Supplementary document

Table S1. Alleles used for making the genetic risk score [1,2]

SNP	Closest gene	Coded allele frequency	Coded allele	Beta
Pulse Pressure				
rs13002573	*FIGN*	0.203	G	-0.31
rs871606	*CHIC2*	0.850	T	0.429
rs17477177	*PIK3CG*	0.717	T	-0.418
rs2071518	*NOV*	0.167	T	0.312
rs11222084	*ADAMTS-8*	0.375	T	0.337
rs1173756	*NPR3*	0.525	T	-0.267
rs9663362	*PLCE-1*	0.533	G	-0.271
rs3824755	*CYP17A1-NT5C3*	0.933	G	0.477
rs17249754	*ATP2B1*	0.892	G	0.392
rs17608766	*GOSR2*	0.908	T	-0.534
Pulse Wave Velocity				
rs1381289	*C14orf64*	0.436	T	-0.073
rs10764094	*C10orf112*	0.471	C	0.057
rs4778983	*EFTUD1*	0.301	C	0.057
rs6485690	*CKAP5*	0.308	A	-0.056
rs7959220	*ELK3*	0.027	G	0.266
rs6472483	*SLCO5A1*	0.452	T	-0.05
rs6101837	*MAFB*	0.416	C	-0.05
rs6947805	*CADPS2*	0.050	T	0.117
rs3742207	*COL4A1*	0.361	G	-0.025

Table S2. Included studies investing the association of markers of arterial stiffness and CKD incident in the general population

Study reference	Sample size	Study population	Country	Mean age	Stiffness index	Modelling of stiffness index	Outcome(s)	Fully adjusted effect estimate(s)	Follow-up time	Adjusted confounders
Pulse Wave Velocity										
Madero, 2013 [3]	2129	Population-based Health ABC	USA	74y	cfPWV	Doubling of PWV	-GFRcys loss of > 3 mml/min per1.73 m^2 -eGFR< 60 mml/min per1.73 m^2	OR: 1.16 (0.89,1.52) IRR: 1.39 (1.09,1.77)	8.5 years	Age, sex, race, site, anti HTN medication, DM, smoking, LDL, HDL, HF, baseline GFR
Upadhyay 2009 [4]	1252 1675	Population-based Framingham Study	USA	47y	cfPWV	per SD SD PWV= 3.1	-UACR>17men, >25 women -eGFR< 60 mml/min per1.73 m^2	OR: 1.14 (0.94, 1.42) OR: 0.94 (0.75, 1.19)	7-10 years	Age, sex, MAP, HR, BMI, DM, fasting glucose, total / HDL cholesterol ratio, triglycerides, CHD, anti-hypertensive and(or) lipid-lowering medication, smoking, hormone replacement therapy, baseline UACR or GFR
Tomiyama, 2010 [5]	2053	Occupational cohort	Japan	40y	baPWV	1 m/s	-GFRcr loss of > 3 mml/min per1.73 m^2 -eGFR< 60 mml/min per1.73 m^2	OR: 1.15 (1.03, 1.29) OR: 1.36 (1.09, 1.70)	5-6 years	Baseline GFR, age, sex, BMI, alcohol, smoking, BP, HR, CHOL, HDL, TG, glucose, medication, CHD, stroke, HTN, DM, dyslipidaemia
Pulse Pressure										
Madero, 2013 [3]	2129	Population-based Health ABC	USA	74y	Brachial PP	10 mmHg	-GFRcys loss of > 3 mml/min per1.73 m^2 -eGFR< 60 mml/min per1.73 m^2	OR: 1.10 (1.04,1.16) IRR: 1.06 (1.01,1.11)	8.5 years	Age, sex, race, site, anti HTN medication, DM, smoking, LDL, HDL, HF, baseline GFR
Upadhyay 2009 [4]	1252 1675	Population-based Framingham Study	USA	47y	Central PP	per SD SD PP= 14.5 mmHg	- ACR>17men, >25 women -eGFR< 60 mml/min per1.73 m^2	OR: 1.33 (0.92, 1.93) OR: 1.08 (0.71, 1.64)	7-10 years	Age, sex, MAP, HR, BMI, DM, fasting glucose, total / HDL cholesterol ratio, triglycerides, CHD, anti-hypertensive and(or) lipid-lowering medication, smoking, hormone replacement therapy, baseline UACR or GFR
Rifkin, 2013 [6]	4365	Population-based Cardiovascular Health Study	USA	72y	Brachial PP	10 mmHg	-GFRcys loss of > 3 mml/min per1.73 m^2 -delta GFR	OR: 1.15 (1.11, 1.20) Beta: -0.15 (-0.21, -0.09)	5-6 years	Baseline GFR, age, sex, BMI, alcohol, smoking, BP, HR, CHOL, HDL, TG, glucose, medication, CHD, stroke, HTN, DM, dyslipidaemia
Peralta, 2012 [7]	4853	Population-based MESA	USA	60y	Brachial PP	per SD SD PP= 16mmHg	Decline in GFR	Beta: 0.35 (-0.43 , -0.28)	4.76 years	Age, sex, race, education, BMI, DM, smoking, anti HTN medication, LDL, HDL, CRP, UACR, SBP

