Arterial Stiffness and Decline in Kidney Function

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Abstract

Background and objectives The independent link between arterial stiffness and CKD remains unknown. We investigated the association of indicators of arterial stiffness with decline in kidney function.

Design, setting, participants, & measurements We studied 3666 participants (mean age =65 years old; 58% women) from the Rotterdam Study. Pulse pressure (PP), carotid stiffness, and pulse wave velocity (PWV) were measured. We created genetic risk scores for PP and PWV. Annual declines in kidney function and incident CKD were assessed using eGFR. To put our findings in context of the literature, we performed a meta-analysis of the available population–based studies.

Results After a median (interquartile range) follow–up time of 11 (10.7–11.3) years, 601 participants with incident CKD were recognized. In the model adjusted for age, sex, mean arterial pressure, heart rate, and baseline GFR, each SD higher PP was associated with 0.15-ml/min per 1.73 m^2 steeper annual eGFR decline (95% confidence interval [95% CI], 0.10 to 0.20) and 11% higher risk of incident CKD (95% CI, 1.05 to 1.18). Each SD greater carotid stiffness was associated with 0.08-ml/min per 1.73 m^2 steeper annual eGFR decline (95% CI, 0.04 to 0.13) and 13% higher risk of incident CKD (95% CI, 1.05 to 1.22). Each SD higher PWV was associated with 7% higher risk of incident CKD (95% CI, 1.00 to 1.14). Incorporating our findings in a meta-analysis, each SD higher PP and PWV were associated with 16% (95% CI, 1.12 to 1.21) and 8% (95% CI, 1.03 to 1.14) higher risks of incident CKD. Each SD higher PP genetic risk score was associated with 0.06-ml/min per 1.73 m^2 steeper annual eGFR decline (95% CI, 0.01 to 0.10) and 8% higher risk of incident CKD (95% CI, 1.03 to 1.14). There was no association between PWV genetic risk score and kidney function decline.

Conclusions Higher indices of arterial stiffness are associated with steeper decline in kidney function. This suggests that vascular stiffness could be considered as a target for delaying decline in kidney function.

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Introduction

Considerable proportions of patients with CKD carry multiple cardiovascular risk factors and die from cardiovascular causes (1). Accumulating evidence suggests a strong association between cardiovascular pathology and CKD. Nevertheless, exact mechanisms linking cardiovascular diseases with kidney impairment remain to be elucidated (2).

The role of vascular risk factors has been implicated in the association between cardiovascular disease and CKD (3). One of the novel risk factors proposed for cardiovascular disease is arterial stiffness (4). Arterial stiffness, independent of mean arterial pressure, results in end organ damage by imposing hemodynamic stress on vascular beds (5). Aortic stiffening, especially in older people, facilitates transmission of excessive pressure and flow pulsatility into the microvascular beds of the kidneys, a high-flow organ, which will potentially lead to microvascular ischemia and tissue damage (6).

Several studies have investigated an independent association between arterial stiffness and decline in kidney function, but the results have been inconsistent (7–14). Heterogeneity in the study populations and the limited power of the individual studies could underlie the inconsistent findings. In addition, all observational studies are subject to confounding and reverse causation. Relevant genetic variants could potentially be used to overcome these flaws (15).

We aimed to investigate the association between arterial stiffness as well as genetic variations related to arterial stiffness with the risk of decline in kidney function in the Rotterdam Study (RS), a population-based study of individuals 55 years old and older. Moreover, to put our findings in the context of the literature, we performed a meta-analysis of population-based studies on the association of arterial stiffness markers and risk of kidney disease.

Materials and Methods

Population for Analysis

This study was performed within the framework of the population–based RS. The cohort originated in 1990 and included 7983 participants from Ommoord, a district of Rotterdam in The Netherlands, age 55 years

old or older (RS-I). In 2000, the first extension of the RS (RS-II) started, adding 3011 new participants. Arterial stiffness was evaluated at the third visit of the RS-I and the first visit of the RS-II. All individuals with available data on arterial stiffness markers at baseline and repeated creatinine measurements (at baseline and the next visit) were included in the analyses. The median (interquartile range) follow–up time elapsed between two creatinine measurements was 11 (10.7–11.3) years. This resulted in 2950 participants with available data on brachial pulse pressure, 2665 participants with pulse wave velocity (PWV) data, and 2344 participants with carotid stiffness data.

