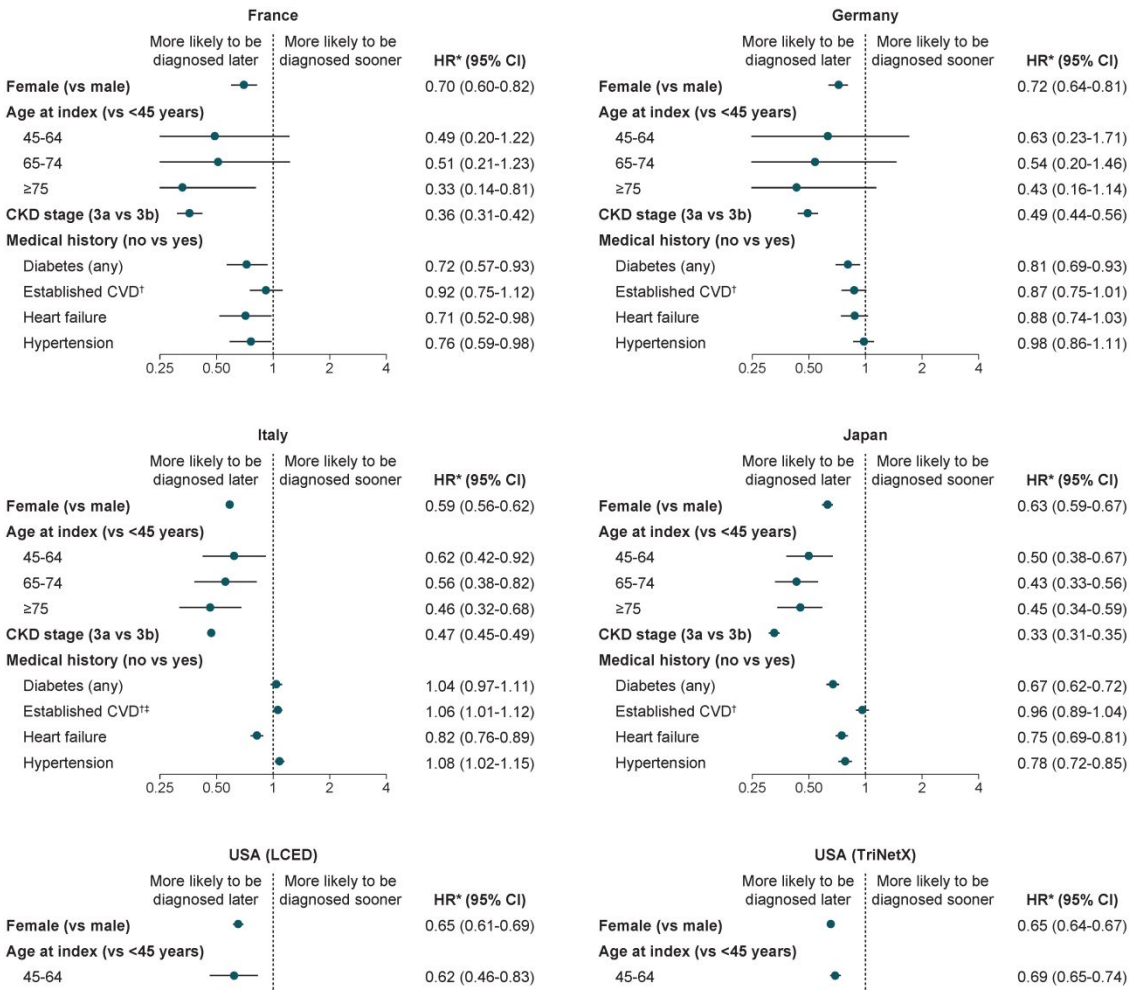
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 3. Factors associated with a lack of CKD diagnosis any time before or up to 6 months after index date according to country and database



Whiskers represent 95% confidence intervals.
*Odds ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors, and other glucose-lowering drugs).
†Upper 95% confidence interval extends beyond the boundary of the graph.
‡Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.
§Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.
CKD, chronic kidney disease; CVD, cardiovascular disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

Supplementary figure 4. Factors associated with time to CKD diagnosis in patients undiagnosed at index according to country and database



Whiskers represent 95% confidence intervals.

[a]Hazard ratios adjusted for covariates at index: sex, age, CKD stage, family history of CKD (not available in France, Germany and Japan), number of clinical visits in year before index, medical history (heart failure, established CVD, diabetes [any type], hypertension, other kidney disease) and medication use (diuretics, β-blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, lipid-lowering drugs, antithrombotic drugs, metformin, glucagon-like peptide receptor-1 inhibitors or sodium-glucose cotransporter-2 inhibitors and other glucose-lowering drugs).

[b]Established CVD includes patients with a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary artery bypass graft and percutaneous coronary intervention.

[c]Owing to a lack of granularity for ICD-9 codes in the database used, established CVD does not include coronary artery bypass graft and percutaneous coronary intervention in patients from Italy.

CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; LCED, Explorys Linked Claims and Electronic Medical Records Data.

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2. Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis.* 2005;46(2):225–32. doi: 10.1053/j.ajkd.2005.04.029

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Title, page 1, and abstract, page 3 [Design section] b) Abstract, page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) Abstract, page 3 (Setting section) 1.2) Abstract, page 3 (Setting and Participants sections) 1.3) N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 5		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Materials and Methods, page 6 (Study Design)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Materials and Methods, page 6 (Study Design)		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	A) Eligibility criteria, follow-up duration and data sources described in Materials and Methods, page 6 and 7 (Study Design)	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1) Materials and Methods, page 7 (Study Design) with full lists of ICD9/10 codes used to identify diagnosed/undiagnosed cases given in Supplementary Materials 6.2) N/A (eligible patients were identified based on eGFR which was calculated from serum creatinine as described in Materials and Methods and according to internationally-recognized equations for eGFR calculations) 6.3) N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Materials and Methods, page 7 (Study Design section)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1) Full list of ICD9/10 codes used in Supplementary Tables 2 and 3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Materials and Methods, page 6 (Study Design section)		

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	Materials and Methods, page 7 (Study Design section); potential bias addressed in Discussion, pages 16 and 17		
Study size	10	Explain how the study size was arrived at	N/A (all eligible patients within specified time frame were included)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	N/A (quantitative variables collected from existing EMR/claims databases; CKD stage groupings based on existing KDIGO guidelines referenced in the manuscript)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how	Materials and Methods, pages 7 and 8 (Study Design and Statistical Analysis sections)		

		matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) Author Contributions section, page 19 12.2) N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3) N/A
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a) Results, page 8 b) N/A c) Figure 1 (cohort selection)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1) Figure 1 (cohort selection); Results, page 8
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic,	a) Results, pages 9 and 12		

		clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(Demographics and Clinical Characteristics of Patients with Diagnosed and Undiagnosed CKD section); Table 1 b) Table 1 c) Results, page 12 (Time to CKD Diagnosis section)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Results, pages 8 and 9		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	a) Results, page 13; confounders for multivariate analyses given in footnotes of supplementary Figure 3 and 4 b) N/A c) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and	Results, pages 12 and 13		

		interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion, page 14		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pages 16 and 17 (Strengths and Limitations)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion, page 17 (Strengths and Limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, page 18 (Conclusions)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, page 17 (Strengths and Limitations)		
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	Funding, page 20		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data Availability Statement, page 19; Supplementary Appendix

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.