Abbreviations: SD standard deviation, PP pulse pressure, cfPWV carotid-femoral pulse wave velocity, baPWV brachial-ankle pulse wave velocity, eGFR estimated glomerular filtration rate, OR odds ratio, IRR incident rate ratio, HTN hypertension, DM diabetes mellitus, LDL low density lipoprotein, HDL high density lipoprotein, HF heart failure, MAP mean arterial pressure, HR heart rate, CHD coronary heart disease, UACR, urine albumin creatinine ratio, BP blood pressure, TG triglyceride, SBP systolic blood pressure

Table S3. Interaction between pulse wave velocity and blood pressure in relation to GFR decline and CKD incidence

		GFR decline	Incident CKD
		P for interaction	**P for interaction**
Pulse wave velocity	Systolic blood pressure	0.13	0.54
	Diastolic blood pressure	0.58	0.60

Analyses are adjusted for age, sex, mean arterial pressure, heart rate, eGFR baseline, pulse pressure/pulse wave velocity, and follow up time (for analyses on incidence of CKD).

Table S4. Association of genetic risk scores for measures of arterial stiffness with annual decline in eGFR and incidence of CKD adjusted for pulse pressure and pulse wave velocity measures.

	eGFR decline			Incident CKD		
	Difference	**95%CI**	**P-value**	**RR**	**95%CI**	**P-value**
Pulse pressure GRS						
Model 1	0.05	0.01, 0.10	0.02	1.08	1.02,1.13	<0.01
Model 2	0.05	0.01, 0.10	0.04	1.07	1.02, 1.13	<0.01
Pulse wave velocity GRS						
Model 1	0.004	-0.01, 0.05	0.85	1.01	0.96, 1.07	0.52
Model 2	0.008	-0.04, 0.05	0.73	1.02	0.97, 1.07	0.45

Abbreviations: CI 95% Confidence interval; GRS Genetic risk score; RR Relative risk

Differences (beta) are per standard deviation of pulse pressure GRS and pulse wave velocity GRS.

Model 1: Adjusted for age, sex, mean arterial pressure, heart rate, eGFR baseline, pulse pressure/pulse wave velocity, and follow up time (for analyses on incidence of CKD).

Model 2: Additionally adjusted for body mass index, alcohol consumption, smoking, high-density lipoprotein cholesterol, total cholesterol, diuretics, ACE inhibitors, beta blockers, calcium channel blockers, and history of diabetes and coronary heart disease.