DNA was extracted from samples taken at the first visit of the RS-I and at the first visit of the RS-II (n=8131). Among them, 3666 had repeated measurements of creatinine for longitudinal assessment of kidney function.

The RS has been approved by the medical ethics committee according to the Population Study Act RS executed by the Ministry of Health, Welfare and Sports of The Netherlands. Written informed consent was obtained from all participants (16).

Measurement of Arterial Stiffness

Carotid femoral PWV was measured with participants in supine position with an automatic device (Complior Artech Medical, Pantin, France) that measures the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid artery and the femoral artery (17). The distance between the recording sites in the carotid and the femoral artery was measured with a tape over the surface of the body. PWV was calculated as the ratio between distance and the foot-to-foot time delay, and it was expressed in meters per second.

Common carotid stiffness was assessed with the participants in supine position with heads tilted slightly to the contralateral side for the measurement in the common carotid artery (18). The vessel wall motion of the right common carotid artery was measured by means of a duplex scanner (ATL Ultramark IV; operating frequency =7.5 MHz) connected to a vessel wall movement detector system (18,19). After 5 minutes of rest, a region at 1.5 cm proximal to the origin of the bulb of the carotid artery was identified with the use of B-mode ultrasound. The displacement of the arterial walls was obtained by processing the radiofrequency signals originating from two selected sample volumes positioned over the anterior and posterior walls. The end diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter ($\Delta D/D$) were computed as the mean of four cardiac cycles of three successive recordings. The cross–sectional arterial wall distensibility coefficient was calculated according to the following equation: distensibility coefficient $=2\Delta D/(D\times$ pulse pressure) (10^{-3} per kilopascal) (18,20). Lower carotid distensibility represents greater carotid stiffness.

Heart rate was measured simultaneously with arterial stiffness measurements. Three observers performed all measurements. In a reproducibility study performed among 47 individuals who were invited two times exactly 1 week apart, the intraclass correlation coefficient was 0.80 for both the PWV and the carotid distensibility coefficient (19,21). After 5 minutes of rest, systolic and diastolic BPs were measured two times on the right arm with a random zero sphygmomanometer, and the mean was taken as the individuals' reading. Pulse pressure was estimated as the difference between systolic and diastolic BPs.

Genetic Risk Score

Genotyping was conducted using the Illumina 550K Array among self–reported white individuals. Imputation was done with reference to HapMap release 22 Utah residents of Northern and Western European ancestry using the maximum likelihood method implemented in MaCH (version 1.0.15).

We selected single-nucelotide polymorphisms (SNPs) reported in genome–wide association studies (GWAS) to be associated with pulse pressure and PWV (22,23). There is no GWAS available on carotid stiffness. Genetic risk score was formed using 10 SNPs associated with pulse pressure and 9 SNPs associated with PWV (Supplemental Table 1). For variants in the same locus, the variant with the smallest P value was selected. We calculated a weighted genetic risk score by multiplying the number of risk alleles at each locus by the corresponding reported coefficient from the previous GWASs and summing the products. The total score was then divided by the average effect size and multiplied by 100 to rescale the scores to a range between 0 and 100.

Measurement of eGFR

Serum creatinine was determined using an enzymatic assay method. Interassay and intra–assay coefficient variations were $<$0.92% and $<$1.37%, respectively. We calibrate creatinine measurements by aligning the mean values of creatinine with creatinine values of the participants of the National Health and Nutrition Examination Survey III in different sex and age groups ($<$60, 60–69, and $\geq$70 years old) (24). eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration Equation (25). To calculate the annual eGFR decline, we first subtracted the eGFR estimates of the follow-up examination from the eGFR estimates at baseline and then divided by the time between the two visits. CKD was defined as eGFR$<$60 ml/min per 1.73 m^2. Patients with incident CKD were defined as individuals free of CKD at baseline (eGFR$>$60 ml/min per 1.73 m^2) who had a decline in eGFR to $<$60 ml/min per 1.73 m^2 between the two periodic examinations (26).

