Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data

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Summary

Background Some evidence suggests that chronic kidney disease is a risk factor for lower-extremity peripheral artery disease. We aimed to quantify the independent and joint associations of two measures of chronic kidney disease (estimated glomerular filtration rate [eGFR] and albuminuria) with the incidence of peripheral artery disease.

Methods In this collaborative meta-analysis of international cohorts included in the Chronic Kidney Disease Prognosis Consortium (baseline measurements obtained between 1972 and 2014) with baseline measurements of eGFR and albuminuria, at least 1000 participants (this criterion not applied to cohorts exclusively enrolling patients with chronic kidney disease), and at least 50 peripheral artery disease events, we analysed adult participants without peripheral artery disease at baseline at the individual patient level with Cox proportional hazards models to quantify associations of creatinine-based eGFR, urine albumin-to-creatinine ratio (ACR), and dipstick proteinuria with the incidence of peripheral artery disease (including hospitalisation with a diagnosis of peripheral artery disease, intermittent claudication, leg revascularisation, and leg amputation). We assessed discrimination improvement through c-statistics.

Findings We analysed 817 084 individuals without a history of peripheral artery disease at baseline from 21 cohorts. 18 261 cases of peripheral artery disease were recorded during follow-up across cohorts (median follow-up was 7·4 years [IQR 5·7–8·9], range 2·0–15·8 years across cohorts). Both chronic kidney disease measures were independently associated with the incidence of peripheral artery disease. Compared with an eGFR of 95 mL/min per 1·73 m², adjusted hazard ratios (HRs) for incident study-specific peripheral artery disease was 1·22 (95% CI 1·14–1·30) at an eGFR of 45 mL/min per 1·73 m² and 2·06 (1·70–2·48) at an eGFR of 15 mL/min per 1·73 m². Compared with an ACR of 5 mg/g, the adjusted HR for incident study-specific peripheral artery disease was 1·50 (1·41–1·59) at an ACR of 30 mg/g and 2·28 (2·12–2·44) at an ACR of 300 mg/g. The adjusted HR at an ACR of 300 mg/g versus 5 mg/g was 3·68 (95% CI 3·00–4·52) for leg amputation. eGFR and albuminuria contributed multiplicatively (eg, adjusted HR 5·76 [4·90–6·77] for incident peripheral artery disease and 10·61 [5·70–19·77] for amputation in eGFR <30 mL/min per 1·73 m² plus ACR ≥300 mg/g or dipstick proteinuria 2+ or higher *vs* eGFR ≥90 mL/min per 1·73 m² plus ACR <10 mg/g or dipstick proteinuria negative). Both eGFR and ACR significantly improved peripheral artery disease risk discrimination beyond traditional predictors, with a substantial improvement prediction of amputation with ACR (difference in c-statistic 0·058, 95% CI 0·045–0·070). Patterns were consistent across clinical subgroups.

Interpretation Even mild-to-moderate chronic kidney disease conferred increased risk of incident peripheral artery disease, with a strong association between albuminuria and amputation. Clinical attention should be paid to the development of peripheral artery disease symptoms and signs in people with any stage of chronic kidney disease.

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Introduction

Lower-extremity peripheral artery disease affects 8–10 million adults in the USA[1] and more than 200 million adults around the world.[2] Its prevalence increased by 24% globally in the past decade.[2] Peripheral artery disease increases the risk of adverse clinical outcomes[3,4] and impairs lower-extremity function.[5] It is especially important for people on haemodialysis and its incidence (about 400 per 1000 patient-years) is much higher than the incidence of coronary heart disease and stroke (about 100–150 per 1000 patient-years each) in this clinical population.[6]

Several previous studies have been done to investigate the association of mild and moderate stages of chronic kidney disease with peripheral artery disease.[7–14] However, most of these studies were cross-sectional[7–10] or investigated either, but not both, of the two kidney measures (estimated glomerular filtration rate [eGFR] or albuminuria) used to define and stage chronic kidney disease.[9–12] This limited evidence might have contributed to chronic kidney disease not being included among the risk factors for peripheral artery disease in the 2016 guidelines on peripheral artery disease from the

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Research in context

Evidence before this study

Lower-extremity peripheral artery disease is an important complication for patients on haemodialysis, and its incidence is much higher than that for coronary heart disease and stroke in this clinical population. No formal systematic review was undertaken; KM searched PubMed for papers published to June 30, 2016, and co-authors provided feedback on relevant articles. For low-severity stages of chronic kidney disease, several previous studies have investigated the risk for peripheral artery disease, but most of them were cross-sectional or investigated either (but not both) of the two kidney measures used to define and stage chronic kidney disease: estimated glomerular filtration rate (eGFR) or albuminuria. This limited evidence might have contributed to 2016 guidelines on peripheral artery disease from the American Heart Association and the American College of Cardiology not including chronic kidney disease among the risk factors for peripheral artery disease.

Added value of this study

In this individual-level data meta-analysis, with 18 261 incident peripheral artery disease cases from 0·8 million participants from 21 cohorts, we examined the prospective and independent associations of eGFR and albuminuria with future risk of peripheral artery disease. Our results showed that both albuminuria and reduced eGFR were independently associated with future risk of peripheral artery disease. Even mild-to-moderate chronic kidney disease (when either of eGFR 30–59 mL/min per 1·73 m^2 or urine albumin-to-creatinine ratio 30–299 mg/g is present) conferred 1·5–4-times higher risk of peripheral artery disease beyond traditional risk factors. Accordingly, both kidney measures improved the prediction of peripheral artery disease risk beyond traditional risk factors, with more evident improvements with albuminuria than with eGFR. Albuminuria was particularly strongly associated with the risk of leg amputation and substantially improved its risk prediction.

Implications of all the available evidence

Our results suggest that individuals with chronic kidney disease, even at mild-to-moderate stages, might warrant clinical attention to leg signs and symptoms of peripheral artery disease. Annual foot care is currently recommended in patients with diabetes, but adherence to this recommendation is low. Thus, as the first step to improve this low adherence, people with both diabetes and chronic kidney disease (particularly when albuminuria is present) might be a reasonable target for strong encouragement of regular foot care. Assessment of kidney function and albuminuria is already recommended in patients with diabetes or hypertension. As such, in these clinical populations, the chronic kidney disease measures should be readily available to classify the risk of peripheral artery disease.

American Heart Association (AHA) and the American College of Cardiology (ACC).[15]

We aimed to quantify the independent and joint associations of eGFR and albuminuria with future risk of peripheral artery disease using data from eligible cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC).[16] These rich data also allowed us to assess improvement of prediction of peripheral artery disease with these measures of chronic kidney disease and to investigate several different definitions of peripheral artery disease such as leg amputation and revascularisation.

