

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 m² (stage 3a/3b CKD using the CKD-EPI¹ 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).
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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.
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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 Winkelmayr et al., 2005²

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 Winkelmayr et al., 2005² according to country and database

Country Database	France THIN Cegecim n=20 012	Germany Disease Analyzer n=26 767	Italy LPD n=65 676	Japan Japan RWD n=90 902	LCED n=22 470	USA 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 Database	USA 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 m², 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 Database	France		Germany		Italy		Japan		USA			
	THIN Cegedim Undiagnosed n=19 120	Diagnosed* n=892	Disease Analyzer Undiagnosed n=22 557	Diagnosed* n=4210	LPD Undiagnosed n=50 547	Diagnosed* n=15 129	Japan RWD Undiagnosed n=83 693	Diagnosed* n=7209	LCED Undiagnosed n=13 845	Diagnosed* n=8625	TriNetX 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 (1.09–1.60)	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 (2.04–3.10)	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.

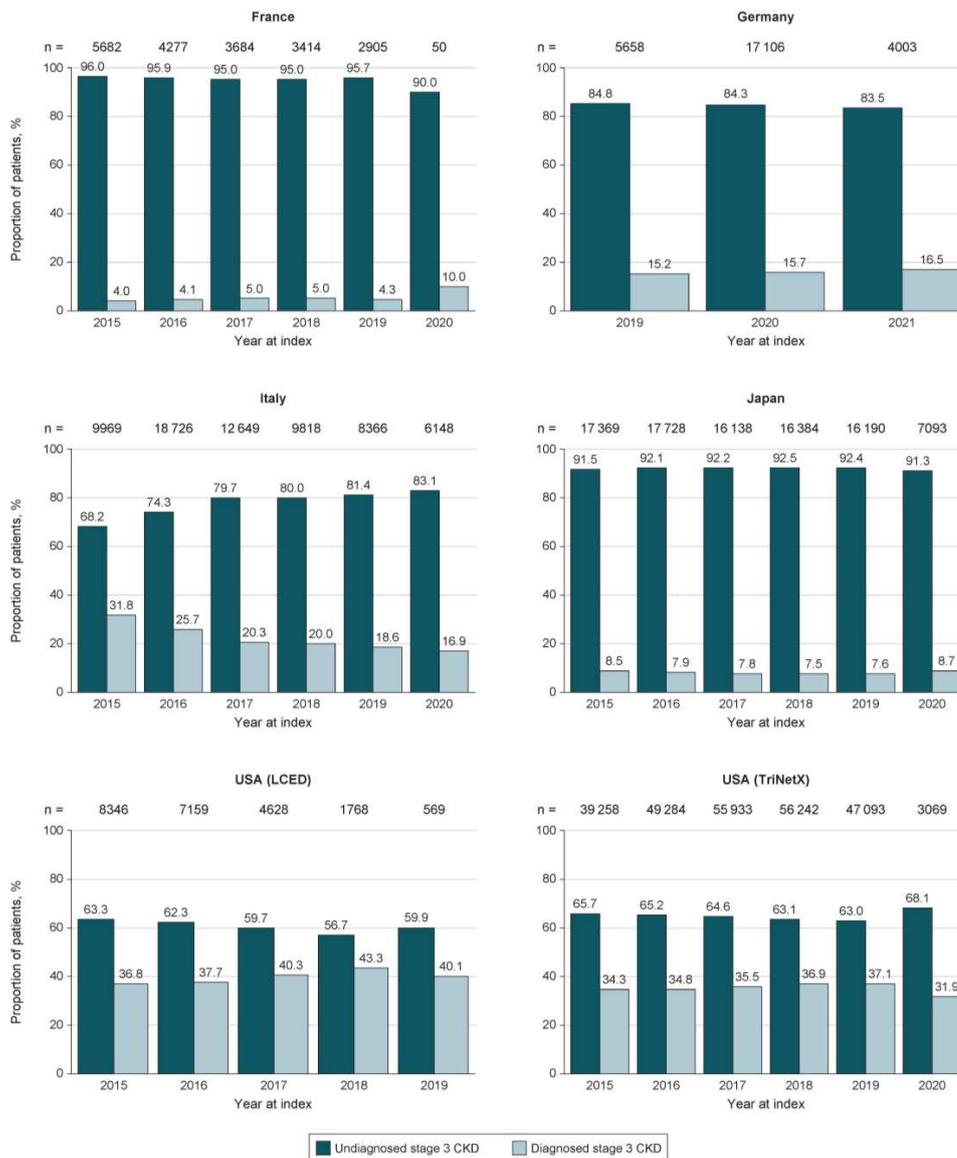
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IQR, interquartile 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)

