Atherosclerosis 272 (2018) 94–100

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Associations between normal range albuminuria, renal function and cardiovascular function in a population-based imaging study

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ARTICLE INFO

Article history:
Received 28 November 2017
Received in revised form
8 March 2018
Accepted 15 March 2018
Available online 16 March 2018

Keywords:
Albuminuria
Glomerular filtration rate
Vascular stiffness
Cardiovascular system
Magnetic resonance imaging

ABSTRACT

Background and aims: In patients with impaired renal function and macroalbuminuria, cardiovascular risk factors are highly prevalent, however, whether this is also present in the general population is unclear. We investigated whether normal-range albuminuria and renal function are associated with cardiovascular function in the general population.

Methods: In this cross-sectional analysis of the NEO study, urinary albumin-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and intima-media thickness were assessed in all participants (n = 6503), and a random subset underwent MRI for pulse wave velocity (n = 2451) and/or cardiac imaging (n = 1138).

Results: Multiple linear regression analysis was performed while adjusting for sex, age, smoking, mean arterial blood pressure, total body fat, and fasting glucose. After adjustment, albuminuria and renal function were positively associated with left ventricle (LV) mass index (UACR, 0.941 g/m^2 [95% CI: 0.21,1.67] $p = 0.012$; eGFR, 0.748 g/m^2 [95% CI: 0.15,1.35] $p = 0.015$) and LV cardiac index (UACR, 0.056 L/min/m^2 [95% CI: 0.00,0.11] $p = 0.038$; eGFR, 0.080 L/min/m^2 [95% CI: 0.03,0.13] $p = 0.001$). Albuminuria showed a weak association with arterial thickness (UACR, 0.003 mm [95% CI: 0.00,0.01] $p = 0.015$) and arterial stiffness (UACR, 0.073 m/s [95% CI: 0.01,0.13] $p = 0.036$), but not with renal function. No associations were observed for LV ejection fraction and LV diastolic function.

Conclusions: Normal-range albuminuria was positively associated with LV mass index, LV cardiac index, arterial thickness and arterial stiffness. Our findings support the hypothesis that even within normal range, albuminuria is a marker of cardiovascular health.

1. Introduction

Chronic kidney disease (CKD), characterized by renal insufficiency and macroalbuminuria, is associated with a substantial risk of cardiovascular morbidity and mortality [1,2]. The exact mechanism underlying the observed excess of cardiovascular disease in chronic kidney disease is unknown, and increasing evidence suggests that this relationship goes beyond indirect associations by hypertension [3,4]. Macroalbuminuria is commonly used as a marker of kidney disease progression. Microalbuminuria [5] and higher levels of albuminuria within 'normal range' are associated with a higher risk of cardiovascular events [6,7]. In non-diabetic patients, microalbuminuria is considered to reflect endothelial damage via degradation of the endothelial glycocalyx [8]. This endothelial glycocalyx degradation could be the biological pathway that explains the continuous relationship between urinary albumin excretion and cardiovascular risk. In this case, cardiac remodeling in advanced renal disease could be preceded by subclinical cardiovascular changes as a consequence of microalbuminuria.

Abbreviations: β, regression coefficient; BMI, body mass index; cIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; E/A, early filling phase/atrial contraction; E deceleration peak, early filling phase deceleration peak; LV, left ventricle; MRI, magnetic resonance imaging; PWV, pulse wave velocity; UACR, urinary albumin creatinine ratio.

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https://doi.org/10.1016/j.atherosclerosis.2018.03.029

However, to what extent normal range albuminuria is related to cardiovascular function in the general population remains unclear. Better understanding of the relationship between albuminuria and cardiac remodeling, requires knowledge of associations in the general population. However, the majority of population-based studies thus far have focused on the presence of hypertension [9,10]. Moreover, these studies lacked functional data, such as LV systolic/diastolic function and arterial stiffness. The aim of this study is to investigate the association between normal range albuminuria, renal function, and cardiovascular imaging parameters in the general population. We hypothesize that also albuminuria within normal range is a marker of cardiovascular function in the middle-aged general population. By improving insight into cardiac remodeling mechanisms in the population at large, preventative strategies might eventually become feasible to reduce cardiovascular risk in CKD patients.