Methods

Study design and data sources

Details of the CKD-PC are described elsewhere.[16,17] Briefly, the CKD-PC is an international consortium established to provide evidence that can improve prevention and management of chronic kidney disease and currently consists of more than 70 prospective cohorts, including participants from 40 countries or regions with data for eGFR, albuminuria, and clinical outcomes. The present study is a collaborative meta-analysis including data from nine general population cohorts, eight cohorts of patients at high risk of cardiovascular disease (such as patients with diabetes), and four cohorts exclusively enrolling patients with chronic kidney disease. These prospective studies had data on incident peripheral artery disease, whereas other cohorts in the CKD-PC did not. This study was approved for use of de-identified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD, USA), and the need for informed consent was waived.

Cohorts with baseline measurements of eGFR and albuminuria, at least 1000 participants (this criterion not applied to cohorts exclusively enrolling patients with chronic kidney disease), and at least 50 peripheral artery disease events were eligible for inclusion. We obtained individual level data from most cohorts but used a distributed data analysis model to include the three cohorts that were unable, for logistic or legal reasons, to send individual level data. We sent out tailored code to individuals responsible for the cohort database to run on their individual participant data and then send us matrices with descriptive data and β-coefficients to be able to meta-analyse across all cohorts. Transfer of individual participant data or standardised analysis of outputs for meta-analysis took place between July 1, 2015, and Jan 31, 2017, with baseline measurements done between 1972 and 2014.

Procedures

We primarily estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based equation,[18] because serum creatinine is the most widely used filtration marker in clinical practice.[19] However,

as a secondary analysis, we analysed eGFR using the CKD-EPI cystatin-C equation in six studies with relevant data because cystatin-C-based eGFR has shown a stronger association with clinical outcomes than creatinine-based eGFR.[20] For measurement of albuminuria, we preferred to use urine albumin-to-creatinine ratio (ACR), as recommended by chronic kidney disease guidelines,[21] but we also accepted semiquantitative assessment of proteinuria with a dipstick test.[16]

We defined the following factors in the AHA/ACC Pooled Cohort Equations[22] as traditional atherosclerotic risk factors: age, sex, race (black *vs* non-black), smoking status (current *vs* former or never), systolic blood pressure, antihypertensive drug use, diabetes (defined as fasting blood glucose ≥7·0 mmol/L, non-fasting blood glucose ≥11·1 mmol/L, HbA_{1c} ≥6·5%, use of antidiabetes drugs, or self-reported diabetes), and blood concentrations of total and HDL cholesterol. A history of other cardiovascular disease (coronary heart disease, stroke, and heart failure) was not an exclusion criterion and was treated as a covariate in our study. We took this approach because risk factor profiles are not necessarily the same between peripheral artery disease and other cardiovascular diseases. For example, smoking and diabetes are particularly strong predictors of peripheral artery disease.[1] Also, diagnostic and monitoring approaches are unique for peripheral artery disease (eg, ankle brachial index and foot examination).[2,23] Notably, a previous risk prediction tool for new development of intermittent claudication from the Framingham Heart Study[24] incorporates a history of coronary heart disease as a predictor.

Outcomes

In view of the heterogeneous scientific literature regarding how to define incident peripheral artery disease,[11,12,24–26] we investigated the following definitions of peripheral artery disease: study-specific peripheral artery disease (comprehensively defined in each study on the basis of International Classification of Diseases [ICD] codes or self-report of peripheral artery disease diagnosis, leg revascularisation, leg amputation, intermittent claudication, or repeated ankle-brachial index, as available); peripheral artery disease-related hospital admissions (ICD-9 codes 440.2 [atherosclerosis of native arteries of the extremities] and 440.4 [chronic total occlusion of an artery of the extremities] or equivalents in ICD-10); leg revascularisation (ICD-9 codes 38.18 [endarterectomy, lower limb arteries], 39.25 [aorta-iliac-femoral bypass], 39.29 [other peripheral vascular shunt or bypass], 39.50 [angioplasty of other non-coronary vessel], or self-report); and leg amputation (ICD codes 84.1x [amputation of lower extremity]). The appendix (pp 3–5) details any deviations in definitions for each cohort.

Statistical analysis

We restricted analyses to patients aged 18 years or older without a history of peripheral artery disease at baseline. We excluded any patient with missing values for eGFR, albuminuria, or traditional cardiovascular risk factors at baseline.[18] However, we included a few studies that systematically did not record data for some traditional risk factors (appendix pp 6–7). All estimates were obtained within each cohort first and then meta-analysed by a fixed-effects model, with the number of events in each cohort as weights, to have consistent weights between the analysis of risk relation and risk prediction.[18,27] We did meta-analyses for peripheral artery disease outcome definitions when estimates were available from three or more cohorts.

Using Cox proportional-hazards models, we first quantified the associations of eGFR and albuminuria with peripheral artery disease outcomes in the general population and high cardiovascular risk cohorts after adjusting for each other and traditional risk factors. We modelled eGFR and ACR with linear splines, with knots for eGFR at 30, 45, 60, 75, and 90 mL/min per 1·73 m², and for ACR at 10, 30, and 300 mg/g. We set an eGFR of 95 mL/min per 1·73 m² and an ACR of 5 mg/g as reference values.[18] ACR values were log-transformed, as were all continuous data for traditional risk factors.[22,28] We used Zellner's seemingly unrelated regression[29] to assess whether the associations of eGFR and ACR with different definitions of peripheral artery disease were significantly different or not. We also quantified risk of peripheral artery disease by cross-categories of eGFR and albuminuria in the context of the new international chronic kidney disease staging system.[21] For this analysis of cross-categories of chronic kidney disease measures, as previously done,[28,30] we combined ACR with dipstick proteinuria: ACR less than 10 mg/g with proteinuria negative (reference); 10–29 mg/g with ± (trace); 30–299 mg/g with 1+; and 300 mg/g or higher with 2+ or higher. We applied the same categories of dipstick proteinuria when general population and high cardiovascular risk cohorts with data on dipstick proteinuria were investigated in other analyses.

Subsequently, we did subgroup analyses by age, sex, race, diabetes, hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications), use of statins, and a history of current cardiovascular diseases. We tested interaction with meta-regression for average coefficients for spline terms weighted on the number of events in each study (for eGFR, only spline terms <90 mL/min per 1·73 m² were taken into account). We also separately analysed the subpopulation with chronic kidney disease, including participants with low eGFR (<60 mL/min per 1·73 m²) or high albuminuria (ACR ≥30 mg/g or dipstick proteinuria ≥1+)[17] from the general population and the high cardiovascular risk cohorts, and all participants in the four chronic kidney disease cohorts. For the analysis of the chronic kidney disease population, we set an eGFR of 50 mL/min per 1·73 m² and an ACR of 100 mg/g as reference values, and

