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## Lipids, inflammation, and the Renin-Angiotensin System

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Chapter 6

**Mild Renal Dysfunction is Associated with  
Electrocardiographic Left Ventricular Hypertrophy**

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**ABSTRACT**

*Background* Both renal dysfunction and left ventricular hypertrophy (LVH) are signs of end-organ damage, risk markers of cardiovascular (CV) disease and chronic heart failure. In selected populations, such as diabetes or hypertension, renal dysfunction was related to LVH. We studied the relation between renal dysfunction and LVH in a cross-sectional study in 8,592 inhabitants from Groningen, The Netherlands.

*Methods* Standard 12-lead electrocardiograms were recorded, and LVH was classified using the Cornell voltage duration product. Renal dysfunction was defined as creatinine clearance  $<60$  mL/min/1.73m<sup>2</sup> and /or microalbuminuria (30-300mg/24h).

*Results* Electrocardiographical signs of LVH were present in 396 (5.3%) subjects. Subjects with LVH were older and had a more extensive CV risk profile. LVH was more prevalent in subjects with renal dysfunction than in those without (8% vs. 4%,  $P < 0.001$ ). Multivariate regression analysis demonstrated that renal dysfunction was independently related to a 1.47 times increased risk of the presence of LVH (95% CI 1.15 to 1.88;  $P = 0.009$ ). In addition, both creatinine clearance (OR 1.56; 95% CI 1.07 to 2.29;  $P = 0.044$ ) and microalbuminuria (OR 1.37; 95% CI 1.04 to 1.80;  $P = 0.024$ ) were independently associated with the presence of LVH.

*Conclusion* Subjects with mild renal dysfunction have a substantially higher risk of LVH on electrocardiogram than those without renal dysfunction.

## INTRODUCTION

Left ventricular hypertrophy (LVH) is a manifestation of sub-clinical cardiovascular (CV) end-organ damage and plays a prominent role in CV disease. Several factors in LVH contribute to ventricular dysfunction and chronic heart failure on the long term.<sup>1,2</sup> The presence of LVH is an important independent risk factor for total and cardiovascular mortality.<sup>3</sup> Impaired renal function is another manifestation of end-organ damage.<sup>4</sup>

Several studies have demonstrated an association between renal dysfunction and LVH.<sup>5,6</sup> However, these studies were only performed in selected populations, such as patients with end-stage renal disease, untreated hypertension or diabetes mellitus type II.<sup>5,7,8</sup> Therefore, we investigated the association cross-sectionally between renal dysfunction and electrocardiographic LVH in a large cohort study.

## METHODS

### *Study design and population*

This study was performed in the subjects participating in the Prevention of RENal and Vascular ENd-stage Disease (PREVEND) study. The PREVEND study is designed to prospectively investigate the natural course of albuminuria and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of the study protocol have been described elsewhere.<sup>9</sup> In summary, in the period 1997-1998, all 85,421 inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years were sent a 1-page postal questionnaire (regarding demographics, use of medication and presence of pregnancy) and a vial to collect an early morning urine sample. 40,856 subjects responded (47.8%; Figure 1). Their vials were sent to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of subjects with type 1 diabetes mellitus (defined as the use of insulin), (possibly) pregnant women and those not able or willing to participate, all subjects with a urinary albumin concentration (UAC) of  $\geq 10$  mg/L ( $n=7,768$ , group A) and a SPSS generated random sample of the 22,492 subjects with a UAC  $< 10$  mg/L (group B) were invited for further investigations in an outpatient clinic and to collect two consecutive 24h urines. Taking into regard an expected non-participation rate of around 15%, the number of subjects invited to form group B was arbitrarily set at 3,395, in order to achieve an overall sample size of approximately 10,000 subjects. Of group A 6,000 subjects completed the screening protocol (77.2%) and of group B 2,592 subjects (76.3%). These 8,592 subjects form the actual PREVEND baseline cohort.