2. Materials and methods

2.1. Study population and study design

The Netherlands Epidemiology of Obesity (NEO) study is a population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases [11]. Men and women living in the greater area of Leiden (the Netherlands) were invited to participate in the study if they were aged between 45 and 65 years and had a self-reported body mass index (BMI) of $\geq$27 kg/m^2. In addition, all inhabitants from one municipality (Leiderdorp) were invited to participate irrespective of their BMI, allowing for a reference distribution of BMI. Participants with potential contra-indications for MRI (i.e. metallic devices, or claustrophobia) were excluded for additional imaging. Of all MRI eligible participants, approximately 30% were randomly selected to undergo arterial stiffness measurement, and a second random subset of approximately 50% had additional cardiovascular magnetic resonance imaging as well. All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 [12]. The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study and all participants gave their written informed consent.

2.2. Data collection

Participants were invited to a baseline visit at the NEO study center of the LUMC after an overnight fasting period. Prior to this study visit, participants collected their urine over 24 h and completed a general questionnaire at home to report demographic, lifestyle and clinical information. The participants were asked to bring all medications they were using to the study visit. At the baseline visit, all participants underwent physical examination including anthropometry and blood pressure measurement. Height was measured with a vertically fixed, calibrated tape measure. Body weight and percent body fat were measured by the Tanita bio impedance balance (TBF-310, Tanita International Division, UK) without shoes, and 1 kg was subtracted to correct for the weight of clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 min rest between consecutive measurements. The mean systolic, diastolic and mean arterial ([(2 $\times$ diastolic blood pressure) + systolic blood pressure]/3) blood pressure was calculated.

2.3. Laboratory measurements

Fasting blood samples were drawn from the antecubal vein after 5 min rest of the participant, and were used to determine serum concentrations of glucose, insulin, triglycerides, creatinine, total cholesterol HDL, and LDL. Serum creatinine (mg/dl) was used to calculate the estimated GFR according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13]. For the measurement of albuminuria, the urinary albumin creatinine ratio (UACR) was derived from a first morning void. Normal range albuminuria was defined as UACR of <3 mg/mmol (<30 mg/g), microalbuminuria (moderately increased albuminuria) as UACR of 3–30 mg/mmol (30–300 mg/g), and macroalbuminuria (severely increased albuminuria) as UACR >30 mg/mmol (>300 mg/g) [14]. All laboratory analyses were performed in the central clinical chemistry laboratory of the LUMC [11].

2.4. Carotid intima-media thickness

Carotid intima-media thickness (cIMT) was assessed by ultrasonography of the far wall of the left and right common carotid arteries along a 15 mm section 10 mm proximal of the bifurcation, using a 7.5–10 MHz linear-array transducer in B-mode setting (Art. Lab version 2.1, Esaote, Maastricht, The Netherlands).

2.5. Pulse wave velocity and cardiovascular magnetic resonance imaging

Magnetic resonance imaging was performed on a 1.5 T whole-body MR scanner (Philips Medical Systems, Best, the Netherlands).

Through-plane flow measurements of the ascending, proximal descending, mid-descending, and distal descending aorta were acquired using multislice, one-directional in-plane velocity-encoded MRI with velocity sensitivity of 150 cm/s. Aortic PWV was calculated by dividing the aortic path length between the measurement sites (Δx) by the transit time between the arrival of the systolic wave front at these sites (Δt), and it is expressed in meters per second [15].