Statistical Analyses

Association of measures of arterial stiffness with annual decline in eGFR and incidence of CKD was evaluated using linear regression models and log binomial regressions, respectively. Coefficients were estimated per SD higher PWV and pulse pressure. Coefficients were estimated per negative SD higher measures of carotid distensibility, which represents greater carotid stiffness. In the first model, analyses were adjusted for age, sex, mean arterial pressure, heart rate, baseline eGFR, and follow-up time (for analyses on incidence of CKD). In the second model, we further adjusted for body mass index, alcohol consumption, smoking, HDL cholesterol, total cholesterol, history of diabetes mellitus and coronary heart disease, and different types of antihypertensive medications (diuretics, β-blockers, angiotensin-converting-enzyme

inhibitors, and calcium channel blockers). Missing values on covariates were imputed using the expectation maximization method (single imputation). The percentage of missing values on covariates was not substantial and ranged from 0.2% to 13.3%. In addition, because an interaction between BP and PWV as biomarkers and indicators of hemodynamic status has been suggested previously (27), we assessed the interaction of PWV and systolic and diastolic BPs by adding an interaction term in the regression model. The interaction term was the product of the PWV and systolic or diastolic BP. In an extra analysis, we adjusted the associations of arterial stiffness genetic risk scores with decline in kidney function for measures of pulse pressure and PWV. All analyses were adjusted for the effect of the two RS cohorts and carried out using STATA 13.1 or R, version 2.15.0.

Meta-Analysis

We searched for studies published in MEDLINE, EMBASE, Web of Science, and Google Scholar using the common key words related to arterial stiffness and incident CKD (Supplemental Appendix). Population-based studies evaluating the association between indicators of arterial stiffness and incidence of CKD were included (Supplemental Table 2) (10–14). Supplemental Figure 1 shows the flow diagram for inclusion of the relevant studies in our meta-analyses. Incident CKD was defined as eGFR<60 ml/min per 1.73 m^2 in all included studies except one study, in which eGFR loss of >3 ml/min per 1.73 m^2 was used (13). We excluded one study from the meta-analysis of pulse pressure, because the outcome was reported continuously for each milliliter per minute per 1.73 meter^2 decline in eGFR (14). We performed random and fixed effect meta–analyses including the current RS. The heterogeneity assumption was investigated using a commonly used statistical method, namely the I^2 statistic. There was no evidence of publication bias using Egger's test.

Results

Baseline characteristics of participants are presented in Table 1. Mean age of the participants was 65±6.7 years old, and 58.3% were women. Figure 1 shows the means and SEMs of pulse pressure and PWV in tertiles of pulse pressure and the PWV genetic risk scores.

Table 2 shows the association between indicators of arterial stiffness and kidney function. In the first model, we observed that higher pulse pressure and greater carotid stiffness were associated with steeper annual decline in eGFR and higher risk of incident CKD. Adjusting for additional potential confounders, in the second model, did not substantially change the association. There was no association between PWV and annual decline in eGFR. Higher PWV was associated with higher risk of incident CKD. Furthermore, we did not observe any statistically significant interaction between PWV and systolic or diastolic BP (Supplemental Table 3). However, the association was not present after adjustment for potential confounders in the second model (Table 2). To provide more reliable estimates, we performed a meta-analysis of the available studies (including this study) to report the association of

Table 1. Baseline characteristics of participants

Characteristics (n=3666)	Value
Age (yr), mean (SD)	65.0 (6.7)
Women, n (%)	2139 (58.3)
Body mass index (kg/m^2), mean (SD)	26.6 (3.6)
Total cholesterol (mg/dl), mean (SD)	246.9 (46.1)
HDL cholesterol (mg/dl), mean (SD)	52.5 (14.5)
Alcohol intake (g/d), median (interquartile range)	4.8 (0.33–16.6)
Smoking, n (%)	
Current	755 (20.6)
Former	1649 (45.0)
Systolic BP (mmHg), mean (SD)	137.3 (19.9)
Diastolic BP (mmHg), mean (SD)	75.4 (10.9)
Pulse rate (beats per minute), mean (SD)	72.2 (11.4)
Mean arterial pressure (mmHg), mean (SD)	96.0 (12.6)
Pulse pressure (mmHg), mean (SD)[a]	62.5 (15.5)
Pulse wave velocity (m/s), mean (SD)[a]	12.2 (2.5)
Carotid distensibility coefficient (10^{-3}/kPa), mean (SD)[a]	12.9 (4.6)
GFR (ml/min per 1.73 m^2), mean (SD)	79.3 (13.7)
Diabetes mellitus, n (%)	279 (7.6)
History of coronary heart disease, n (%)	327 (8.9)
Antihypertensive medication, n (%)	
Diuretics	355 (9.7)
ACE inhibitors	204 (5.6)
Calcium channel blocker	177 (4.8)
β-Blocker	503 (13.7)

ACE, angiotensin-converting-enzyme.
[a]Data are on the basis of the correspondence sample size (pulse pressure, n=2950; pulse wave velocity, n=2665; and carotid distensibility, n=2344).