All subjects filled in a questionnaire concerning demographics, cardiovascular and renal history. Anthropometrical measurements were performed, as were blood pressure measurements.<sup>9</sup>

Fasting blood samples were taken and subjects collected twice 24h urine. We excluded 451 subjects because of erythrocyturia or leucocyturia since these laboratory abnormalities may indicate the presence of urinary tract infection, which makes the assessment of the exact amount of albuminuria unreliable. 117 subjects were excluded, because of the presence

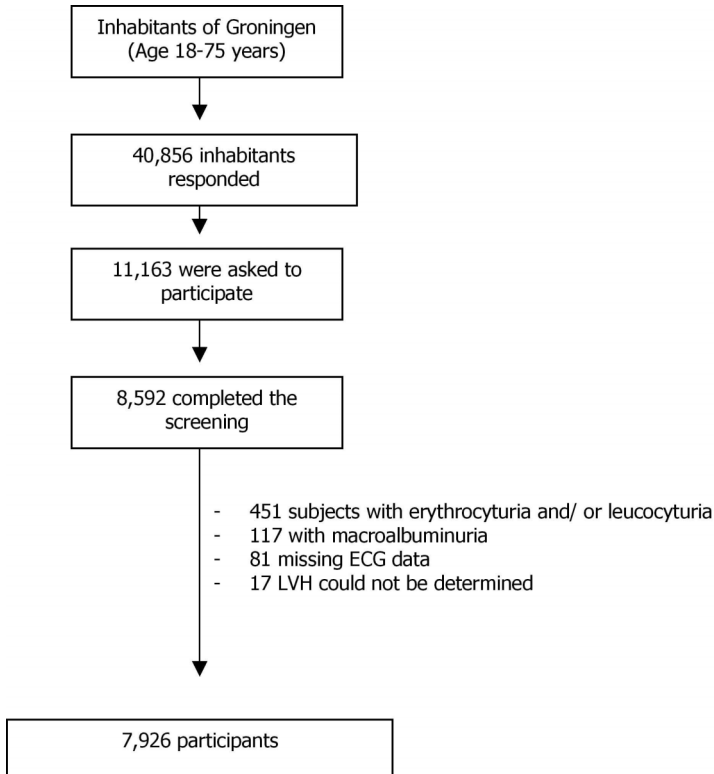


Figure 1. Schematic overview of patient selection of the PREVEND-study.

of macroalbuminuria, to exclude overt nephropathy. Furthermore, 81 subjects were excluded because of missing electrocardiographic data and 17 subject because LVH could not be determined on the electrocardiogram. In total 7,926 subjects were eligible for the analysis.

All subjects gave written informed consent. The local medical ethics committee approved the PREVEND study and the study was conducted in accordance with the guidelines of the declaration of Helsinki.

#### *Laboratory methods*

Urinary volume and albumin were measured in each collection.<sup>9</sup> UAC and high sensitive C-reactive protein were determined by nephelometry (Dade Behring Diagnostics, Marburg, Germany). Leukocytes and erythrocytes were determined by urine stick (Nepthur + leuco, Boehringer Mannheim). Serum glucose, cholesterol, creatinine and urine creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, U.S.A.).

#### *Definitions*

Urinary albumin excretion was measured as the mean of two 24h urine collections. Normoalbuminuria was defined as urinary albumin excretion of <15 mg per 24h, high

normoalbuminuria as urinary albumin excretion of 15-29.9 mg per 24h, microalbuminuria as 30-300 mg per 24h and macroalbuminuria as urinary albumin excretion of >300 mg per 24h. Albumin measurements were considered unreliable when more than 75 leukocytes  $\mu\text{L}^{-1}$  or more than 50 erythrocytes  $\mu\text{L}^{-1}$  were measured in the urine. Creatinine clearance (CrCl) was calculated as the mean of two 24h urine creatinine excretions divided by plasma creatinine. CrCl was adjusted for body surface area,  $\text{BSA} = 0.007184 \times \text{weight}^{0.425} \times \text{length}^{0.725}$ , by dividing CrCl by BSA. Mild renal dysfunction was defined as  $\text{CrCl} < 60 \text{ mL/min/1.73m}^2$  and/ or the presence of microalbuminuria.<sup>5,9,10</sup> To obtain body mass index (BMI) weight (kg) was divided by the square of height ( $\text{m}^2$ ). Obesity was defined as BMI greater than  $30 \text{ kg/m}^2$ . Diabetes was defined as a fasting plasma glucose level of  $\geq 7.0 \text{ mmol/L}$  or a non-fasting plasma glucose level of  $\geq 11.1 \text{ mmol/L}$  or the use of oral antidiabetic drugs. Hypertension was defined as having a systolic blood pressure  $\geq 140 \text{ mm Hg}$  and/ or diastolic blood pressure  $\geq 90 \text{ mm Hg}$  and/ or use of anti-hypertensive medication. Hypercholesterolemia was defined as a serum cholesterol  $\geq 6.5 \text{ mmol/L}$  or a serum cholesterol  $\geq 5.0 \text{ mmol/L}$  if a history of myocardial infarction was present or the use of lipid lowering medication.