The entire heart was imaged in short-axis orientation using electrocardiographically gated breath-hold balanced steady-state free precession (Repetition Time 3.4 ms, Echo Time 1.7 ms; Flip Angle 35°; slice thickness 10 mm; slice gap 0 mm; Field of View 400 $\times$ 400 mm; matrix size = 256 $\times$ 256). LV mass determined by the sum of myocardial area times slice thickness multiplied by the myocardial gravity (1.05 g/ml), and LV mass index was calculated by dividing LV mass by body surface area (BSA). LV hypertrophy was defined as LV mass index >84.1 g/m^2 for men and >76.4 g/m^2 for women. LV cardiac output was calculated by multiplying stroke volume by heart rate, and LV cardiac index by dividing LV cardiac output by body surface area (BSA). LV ejection fraction by dividing stroke volume by the end-diastolic volume multiplied by 100%. An electrocardiographically gated gradient-echo sequence with velocity encoding was used to measure blood flow across the mitral valve (Repetition Time 6.5 ms, Echo Time 1 ms; Flip Angle 20°; section thickness 8 mm, Field of View 350 $\times$ 350 mm; matrix size 256 $\times$ 256 mm; velocity encoding gradient 150 cm/s). Subsequent wave-form analysis of mitral inflow pattern was performed, resulting in the quantification of early (E) and atrial (A) peak filling velocity, E/A ratio, and the E deceleration peak [16]. Image post processing was performed with in-house developed software (MASS and FLOW, Medis, Leiden, the Netherlands) with consensus between two experienced radiologists. Imaging analysis of the cIMT, PWV and cardiac MRI group are visualized in Fig. 1B.

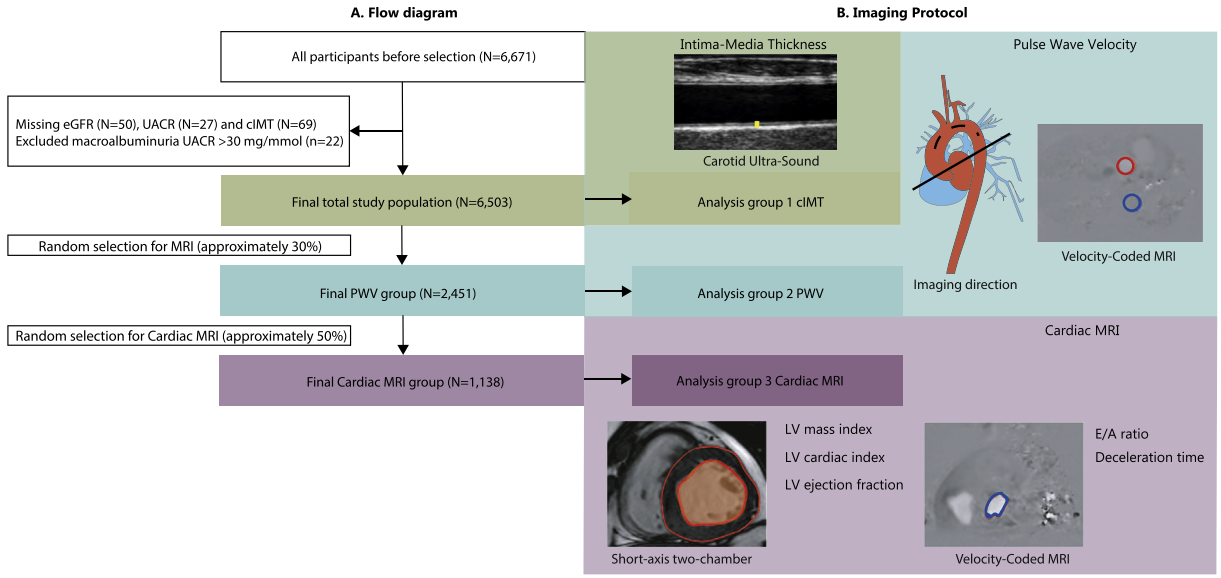

Fig. 1. Flow diagram and imaging protocol for the total population, and PWV and cardiac MRI analysis subgroups.
(A) Study flow diagram for the final carotid intima-media thickness (total population), pulse wave velocity subgroup (PWV), and cardiac MRI aubgroup. (B) Overview of the imaging protocol per analysis group; for the cIMT group, this consisted of carotid ultrasound for the measurement of the intima-media thickness (yellow bar in the B-mode ultrasound image of the common carotid artery); for the PWV group, this consisted of velocity-encoded MRI of the ascending aorta (red contour) and descending aorta (blue contour) with an imaging direction similar to the anatomical drawing of the aorta; for the cardiac MRI group, this consisted of a short-axis two-chamber images of heart for the assessment of LV mass index (LV myocardial area contours in red) and volumetric derived LV systolic function (LV volume shaded in red), and velocity-encoded MRI of the mitral valve for the assessment of LV diastolic function (mitral valve contour in blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.6. Statistical analysis

