Published in final edited form as:

Am J Kidney Dis. 2015 May ; 65(5): 692–700. doi:10.1053/j.ajkd.2014.11.021.

Parental History of Premature Cardiovascular Disease, Estimated GFR, and Rate of Estimated GFR Decline: Results From the Aerobics Center Longitudinal Study

Xiaoyan Huang, MD, PhD^{1,2}, Xuemei Sui, MD, MPH, PhD³, Jonatan R. Ruiz, PhD⁴, Victor Hirth, MD⁵, Francisco B. Ortega, PhD⁴, Steven N. Blair, PED^{3,6}, and Juan J. Carrero, PhD^{2,7}

¹Division of Nephrology, Peking University Shenzhen Hospital, Peking University, Shenzhen, China

²Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

³Department of Exercise Science, University of South Carolina, Columbia, South Carolina, USA

⁴The PROFITH Research Group “PROmoting FITness and Health through physical activity”. Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain

⁵Division of Geriatrics, School of Medicine, University of South Carolina, Columbia, South Carolina, USA

⁶Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina, USA

⁷Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

© 2014 by the National Kidney Foundation, Inc. All rights reserved.

Correspondence to: Xiaoyan Huang, Division of Nephrology, Peking University Shenzhen Hospital, Peking University, CN-518036 Shenzhen, China, Tel.: +86-755-83923333-5403; Fax: +86-755-83923333-5406, huangxy@bjmu.edu.cn And Juan Jesus Carrero, Division of Renal Medicine, Karolinska University Hospital at Huddinge K56, Karolinska Institutet, SE-14186 Stockholm, Sweden, Tel.: +46-8-58583982; Fax: +46-8-58583925, juan.jesus.carrero@ki.se.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: XH, JJC; data acquisition: SNB, XS; data analysis/interpretation: XH, XS, JRR, VH, FBO, SNB, JJC; statistical analysis: XH; supervision or mentorship: SNB, JJC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. XH takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary Material

Table S1: General characteristics of individuals included in and excluded from cross-sectional analysis.

Table S2: Baseline characteristics of participants reporting consistent and inconsistent parental CVD history across visits.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Descriptive Text for Online Delivery of Supplementary Material

Supplementary Table S1 (PDF)

General characteristics of individuals included in and excluded from cross-sectional analysis. Supplementary Table S2 (PDF)

Baseline characteristics of participants reporting consistent and inconsistent parental CVD history across visits.

Abstract

Background—Despite cardiovascular disease (CVD) and chronic kidney disease (CKD) sharing similar etiologies and interplay, it remains unknown if a broader relationship between these diseases exists across generations. We investigated the association between parental CVD history and estimated glomerular filtration rate (eGFR) in the community.

Study Design—Cross-sectional and longitudinal analyses.

Setting & Participants—A total of 13,241 community-based adults with serum creatinine measurement and follow-up visits (from 1 to 8 visits, approximately 2 years apart) from the Aerobics Center Longitudinal Study.

Predictors—Premature parental CVD history (before age of 50 years).

Outcomes—eGFR, decreased eGFR (<60 mL/min/1.73m²), and rate of eGFR decline.

Measurements—Information of parental history was collected by protocol-standardized questionnaires. eGFR was assessed with serum creatinine.

Results—A total of 3,339 (25.2%) participants reported a history of parental CVD. Individuals with parental CVD had significantly lower eGFR compared with those without parental CVD (69.4 ± 12.9 vs. 74.8 ± 14.2 mL/min/1.73m²; $P < 0.001$). After multivariable adjustment, parental CVD was independently associated with higher odds of having decreased eGFR (adjusted OR, 1.68; 95% CI, 1.52–1.86). Random-coefficient models showed that individuals with parental CVD had a faster decline in eGFR compared with those without parental CVD (sex- and ethnicity-adjusted annual change of -0.47 vs. -0.41 mL/min/1.73 m²; $P = 0.06$).

Limitations—Approximately 70% of the participants did not attend a second examination.

Conclusions—Parental history of CVD was associated with lower baseline eGFR, higher odds of decreased eGFR, and a nominally faster rate of eGFR decline in the offspring. Such findings may imply previously unrecognized cross-generational links between both diseases and be of support in community screening programs.