### *Electrocardiography*

Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Rijswijk, The Netherlands), stored digitally using the computer program MEANS (Modular electrocardiogram Analysis System). Infarct patterns, suggestive of myocardial infarction, were defined by Minnesota codes 1.1 and 1.2. Minnesota Codes 1.3, 4.1, 4.2, 4.3, 5.1, 5.2, and 5.3 were considered to be indicative for the potential presence for ischemia. LVH was identified using Cornell voltage-duration product, which was calculated as follows:  $\text{RaVL} + \text{SV}_3$  (with 6 mm added in women) times QRS duration. A threshold of 2440 mm·ms was used to identify LVH.<sup>11</sup>

### *Statistical analyses*

Differences between continuous variables were tested by a Student's t-test or Mann-Whitney U test when appropriate. Differences in proportions were tested using a Chi-square test or Fisher's exact test. Continuous variables were modeled with indicator variables into tertiles, and odds ratios (OR) were calculated for the two highest tertiles compared with the lowest (reference) tertile. Logistic regression analysis was performed to determine independent associations with electrocardiographic LVH. Data are expressed as OR and corresponding 95% confidence intervals (CIs). The variables with  $P < 0.10$  in the univariate regression analysis were used in the multivariate regression analysis. A  $P < 0.05$  was considered as significant. Analyses were performed using the statistical package SPSS 11.0.

## **RESULTS**

### *Baseline characteristics*

Using the Cornell voltage-duration product 396 (5.3%) subjects were identified with electrocardiographic LVH. Mild renal dysfunction was present in 1311 subjects (16.6% of

the total population). Creatinine clearance  $< 60\text{mL}/\text{min}/1.73\text{m}^2$  was present in 5.0% and microalbuminuria in 12.9% of the total population. The baseline characteristics of subjects identified with or without LVH are presented in Table 1. Subjects with LVH were significantly older, more frequently male, and had higher blood pressures. Also, diabetes and history of myocardial infarction were more frequently present in subjects with LVH. Smoking was less frequently present in subjects with LVH (40% vs. 45%).

Subjects with mild renal dysfunction had more often LVH (8% vs. 4%;  $P < 0.001$ ). Of the subjects with LVH, 186 (47%) did not have hypertension.

**Table 1.** Baseline characteristics of participants of PREVEND with and without left ventricular hypertrophy (LVH) on electrocardiogram.

	No LVH (n=7530)	LVH (n=396)	P-value
Age (years)	49 (12)	53 (14)	$<0.001$
Sex (male, %)	3858 (51)	206 (52)	0.023
Smoking (n, %)	3364 (45)	155 (40)	0.008
Medical History			
Diabetes (n, %)	111 (1.5)	12 (3.0)	0.007
Myocardial infarction (n, %)	289 (4)	46 (12)	$<0.001$
Hypertension (n, %)	2208 (30)	206 (53)	$<0.001$
Hypercholesterolemia (n, %)	1816 (25)	111 (29)	0.096
Obesity (n, %)	1114 (15)	62 (16)	0.668
Anti-hypertensive medication (n, %)	818 (11)	75 (19)	$<0.001$
Lipid lowering therapy (n, %)	434 (6)	29 (8)	0.163
Physical examination			
Heart rate (bpm)	67 (12)	67 (14)	0.573
Systolic BP (mm Hg)	128 (19)	139 (25)	$<0.001$
Diastolic BP (mm Hg)	74 (10)	77 (11)	$<0.001$
Body Mass Index ( $\text{kg}/\text{m}^2$ )	26.0 (4.2)	25.7 (4.4)	0.253
Creatinine ( $\mu\text{mol}/\text{L}$ )	83 (15)	86 (31)	0.098
Creatinine clearance ( $\text{mL}/\text{min}/1.73\text{m}^2$ )	93 (21)	89 (23)	$<0.001$
Creatinine clearance $< 60$ ( $\text{mL}/\text{min}/1.73\text{m}^2$ ) (n, %)	358 (5)	36 (9)	
UAE ( $\text{mg}/\text{L}/24\text{h}$ )*	9.0 (6.2-16.3)	11.0 (7.3-24.9)	$<0.001$
UAE 0.0-14.9 (n, %)	5468 (73)	252 (63)	
UAE 15.0-29.9 (n, %)	1123 (15)	58 (15)	
UAE 30.0-300 (n, %)	939 (12)	86 (22)	
Mild renal dysfunction (n, %)	1211 (15)	108 (27)	$<0.001$
C-Reactive Protein ( $\text{mg}/\text{L}$ )*	1.2 (0.5-2.9)	1.3 (0.5-2.8)	0.899
Cholesterol ( $\text{mmol}/\text{L}$ )	5.6 (1.1)	5.7 (1.1)	0.648