In the NEO study, individuals with a BMI of 27 kg/m^2 or higher were oversampled. First, inhabitants of Leiden and its surroundings, between 45 and 65 years of age, and with a self-reported BMI of 27 kg/m^2 or higher, were invited to participate in the NEO study. In addition, we included a reference population. To that extent, all inhabitants between 45 and 65 years living in one municipality, Leiderdorp, were asked to participate irrespective of their BMI. This resulted in an additional sample of 1671 participants with a BMI distribution that was similar to the BMI distribution of the general Dutch population [17]. If inference is made on the general population, the over-representation of overweight and obese participants in the NEO study may introduce bias, because of the skewed BMI distribution in the NEO population. Weighting towards the BMI distribution of the general population may solve this problem [18]. Using the BMI distribution of the reference population, we calculated weight factors for the NEO population, resulting in a higher weight factor for participants with a lower BMI [19]. Use of sampling weights yield results that apply to a population-based study without oversampling of individuals with a high BMI [20]. UACR was log-2 transformed to account for the skewed distribution of the data, and because after log-2 transformation the regression coefficient (β) can be interpreted as a two-fold increase in UACR. Multiple linear regression was performed with UACR or eGFR as the exposure and cardiovascular imaging parameters as the outcome. Regression coefficients with corresponding 95% confidence intervals (CI) were calculated and reflect the change in cardiovascular outcome variable per two-fold increase in UACR or per 10 ml/min/1.73 m^2 change in eGFR. Analyses were adjusted for sex, age, smoking, blood pressure, total body fat, and fasting glucose. Sensitivity analyses were performed by excluding participants with hypertension (blood pressure ≥140/90 mmHg or on antihypertensive treatment) or highest quintile of eGFR, indicating supranormal renal function (hyperfiltration). Analyses were performed using STATA (Statacorp, College Station, Texas, USA, version 12.0) and results are presented according to the STROBE guidelines [21].

3. Results

3.1. Baseline characteristics

The total NEO study population consisted of 6671 participants. After consecutive exclusion of participants with missing data on carotid ultrasound (n = 69), urinary albumin creatinine ratio (n = 27), eGFR (n = 50), or with macroalbuminuria (UACR >30 mg/mmol) (n = 22), the final cIMT group consisted of 6503 participants. Of these participants, a random subset (approximately 30%) underwent PWV measurement, resulting in the final PWV group of 2451 participants. Of the participants who underwent PWV measurement, a second random subset of approximately 50% was selected for additional cardiac MRI, resulting in a final cardiac MRI group of 1308 participants (Fig. 1A). Mean (SD) age was 55.7 (6.0) years, median UACR was 0.45 mg/mmol (25th, 75th percentile; 0.30, 0.70), and mean eGFR was 86.3 (12.3) ml/min/1.73 m^2 in the total group. Microalbuminuria (UACR 3–30 mg/mmol or 30 mg/g) was present in 2.0% of the total group, and 0.2% of the participants had a moderately impaired renal function (eGFR <60 ml/min/1.73 m^2). Self-reported history of CVD (defined as myocardial infarction, angina, congestive heart failure, stroke and peripheral vascular disease) was present in 6% of the total group. Participant characteristics of the total group are provided in Table 1. Participant characteristics of the PWV and cardiac MRI group were not different from the total group and excluded participants were not different from the included population (data not shown). An overview of the cardiovascular imaging parameters is presented in Table 2.

3.2. Associations between albuminuria and cardiovascular imaging parameters

Table 3 shows the crude and adjusted regression coefficients

Table 1
Characteristics of the total study population.