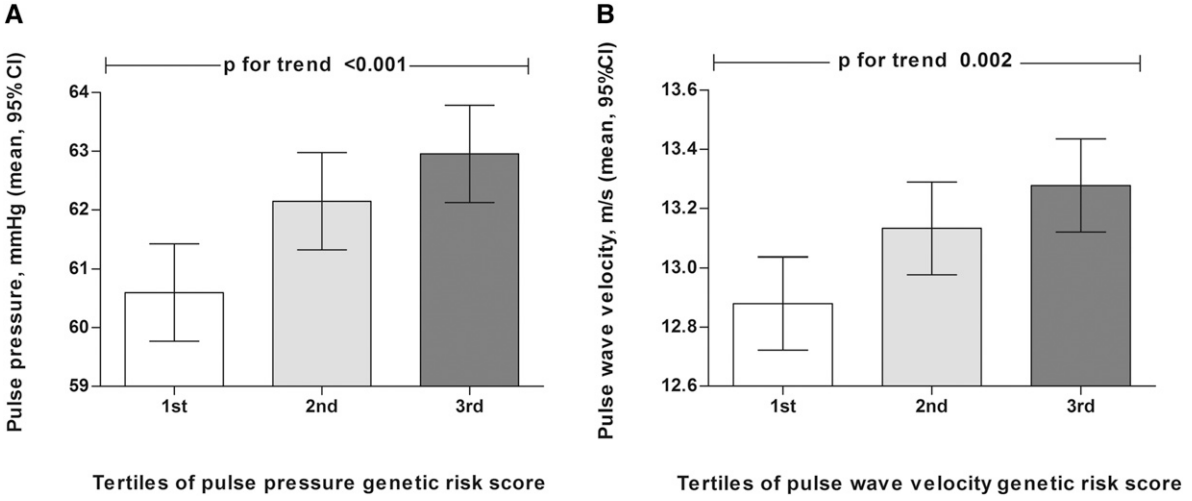

Figure 1. | Linear association between arterial stiffness measures and their corresponding genetic risk scores. (A) Mean and SEM of pulse pressure in tertiles of pulse pressure genetic risk score. (B) Mean and SEM of pulse wave velocity in tertiles of pulse wave velocity genetic risk score. Analyses are adjusted for age and sex. 95% CI, 95% confidence interval.

pulse pressure and PWV with incident CKD (Figure 2). Combining the effect estimates of our study with three previous population–based studies, we observed the overall relative risk of 1.16 (95% confidence interval [95% CI], 1.12 to 1.21) for each SD higher pulse pressure in respect to incident CKD. Test for heterogeneity resulted in moderate estimates (I^2=75%; 30.6%–91%). Excluding the study with outcome defined as eGFR loss of >3 ml/min per 1.73 m^2 resulted in no heterogeneity (Supplemental Figure 2). Regarding PWV, we observed the overall relative risk of 1.08 (95% CI, 1.03 to 1.14) for incident CKD per each SD higher PWV. The test for heterogeneity resulted in moderate estimates (I^2=59.5%; 0%–86.5%). Excluding the study with carotid brachial PWV measures reduced the heterogeneity (I^2=24%; 0%–92.1%) (Supplemental Figure 2).

Pulse pressure genetic risk score was associated with steeper annual decline in eGFR and higher risk of incident CKD (relative risk, 1.08; 95% CI, 1.03 to 1.14) (Table 3). There was no association between PWV genetic risk score and kidney function. Adjusting the associations for pulse pressure and PWV measurements changed the associations minimally (Supplemental Table 4).