See Online for appendix

	n	Age (years)	Female	Black	Smokers	Hypertension	Diabetes	Total cholesterol (mmol/L)	HDL cholesterol (mmol/L)	History of CVD	eGFR <60 mL/min per 1·73 m²	ACR ≥30 mg/g	Study-specific PAD events	PAD hospital admission	PAD revascularisation	PAD amputation	Follow-up (years)
General population																	
ARIC	10 256	63 (6)	5668 (55%)	2251 (22%)	1481 (14%)	4770 (47%)	1656 (16%)	5·2 (1·0)	1·3 (0·4)	1349 (13%)	616 (6%)	796 (8%)	307	214	170	73	15·8 (14·2–16·8)
BIS	1553	80 (6)	842 (54%)	0	76 (5%)	1419 (91%)	362 (23%)	5·6 (1·2)	1·5 (0·5)	367 (24%)	533 (34%)	359 (23%)	101	NA	NA	NA	4·0 (3·9–4·1)
CHS	2824	78 (5)	1680 (59%)	459 (16%)	209 (7%)	1448 (51%)	486 (17%)	5·3 (1·0)	NA	843 (30%)	1162 (41%)	551 (20%)	135	NA	NA	NA	9·9 (5·6–15·0)
ESTHER*	5467	62 (7)	2958 (54%)	0	797 (15%)	3281 (60%)	993 (18%)	5·7 (1·3)	1·4 (0·4)	967 (18%)	598 (11%)	608 (11%)	67	NA	67	NA	10·7 (5·3–10·9)
KHS*	244 763	44 (10)	163 356 (67%)	0	93 459 (38%)	63 408 (26%)	15 021 (6%)	4·9 (0·9)	1·3 (0·3)	2706 (1%)	50 608 (21%)	8790 (4%)	1695	1695	NA	NA	12·4 (10·6–14·2)
MESA	6693	62 (10)	3532 (53%)	1836 (27%)	871 (13%)	3005 (45%)	839 (13%)	5·0 (0·9)	1·3 (0·4)	0	874 (13%)	638 (10%)	72	NA	NA	NA	8·5 (7·7–8·6)
PREVEND	6481	51 (13)	3449 (53%)	63 (1%)	2173 (34%)	2313 (36%)	270 (4%)	5·7 (1·1)	1·3 (0·4)	377 (6%)	172 (3%)	742 (11%)	63	NA	63	NA	12·5 (12·2–12·8)
Rancho Bernardo	1427	70 (12)	857 (60%)	1 (0%)	112 (8%)	719 (50%)	196 (14%)	5·5 (1·0)	1·4 (0·4)	181 (13%)	521 (37%)	203 (14%)	157	NA	NA	NA	13·7 (6·4–18·2)
SCREAM_DIP*	106 300	51 (14)	57 102 (54%)	0	NA	71 857 (68%)	19 131 (18%)	5·4 (1·1)	1·4 (0·4)	13 471 (13%)	9842 (9%)	5227 (5%)	1263	1150	396	216	4·3 (2·8–5·7)
Total	385 764	48 (11)	239 444 (62%)	4610 (1%)	99 178 (26%)	152 220 (39%)	38 954 (10%)	5·1 (1·0)	1·3 (0·3)	20 261 (5%)	64 926 (17%)	17 914 (5%)	3860	3059	696	289	10·1 (8·4–11·7)
High cardiovascular risk population																	
ADVANCE	10 580	66 (6)	4489 (42%)	35 (0%)	1586 (15%)	8732 (83%)	10 580 (100%)	5·2 (1·2)	1·3 (0·4)	2641 (25%)	1656 (16%)	3246 (31%)	665	NA	NA	NA	5·0 (4·5–5·0)
Geisinger	40 704	61 (14)	20 737 (51%)	1101 (3%)	6182 (15%)	30 132 (74%)	31 381 (77%)	4·8 (1·1)	1·2 (0·4)	11 882 (29%)	8191 (20%)	10 839 (27%)	911	667	387	249	3·2 (1·7–5·0)
GLOMMS-II	9752	66 (14)	4896 (50%)	0	85 (1%)	442 (5%)	646 (7%)	NA	NA	774 (8%)	3622 (37%)	2650 (27%)	271	NA	198	115	4·9 (2·7–7·5)
Maccabi	212 198	58 (14)	104 245 (49%)	0	4588 (2%)	122 703 (58%)	80 188 (38%)	4·9 (1·1)	1·3 (0·3)	8080 (4%)	27 717 (13%)	34 820 (16%)	6669	NA	NA	NA	5·0 (2·3–8·1)
Mt Sinai BioMe	4086	57 (13)	2481 (61%)	1395 (34%)	719 (18%)	3510 (86%)	2358 (58%)	4·8 (1·1)	1·4 (0·5)	693 (17%)	1127 (28%)	1249 (31%)	543	156	66	NA	4·1 (2·6–5·3)
NZDCS	25 904	61 (14)	12 796 (49%)	67 (0%)	3755 (14%)	19 171 (80%)	25 904 (100%)	5·3 (1·1)	1·3 (0·4)	4825 (19%)	6234 (24%)	1954 (8%)	2021	1592	415	468	9·3 (7·3–10·6)
RCAV	54 114	63 (12)	1761 (3%)	9405 (17%)	NA	40 839 (75%)	39 926 (74%)	4·6 (1·1)	NA	7029 (13%)	NA	11 583 (21%)	1529	1313	302	334	7·4 (6·4–8·3)
SCREAM ACR	61 321	53 (13)	26 795 (44%)	0	NA	52 313 (85%)	34 173 (56%)	5·1 (1·1)	1·3 (0·4)	11 426 (19%)	8217 (13%)	16 196 (26%)	1283	1148	392	272	3·6 (2·3–5·1)
SMART	3181	57 (13)	921 (29%)	0	922 (29%)	2075 (66%)	801 (25%)	5·1 (1·4)	1·2 (0·4)	1808 (57%)	602 (19%)	987 (31%)	105	NA	93	27	5·8 (2·4–9·6)
Total	421 840	59 (13)	179 121 (42%)	12 003 (3%)	17 837 (4%)	279 917 (66%)	225 957 (54%)	4·9 (1·1)	1·3 (0·3)	49 158 (12%)	57 366 (14%)	83 524 (20%)	13 997	4876	1853	1465	4·9 (3·3–6·3)

(Table continues on next page)

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categorised dipstick proteinuria into negative or trace (reference), 1+, 2+, and 3+ or higher, as done previously.[31]

Next, we estimated the difference in Harrell's c-statistics,[32] a parameter of risk discrimination accounting for censoring, between prediction models that included or excluded kidney measures (eGFR, albuminuria, or both). To mitigate the methodological advantage for kidney measures having several spline terms, in these prediction analyses, eGFR was modelled with two linear terms with a knot at 60 mL/min per 1·73 m², as previously done.[18]

All models showed good calibration according to visual assessment of predicted versus observed risk in almost all cohorts.[33] The assessment of heterogeneity was based on the I^2 statistic and the χ^2 test. We did a random-effects meta-regression analysis to assess sources of heterogeneity when heterogeneity was high (I^2 statistic >75%[34]). All analyses were done with Stata/MP 13 and p values of less than 0·05 were regarded as significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KM and JC had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication, informed by discussions with collaborators.