Characteristics	Total population (n = 6503)
Age (years)	55.7 (6.0)
Sex (% men)	44
Ethnicity (% whites)	95
Medical history	
Cardiovascular disease (%)	6
myocardial infarction	2
congestive heart failure	0.5
stroke	3
peripheral vascular disease	2
Hypertension (BP ≥ 140/90 mmHg) (%)	34
Diabetes (fasting glucose >8.0 mmol/L) (%)	3
Hypertriglyceridemia (fasting triglyceride ≥2.3 mmol/L) (%)	8
Anthropometrics	
Total body fat (%) in men	30.0 (6.1)
Total body fat (%) in women	36.9 (6.5)
Body mass index (kg/m^2)	26.3 (4.4)
Normal weight (%)	42
Overweight (%)	42
Obese (%)	16
Smoking	
Never (%)	39
Former (%)	46
Current (%)	16
Blood pressure	
Systolic blood pressure (mmHg)	130.2 (17.0)
Diastolic blood pressure (mmHg)	83.2 (10.3)
Mean arterial pressure (mmHg)	98.9 (11.9)
Use of medication	
Antihypertensives (%)	23
Glucose lowering medication (%)	3
Lipid lowering medication (%)	11
Statins (%)	11
Beta blockers (%)	11
Calcium channel blockers (%)	3
ACE inhibitors (%)	14
Diuretics (%)	8
Fasting serum measurements	
Glucose (mmol/L)	5.5 (1.0)
Insulin (mU/L)	9.7 (8.1)
Triglyceride (mmol/L)	1.2 (0.8)
HDL cholesterol (mmol/L)	1.6 (0.5)
LDL cholesterol (mmol/L)	3.5 (1.0)
Total cholesterol (mmol/L)	5.7 (1.1)
Renal parameters	
Creatinine (umol/L)	76.4 (14.0)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	86.3 (12.3)
Urinary albumin excretion (mg/L)	3.62 (2.99, 4.79)
Urinary albumin-creatinine ratio (mg/mmol)	0.44 (0.30, 0.70)

Results were weighed toward the BMI distribution of the general population. Data are shown as percentage, mean (SD) or median (25th, 75th percentile). Normal weight: BMI<25 kg/m^2, overweight: BMI 25–30 kg/m^2, and obese: BMI>30 kg/m^2.
ACE; angiotensin-converting-enzyme, BP; blood pressure, HDL; High-density-lipoprotein, LDL; low-density-lipoprotein.
Cardiovascular disease was defined as myocardial infarction, angina, congestive heart failure, stroke, and peripheral vascular disease.

between UACR (per two-fold change) and cardiovascular parameters. In unadjusted analysis, albuminuria was associated with an increase of 0.006 mm [95% CI: 0.00, 0.01] in arterial thickness (cIMT), which after adjustment changed to 0.003 mm [95% CI: −0.00, 0.01]. In crude analysis, a two-fold increase in UACR arterial stiffness (PWV) was associated with an increase of 0.246 m/s [95% CI: 0.18, 0.31], which diminished after adjustment. UACR was not associated with LV mass index in crude analysis (β −0.126 [95% CI: −0.93, 0.68]), however, UACR did relate to LV mass index after adjustment for sex, and this association was attenuated after further adjustment for the remaining confounding variables (β 0.941 [95% CI: 0.21, 1.67]). This means that per two-fold increase in UACR, LV mass index is associated with an increase of 0.941 g/m^2.

Table 2
Mean (SD) of different cardiovascular imaging parameters measured in the cIMT, PWV and cardiac MR group.

Outcome parameter	n	Mean (SD)
Arterial thickness	6503	
Carotid intima-media thickness (mm)		0.6 (0.1)
Arterial stiffness	2451	
Pulse wave velocity total (m/s)		6.6 (1.3)
Cardiovascular magnetic resonance	1138	
Dimensions		
LV mass (g)		99.8 (26.1)
LV mass index; LV mass/BSA (g/m^2)		51.1 (10.2)
Systolic function		
LV ejection fraction (%)		63.7 (5.9)
LV cardiac output (L/min)		6.2 (1.4)
LV cardiac index; LVCO/BSA (L/min/m^2)		3.2 (0.6)
Diastolic function		
E/A ratio		1.3 (0.5)
E deceleration peak (ml/s^{2*} 10^{-3})		−3.5 (1.1)

Results were weighed toward the BMI distribution of the general population. Data are shown as mean (SD).
BSA; body surface area, E/A ratio; ratio of early peak filling rate and atrial peak filling rate, UACR; urinary albumin creatinine ratio. LV hypertrophy, LV mass index >84.1 g/m^2 for men and >76.4 g/m^2 for women.

Table 3
Differences (with 95% confidence intervals) in cardiovascular imaging parameters per two-fold increase in UACR.