Keywords

cardiovascular disease (CVD); chronic kidney disease (CKD); glomerular filtration rate (GFR); renal function; kidney disease progression; heart; kidney; random-coefficient model; parental history; risk factor; Aerobics Center Longitudinal Study (ACLS)

Complex, multifactorial links between the heart and the kidneys have long been established and recognized.¹ Besides traditional mechanisms such as hemodynamic interactions, many other components are involved in the pathophysiology of both cardiac and kidney disorders.² In particular, cardiovascular disease (CVD) risk factors such as obesity, cigarette smoking, physical inactivity, diabetes and hypertension are associated with the development and progression of chronic kidney disease (CKD).^{3,4}

Parental history of CVD, especially with premature onset, is a well-documented risk factor for cardiovascular events in offspring.^{5,6} Similarly, family history of CKD is reported as an independent predictor of offspring CKD development.^{7,8} Familial aggregation of CVD or

CKD suggests both genetic susceptibility and clustering of environmental exposures, lifestyle and behavioral factors shared within a family that may increase the risk of these conditions.⁹ Current guidelines recommend that individuals with a positive parental history of CVD or CKD should be considered at risk of developing CVD or CKD, respectively.^{3,4,10,11}

Prior studies have associated parental CVD with hyperlipidemia,¹² inflammation,¹³ and endothelial dysfunction¹⁴, all of which usually accompany CKD. Despite similar etiologies and interplay, it remains unknown if a broader relationship between these diseases exists across generations. In this study, we hypothesized that a positive parental CVD history predisposes to reduced estimated glomerular filtration rate (eGFR) as well as more rapid decline in eGFR over time in the offspring. We addressed this issue in the Aerobics Center Longitudinal Study (ACLS), a study of adult US men and women.

METHODS

Population and Data Sources

The ACLS is an observational epidemiological study established in the 1970s. Participants came to the Cooper Clinic in Dallas, Texas, from all 50 US states for periodic preventive health examinations and for counseling regarding factors associated with increased risk of chronic disease. Participants were volunteers, not paid, and not recruited to the study as they would be for a clinical trial. Many were sent by their employers for the examination, some were referred by their physicians, and others were self-referred. No inclusion criteria were *a priori* applied. From April 1994 through February 2004, 21,578 men and women older than 20 years underwent comprehensive medical examinations and were enrolled in the ACLS.¹⁵ All of these participants had reached at least 85% age-predicted maximal heart rate. All participants in the current study gave written, informed consent, which was approved annually by the Cooper Institute Institutional Review Board. This is an ancillary study of the ACLS cohort when data already had been collected. Study hypotheses arose before inspection of the data.

Figure 1 shows the inclusion and exclusion of study participants. We performed a cross-sectional analysis to investigate the association between parental CVD history, eGFR, and the presence of decreased eGFR. For this reason, we excluded 5,920 ACLS participants without creatinine measurements and 2,417 without race records, information necessary for estimating glomerular filtration rate. The cross-sectional analysis thereafter includes a population of 13,241 adults for the primary analyses. As shown in Table S1 (provided as online supplementary material), waist circumference, blood pressure, fasting glucose, total and high-density cholesterol, and the prevalence of heavy drinkers and individuals with hypertensive or hypercholesterolemia were not significantly different between the included participants and the entire population. However, the current sample was older, had a lower percentage of women, and was more likely to have parental history of CVD.

A total of 4,173 participants attended subsequent re-examinations, approximately two years apart, allowing us to perform longitudinal analyses on eGFR decline. Among those, 1,090 subjects did not consistently report parental CVD history during re-examinations. We *a*

priori excluded them, leaving 12,151 individuals with at least one visit for the longitudinal analyses. As shown in Table S2, these 12,151 participants were younger, less likely to be men and have a parental CVD history, and had higher baseline eGFR (and thus had lower prevalence of decreased eGFR) compared to those only included in the cross-sectional analysis. There were no significant differences in race.