BP, blood pressure. UAE, urinary albumin excretion. Mild renal dysfunction; creatinine clearance  $< 60\text{mL}/\text{min}/1.73\text{m}^2$  and/or microalbuminuria. All continuous variables are presented as mean (SD), if \* is present continuous variable are presented in median value (25<sup>th</sup>-75<sup>th</sup>)

*LVH regression analysis*

After adjustment of confounding factors, such as age, sex, diabetes, myocardial infarction, systolic and diastolic blood pressure and anti-hypertensive medication, mild renal dysfunction remained associated with a 1.47 times ( $P = 0.003$ ) increased risk for LVH (Table 2). Since we used a composite parameter renal function we studied the subjects with microalbuminuria or with a creatinine clearance  $< 60\text{mL/min}/1.73\text{m}^2$  in more detail. In both populations LVH was equally present. Also no differences were found in age, diabetes or history of myocardial infarction. In subjects with microalbuminuria males were frequently more present and also had higher blood pressures. We therefore subdivided the composite parameter renal function (microalbuminuria and creatinine clearance  $< 60\text{mL/min}/1.73\text{m}^2$ ) and both

Table 2. Multivariate associations with left ventricular hypertrophy.

	Mild renal dysfunction OR (95% CI)	Microalbuminuria OR (95% CI)	CrCl $< 60\text{ mL/min}/1.73\text{m}^2$ OR (95% CI)
Model 1	1.97 (1.56-2.48)***	1.95 (1.52-2.50)***	2.01 (1.40-2.88)***
Model 2	1.73 (1.36-2.19)***	1.70 (1.31-2.20)***	1.72 (1.19-2.49)**
Model 3	1.47 (1.15-1.88)**	1.37 (1.04-1.80)* #	1.56 (1.07-2.29)* #

Data are expressed as Odds ratio (95% confidence interval).

Model 1: Univariate analysis

Model 2: Multivariate model adjusted for age and sex.

Model 3: Multivariate model final model: adjusted for age, sex, diabetes, myocardial infarction, systolic and diastolic blood pressure and anti-hypertensive medication.

\*  $P < 0.05$ , \*\*  $P < 0.01$  and \*\*\*  $P < 0.001$

# both included into the same model.

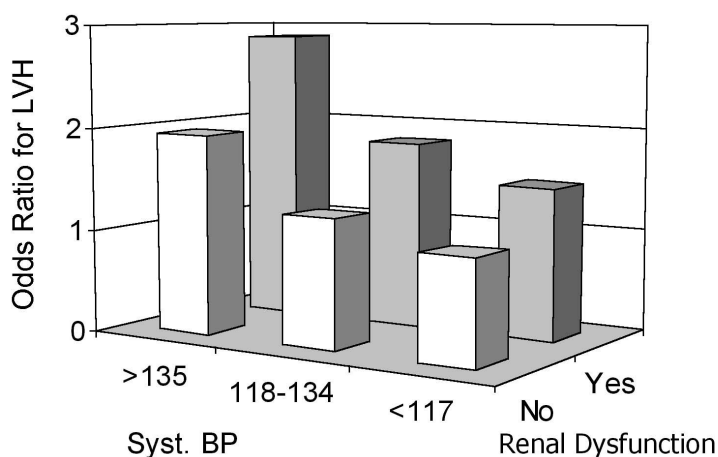


Figure 2. Bar graph of the additional value of mild renal dysfunction with increasing tertiles of systolic blood pressure for diagnosing LVH in this population.