Results

A total of 817 084 individuals without a history of peripheral artery disease from 21 cohorts in the CKD-PC, with a mean age of 54 years (SD 12), were followed up for a median of 7·4 years (IQR 5·7–8·9, table). Overall, 268 385 (33%) had diabetes and 72 183 (9%) had a history of cardiovascular disease. The prevalence of an eGFR of less than 60 mL/min per 1·73 m² was 17% (64 926 of 385 764 patients) in the general population cohorts, 14% (57 366 of 421 840) in high cardiovascular risk cohorts, and 84% (7994 of 9480) in chronic kidney disease cohorts. The prevalence of high albuminuria (≥30 mg/g) was 5% (17 914 of 385 764 patients) in the general population cohorts, 20% (83 524 of 421 840) in high cardiovascular risk cohorts, and 66% (6279 of 9480) in chronic kidney disease cohorts.

During follow-up, 18 261 incident cases of peripheral artery disease were reported on the basis of study-specific definitions across all cohorts, in addition to 8014 cases of peripheral artery disease-related hospital admissions from eight cohorts, 2549 cases of leg revascularisation from ten cohorts, and 1754 cases of leg amputation from seven cohorts.

The adjusted risk of incident peripheral artery disease was largely constant above an eGFR of 60 mL/min per 1·73 m² and steadily increased below an eGFR of 60 mL/min per 1·73 m², with a similar risk gradient across the four definitions of peripheral artery disease (figure 1). Compared with an eGFR of 95 mL/min per 1·73 m², the hazard ratio (HR) of incident study-

	n	Age (years)	Female	Black	Smokers	Hypertension	Diabetes	Total cholesterol (mmol/L)	HDL cholesterol (mmol/L)	History of CVD	eGFR <60 mL/min per 1·73 m²	ACR ≥30 mg/g	Study-specific PAD events	PAD hospital admission	PAD revascularisation	PAD amputation	Follow-up (years)
(Continued from previous page)																	
Chronic kidney disease population																	
CanPREDDICT	1468	67 (13)	570 (39%)	25 (2%)	NA	1434 (98%)	704 (48%)	4·3 (1·3)	1·2 (0·4)	440 (30%)	1463 (100%)	1079 (74%)	74	NA	NA	NA	4·8 (2·7–5·0)
GCKD	4502	60 (12)	1845 (41%)	0	695 (15%)	4325 (96%)	1498 (33%)	5·5 (1·3)	1·4 (0·5)	1391 (31%)	3545 (79%)	2565 (57%)	130	NA	NA	NA	2·0 (2·0–2·1)
SRR-CKD	2527	67 (15)	848 (34%)	0	NA	2436 (96%)	876 (35%)	5·1 (1·5)	NA	576 (23%)	2497 (99%)	2006 (79%)	127	79	NA	NA	2·8 (2·0–4·4)
Sunnybrook	983	61 (18)	447 (45%)	0	93 (9%)	841 (86%)	396 (40%)	4·9 (1·3)	1·4 (0·5)	357 (36%)	489 (50%)	629 (64%)	73	NA	NA	NA	2·9 (1·7–4·8)
Total	9480	63 (14)	3710 (39%)	25 (0%)	788 (8%)	9036 (95%)	3474 (37%)	5·1 (1·4)	1·3 (0·4)	2764 (29%)	7994 (84%)	6279 (66%)	404	79	0	0	2·8 (2·0–3·4)
All cohorts																	
Total	817 084	54 (12)	422 275 (52%)	16 638 (2%)	117 803 (14%)	441 173 (54%)	268 385 (33%)	5·0 (1·0)	1·3 (0·3)	72 183 (9%)	130 286 (16%)	107 717 (13%)	18 261	8014	2549	1754	7·4 (5·7–8·9)

Data are n, n (%), mean (SD), or median (IQR). SCREAM Dip and SCREAM ACR are subsets of the same cohort. See appendix for definitions of study acronyms and references. CVD=cardiovascular disease. eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio. PAD=peripheral artery disease. NA=not applicable. *Studies with dipstick proteinuria.

Table: **Demographic characteristics of included cohorts**

specific peripheral artery disease was 1·22 (95% CI 1·14–1·30; p<0·0001) at an eGFR of 45 mL/min per 1·73 m², 1·68 (1·52–1·86; p<0·0001) at an eGFR of 30 mL/min per 1·73 m², and 2·06 (1·70–2·48; p<0·0001) at an eGFR of 15 mL/min per 1·73 m² (figure 1). The risk gradient was slightly steeper for an eGFR based on cystatin C than when based on a serum creatinine concentration of less than 90 mL/min per 1·73 m² (appendix p 11), although we were only able to meta-analyse study-specific peripheral artery disease in this analysis because of the limited availability of cystatin C measurements.