Given the correlation between pulse pressure and BP, we investigated if any of the pulse pressure genes are associated with systolic or diastolic BP in our sample (Supplemental Table 5). After Bonferroni correction (adjusted *P* value of 0.002), none of the variants were significantly associated with BP measures; however, an SNP in the *PIK3CG* gene and an SNP in the *PLCE-1* gene were suggestively associated with systolic BP (*P*=0.003). Excluding these

Table 2. Association of measures of arterial stiffness with decline in eGFR and incidence of CKD

Regression Models	eGFR Decline			Incident CKD		
	Difference	95% Confidence Interval	*P* Value	Relative Risk	95% Confidence Interval	*P* Value
Pulse pressure (*n*=2950)						
Model 1	0.15	0.10 to 0.20	<0.001	1.11	1.05 to 1.18	<0.001
Model 2	0.13	0.09 to 0.18	<0.001	1.10	1.03 to 1.17	0.002
Carotid stiffness (*n*=2342)						
Model 1	0.08	0.04 to 0.13	<0.001	1.13	1.05 to 1.22	0.001
Model 2	0.07	0.02 to 0.11	0.002	1.13	1.05 to 1.22	0.001
Pulse wave velocity (*n*=2665)						
Model 1	0.04	−0.00 to 0.09	0.07	1.07	1.01 to 1.14	0.04
Model 2	0.02	−0.02 to 0.07	0.33	1.05	0.99 to 1.31	0.10

Differences (coefficients) and relative risks are calculated per each SD of arterial stiffness measures. Model 1 is adjusted for age, sex, mean arterial pressure, heart rate, baseline eGFR, and follow-up time (for analyses on incidence of CKD). Model 2 is additionally adjusted for body mass index, alcohol consumption, smoking, HDL cholesterol, total cholesterol, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, and history of diabetes and coronary heart disease.

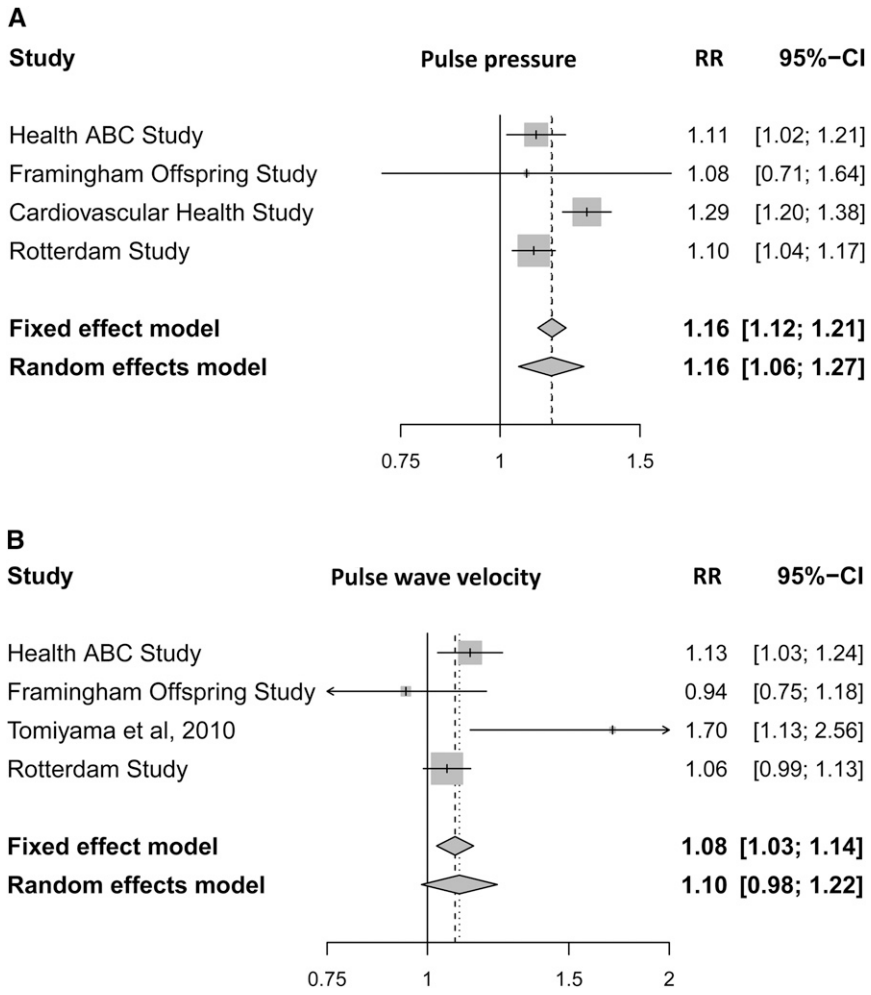

Figure 2. | Higher pulse pressure and pulse wave velocity are associated with higher risk of incident CKD. Forest plots of multivariate–adjusted relative risks (RRs) for the association of each SD of (A) pulse pressure and (B) pulse wave velocity with incident CKD (11). Health ABC, health, aging, and body composition; 95% CI, 95% confidence interval.

