The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly

Elisabet Nerpin1,2, Erik Ingelsson3, Ulf Risérs4, Johan Sundström5, Bertil Andren5, Elisabeth Jobs1,2, Anders Larsson5, Lind Lars5 and Johan Ärnlöv1,2

1Department of Public Health and Caring Sciences/Geriatrics, Uppsala Science Park, Uppsala, Sweden, 2Department of Health and Social Sciences, Högskolan Dalarna, Falun, Sweden, 3Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden, 4Department of Public Health and Caring Sciences/Section of Clinical Nutrition and Metabolism, Uppsala Science Park, Uppsala, Sweden and 5Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Correspondence and offprint requests to: Elisabet Nerpin; E-mail: ene@du.se

ABSTRACT

Background. The cardiorenal syndrome, the detrimental bi-directional interplay between symptomatic heart failure and chronic kidney disease, is a major clinical challenge. Nonetheless, it is unknown if this interplay begins already at an asymptomatic stage. Therefore we investigated whether the glomerular filtration rate (GFR) is associated with left ventricular function in participants free from clinical heart failure and with a left ventricular ejection fraction (LVEF) >40% and with pre-specified sub-group analyses in individuals with a GFR >60 mL/min/1.73 m².

Methods. Two independent community-based cohorts were used; the Prospective Investigation of the Vasculature in Communities, Högskolan Dalarna, Falun, Sweden, 3Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden and 5Department of Medical Sciences, Uppsala University, Uppsala, Sweden

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39. Li MX, Kwan JS, Bao SY et al. The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly
41. Chan PA, Duraisamy S, Miller PJ et al. Prediction of missense mutation functionality depends on both the algorithm and sequence alignment employed. Hum Mutat 2011; 32: 661–668

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Correspondence and offprint requests to: Elisabet Nerpin; E-mail: ene@du.se

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Uppsala Seniors (PIVUS; \( n = 911 \); 50% women; mean age: 70 years) and the Uppsala Longitudinal Study of Adult Men (ULSAM; \( n = 538 \); mean age: 71 years). We investigated cross-sectional association between cystatin C-based GFR (estimated glomerular function \( \text{eGFR} \)) and systolic (LVEF), diastolic-(isovolumic relaxation time \( \text{IVRT} \)) and global left ventricular function (myocardial performance index \( \text{MPI} \)) determined by echocardiography.

**Results.** In both PIVUS and ULSAM, higher eGFR was significantly associated with higher LVEF \( (P = 0.004 \ [\text{PIVUS} \text{]} \text{and} \ P = 0.005 \ [\text{ULSAM}] \). In PIVUS, higher eGFR was significantly associated with lower IVRT \( (P = 0.001) \text{and} \ MPI \ (P = 0.006) \), in age- and sex-adjusted models. After further adjustment for cardiovascular risk factors, the association between higher eGFR and higher LVEF was still statistically significant \( (P = 0.008 \ [\text{PIVUS} \text{]} \text{and} \ P = 0.02 \ [\text{ULSAM}] \). In PIVUS, the age- and sex-adjusted association between eGFR and left ventricular function was similar in participants with eGFR >60 mL/min/m².

**Conclusions.** Our data suggest that the interplay between kidney and heart function begins prior to the development of symptomatic heart failure and kidney disease.

**Keywords:** chronic kidney disease, cystatin C, glomerular filtration rate, left ventricular dysfunction, heart failure

**INTRODUCTION**

Chronic kidney disease (CKD) is recognized as a global public health problem and is known to be an independent risk factor for cardiovascular disease (CVD) including heart failure [1]. It is also known that worsening heart failure or acute decompenated heart failure can accelerate deterioration of renal function or vice versa—often referred to as the cardiorenal syndrome [2, 3]. Anomalies of left ventricular function have been shown to be very prevalent among CKD patients in stages 3–5 (estimated glomerular function rate \( \text{eGFR} \) \(<60 \text{ mL/min/1.73 m}^2 \)) [3, 4]. However, whether eGFR is associated with left ventricular function in the community is less studied.