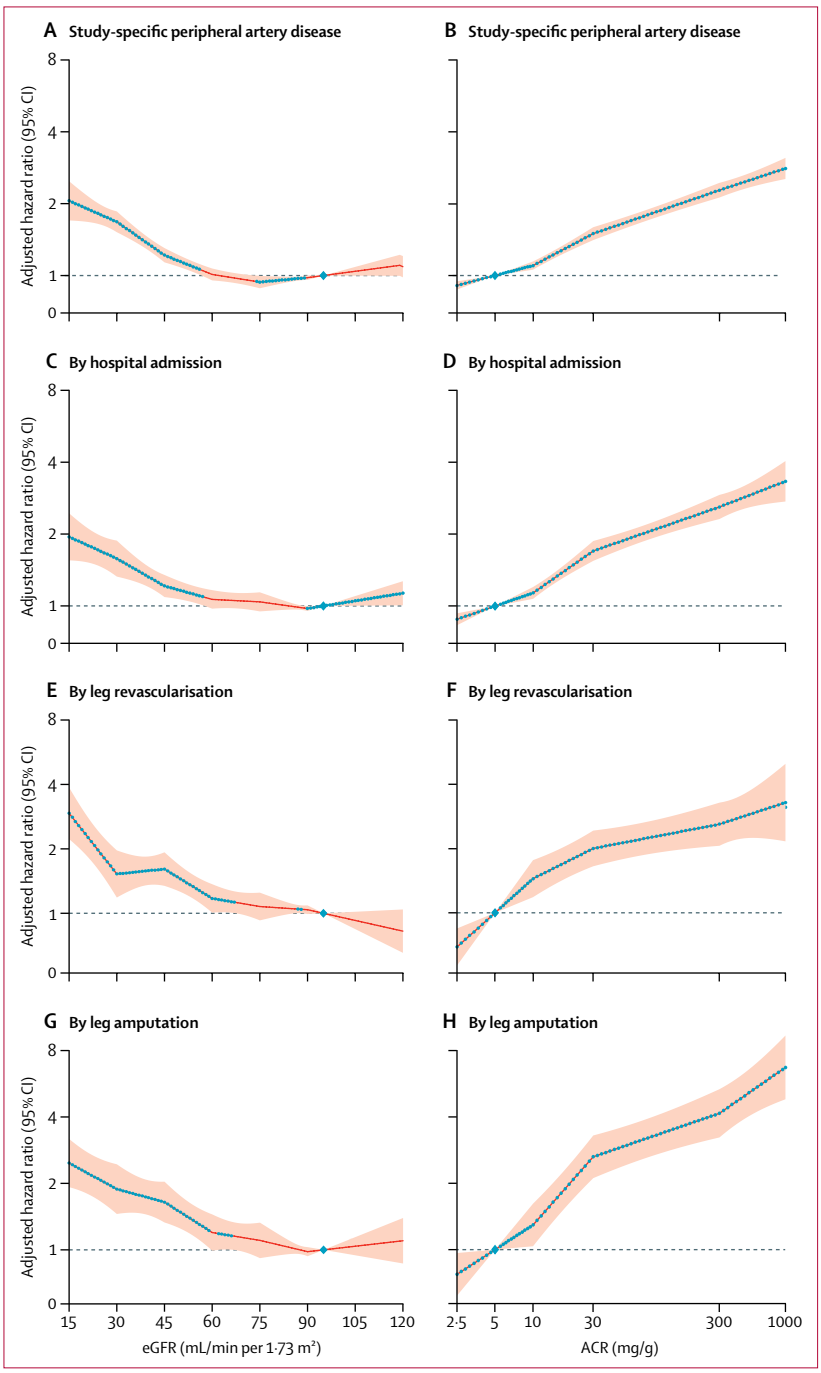

Figure 1: **Relative risk of incident peripheral artery disease, by eGFR and ACR**
Graphs show adjusted hazard ratios (red lines) and 95% CIs (shaded areas) for the four definitions of peripheral artery disease, according to eGFR (A,C,E,G) and ACR (B,D,F,H). The reference value is an eGFR of 95 mL/min per 1·73 m² and an ACR of 5 mg/g (diamonds), and blue dots indicate statistical significance compared to the reference. Analyses are adjusted for age, sex, race or ethnic origin, smoking status, systolic blood pressure, antihypertensive drug use, diabetes, total and HDL cholesterol concentrations, and albuminuria (ACR or dipstick) or eGFR, as appropriate. Panels A, C, E, and G included cohorts with dipstick proteinuria, and panels B, D, F, and H were based on cohorts with ACR data. eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio.

The associations of ACR with peripheral artery disease outcomes were generally linear on the log-log scale (figure 1), with significantly increased risk even within the range below the current clinical threshold of abnormality (<30 mg/g). Compared with an ACR of 5 mg/g, the HR for incident study-specific peripheral artery disease was 1·10 (95% CI 1·06–1·14; p<0·0001) at an ACR of 10 mg/g, 1·50 (1·41–1·59; p<0·0001) at an ACR of 30 mg/g, and 2·28 (2·12–2·44; p<0·0001) at an ACR of 300 mg/g (figure 1). The risk association seemed largely similar for study-specific peripheral artery disease, peripheral artery disease-related hospital admission, and leg revascularisation, but was steepest for leg amputation (figure 1). For example, the adjusted HR at an ACR of 300 mg/g versus 5 mg/g was 3·68 (95% CI 3·00–4·52; p<0·0001) for leg amputation and about 2·5 for the other three outcomes. Moreover, the adjusted HR for leg amputation for log-ACR as a linear term was significantly greater than that of study-specific peripheral artery disease (p<0·0001 by the seemingly unrelated regressions).

Although qualitatively consistent associations were seen in most cohorts, we saw high heterogeneity (I^2 statistic >75%) for HR at an eGFR of 45 mL/min per 1·73 m² versus 95 mL/min per 1·73 m² for study-specific peripheral artery disease and peripheral artery disease-related hospital admission (appendix p 12). However, in the meta-regression analyses, none of the covariates seemed to account for the difference in HRs across studies (appendix p 27). HR at an ACR of 30 mg/g versus 5 mg/g did not show high heterogeneity in any peripheral artery disease outcomes (appendix p 13). Regarding subgroups, although significant interactions were seen in some combinations of peripheral artery disease definitions and subgroups (appendix pp 14–20), chronic kidney disease measures were generally associated with increased risk of incident peripheral artery disease in every subgroup tested. Similar patterns were seen when we analysed the chronic kidney disease population (appendix p 21).

We confirmed multiplicative contributions of eGFR and albuminuria to increased risk of peripheral artery disease by modelling their cross-categories in the general and high cardiovascular risk cohorts, including cohorts with dipstick proteinuria (figure 2). Irrespective of peripheral artery disease definition, the highest risk was seen in the category of severely reduced eGFR (<30 mL/min per 1·73 m²) plus severely raised ACR (≥300 mg/g) or dipstick proteinuria (≥2+), with, for example, adjusted HRs of 5·76 (4·90–6·77) for incident peripheral artery disease and 10·61

(5·70–19·77) for amputation compared with the reference category of an eGFR of 90 mL/min per 1·73 m² or higher plus an ACR of less than 10 mg/g or negative dipstick proteinuria. The categories with mild-to-moderate abnormality of both eGFR (30–59 mL/min per 1·73 m²) and ACR (30–299 mg/g) showed 2·1–4·4 times higher risk of peripheral artery disease outcomes. Lower eGFR and higher ACR were associated with increased risk of peripheral artery disease, even when the other chronic kidney disease measure was normal (eg, an eGFR of 30–59 mL/min per 1·73 m² showed HRs of 1·2–2·4, even when the ACR was less than 10 mg/g; and an ACR of 30–299 mg/g showed a HR of 1·8–2·2, even when the eGFR was 90 mL/min per 1·73 m² or higher). Generally similar patterns were apparent when we analysed the chronic kidney disease population (appendix p 22).

C-statistics based on traditional risk factors ranged from 0·750 to 0·772 across the four peripheral artery disease outcomes in the general and high cardiovascular risk cohorts with ACR data (figure 3). The addition of chronic kidney disease measures significantly improved peripheral artery disease risk discrimination beyond traditional risk factors. For all peripheral artery disease outcomes, the improvement in risk discrimination was more evident with ACR than with eGFR (eg, difference in the c-statistic was 0·018 [95% CI 0·015–0·020] *vs* 0·010 [0·008–0·011] for study-specific peripheral artery disease). The improvement was especially evident for leg amputation when ACR was added, with a difference in the c-statistic of 0·058 (95% CI 0·045–0·070). We identified some incremental improvements in c-statistics when eGFR and ACR were added simultaneously (figure 3). The greater risk discrimination with ACR over eGFR was also seen when cystatin C was taken as the filtration marker rather than serum creatinine (appendix p 23).