Imaging parameter		Log2-UACR (mg/mmol)		
	n	β	95% CI	*p*
Carotid intima-media thickness (mm)	6503			
Crude		0.006	0.00; 0.01	<0.001
Adjusted		0.003	0.00; 0.01	0.036
Pulse wave velocity (m/s)	2541			
Crude		0.246	0.18; 0.31	<0.001
Adjusted		0.073	0.01; 0.13	0.015
Cardiovascular magnetic resonance	1138			
LV mass index (g/m^2)				
Crude		−0.126	−0.93; 0.68	0.760
Adjusted		0.941	0.21; 1.67	0.012
LV ejection fraction (%)				
Crude		0.350	−0.04; 0.74	0.082
Adjusted		0.074	−0.36; 0.51	0.741
LV cardiac index (L/min/m^2)				
Crude		0.020	−0.03; 0.07	0.445
Adjusted		0.056	0.00; 0.11	0.038
E/A ratio				
Crude		−0.057	−0.10;-0.01	0.008
Adjusted		−0.031	−0.06;-0.00	0.055
E deceleration peak (ml/s^2*10^{-3})				
Crude		0.175	0.10; 0.25	<0.001
Adjusted		0.038	−0.03; 0.11	0.286

Results were weighed toward the BMI distribution of the general population. Crude and adjusted analysis (sex, age, smoking, mean arterial blood pressure, total body fat and fasting glucose) with linear regression coefficients and 95% confidence intervals are shown. Regression coefficients reflect the change in cardiovascular outcome variable with a 2-fold increase in UACR.
E/A ratio; ratio of early peak filling rate and atrial peak filling rate, UACR; urinary albumin creatinine ratio.

UACR was not related to LV ejection fraction in both unadjusted and adjusted analysis. UACR was not related to LV cardiac index in the unadjusted analysis, but after adjustment UACR did relate to LV cardiac index (β 0.056 L/min/m^2 [95% CI: 0.00, 0.11]). In unadjusted analyses UACR was minimally associated with E deceleration peak (β 0.175 [95% CI: 0.10, 0.25]), which diminished in adjusted analyses. Results from sensitivity analyses evaluating the associations between albuminuria and LV mass index without participants with hypertension (blood pressure ≥140/90 mmHg or on antihypertensive treatment) are presented in Supplementary Table 1.

3.3. Associations between renal function and cardiovascular imaging parameters

Table 4 shows the unadjusted and adjusted regression coefficients between renal function (per 10 ml/min/1.73 m^2 higher eGFR) and cardiovascular parameters. In crude analysis, renal function was associated with a decrease of −0.004 mm [95% CI: −0.01, −0.00] of arterial thickness (cIMT) and with a decrease of −0.149 m/s [95% CI: −0.21, −0.09] of arterial stiffness (PWV). These associations diminished after adjusting for confounding variables. In crude analysis, renal function was associated with LV mass index (β 0.969 [95% CI: 0.26, 1.67]) and after adjustment for confounding variables, per 10 ml/min/1.73 m^2 higher eGFR, LV mass index increased with 0.748 g/m^2 [95% CI: 0.15, 1.35]. Renal function was not associated with LV ejection fraction in both crude (β −0.374 [95% CI: −0.79, 0.04]) and adjusted analysis (β −0.294 [95% CI: −0.72, 0.13]). In crude analysis, renal function was associated with the LV cardiac index (β 0.08 [95% CI: 0.03, 0.13]), which remained the same in the adjusted analysis. In crude analysis, higher renal function was associated with an increase in the E/A ratio (β 0.07 [95% CI: 0.03, 0.11]) and negatively associated with the E deceleration peak (β −0.133 [95% CI: −0.20, −0.06]). These associations diminished after adjusting for confounding variables. Results from sensitivity analyses in the cardiac MRI group, evaluating the associations between renal function and LV mass index, after exclusion of participants with hypertension (blood pressure ≥140/90 mmHg or on antihypertensive treatment), and after exclusion of individuals in the highest quintile of eGFR (eGFR ≥97.1 ml/min/1.73 m^2), are presented in Supplementary Tables 1 and 2

4. Discussion

In this large cross-sectional study of the middle-aged general population, we found that normal range albuminuria and renal function were positively associated with LV mass index and LV cardiac index. Weak positive associations were found between normal range albuminuria, arterial thickness, and arterial stiffness, and no associations were observed for LV ejection fraction and diastolic function.