Table S5. Association of the pulse pressure genes with systolic and diastolic blood pressure

SNP name	Closest gene	Coded Allele	Systolic blood pressure		Diastolic blood pressure	
			Difference	*P value*	*Difference*	*P value*
rs13002573	*FIGN*	G	0.653	0.117	-0.061	0.781
rs871606	*CHIC2*	T	0.051	0.930	-0.345	0.252
rs17477177	*PIK3CG*	T	-1.303	**0.003**	0.087	0.709
rs2071518	*NOV*	T	-0.087	0.831	0.213	0.315
rs11222084	*ADAMTS-8*	T	-0.329	0.379	0.461	0.018
rs1173756	*NPR3*	T	0.074	0.832	0.209	0.253
rs9663362	*PLCE-1*	G	1.031	**0.003**	0.368	0.046
rs3824755	*CYP17A1-NT5C3*	G	0.721	0.246	0.156	0.633
rs17249754	*ATP2B1*	G	0.742	0.125	0.252	0.319
rs17608766	*GOSR2*	T	0.610	0.226	0.186	0.480

To account for multiple testing, we used Bonferroni corrected P-value (0.05/ number of SNPs ×2 (10×2) = 0.002).

Table S6. Association of pulse pressure genetic risk score excluding *PIK3CG* and *PLCE-1* gene with annual decline in eGFR and incidence of CKD.

	eGFR decline			Incident CKD		
	Difference	**95%CI**	**P-value**	**RR**	**95%CI**	**P-value**
Pulse pressure GRS						
Model 1	0.06	0.01, 0.11	0.01	1.08	1.03,1.14	<0.01
Model 2	0.06	7.9×10^{-3}, 0.11	0.01	1.08	1.02, 1.14	<0.01

Abbreviations: CI Confidence interval, GRS Genetic risk score, RR Relative risk

Differences (beta) are per standard deviation.

Model 1: Adjusted for age, sex, mean arterial pressure, heart rate, eGFR baseline and follow up time (for analyses on incidence of CKD).

Model 2: Additionally adjusted for diuretics, ACE inhibitors, beta blockers, calcium channel blockers, body mass index, alcohol consumption, smoking, high density lipoprotein cholesterol, total cholesterol, history of diabetes and coronary heart disease, and follow up time (for analyses on incidence of CKD).

Figure S1. Follow diagram of studies through the different phases of the meta-analyses