Study-specific peripheral artery disease
ACR/dipstick measurement

eGFR	<10/dipstick measurement –	10–29/dipstick measurement ±	30–299/dipstick measurement 1+	≥300/dipstick measurement ≥2+	Overall
≥90	Reference	**1·31 (1·19–1·45)**	**1·82 (1·65–2·01)**	**3·16 (2·61–3·84)**	Reference
75–89	0·94 (0·87–1·01)	**1·22 (1·11–1·34)**	**1·84 (1·68–2·03)**	**3·14 (2·61–3·79)**	0·95 (0·91–1·01)
60–74	0·97 (0·89–1·04)	**1·29 (1·18–1·41)**	**1·87 (1·71–2·05)**	**2·97 (2·54–3·48)**	0·98 (0·93–1·04)
45–59	**1·24 (1·13–1·36)**	**1·63 (1·46–1·81)**	**2·07 (1·87–2·29)**	**3·39 (2·93–3·92)**	1·23 (1·16–1·31)
30–44	**1·78 (1·58–2·01)**	**1·99 (1·72–2·30)**	**2·51 (2·23–2·83)**	**3·92 (3·36–4·58)**	1·57 (1·46–1·70)
<30	**2·84 (2·28–3·53)**	**2·84 (2·18–3·71)**	**3·58 (3·06–4·19)**	**5·76 (4·90–6·77)**	2·42 (2·20–2·66)
Overall	Reference	1·31 (1·25–1·37)	1·79 (1·71–1·86)	2·80 (2·62–3·00)	

Hospital admissions
ACR/dipstick measurement

<10/dipstick measurement –	10–29/dipstick measurement ±	30–299/dipstick measurement 1+	≥300/dipstick measurement ≥2+	Overall
Reference	**1·38 (1·19–1·60)**	**2·06 (1·76–2·41)**	**4·35 (3·16–5·98)**	Reference
1·01 (0·91–1·13)	**1·45 (1·25–1·68)**	**2·42 (2·08–2·80)**	**3·42 (2·40–4·88)**	1·03 (0·96–1·12)
1·16 (1·04–1·30)	**1·48 (1·27–1·73)**	**2·41 (2·08–2·79)**	**4·01 (3·07–5·23)**	1·14 (1·05–1·24)
1·57 (1·35–1·83)	**2·05 (1·67–2·51)**	**2·82 (2·35–3·38)**	**4·49 (3·34–6·03)**	1·49 (1·34–1·66)
2·15 (1·76–2·63)	**2·46 (1·90–3·20)**	**3·02 (2·41–3·79)**	**6·09 (4·49–8·26)**	1·77 (1·56–2·02)
2·53 (1·80–3·57)	**3·83 (2·70–5·42)**	**4·82 (3·79–6·12)**	**7·21 (5·50–9·46)**	2·31 (1·95–2·75)
Reference	1·35 (1·25–1·45)	2·00 (1·86–2·15)	3·27 (2·90–3·69)	

Leg revascularisation
ACR/dipstick measurement

eGFR	<10/dipstick measurement –	10–29/dipstick measurement ±	30–299/dipstick measurement 1+	≥300/dipstick measurement ≥2+	Overall
≥90	Reference	**1·63 (1·30–2·03)**	**1·79 (1·41–2·28)**	**4·64 (3·37–6·41)**	Reference
75–89	0·99 (0·82–1·19)	**1·40 (1·09–1·79)**	**2·29 (1·82–2·88)**	**2·65 (1·53–4·59)**	0·97 (0·86–1·10)
60–74	1·15 (0·95–1·40)	**1·40 (1·09–1·81)**	**2·08 (1·64–2·65)**	**3·45 (2·16–5·51)**	1·06 (0·93–1·21)
45–59	**1·52 (1·18–1·96)**	**2·34 (1·75–3·13)**	**2·44 (1·82–3·28)**	**3·51 (2·27–5·45)**	1·42 (1·21–1·66)
30–44	**2·42 (1·76–3·33)**	**2·42 (1·63–3·58)**	**2·78 (1·85–4·17)**	**4·96 (3·25–7·57)**	1·60 (1·31–1·96)
<30	**2·65 (1·46–4·81)**	**2·94 (1·46–5·89)**	**3·18 (2·03–4·97)**	**7·14 (4·59–11·11)**	2·60 (2·04–3·31)
Overall	Reference	1·45 (1·29–1·62)	1·77 (1·58–1·99)	2·99 (2·47–3·64)	

Leg amputation
ACR/dipstick measurement

<10/dipstick measurement –	10–29/dipstick measurement ±	30–299/dipstick measurement 1+	≥300/dipstick measurement ≥2+	Overall
Reference	**1·59 (1·21–2·08)**	**2·17 (1·62–2·90)**	**8·02 (5·45–11·80)**	Reference
0·90 (0·72–1·13)	**1·94 (1·47–2·55)**	**3·16 (2·44–4·11)**	**7·21 (4·34–11·99)**	1·04 (0·90–1·20)
1·02 (0·81–1·30)	**1·83 (1·36–2·48)**	**3·25 (2·50–4·23)**	**5·17 (3·02–8·86)**	1·09 (0·93–1·27)
1·54 (1·12–2·14)	**2·81 (1·95–4·06)**	**3·96 (2·87–5·48)**	**9·30 (6·11–14·15)**	1·61 (1·32–1·96)
2·12 (1·33–3·38)	**4·37 (2·84–6·74)**	**4·43 (2·90–6·76)**	**10·27 (6·03–17·50)**	2·13 (1·68–2·69)
3·16 (1·67–5·99)	**5·77 (2·87–11·60)**	**7·39 (4·72–11·57)**	**10·61 (5·70–19·77)**	2·59 (1·97–3·40)
Reference	1·88 (1·64–2·16)	2·82 (2·47–3·23)	6·04 (4·97–7·35)	

Figure 2: **Categorical analysis of outcome definitions of peripheral artery disease with eGFR and ACR in the combined general population and high cardiovascular risk cohorts**
Panels show adjusted hazard ratios derived from categorical analysis of the general population and high cardiovascular risk cohorts. Dipstick proteinuria categories (negative, trace, 1+, and ≥2+) were combined with ACR categories, as appropriate. Units for ACR are mg/g. Colour coding is based on the following cutoffs: green indicating less than 1·5; yellow indicating 1·5 to less than 2; orange indicating 2 to less than 4; and red indicating 4 or higher. Bold indicates statistical significance (p<0·05). eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio.

To compare the contributions of the kidney measures and traditional risk factors to predicting risk of peripheral artery disease, we added each of them in turn to demographic predictors (age, sex, and race; figure 4). Of the traditional risk factors, diabetes and a history of other cardiovascular diseases were consistently the strongest predictors. Notably, ACR consistently improved the risk prediction more than these two potent predictors, irrespective of peripheral artery disease outcome assessed. The contribution of eGFR to risk prediction of peripheral artery disease was similar to or slightly greater than traditional risk factors, other than diabetes and history of cardiovascular disease. The risk discrimination improvement of peripheral artery disease was confirmed with dipstick, but not as much as with ACR data (appendix pp 24–25). When we investigated the chronic kidney disease population, the pattern for the contributions of eGFR, ACR, and traditional risk factors to peripheral artery disease risk prediction was largely similar (appendix p 26), with ACR as one of the most potent predictors.