We found that normal range albuminuria was independently associated with LV mass index even after adjustment of various confounders, such as mean arterial blood pressure and serum glucose. In addition, subsequent sensitivity analyses, excluding all participants with hypertension and/or using antihypertensives, did not materially change our findings (Supplementary Table 1). Previous cardiovascular magnetic resonance-based studies, evaluating the relationship between normo- to microalbuminuria and LV mass in non-CKD populations, were performed solely in hypertensive individuals [9,10], limiting conclusions on whether found associations were independent of blood pressure. Our findings are supported by the improved cardiac function and decrease in LV mass index after renal transplantation [22,23]. Moreover, elevated circulating levels of endothelial glycocalyx degrading enzyms, such as syndecan-1 and thrombomodulin, have shown to normalize after kidney transplantation, indicating an improved systemic endothelial function [24].

The observed weak positive association between eGFR and LV mass index in our study is contra-intuitive compared to the inverse relationship in the CKD population [25]. Previous population-based studies, evaluating renal function measured by cystatin C rather than eGFR, also found a positive relationship with a concentric LV hypertrophy phenotype [3,4,26]. However, this may be confounded by the association of cystatin C, as the endogenous cathepsin inhibitor with a role in adipose tissue or cardiac remodeling [27]. We thus hypothesized this finding to be an effect of the cross-sectional design including relatively early renal hyperfiltrate in obese subjects [28]. However, exclusion of individuals within the highest eGFR quintile did not change the observed associations, and can thus not be clearly attributed to glomerular hyperfiltration (Supplementary Table 2). Other explanations are the presence of a U-shaped association or overestimation of renal function given that the CKD-EPI formula is not validated for an eGFR >90 ml/min/1.73 m^2 [29].

In our study, normal range albuminuria and renal function showed a moderately positive association with LV cardiac index, but not with LV ejection fraction. LV cardiac index is corrected for body surface area and heart rate in contrast to LV ejection fraction, which does not take this into account and has a relatively larger variance compared to LV cardiac index, making it a less sensitive measure of LV systolic function. In the present study, no associations were demonstrated between normal range albuminuria, renal function and LV diastolic function. These observations suggest that the association between normal range albuminuria and LV systolic function is more linked to physiological endothelial function than LV diastolic function.

Vascular lipoprotein deposition and atherosclerosis have also been linked to loss of endothelial glycocalyx, which might explain the accelerated vascular aging in CKD, ultimately leading to systemic arteriosclerosis [30,31]. Moreover, increased arterial stiffness reflecting impaired elastic vessel properties has been observed in the early stages of CKD, suggesting that arterial remodeling occurs early in the disease process [32]. Older studies using tonometry observed associations between microalbuminuria, renal function and arterial stiffness [33,34], and in the present study, we elaborated on these findings by the observed weak associations between normal-range albuminuria, arterial thickness and arterial stiffness in the general population.

Strengths of our study are the extensive cardiovascular imaging

Table 4
Differences (with 95% confidence intervals) in cardiovascular imaging parameters per 10 ml/min/1.73 m^2 higher eGFR.

Imaging parameters		eGFR (10 ml/min/1.73 m^2)		
	n	β	95% CI	*p*
Carotid intima media thickness (mm)	6503			
Crude		−0.004	−0.01;-0.00	0.002
Adjusted		0.002	−0.00; 0.00	0.137
Pulse wave velocity (m/s)	2541			
Crude		−0.149	−0.21;-0.09	<0.001
Adjusted		−0.005	−0.06; 0.05	0.856
Cardiovascular magnetic resonance	1138			
LV mass index (g/m^2)				
Crude		0.969	0.26; 1.67	0.007
Adjusted		0.748	0.15; 1.35	0.015
LV ejection fraction (%)				
Crude		−0.374	−0.79; 0.04	0.075
Adjusted		−0.294	−0.72; 0.13	0.177
LV cardiac index (L/min/m^2)				
Crude		0.078	0.03; 0.13	0.001
Adjusted		0.080	0.03; 0.13	0.001
E/A ratio				
Crude		0.07	0.03; 0.11	0.001
Adjusted		0.01	−0.02; 0.05	0.449
E deceleration peak (ml/s^{2}*10^{-3})				
Crude		−0.133	−0.20;-0.06	<0.001
Adjusted		−0.040	−0.11; 0.03	0.257