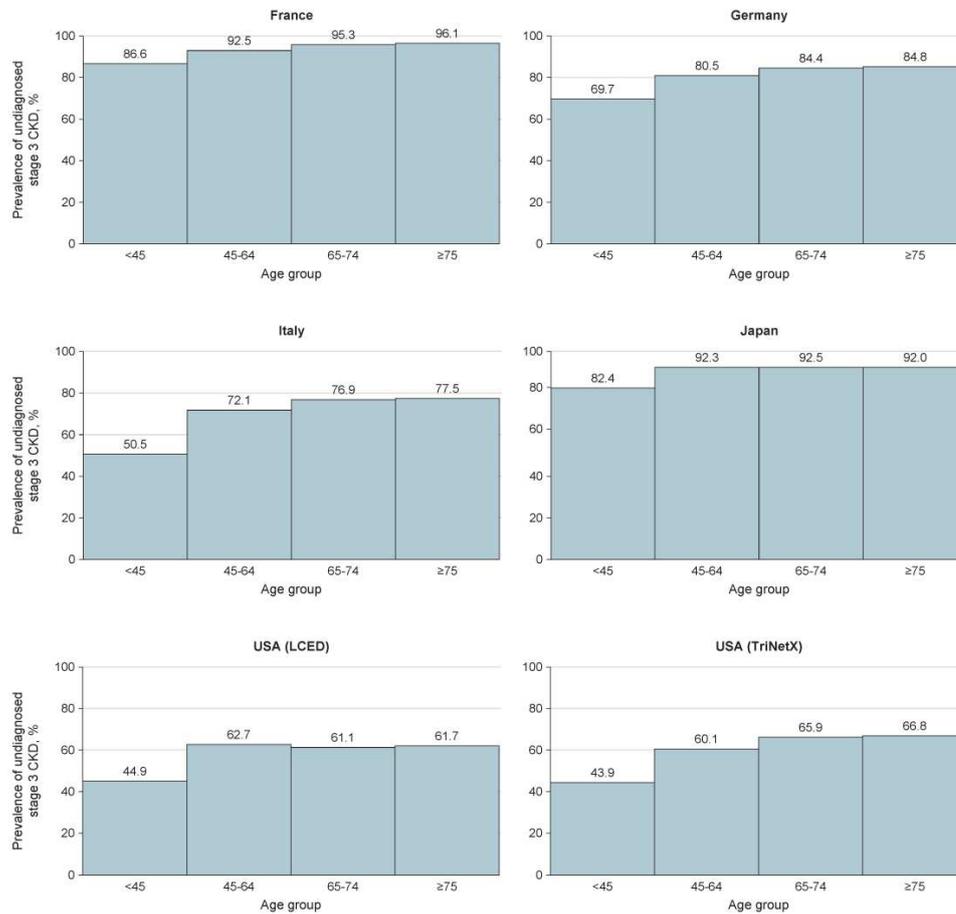
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

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



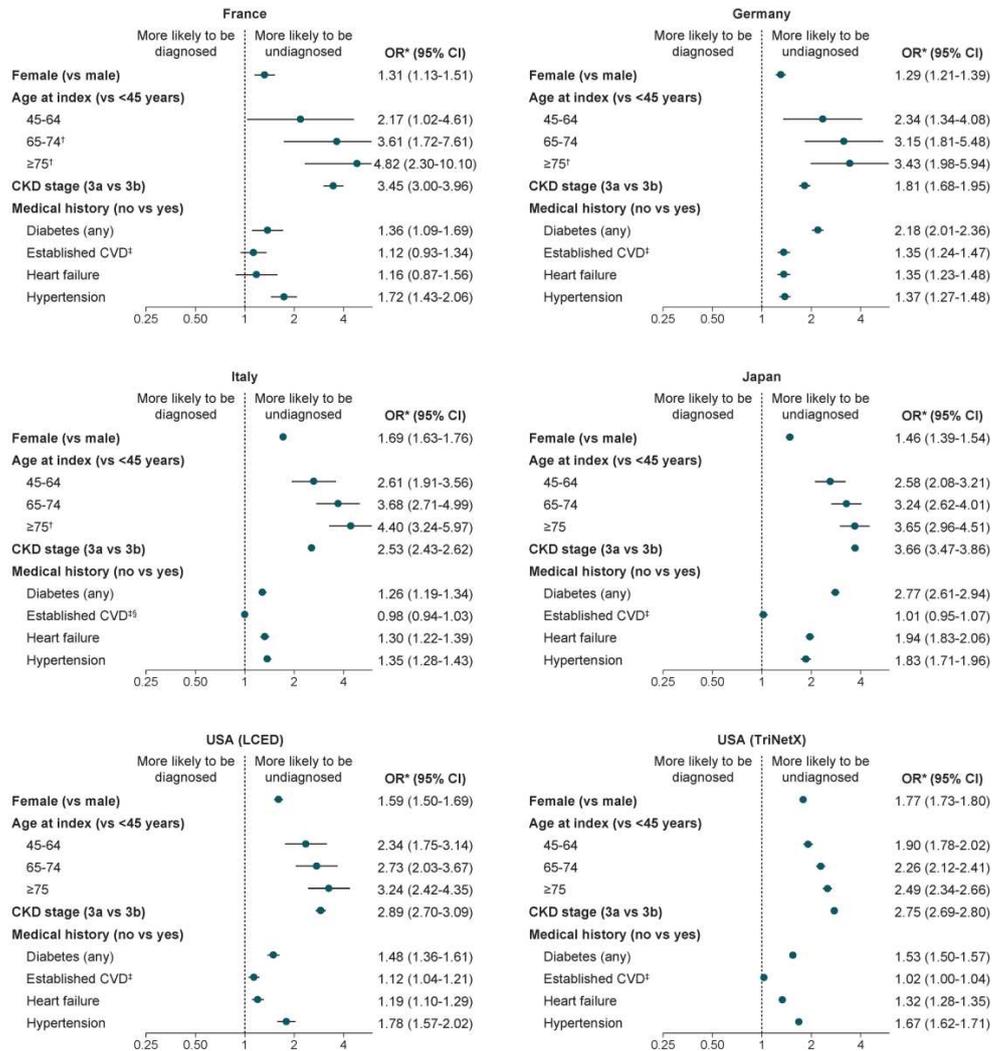
CKD, chronic kidney disease; LCED, Explorys Linked Claims and Electronic Medical Records Data.