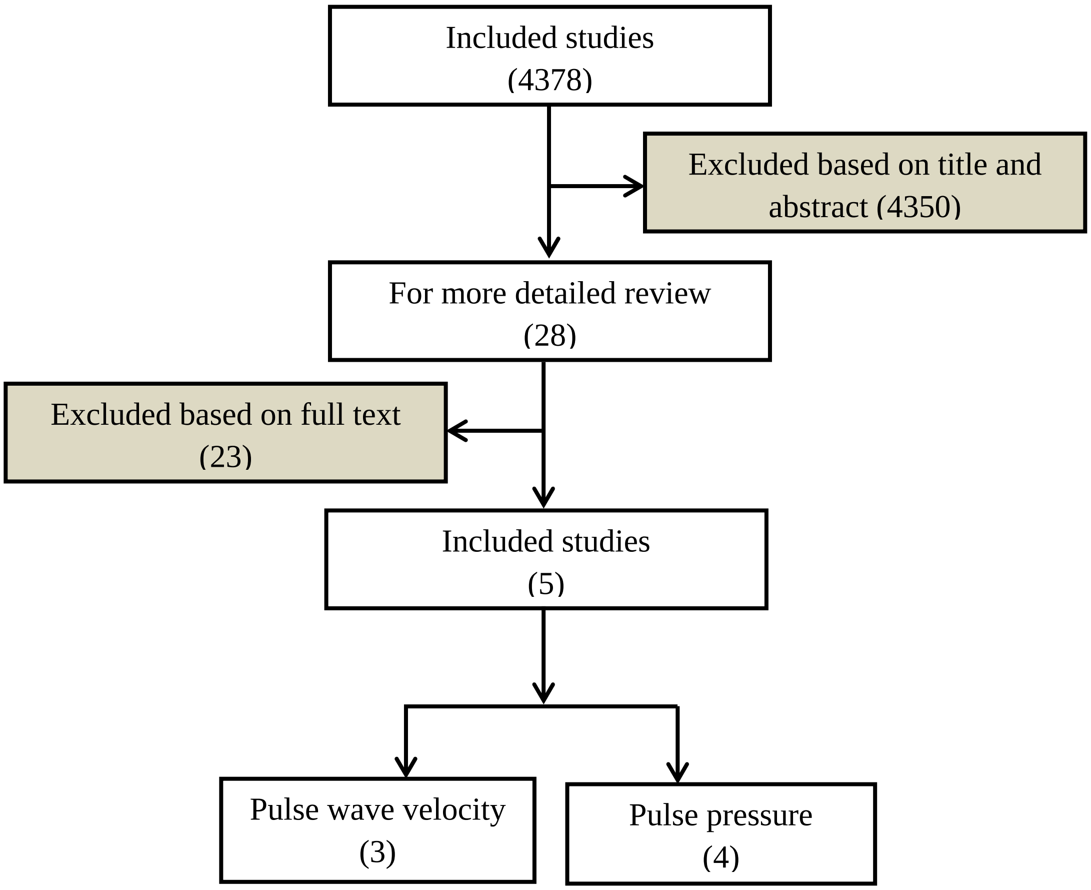
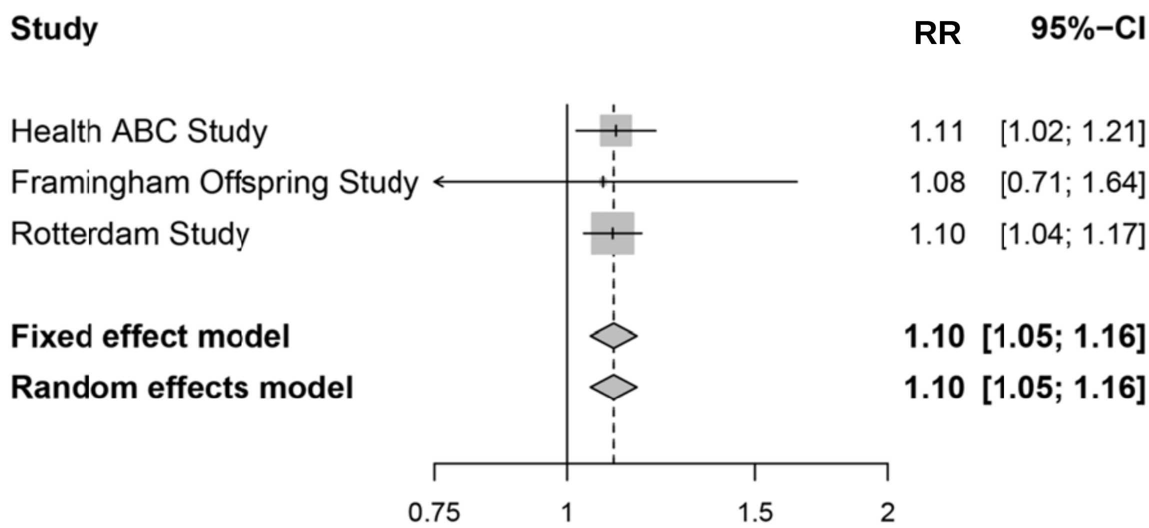