Results were weighed toward the BMI distribution of the general population. Crude and adjusted analysis (sex, age, smoking, mean arterial blood pressure, total body fat and fasting glucose) with linear regression coefficients and 95% confidence intervals are shown. Regression coefficients reflect the change in cardiovascular outcome variable per 10 ml/min/1.73 m^2 increase in eGFR. E/A ratio; ratio of early peak filling rate and atrial peak filling rate, eGFR; estimated glomerular filtration rate according to CKD-EPI.

protocol, and the large sample size based on a random subset of the general population without contra-indications for MRI. Moreover, previous studies have mainly used echocardiography rather than cardiovascular magnetic resonance, which is considered the gold standard for assessment of LV mass, volume, and function [35]. Arterial stiffness assessed by MRI is considered a superior technique regarding accuracy and precision [36,37] compared to conventional tonometry. Inaccurate measurement of the pressure wave path length by tonometry can lead to substantial measurement error in PWV of up to 30% [38,39]. The use of MRI-based PWV measurements enabled us to detect weak associations between normal-range albuminuria and arterial stiffness in a relatively healthy sample of the general population. The quantitative nature of cardiovascular magnetic resonance makes this technique very suitable for the detection of early changes in cardiovascular morphology and functioning in large population based analyses.

There are several limitations that need to be considered. The observational cross-sectional nature of our study precludes causal inference. We thus cannot exclude that observed associations result from residual confounding or reverse causation (e.g. decreased renal perfusion and/or arterial remodeling due to lower cardiac output). Prospective analyses with repeated measurements over time are needed to determine the direction of the observed associations between normal range albuminuria, renal function and cardiovascular health. Furthermore, it should be recognized that residual confounding by hypertension cannot be eliminated since blood pressures levels were based on office measurements rather than 24-h ambulatory or home blood pressure monitoring. Although the present study is based on a study population with oversampling of obesity, we adjusted for this by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality, whose BMI distribution was similar to that of the general Dutch population. The results of the present study, therefore, apply to a population-based study without oversampling of individuals with a high BMI. Another important limitation is the use of estimated GFR, although the CKD-EPI formula has proven to be more accurate and precise than the MDRD formula, it has not been validated above 90 ml/min/1.73 m^2 and might underestimate hyperfiltration in obesity [29]. Gold standard exogenous clearance measurements are seldom used in epidemiological research due to invasiveness, time and high-cost, and cystatin C derived equations lack an international standardized calibrator.

In conclusion, normal-range albuminuria was positively associated with LV mass index, LV cardiac index, arterial thickness and arterial stiffness in the middle-aged general population. Our findings support the hypothesis that normal range albuminuria is a marker of cardiovascular health, even before adverse changes in the setting of advanced kidney disease or cardiovascular disease occur.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Centre, and by the Leiden University, Research Profile Area 'Vascular and Regenerative Medicine'.

Author contributions

I. A. Dekkers designed and performed research, analyzed and interpreted data, and wrote the manuscript. R. de Mutsert, F. R. Rosendaal, A. de Roos, J. W. Jukema, T. J. Rabelink, H. J. Lamb, and A. P. J. de Vries designed research, interpreted data, and provided vital reviews of the manuscript. All authors gave final approval of the version to be published.

Acknowledgements

We express our gratitude to all individuals who participate in the Netherlands Epidemiology of Obesity (NEO) study. We are grateful to all participating general practitioners for inviting eligible participants. We furthermore thank all research nurses for collecting the data, I. de Jonge, MSc, Leiden University Medical Center, for all data management of the NEO study, R.C.A. Rippe, PhD, Leiden University, for statistical input and guidance, and R.L. Widya, MD PhD, J. Amersfoort, MSc, E. Ghariq, MD, M.F. Rodrigues, MD, and R.P.B. Tonino, all Leiden University Medical Center, for their help in MR data collection.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.03.029.

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