Covariates and eGFR Estimates

The ACLS clinical examinations are described in detail elsewhere.¹⁵ In brief, participants completed a comprehensive health evaluation that included self-reported personal and family health histories, a standardized medical examination by a physician, and fasting blood clinical chemistry tests. Parental CVD history was defined as the occurrence of heart attacks, coronary bypass, angioplasty, angina, or stroke before the age of 50 years in either father or mother.¹⁶ Other baseline medical conditions, such as previous hypertension, diabetes, and hypercholesterolemia, were defined as a history of physician diagnosis, measured phenotypes that met clinical thresholds for a specific condition, or, when appropriate, the combination of both methods. Smoking habits (current smoker or not), alcohol drinking habits (heavy drinker or not), and physical activity habits (physically inactive or not) were obtained from a standardized questionnaire. Heavy drinkers were defined as consuming more than 14 and more than 7 alcoholic drinks per week for men and women, respectively. Physical inactivity was defined as no leisure-time physical activity during the last three months. Body mass index (BMI) was calculated as the ratio of the body weight (in kg) to the height (in m²). Waist circumference was measured midway between the lowest rib and the iliac crest. Percent body fat was assessed using hydrostatic weighing, the sum of seven skinfold measures, or both methods, following standardized protocols.¹⁷ These 2 measures were highly correlated ($\rho > 0.90$) for participants who had both measurements.¹⁸ Resting blood pressure was measured in the seated position by trained technicians using auscultatory methods with mercury sphygmomanometer.

Clinical chemistry tests were performed in the Cooper Clinic clinical chemistry laboratory, which participates in and meets the quality control standards of the US Centers for Disease Control and Prevention lipid standardization program. Creatinine in serum was measured with spectrophotometry using Jaffe's reaction. The eGFR was calculated by using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.¹⁹ Decreased eGFR was defined as an eGFR < 60 mL/min/1.73 m², according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.^{3,4} Serum concentrations of triglycerides, total cholesterol, high-density lipoprotein, and glucose were enzymatically and centrally determined.

Statistical Analyses

After evaluating the distribution with the Kolmogorov-Smirnov test, data are expressed as mean $\pm$ standard deviation, median (interquartile range), or percentage of total, as appropriate. Study participants were divided into two groups based on the presence/absence of parental CVD history, and general characteristics between the two groups were compared by Student's unpaired *t* tests for normally distributed continuous variables, nonparametric

Mann–Whitney tests for non-normally distributed continuous variables, and chi-square tests for nominal variables. Differences in eGFR between individuals with and without parental CVD history stratified by sex, age categories (<45, 45–<65, and ≥65 years), race, and comorbidities (diabetes, hypertension and hypercholesterolemia) were determined by separated two-way analysis of variance (ANOVA), including the corresponding interaction term between parental CVD history and these categorical variables.

A series of logistic regression models were fitted to assess the cross-sectional association of parental CVD history with the presence of decreased eGFR: *i*) crude model; *ii*) adjusted for sex and race; *iii*) further adjusted for age; *iv*) model *iii* further adjusted for lifestyle parameters: smoking status, alcohol drinking, and physical inactivity; *v*) model *iii* further adjusted for metabolic factors: BMI, percentage of fat mass, systolic BP, fasting glucose, triglyceride, and total cholesterol. Models *iv* and *v* aimed to examine two sets of presumed causal pathways underlying parental CVD and eGFR, representing environmental and heritable factors, respectively. As an exploratory analysis, a term was incorporated into the model to assess possible interactive effects of parental CVD history and sex, age categories, race, as well as separate comorbidities. Data are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

In longitudinal analysis, we performed a random-coefficient model with an unstructured covariance matrix to determine the overall difference in eGFR between individuals with and without parental CVD history across multiple visits in 12,151 participants with consistent reports of parental CVD history. The model was fitted by maximum likelihood estimation. The dependent variable in this model was the serial eGFR and the predictor was the presence of parental CVD history. Covariates considered were age, sex and race. The random part of the model consisted of the participant's identity number and age. A log-likelihood ratio test was used to determine whether the model improved the fit. Each fixed-effect regression coefficient was tested with a *z* statistic to determine whether it was significantly different from 0.²⁰ Results are expressed as regression coefficients (β) and 95% CI.