We are aware of a few previous community-based studies that have reported the association between impaired kidney function and left ventricular function. However, these studies have included patients with CKD [5–7] or patients with clinical heart failure at baseline [7] making it difficult to fully evaluate whether the association between eGFR and anomalies of left ventricular function is present prior to the development of symptomatic heart failure and CKD.

Based on previous data, we hypothesized that the interplay between impaired kidney function and left ventricular function begins already at the asymptomatic stages of heart failure and with eGFR >60 mL/min/1.73 m². Accordingly, we investigated cross-sectional associations between eGFR and ventricular function in two community-based samples of elderly free from a clinical heart failure and with a left ventricular ejection function (LVEF) >40%. In secondary analyses, we also investigated associations between eGFR and ventricular function in pre-specified sub-groups of the cohorts with eGFR >60 mL/min/1.73 m².

**MATERIALS AND METHODS**

**Study samples**

**Prospective Investigation of the Vasculature in Uppsala Seniors.** All 70-year-old residents of Uppsala County (Sweden), between April 2001 and June 2004, were invited to participate in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, described in detail elsewhere [8]. Of 2025 subjects invited, 1016 were examined within 1 month of their 70th birthday. For this study, we excluded 49 participants who had not undergone the echocardiography examination, 8 participants with LVEF <20%, 33 participants with a previous diagnosis of heart failure, 14 participants with missing data on cystatin C and 1 participant with eGFR >270 mL/min/1.73 m². After these exclusions, 911 individuals aged 70 (50.6% women) were eligible. Of these individuals, 785 had valid measurement of LVEF, 850 isovolumic relaxation time (IVRT) and 732 global ventricular function (myocardial performance index, MPI).

**Uppsala Longitudinal Study of Adult Men.** The Uppsala Longitudinal Study of Adult Men (ULSAM) is a community-based study aimed at identifying risk factors for CVD. All men born in 1920–24 and living in Uppsala were invited to participate in a health survey in between 1970 and 1973, of the 2841 invited subjects, 2322 participated (82%). At a re-investigation after approximately 20 years, 1221 men (mean age 71 years) were investigated. At this re-investigation, an echocardiographic Doppler examination was performed on the first consecutive 583 participants. We excluded 15 participants where it was not possible to obtain reliable data from the echocardiographic examination, 14 participants with LVEF <40%, 4 participants who had previously been hospitalized for heart failure and 12 participants for missing data on cystatin C. After these exclusions, 538 individuals aged 70 were eligible. Of these individuals, 407 had valid measurement of LVEF, 494 IVRT and 424 MPI.

All participants gave written informed consent and the Ethics Committee of Uppsala University approved the study protocols.

**Clinical and biochemical evaluation**

The investigations in PIVUS and ULSAM were performed using the same standardized methods, which included anthropometrical measurements, blood pressure, fasting blood and a questionnaire regarding their medical history, smoking habits and regular medication.

All participants were investigated in the morning after an overnight fast, with no medication or smoking allowed after midnight. Venous blood samples were drawn in the morning after an overnight fast and stored at –70°C.

Body mass index (BMI) was calculated as the ratio of the weight to the height squared (kg/m²). Blood pressure was measured by a calibrated mercury sphygmomanometer to the nearest even mmHg after at least 10 min of rest and the average of three (PIVUS) or two (ULSAM) recordings were used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques.
Use of diabetes medication was ascertained through self-report questionnaires. Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L or use of insulin or oral hypoglycaemic agents. Hypertension was defined as ≥140 mmHg systolic blood pressure, ≥90 mmHg diastolic blood pressure or treatment for hypertension.

Estimations of glomerular filtration rate (eGFR) were measured from serum cystatin C performed by Gentien (Moss, Norway) using an Architect Ci8200 (Abbott Park, IL, USA), with the corresponding formula eGFR = 79.901 × cystatin C\(^{-1.4389}\) (PIVUS), and late enhanced reagents from Dade Behring (Deerfield, IL, USA) using a Behring BN ProSpec analyzer (Dade Behring) with the formula: eGFR = 77.24 * cystatin C\(^{-1.2623}\) (ULSAM) and which both have been shown to be closely correlated with iohexol clearance [9, 10].