remained statistically significant in the multivariate analyses (Table 2). In addition, LVH was significantly associated with systolic blood pressure (respectively for the 2<sup>nd</sup> and 3<sup>rd</sup> tertile: odds ratio 1.24 (0.89-1.73) and 1.95 (1.34-2.82);  $P = 0.001$ ) and a history of myocardial infarction (odds ratio 2.82 (1.99-4.01);  $P < 0.001$ ). Figure 2 illustrates the additional value of mild renal dysfunction in subjects of various degrees of systolic blood pressure.

The association of mild renal dysfunction with LVH was consistent across pre-specified subgroups, including men and women, patients with a history of myocardial infarction, those with and without diabetes, those with younger and older age or among various blood pressure levels (Figure 3).

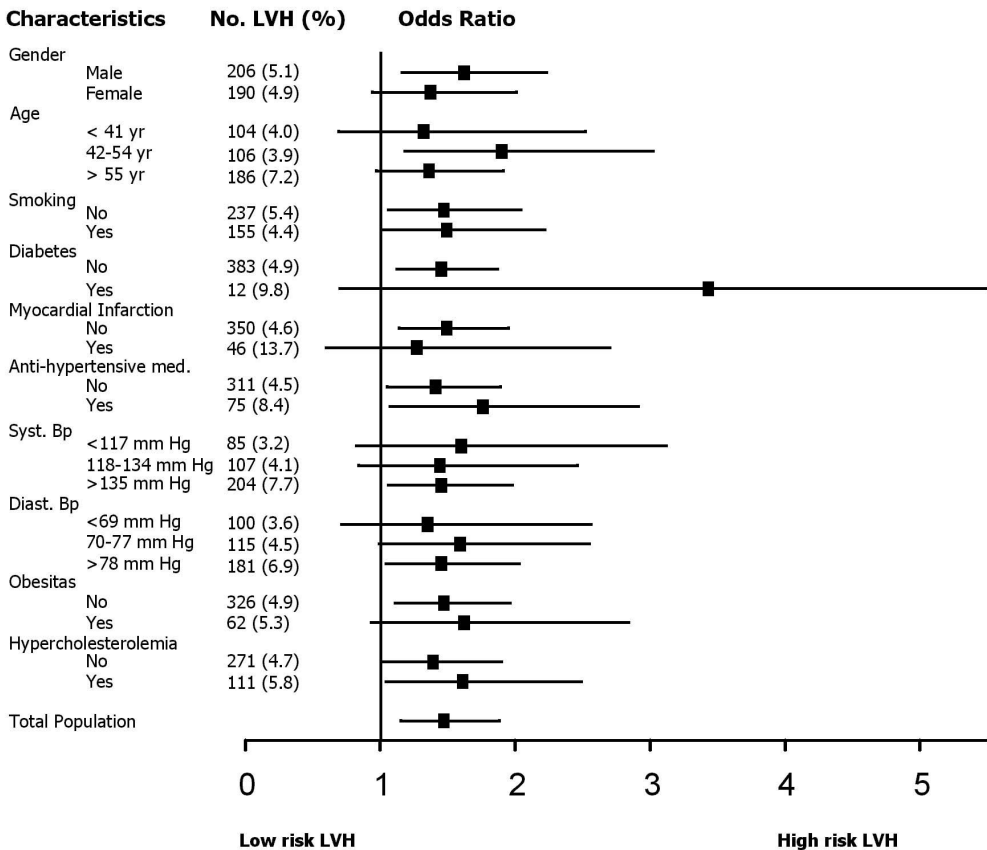


Figure 3. Odds Ratio's of mild renal dysfunction for LVH in prespecified subgroups. Presented are the odds ratio's of the multivariate analysis within each subgroup, adjusted for age, sex, diabetes, myocardial infarction, systolic and diastolic blood pressure, and anti-hypertensive medication.