SNPs from the genetic risk score of pulse pressure did not essentially change the associations (Supplemental Table 6).

Discussion

We showed that markers of arterial stiffness are independently associated with future decline in kidney function. This study provides additional evidence for the association between pulse pressure and decline in kidney function using genetic variability in pulse pressure.

Previous studies on the association between arterial stiffness and decline in kidney function have been inconsistent (7,9–14,28). In a study including patients with CKD, Ford *et al.* (9) showed that higher PWV but not pulse pressure was associated with the rate of change in kidney function. Similarly, in a Japanese cohort, an association was observed between higher brachial PWV and steeper decline in eGFR (11). In contrast, results of the Framingham Offspring Cohort showed that PWV is associated with the incidence of albuminuria but not mild to moderate CKD (12). In this study, we observed an association between pulse pressure and decline in kidney function, but the association between PWV and CKD disappeared after adjustment for cardiovascular risk factors. To improve the power, increase generalizability, and decrease heterogeneity, we combined our results with the effect estimates of the population–based studies and provided additional support for an independent link between PWV and decline in kidney function.

Pulse pressure and PWV are two commonly used measures of arterial stiffness. Arterial stiffness is not uniform along the arterial tree; therefore, assessment of arterial stiffness at different sites in relation to clinical outcomes is important (29). We have previously shown that arterial stiffness measured as carotid femoral PWV is associated with cardiovascular morbidity and mortality; however, we did not observe such an association with stiffness in the carotid artery. Previous studies showed that local carotid arterial stiffness is associated with brain outcomes (direct organ supplies by carotid arteries). In this study, we showed an independent association between carotid stiffness and decline in kidney function. Both kidney and brain are low–resistance, high–flow end organs, which renders them vulnerable to pulsatile changes in the blood flow. This might suggest that systemic pulsatile pressure can cause vascular injury in both organs.

Table 3. Association of genetic risk scores for measures of arterial stiffness with annual decline in eGFR and incidence of CKD

Regression Models	eGFR Decline			Incident CKD		
	Difference	95% Confidence Interval	*P* Value	Relative Risk	95% Confidence Interval	*P* Value
Pulse pressure GRS (*n*=3666)						
Model 1	0.06	0.01 to 0.10	0.01	1.08	1.03 to 1.14	0.003
Model 2	0.05	0.01 to 0.11	0.02	1.07	1.02 to 1.13	<0.01
Pulse wave velocity GRS (*n*=3666)						
Model 1	-7.4×10^{-4}	−0.04 to 0.04	0.99	1.03	0.98 to 1.08	0.18
Model 2	3.6×10^{-3}	−0.04 to 0.05	0.87	1.03	0.98 to 1.08	0.17

Differences (coefficients) are per SD of pulse pressure genetic risk score (GRS) and pulse wave velocity GRS. Model 1 is adjusted for age, sex, mean arterial pressure, heart rate, baseline eGFR, and follow-up time (for analyses on incidence of CKD). Model 2 is additionally adjusted for body mass index, alcohol consumption, smoking, HDL cholesterol, total cholesterol, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, and history of diabetes and coronary heart disease.

Future studies are needed to investigate the mechanism behind the association between carotid stiffness and decline in kidney function.

We observed that pulse pressure genetic variants but not PWV genetic variants are associated with kidney function decline. Our findings can be explained by relatively more power for pulse pressure given the stronger association of pulse pressure with kidney function compared with PWV. It is also known that pulse pressure is not only the indicator of arterial stiffness but also, influenced by peak systolic BP (30). Some of the genes found for pulse pressure are known to be associated with BP variation (31–33). However, adjustment for BP and excluding SNPs with suggestive association with systolic BP did not change the associations.

There are different putative mechanisms suggesting a role for arterial stiffness in the deterioration of kidney function. A plausible mechanism is that arterial stiffness increases circumferential and shear stresses in the arterial lumen. This hemodynamic stress on the kidney vasculature may result in endothelial dysfunction and microvascular ischemia, leading to kidney injury (34). Other possible mechanisms include chronic inflammation, oxidative stress, and activation of the renin-angiotensin system (12).