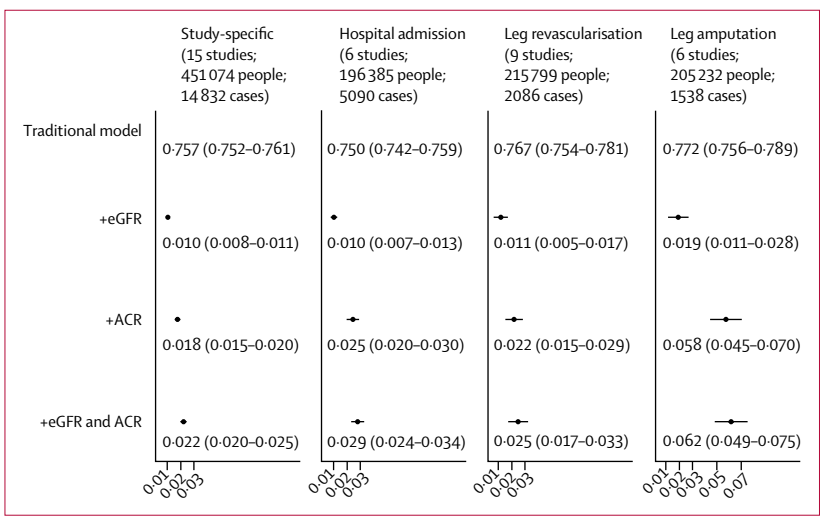

Figure 3: **Difference in c-statistics for each definition of peripheral artery disease after addition of kidney measures to traditional models**
Analyses shown were in the combined general population and high cardiovascular risk cohorts. Traditional models included adjustment for age, sex, race, smoking status, systolic blood pressure, antihypertensive drug use, diabetes, total and HDL cholesterol concentrations, and history of cardiovascular disease. Bars show 95% CI. eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio.

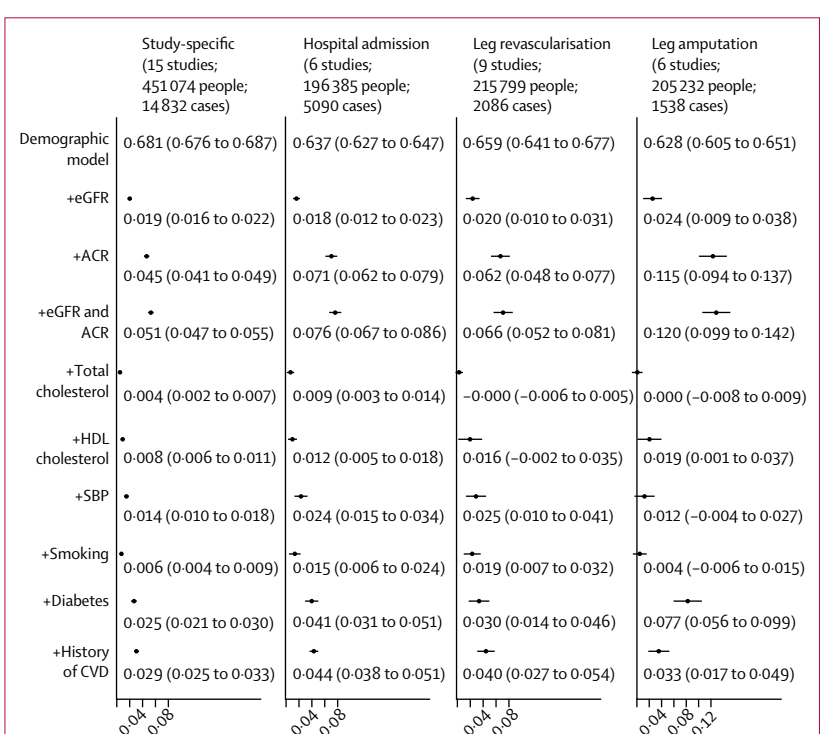

Figure 4: **Difference in c-statistics for each definition of peripheral artery disease after addition of kidney measures and traditional risk factors to the demographic model**
Analyses shown were in the combined general population and high cardiovascular risk cohorts. The demographic model includes age, sex, and race. Bars show 95% CI. eGFR=estimated glomerular filtration rate. ACR=urine albumin-to-creatinine ratio. SBP=systolic blood pressure. CVD=cardiovascular disease.

Discussion

This international collaborative meta-analysis of individual-level data in about 0·8 million individuals without peripheral artery disease at baseline shows that both eGFR and ACR were independently associated with future risk of peripheral artery disease. Even mild-to-moderate chronic kidney disease conferred 1·5–4-times increased risk of peripheral artery disease beyond traditional risk factors. For ACR, we identified a risk gradient even within the range currently regarded as normal or mildly raised (ie, <30 mg/g).[21] The associations were largely consistent across different cohorts and across key demographic and clinical subgroups such as participants with versus without diabetes or hypertension. Reflecting their strong associations, both kidney measures improved the prediction of peripheral artery disease risk beyond traditional risk factors, with more evident improvements with ACR than with eGFR. Notably, the contribution of these kidney measures (particularly ACR) to peripheral artery disease risk prediction was greater than or similar to any modifiable traditional risk factors, including diabetes and history of cardiovascular disease. Additionally, ACR substantially improved the prediction of leg amputation.

Although most previous studies have not analysed the chronic kidney disease–peripheral artery disease association longitudinally with both eGFR and albuminuria,[7–12] two previous investigations by Bello and colleagues[13] and Garimella and colleagues[14] have observed their prospective association. However, Bello and colleagues' study[13] included individuals with a history of peripheral artery disease at baseline and used a wide definition of peripheral artery disease, including atherosclerotic events beyond lower-extremity peripheral artery disease such as aortic aneurysm and renal artery stenosis. Garimella and colleagues' study[14] used a decrease in ankle-brachial index below 0·9 as an outcome variable.

Therefore, our study expanded these findings to clinical lower-extremity peripheral artery disease, including leg amputation. Other unique aspects of our study include a meta-analysis of individual-level data (mostly unpublished data), a collaborative investigation of international cohorts, detailed subgroup analyses, and a sophisticated evaluation of c-statistics.

Overall, our results suggest important pathophysiological contributions of chronic kidney disease to the development of peripheral artery disease above and beyond traditional risk factors, although the present study is not designed to elucidate mechanisms. Nonetheless, it is worth emphasising that both chronic kidney disease measures contributed to peripheral artery disease risk, even among participants without diabetes or hypertension, suggesting that eGFR and albuminuria are not merely end-organ damage markers of these traditional atherosclerotic risk factors. Several plausible mechanisms exist linking chronic kidney disease to peripheral artery disease, including, but not limited to, activation of the renin–angiotensin system, oxidative stress, inflammation, hypercoagulability, abnormal calcium-phosphate metabolism, increase of lipoprotein(a), and accumulation of uraemic toxins.[35] Additionally, albuminuria is linked to endothelial dysfunction and microvascular damage.[36] This link might account for the particularly strong contribution of albuminuria to the risk of leg amputation. The development of critical limb ischaemia as a severe form of peripheral artery disease has been suggested to be due to a compromised microcirculation, resulting in an impaired collateral formation and wound healing.[37,38]

Notably, increased ACR was associated with incident peripheral artery disease even within the range currently considered normal or mildly raised (ie, <30 mg/g).[21] This pattern was also seen for other cardiovascular outcomes (eg, cardiovascular mortality, coronary heart disease, and heart failure),[18,28] prompting some experts to propose a lower threshold of "elevated" albuminuria.[39] Decisions about thresholds for albuminuria should involve comprehensive consideration of the distribution of a relevant biomarker in the target population, the need for age-specific or sex-specific thresholds, the contribution to clinical outcomes, and the cost-effectiveness of clinical management triggered by identification of abnormal values of that biomarker.[28,40–42] In terms of distribution, 19·1% of participants in our general population cohorts had an ACR of less than 10 mg/g. Nonetheless, it seems worth paying attention to any future evidence informing this important issue, particularly the cost-effectiveness of any interventions targeting mildly raised ACR below 30 mg/g.