Since electrocardiographic LVH have some similar ECG patterns as the presence of possible electrocardiographic myocardial ischemia, we adjusted the association of mild renal dysfunction for the presence of ischemia. This did not alter the observed association indicating electrocardiographic ischemia was not a confounder (OR; 1.74[1.36-2.21]).

Additionally, we explored whether the association of mild renal dysfunction and LVH was confounded by the selection criteria of our study population (UAC  $\geq$  10 mg/L or  $<$  10 mg/L). The addition of these selection criteria into the multivariate analysis did not alter the association between renal dysfunction and LVH (OR; 1.41 [1.08-1.82]) and has, therefore, no effect on the observed association. In a secondary analysis we evaluated interaction terms between the variables of the multivariate analysis and also the selection criteria. No significant interaction term was found in the multivariate analysis.

## DISCUSSION

This study shows a clear relationship between two manifestations of early cardiovascular end-organ damage, LVH and renal dysfunction, in an apparently healthy population at large. This association remained statistically significant after adjustment for several confounding factors, such as age, gender, systolic blood pressure and myocardial infarction. Interestingly, almost half of the subjects with LVH did not have hypertension.

Importantly, both mild renal dysfunction and LVH are markers of end-organ damage and are known to be well-established risk markers for cardiovascular morbidity and mortality.<sup>3,4</sup> The association between mild renal dysfunction and LVH can be explained by several mechanisms. If we assume a causal relationship, a bidirectional interaction is suggested. First, LVH might be caused by renal dysfunction, for example by renal anemia<sup>12</sup> or increased sodium retention, both leading to an increased cardiac workload. Second, renal dysfunction might be caused by LVH, for instance through forward failure by primary conditions, such as hypertrophic cardiomyopathy, or secondary conditions, such as myocardial infarction/ischemia<sup>13</sup> and aortic valve stenosis. The most probable explanation however for the association between LVH and mild renal dysfunction is an intermediate factor, which is both associated with renal dysfunction and LVH. For example, hypertension, diabetes, endothelial dysfunction, activated renin-angiotensin system.<sup>14-17</sup> Interestingly, AT1-antagonist have been proven beneficial in both renal dysfunction and LVH<sup>18,19</sup>, this may therefore suggest that angiotensin II may play a causal role in the pathophysiology of renal dysfunction, LVH and their associated increased risk for cardiovascular morbidity and mortality.

The broad definition of renal dysfunction reflects a spectrum of renal conditions, which are the result of several pathophysiological mechanisms in the kidney. Currently it is believed that microalbuminuria is, besides a marker of generalised vascular disease, a reflection of abnormalities in glomerular filtration rate e.g. glomerular hyperfiltration. Glomerular hyperfiltration is considered as one of the pathophysiological mechanisms for the development of diabetic and nondiabetic renal disease.<sup>9,20</sup>

The results of this study might have clinical implications. The increased prevalence of LVH in patients with mild renal dysfunction, might explain the increased risk for

cardiovascular death.<sup>21</sup> Therefore, physicians should be aware of this association and actively screen for other signs of LVH if mild renal dysfunction is detected. Importantly, even in the lowest tertile of systolic blood pressure (<117 mm Hg), mild renal dysfunction tended to be associated with LVH, illustrating an independence of blood pressure. Nevertheless, the risk accumulated with increasing blood pressure (Figure 2).

### *Limitations*

This study provides cross-sectional observational data and therefore can only be used to generate new hypotheses. Due to the epidemiological nature of the study, no clinical data or data about known predictors of LVH, e.g. valve disorders or presence of myocardial ischemia, were obtained. We used electrocardiogram to identify subjects with LVH, not echocardiograms. Therefore, the possibility exists that several subjects with LVH were not detected or falsely identified.

However, strong points of this study are the large size of the population, the reliable way of measuring microalbuminuria by two 24h urine collections, and the computerised electrocardiogram analysis thereby avoiding intra- and inter-observer bias.

## CONCLUSIONS

Our study shows that in this large population subjects with mild renal dysfunction have a higher prevalence of LVH on electrocardiogram than those without renal dysfunction. We hypothesized that this finding may, in part, explain the increased risk for cardiovascular morbidity and mortality that is observed in subjects with mild renal dysfunction.

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