Information about hospitalization due to myocardial infarction, angina pectoris, ischaemic stroke and heart failure was obtained from the Swedish Hospital Discharge Register (ULSAM). The validity of myocardial infarction and stroke in the Swedish Hospital Discharge Register has been demonstrated to be high [11]. In PIVUS, information on prior CVD was collected from a questionnaire.

**Echocardiography.** A 2–5 MHz transducer was used for two-dimensional and Doppler echocardiography and was performed with an Acuson XP124 cardiac unit (Acuson, CA) in PIVUS and a Hewlett-Packard Sonos 1500 cardiac ultrasound unit (Hewlett-Packard, Andover, MA) in ULSAM.

Left ventricular dimensions were measured with M-mode. Left ventricular volumes (LVEDV, LVESV) were calculated according to the Teichholz M-mode formula; volume = \(7D^3/3\) (2.4 + \(D\), \(D\) = diameter LVEF, reflecting left ventricular systolic function, was calculated as left ventricular diastolic volume − left ventricular systolic volume/ left ventricular diastolic volume. Impaired LVEF was defined as LVEF <40% [12]. Ventricular diastolic function was measured with isovolumic relaxation time as the interval between aortic valve closure and the onset of mitral flow, using the Doppler signal from the area between the LV outflow tract and mitral flow. MPI, reflecting global left ventricular function, was calculated as isovolumic contraction time + isovolumic relaxation time/ left ventricular ejection time. Examinations and readings of the images were performed by two experienced physicians (Dr Lind, PIVUS and Dr Andrén, ULSAM) who were unaware of the other data of the subjects.

**Statistical analysis**

Variables with a skewed distribution (NT-proBNP and glucose) were logarithmically transformed to achieve normal distribution, and these transformed variables were used in all analyses. Missing data on covariates were handled via multiple imputation techniques to deal with the loss of information on covariates in the data set. Two-tailed 95% confidence intervals (CIs) and significance values were given, with a value of \(P < 0.05\) regarded as significant.

Linear regression analyses were used to assess the cross-sectional associations of eGFR (independent variable) with LVEF, IVRT and MPI (dependent variables in separate models).

We used the directed acyclic graph (DAG) approach to establish a parsimonious model with minimized confounding of the effect estimates in the statistical model B.

The following models were performed:

- **Model A:** adjusted for age (continuous) and sex (binary [PIVUS]).
- **Model B:** DAG-adjusted; adjusted for age (continuous), sex (binary [PIVUS]), systolic and diastolic blood pressure (continuous), BMI (continuous), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) (continuous), smoking (binary), diabetes (binary).

In our analysis, we modelled eGFR, LVEF, IVRT and MPI as continuous variables (expressed as a 1 SD increase). In secondary models we also added to the whole cohort and to participants with eGFR >60 mL/min/1.73 m\(^2\), the use of angiotensin converting enzyme (ACE) inhibitors, beta-blockers, Ca-antagonist or diuretics to multivariable model B. To gain additional insights into the potential nonlinearity of the associations, we examined the regression models using splines.

We also performed the above analyses in a pre-specified sub-group with normal eGFR (>60 mL/min/1.73 m\(^2\)), PIVUS: \(n = 743/802/688\) for LVEF/IVRT/MPI analyses, respectively; ULSAM: \(n = 224/268/243\) analyses, respectively. Moreover, we also investigated the association between creatinine-based eGFR (Chronic Kidney Disease Epidemiology Collaboration formula [CKD-EPI]) [13] and LVEF.

In secondary analyses, we performed tests for effect modification by gender by including a multiplicative interaction term in multivariable model B.

**RESULTS**

Baseline characteristics for the whole cohort in PIVUS and ULSAM are shown in Table 1.