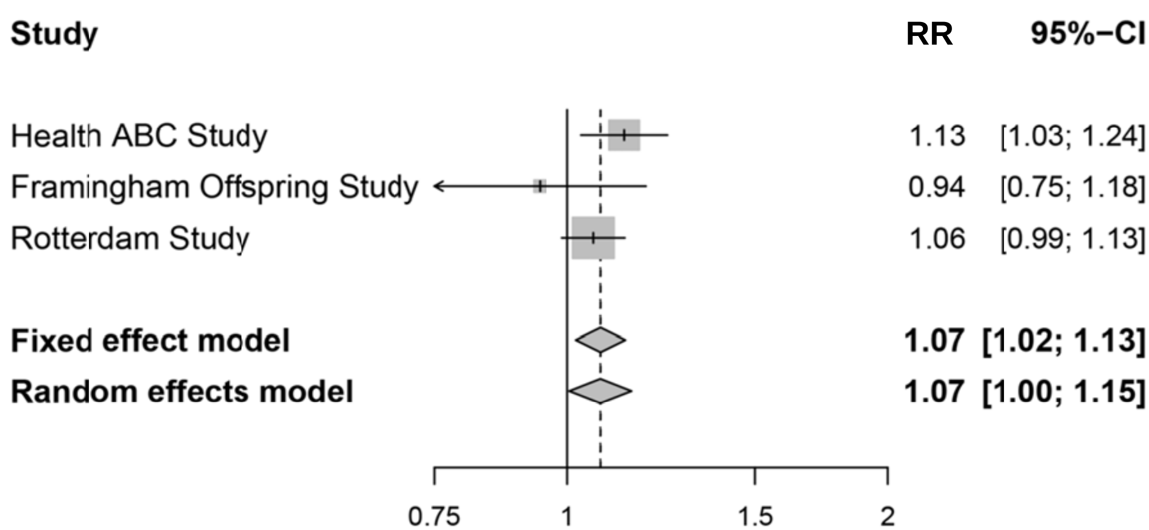
Figure S2. (A) Forest plot of multivariate adjusted relative risk for the association of pulse pressure with new onset CKD excluding the study with outcome definition of GFR loss of > 3 ml/min/1.73 m^2

(B) Forest plot of multivariate adjusted relative risk for the association of pulse wave velocity with new onset CKD excluding the study with ankle brachial pulse wave velocity.

A)



B)



Appendix. Search terms for the association between markers of arterial stiffness and incidence kidney disease in the population-based study.

Embase.com

('arterial stiffness'/de OR 'pulse pressure'/de OR 'arterial pressure'/de OR 'blood vessel compliance'/exp OR 'blood vessel calcification'/exp OR 'augmentation index'/de OR 'Young modulus'/de OR 'pulse wave'/de OR 'pulsatile flow'/de OR (((aort* OR arter* OR vascul* OR vessel*) NEAR/6 (stiff* OR complian* OR calcif*)) OR (wave NEXT/1 (velocit* OR reflection*)) OR ('internal carotid' NEAR/3 index) OR (pulse NEAR/3 (pressure* OR tension*)) OR distensibil* OR augmentation OR 'stiffness index' OR ((capacit* OR oscillat*) NEAR/3 complian*) OR ((elastic* OR young) NEXT/1 modul*) OR PWV OR CPP OR 'pulsatile flow'):ab,ti) AND (kidney/exp OR 'kidney function'/exp OR 'kidney function test'/exp OR 'kidney disease'/de OR 'chronic kidney disease'/exp OR 'chronic kidney failure'/exp OR microalbuminuria/exp OR ('albumin'/exp AND 'creatinine'/exp) OR 'cystatin C'/exp OR (kidney* OR renal OR nephro* OR glomeru* OR ckd OR microalbuminuri* OR (micro NEXT/1 albuminuri*) OR (albumin* NEAR/3 creatinin*) OR 'cystatin C'):ab,ti) AND ('cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR (population* OR cohort* OR longitudinal* OR prospectiv* OR 'follow up')) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim)

Medline (OvidSP)