We performed these analyses in a large population–based study, which enables us to control for several potential confounders and see the small effects of the genes. In addition, we performed a meta-analysis to provide a more precise estimate of the association. We confirmed the association between pulse pressure and kidney function using genetic variants as the less-biased proxies for the arterial stiffness parameters. As a limitation, data on albuminuria were unavailable, and it is an important element in defining CKD. However, eGFR<60 ml/min per 1.73 m^2 is a well accepted definition for CKD in population–based research settings (35). Furthermore, adjustments for pulse pressure changed the association between genetic variants of pulse pressure and kidney disease only minimally; this might indicate that our findings with pulse pressure genetic risk score could be partially explained by pleiotropic effects in the genetic risk score, such as BP genetic variants. In computing the carotid distensibility coefficient, we used the brachial pulse pressure rather than the carotid pulse pressure. Substantial differences have been reported between carotid and brachial pulse pressures, which can lead to an underestimation of the distensibility measurements and subsequently, an underestimation of the association with the disease (4).

Currently, major strategies to prevent CKD are focused on conventional cardiovascular risk factors, and in this study, we showed that vascular stiffness independent of cardiovascular risk factors is associated with decline in kidney function. This highlights that vascular stiffness can be considered as a target for delaying decline in kidney function.

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Disclosures

None.

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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 ml/min per1.73 m^2 -eGFR< 60 ml/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 ml/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 ml/min per1.73 m^2 -eGFR< 60 ml/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 ml/min per1.73 m^2 -eGFR< 60 ml/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 ml/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 ml/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

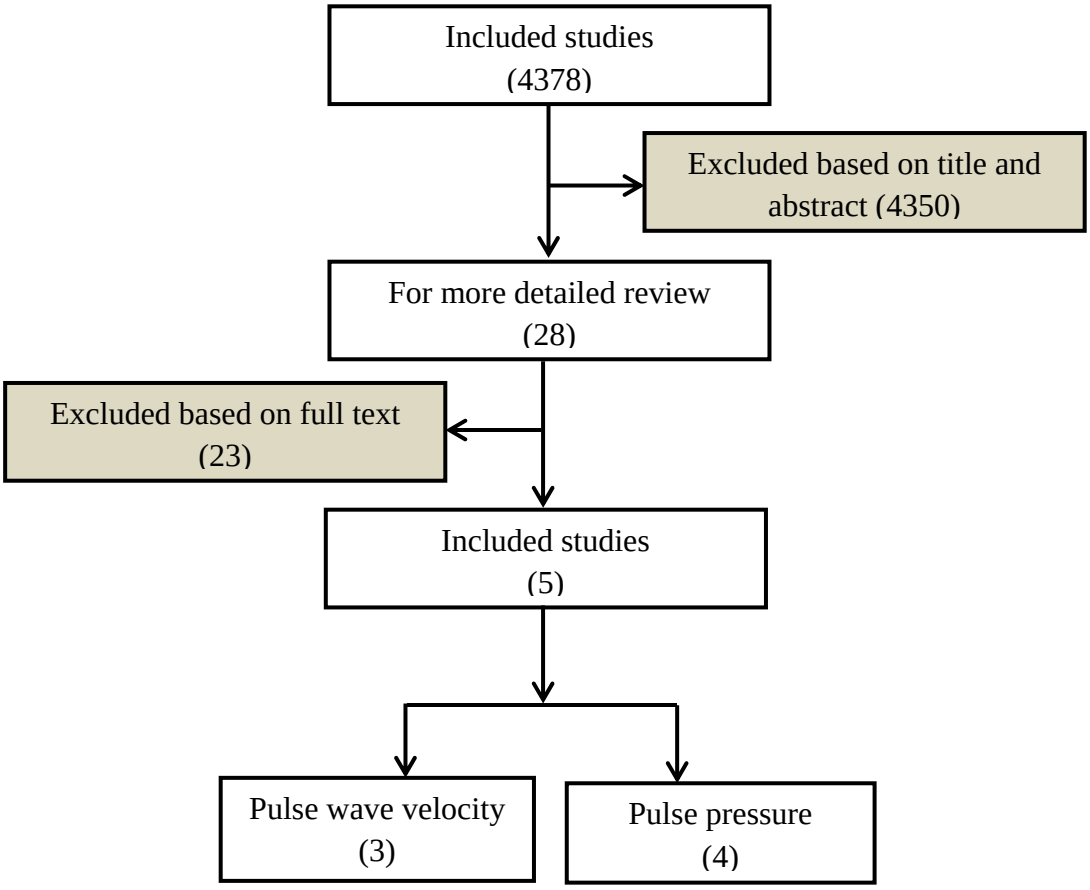
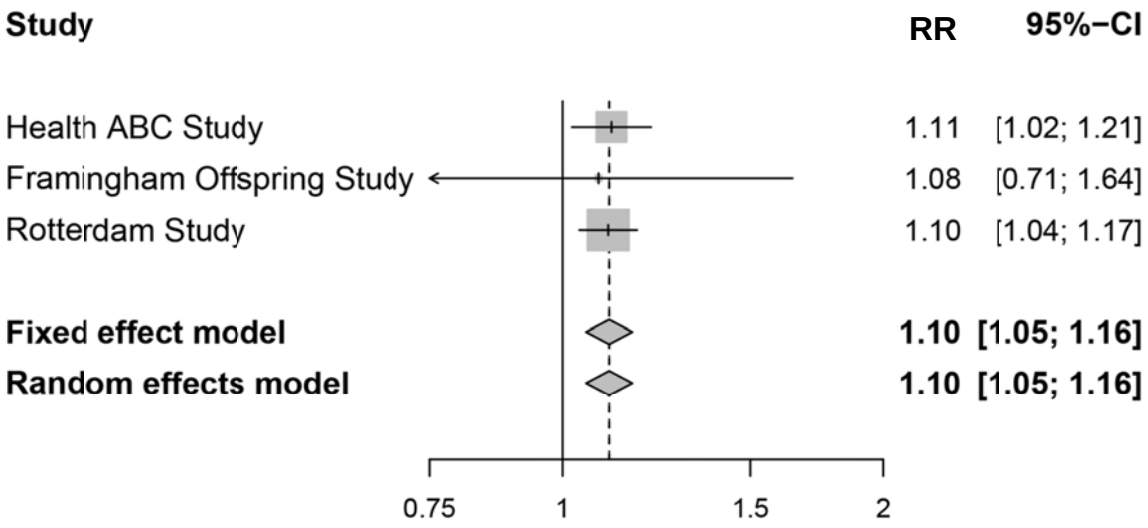