In both PIVUS and ULSAM, higher eGFR was significantly associated with higher LVEF, adjusted for age and sex (model A, Table 2). Further, higher eGFR was significantly associated with lower IVRT and MPI (reflecting better ventricular function) in PIVUS. After further adjustment of systolic and diastolic blood pressure, BMI, diabetes, LDL- and HDL-cholesterol and smoking, a significant association was seen between eGFR and LVEF (model B, Table 2) in both cohorts. Further, in sub-group analyses of participants with eGFR >60 mL/min/1.73 m\(^2\) a significant association between eGFR and LVEF, IVRT and MPI was seen in PIVUS but not in ULSAM after adjustment for age and sex (model A, supplementary data, Table S1). These associations were similar when the use of ACE inhibitors, beta-blockers, Ca-antagonist or diuretics was added to multivariable model B in the whole cohort and in sub-group analyses of participants with eGFR >60 mL/min/1.73 m\(^2\) (data not shown).

The association between creatinine-based eGFR with LVEF in PIVUS and ULSAM was similar to cystatin C-based eGFR adjusted for age and sex but of borderline significance.
(multivariable regression coefficient for 1 SD increase of LVEF 0.07 [95% CI –0.07 to 0.14, P = 0.08] in PIVUS and 0.09 [95% CI –0.01 to 0.19, P = 0.08] in ULSAM).

No evidence of effect modification by gender on the association between eGFR and LVEF was observed in PIVUS. Examination of regression splines suggests no obvious deviation from linearity in the association between eGFR and the different indices of left ventricular function (LVEF, IVRT and MPI, data not shown).

**DISCUSSION**

In two independent community-based cohorts of elderly individuals free from clinical heart failure and with LVEF >40%, we found a positive association between eGFR and different echocardiographic indices of left ventricular systolic, diastolic and global function. However, after adjustment for cardiovascular risk factors only the association between eGFR and left ventricular systolic function (LVEF) was statistically significant in the two cohorts. Interestingly, an association between eGFR and systolic function was seen also in participants with eGFR >60 mL/min/m² in the PIVUS cohort. Our data suggest that the interplay between the kidney and heart may be evident already prior to the development of symptomatic heart failure and CKD.

**Comparison with the literature**

Clinical studies have indicated that impaired left ventricular function is observed among individuals with moderate-to-severe kidney function in patients with hypertension [14, 15], heart failure [16–19], chronic glomerulonephritis [20], diabetes [21] and anaemia [22]. However, previous community-based data are scarce and inconsistent [5–7].

Our findings are in accordance with one previous community-based study [6] measuring LV function with echocardiography in 818, 60–70-year-old participants with coronary heart disease, but free from heart failure. Circulating cystatin C was associated with both diastolic and systolic dysfunction in both crude and multivariable models.

In contrast, the Multi-Ethnic Study of Atherosclerosis by Agarwal et al. [5], an analysis of 4970 participants age 44–80 years, demonstrated no significant association between mild-to-moderate reduction in kidney function measured with cystatin C and LVEF using cardiac magnetic resonance imaging. Similarly, in the Dallas Heart Study [7] a cohort of 2548 individuals aged 30–65 years showed no significant associations between cystatin C and LVEF. Perhaps differences in clinical characteristics, such as age and prevalence of CVD and CKD, could explain these discrepant results between the studies. The participants of the previous negative studies were younger, healthier and with less CVD and CKD comorbidities. We are not aware of any previous study that have reported the association between glomerular filtration rate and left