("Vascular Stiffness"/ OR exp Elasticity/ OR "Arterial Pressure"/ OR "Vascular Calcification"/ OR "Pulse Wave Analysis"/ OR "pulsatile flow"/ OR (((aort* OR arter* OR vascul* OR vessel*) ADJ6 (stiff* OR complian* OR calcif*)) OR (wave ADJ (velocit* OR reflection*)) OR ("internal carotid" ADJ3 index) OR (pulse ADJ3 (pressure* OR tension*)) OR distensibil* OR augmentation OR "stiffness index" OR ((capacit* OR oscillat*) ADJ3 complian*) OR ((elastic* OR young) ADJ modul*) OR PWV OR CPP OR "pulsatile flow").ab,ti.) AND (exp kidney/ OR exp Kidney Function Tests/ OR kidney diseases/ OR Renal Insufficiency, Chronic/ OR (albumins/ AND creatinine/) OR cystatin C/ OR (kidney* OR renal OR nephro* OR glomeru* OR ckd OR microalbuminuri* OR (micro ADJ albuminuri*) OR (albumin* ADJ3 creatinin*) OR cystatin C).ab,ti.) AND (exp Cohort Studies/ OR (population* OR cohort* OR longitudinal* OR prospectiv* OR "follow up")) NOT (exp animals/ NOT humans/) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Web-of-science

TS=(((((aort* OR arter* OR vascul* OR vessel*) NEAR/6 (stiff* OR complian* OR calcif*)) OR (wave NEAR/1 (velocit* OR reflection*)) OR ("internal carotid" NEAR/3 index) OR (pulse NEAR/3 (pressure* OR tension*)) OR distensibil* OR augmentation OR "stiffness index" OR ((capacit* OR oscillat*) NEAR/3 complian*) OR ((elastic* OR young) NEAR/1 modul*) OR PWV OR CPP OR "pulsatile flow")) AND ((kidney* OR renal OR nephro* OR glomeru* OR ckd OR microalbuminuri* OR (micro NEAR/1 albuminuri*) OR (albumin* NEAR/3 creatinin*) OR "cystatin C")) AND ((population* OR cohort* OR longitudinal* OR prospectiv* OR "follow up"))) AND DT=(Article) AND LA=(english)

PubMed publisher

("Vascular Stiffness"[mh] OR Elasticity[mh] OR "Arterial Pressure"[mh] OR "Vascular Calcification"[mh] OR "Pulse Wave Analysis"[mh] OR "pulsatile flow"[mh] OR (((aort*[tiab] OR arter*[tiab] OR vascul*[tiab] OR vessel*[tiab]) AND (stiff*[tiab] OR complian*[tiab] OR calcif*[tiab])) OR (wave ADJ (velocit*[tiab] OR reflection*[tiab])) OR ("internal carotid" AND index) OR (pulse AND (pressure*[tiab] OR tension*[tiab])) OR distensibil*[tiab] OR augmentation OR "stiffness index" OR ((capacit*[tiab] OR oscillat*[tiab]) AND complian*[tiab]) OR ((elastic*[tiab] OR young) ADJ modul*[tiab]) OR PWV OR CPP OR "pulsatile flow")) AND (kidney[mh] OR Kidney Function Tests[mh] OR kidney diseases[mh] OR Renal Insufficiency, Chronic[mh] OR (albumins[mh] AND creatinine[mh]) OR cystatin C[mh] OR (kidney*[tiab] OR renal OR nephro*[tiab] OR glomeru*[tiab] OR ckd OR microalbuminuri*[tiab] OR (micro ADJ albuminuri*[tiab]) OR (albumin*[tiab] AND creatinin*[tiab]) OR cystatin C)) AND (Cohort Studies[mh] OR (population*[tiab] OR cohort*[tiab] OR longitudinal*[tiab] OR prospectiv*[tiab] OR "follow up")) NOT (animals[mh] NOT humans[mh]) AND english[la] AND publisher[sb]

Google scholar

"arterial|pulse|aorta|aortic|artery stiffness|pressure|compliance|calcification"|"wave velocity|reflection"|distensibility|augmentation|"pulsatile flow" kidney|renal|glomerular cohort|longitudinal|prospective|"follow up"

Supplementary references

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