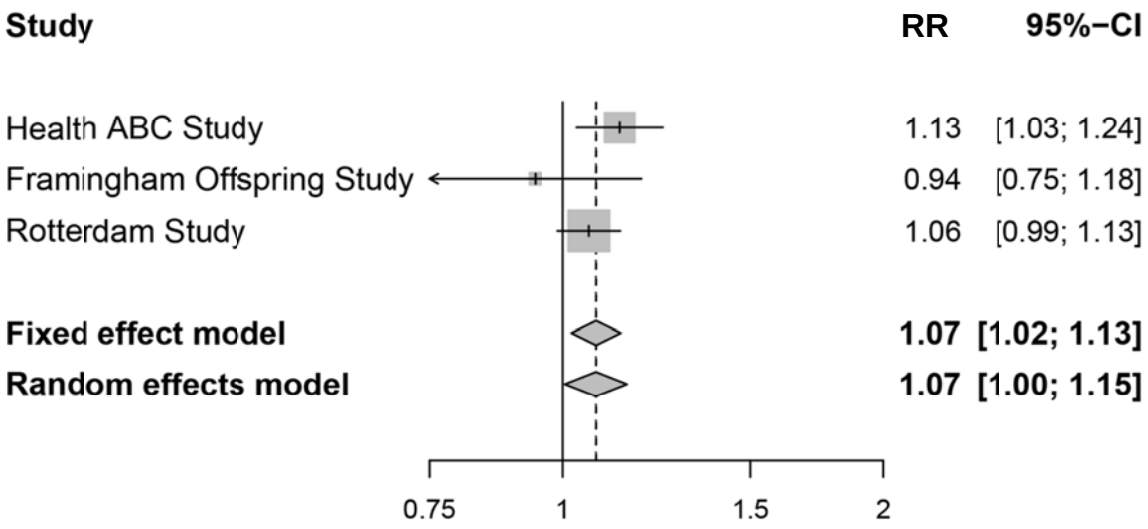
Figure S2. (A) Forest plot of multivariate adjusted relative risk for the association of pulse pressure with new onset CKD excluding the study with outcome definition of GFR loss of > 3 ml/min/1.73 m^2

(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"

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