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**Table 1. Baseline characteristics of two cohorts**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PIVUS Whole sample (n = 911)</th>
<th>ULSAM Whole sample (n = 538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>70.2 ± 0.2</td>
<td>71.2 ± 0.5</td>
</tr>
<tr>
<td>Females no (%)</td>
<td>461 (50.6)</td>
<td>NA</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 7</td>
<td>65 ± 8</td>
</tr>
<tr>
<td>IVRT</td>
<td>121 ± 21</td>
<td>123 ± 22</td>
</tr>
<tr>
<td>MPI</td>
<td>0.60 ± 0.16</td>
<td>0.69 ± 0.16</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.90 ± 0.17</td>
<td>1.24 ± 0.25</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>93 ± 22</td>
<td>62 ± 14</td>
</tr>
<tr>
<td>eGFRCKD-EPI (mL/min/1.73 m²)</td>
<td>79 ± 14</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150 ± 23</td>
<td>149 ± 19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 10</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.5 ± 0.4</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.4 ± 0.9</td>
<td>3.9 ± 0.9</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>101 (11.1)</td>
<td>76 (14.1)</td>
</tr>
<tr>
<td>Diabetes medication, no. (%)</td>
<td>61 (6.7)</td>
<td>26 (4.8)</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>95 (10.4)</td>
<td>113 (21.0)</td>
</tr>
<tr>
<td>Dyslipidaemia, no (%)</td>
<td>699 (76.7)</td>
<td>475 (88.3)</td>
</tr>
<tr>
<td>Lipid-lowering treatment, no. (%)</td>
<td>138 (15.1)</td>
<td>39 (7.3)</td>
</tr>
<tr>
<td>Cardiovascular disease, no. (%)</td>
<td>117 (12.8)</td>
<td>183 (34.0)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>655 (71.9)</td>
<td>407 (75.7)</td>
</tr>
</tbody>
</table>
| Anti-hypertensive treatment, no. (%)| 270 (29.6) | 185 (34.4)  
| Beta-blocker, no. (%)           | 181 (19.9)                  | 103 (19.1)                    |
| Calcium channel blockers, no. (%)| 99 (10.9)                   | 64 (11.9)                     |
| Diuretic, no. (%)               | 93 (10.2)                   | 64 (11.9)                     |
| ACE-antagonist, no. (%)         | 67 (7.4)                    | 28 (5.2)                      |
| A-1 antagonist, no. (%)         | 75 (8.2)                    | NA                            |

Data are mean ± SD for continuous variables and no (%) for dichotomous variables.

BMI, body mass index; LVEF, left ventricular ejection fraction; IVRT, isovolumic relaxation time; MPI, myocardial performance index; NA, not available.

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**Table 2. Cross-sectional associations between cystatin C-based glomerular filtration rate (eGFR) and LVEF, IVRT or MPI at age 70 in PIVUS and ULSAM: multivariable regression, whole cohort with LVEF >40%**

<table>
<thead>
<tr>
<th>Estimated glomerular filtration rate (eGFR) Whole cohort</th>
<th>β-coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIVUS Model A; sex and age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.11 (0.03 to 0.18)</td>
<td>0.004</td>
</tr>
<tr>
<td>IVRT</td>
<td>−0.12 (−0.18 to −0.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>MPI</td>
<td>−0.10 (−0.17 to −0.03)</td>
<td>0.006</td>
</tr>
<tr>
<td>PIVUS Model B; DAG-adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.10 (0.03 to 0.17)</td>
<td>0.008</td>
</tr>
<tr>
<td>IVRT</td>
<td>−0.07 (−0.14 to −0.01)</td>
<td>0.02</td>
</tr>
<tr>
<td>MPI</td>
<td>−0.07 (−0.14 to 0.0001)</td>
<td>0.051</td>
</tr>
<tr>
<td>ULSAM Model A; sex and age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.14 (0.04 to 0.23)</td>
<td>0.005</td>
</tr>
<tr>
<td>IVRT</td>
<td>−0.05 (−0.14 to 0.04)</td>
<td>0.24</td>
</tr>
<tr>
<td>MPI</td>
<td>−0.09 (−0.18 to 0.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>ULSAM Model B; DAG-adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.11 (0.02 to 0.21)</td>
<td>0.02</td>
</tr>
<tr>
<td>IVRT</td>
<td>−0.03 (−0.12 to 0.06)</td>
<td>0.50</td>
</tr>
<tr>
<td>MPI</td>
<td>−0.06 (−0.15 to 0.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Data are regression coefficients for a 1-SD higher eGFR. LVEF, left ventricular ejection fraction; IVRT, isovolumetric relaxation time; MPI, myocardial performance index.