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).

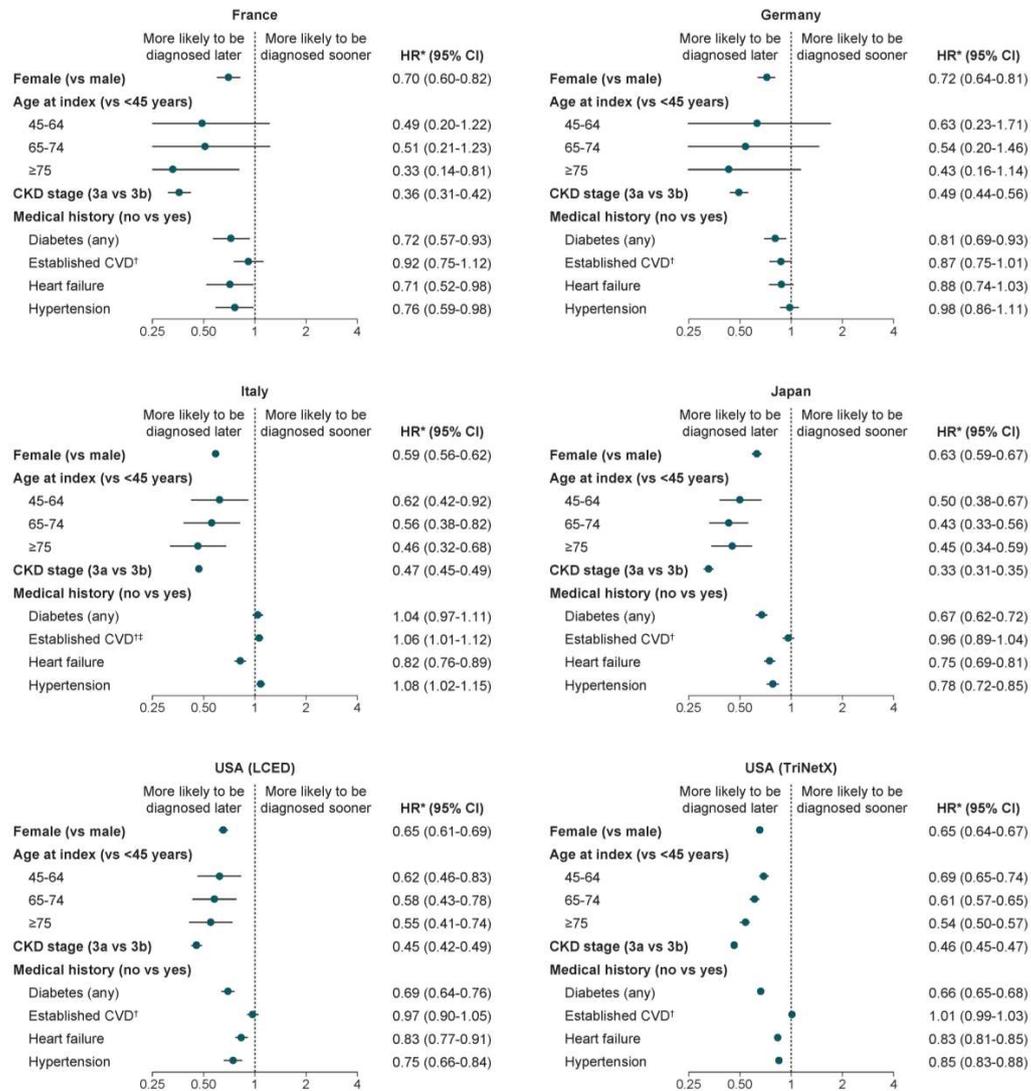
[†]Upper 95% confidence interval extends beyond the boundary of the graph.

[‡]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.

^aHazard 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).

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

^cOwing 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

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