The strong association between chronic kidney disease and peripheral artery disease might not be surprising because chronic kidney disease is sometimes regarded as an equivalent atherosclerotic disease in terms of prognosis;[43] however, our study has clinical implications because the diagnosis and management of peripheral artery disease has some unique features. Although the AHA/ACC 2016 guideline on peripheral artery disease does not specify chronic kidney disease as a risk factor of peripheral artery disease,[15] our results suggest that individuals with chronic kidney disease, even at mild-to-moderate stages, might warrant clinical attention to leg signs and symptoms of peripheral artery disease. Annual foot care is currently recommended in patients with diabetes,[23] but adherence to this recommendation is only about 30%.[44] As such, a reasonable first step to improve this low adherence could be to target people with both diabetes and chronic kidney disease (particularly when albuminuria is present). From a practical point of view, it is important that the assessment of kidney function and albuminuria is already recommended in patients with diabetes and in patients with hypertension.[21,23,45] As such, in these clinical populations, chronic kidney disease measures should be readily available to classify the risk of peripheral artery disease. Moreover, a few research groups have proposed prediction models for the risk of peripheral artery disease in the general population,[24,33] but none of these models take into consideration measures of chronic kidney disease. In this context, the improvement of peripheral artery disease risk prediction with measures of chronic kidney disease in our study, even among individuals without diabetes or hypertension, is an important finding.

Although to our knowledge this is the most comprehensive study done so far to investigate the prospective association of chronic kidney disease with incident peripheral artery disease, the results should be interpreted with appropriate caution. As mentioned, the definitions of peripheral artery disease outcomes varied across cohorts. Additionally, some definitions (eg, clinical diagnosis and hospital admission for peripheral artery disease included as a part of study-specific peripheral artery disease in several studies) might be prone to ascertainment bias, particularly among patients with advanced chronic kidney disease. Nonetheless, it is important that the results were consistent across different peripheral artery disease outcomes, including a harder outcome of leg amputation. Similarly, the methods used to assess creatinine, albuminuria, and traditional risk factors were not necessarily consistent across cohorts, although we standardised their definitions as much as possible (appendix pp 6–7). Our study population predominantly consisted of white and black people, and, as such, confirmatory investigation is needed for other racial and ethnic groups. Additionally, as with any observational study, residual confounding due to unassessed potential confounders (eg, physical activity) could have occurred.

In conclusion, our results show that even mild-to-moderate chronic kidney disease conferred about 1·5–4 times higher risk of incident peripheral artery

disease beyond and above traditional atherosclerotic risk factors. The association between albuminuria and amputation was remarkably strong. Our results suggest that clinical attention should be paid to the development of leg symptoms and clinical signs of peripheral artery disease in people with any stage of chronic kidney disease.

Contributors

KM, JC, RTG, CPK, VS, and MW conceived the study concept and design. KM, SHB, JC, and the Chronic Kidney Disease Prognosis Consortium (CKD-PC) investigators and collaborators acquired the data. KM and the Data Coordinating Center members analysed the data. All authors contributed to the interpretation of the data. KM, SHB, JC, and FK drafted the report, and all authors provided critical revisions of the report for important intellectual content. All collaborators shared data and were given the opportunity to comment on the report. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in the appendix (pp 9–10).

Chronic Kidney Disease Prognosis Consortium (CKD-PC)

CKD-PC investigators and collaborators (study acronyms and abbreviations are listed in the appendix p 8)—ADVANCE (John Chalmers, Mark Woodward, Hisatomi Arima, Vlado Perkovic); ARIC (Josef Coresh, Kunihiro Matsushita, Morgan E Grams, Yingying Sang); BIS (Elke Schaeffner, Natalie Ebert, Peter Martus); CanPREDDICT (Adeera Levin, Ognjenka Djurdjev, Mila Tang); CARE FOR HOMe (Gunnar Heine, Sarah Seiler, Adam Zawada, Insa Emrich); CHS (Michael Shlipak, Mark Sarnak, Ronit Katz, Jade Hiramoto); ESTHER (Hermann Brenner, Ben Schöttker, Dietrich Rothenbacher, Kai-Uwe Saum); GCKD (Anna Köttgen, Florian Kronenberg, Markus Schneider, Kai-Uwe Eckardt); Geisinger (Jamie Green, H Lester Kirchner, Alex R Chang); GLOMMS-II (Corri Black, Angharad Marks, Gordon Prescott, Laura Clark, Nick Fluck); Gubbio (Massimo Cirillo); KHS (Sun Ha Jee, Heejin Kimm, Yejin Mok); Maccabi (Gabriel Chodick, Varda Shalev); MASTERPLAN (Jack F M Wetzels, Peter J Blankestijn, Arjan D van Zuilen, M Bots); MESA (Carmen Peralta, Jade Hiramoto, Ronit Katz, Mark Sarnak); Mt Sinai BioMe (Erwin Bottinger, Girish N Nadkarni, Stephen B Ellis, Rajiv Nadukuru); NZDCS (Timothy Kenealy, C Raina Elley, John F Collins, Paul L Drury); PREVEND (Ron T Gansevoort, Stephan JL Bakker, Hiddo J Lambers Heerspink); Rancho Bernardo (Simerjot K Jassal, Jaclyn Bergstrom, Joachim H Ix, Elizabeth Barrett-Connor); RCAV (Csaba Kovesdy, Kamyar Kalantar-Zadeh); SCREAM (Juan J Carrero, Alessandro Gasparini, Abdul Rashid Qureshi, Peter Barany); SMART (Frank Visseren, Ale Algra, Yolanda van der Graaf); SRR-CKD (Marie Evans, Mårten Segelmark, Maria Stendahl, Staffan Schön); Sunnybrook (Navdeep Tangri, Maneesh Sud, David Naimark); and ULSAM (Johan Ärnlöv, Lars Lannfelt, Anders Larsson).
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CKD-PC Data Coordinating Center—Shoshana H Ballew (assistant project director), Jingsha Chen (programmer), Josef Coresh (principal investigator), Morgan E Grams (director of nephrology initiatives), Lucia Kwak (programmer), Kunihiro Matsushita (director), Yingying Sang (lead programmer), and Mark Woodward (senior statistician).

Declarations of interest

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