Model A: adjusted age, sex. Model B: DAG-adjusted; age, sex, systolic and diastolic blood pressure, BMI, diabetes, LDL-cholesterol and smoking. Whole cohort PIVUS: LVEF (n = 785), IVRT (n = 850), MPI (n = 732); ULSAM: LVEF (n = 407), IVRT (n = 494), MPI (n = 424).
ventricular function in individuals free from clinical heart failure and GFR >60 mL/min/1.73 m².

Possible mechanisms for the observed associations

The mechanisms of association between impaired kidney function and CVD are not fully understood:

A chronic activation of the renin–angiotensin system (RAAS) is a hallmark of CKD. RAAS activation leads to sodium retention and increased extracellular fluid volume which may further exacerbate LV function. A persistent activation of RAAS also has direct damaging effects on cardiac function and contributes to the progression of heart failure via promotion of cardiac remodelling and myocardial fibrosis [2]. An experimental study by Martin et al. [23] demonstrated that mild renal insufficiency in rats resulted in an early cardiac fibrosis and impaired diastolic function, which progresses to more global LV remodelling and dysfunction and further on to heart failure.

CKD often coexists with cardiovascular risk factors, such as dyslipidaemia, hypertension, smoking and diabetes [24], all of which have been shown to be important risk factors for heart failure [25]. In this study, the association between renal function and ventricular function was attenuated after adjustment for cardiovascular risk factors (in particular the association between eGFR and diastolic or global ventricular function), which could indicate that these factors are deleterious for both the heart and the kidney and provide a common pathophysiological link. Elevated cardiovascular risk factors contribute to accelerated atherosclerosis in these patients through increased production of reactive oxygen species, which then could lead to increased incidence of heart failure in the general population [26].

Clinical implications

Cardiorenal syndrome is a major clinical challenge and early diagnosis by assessing biomarkers of cardiac and renal injury may be critical for timely therapeutic intervention. A better understanding of the cardiorenal interplay in the early stages of the disease may in the long term improve the patients’ outcome, delaying not only early renal disease but also the progression of heart failure. Studies have shown that therapeutic interventions introduced before the presence of left ventricular dysfunction or symptoms can reduce the population morbidity and mortality of heart failure [27, 28].

In our study, the cross-sectional regression coefficients suggest that the magnitude of the association between eGFR and left ventricular heart function appears modest even though it was statistically significant. Yet, no firm conclusions on effect size should be drawn from observational data, additional intervention trials are needed to properly investigate this issue.

Strengths and limitations

The strengths of our investigation include the use of two independent community-based study samples with longitudinal data and the detailed characterization regarding cardiovascular risk factors, which allowed adjustment for many potential confounders.

Some limitations are also worth noting. The study design was cross-sectional; thus, we cannot assess causality between eGFR and left ventricular function. The present sample consisted of individuals of Northern European descent and 70 years of age, so generalizability to other ethnic and age groups is unknown. The PIUS cohort had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population in terms of most cardiovascular disorders and medication [8]. Cystatin C is an indirect approximation for eGFR, and direct measures of eGFR through the gold standard method (exogenous clearance measurements) were unavailable. Yet, exogenous clearance measurements are seldom used in epidemiological research as it is a time-consuming and costly procedure. In this study, we used a cystatin C-based eGFR formula, which has been shown to be closely correlated with eGFR assessed by isotope clearance measurements also in the normal range of eGFR [9, 10]. We did not use the CKD-EPI formula that incorporates both creatinine and cystatin C as this formula is based on standardized cystatin C or creatinine measurements and these were not available at the baseline of this study.

CONCLUSION

Among elderly individuals in two independent community-based cohorts, lower levels of eGFR were independently associated with decreased left ventricular function. Our data suggest that the detrimental interplay between the kidney and the heart begins at the early stages of left ventricular dysfunction, prior to the development of symptomatic heart failure and CKD.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have previously been published in Elisabet Nerpin’s thesis.

REFERENCES

2. Sun Y. The renin–angiotensin–aldosterone system and vascular remodeling. Congest Heart Fail 2002; 8: 11–16

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