In subgroup analysis, we fitted separate random-coefficient models to evaluate annual changes in eGFR in participants with and without parental CVD history.²⁰ The participant's age was the measure of time for the growth model. The dependent variable was eGFR. Age as the variable of time was entered the models, and its coefficient was regarded as annual change rate of eGFR. The following models were fitted: *i*) crude model; *ii*) adjusted for sex and race; *iii*) further adjusted for baseline eGFR. According to our hypothesis, model *iii* may lie within the causal pathway. The analyses were stratified by the presence/absence of parental CVD history, and the difference in regression coefficients for age was tested with a likelihood test. *P* values for (parental CVD history $\times$ age) interaction were reported. Moreover, subgroup random-coefficient models stratified by sex, age categories, and baseline eGFR categories (>90, 60–<90, and <60 mL/min/1.73 m²) were performed. Also, as a sensitivity analysis, we repeated the random-coefficient models in those with at least 2 visits during follow-up. Data are presented as regression coefficients, *i.e.* adjusted annual changes in eGFR in mL/min/1.73 m², and 95% CI.

Statistical analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, USA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Cross-sectional Analyses

There were 3,339 (25.2%) participants who reported a history of parental CVD. As shown in Table 1, individuals with parental CVD history were older, fatter (depicted by higher BMI, waist circumference, and percent body fat), and more likely to be physically inactive compared with those without a parental history of CVD. They are also more likely to have diabetes, hypertension, hypercholesterolemia, and presented higher fasting glucose, systolic BP, diastolic BP, triglycerides and total cholesterol levels. In addition, participants with parental CVD history had significantly lower eGFR levels and, as a result, were more likely to have decreased eGFR. There were no significant differences observed with respect to sex, race, smoking status, alcohol consumption, and serum HDL cholesterol concentration between the two groups.

As depicted in Figure 2, eGFR in individuals with a parental history of CVD was consistently lower than in those without a parental history of CVD (all P values < 0.001), irrespective of their sex, age, race, and state of diabetes, hypertension and hypercholesterolemia (all P values for interaction between parental history of CVD and these stratified variables > 0.4). A series of logistic regression models were constructed to determine the cross-sectional association between parental history of CVD and the presence of decreased eGFR (Table 2). In the crude model, parental history of CVD was associated with 89% higher odds of decreased eGFR (OR, 1.89; 95% CI, 1.72–2.09). This relationship held constant when adjusted for sex and race, but was attenuated (although it was still statistically significant) after further adjustment for age (OR, 1.68; 95% CI, 1.52–1.86). In the two subsequent adjusted models exploring potential causal pathways, the association between parental history of CVD and the presence of decreased eGFR was little affected when lifestyle parameters were considered, but became further weakened after correction of metabolic risk factors (OR, 1.61; 95% CI, 1.44–1.80).

Longitudinal Analyses

A total of 12,151 participants who consistently reported parental history of CVD throughout the visits were included in the longitudinal analyses. Among them, 3,083 attended at least two visits. During follow-up, a total of 17,154 individual visits were considered. The mean number of tests completed by each participant was 1.4 (range, 1–8). In those attending re-examination, the mean time interval between tests was 2.45 (median, 1.96) years, and the mean length of follow-up was 4.02 (median, 3.62) years.

A random-coefficient model was fitted to calculate the average difference in eGFR across multiple visits between individuals with and without parental history of CVD. After adjustment for age, sex, and ethnicity, parental history of CVD overall was independently associated with 4.17 (95% CI, 3.65–4.69) mL/min/1.73 m² lower eGFR during follow-up.

Random-coefficient models were constructed to estimate the rates of decline in eGFR. As shown in Table 3, in crude models, the annual changes in eGFR in individuals with and without parental history of CVD were -0.48 (95% CI, -0.52 to -0.43) and -0.42 (95% CI, -0.45 to -0.40) mL/min/1.73 m², respectively. Such a difference in rate of eGFR decline between the two groups was statistically significant (P for interaction term between age and presence/absence of parental CVD history = 0.04). Adjustment of sex and race had little impact on the magnitude of yearly eGFR declines in both groups as well as the difference between them, but the interaction term became not statistically significant (P for interaction = 0.06). In a sensitivity analysis considering only participants with at least 2 visits, results were similar but held after multivariable adjustment: The sex- and ethnicity-adjusted annual changes in eGFR were -0.33 (95% CI, -0.43 to -0.24) and -0.25 (95% CI, -0.29 to -0.21) mL/min/1.73 m² in individuals with and without parental history of CVD, respectively (P for interaction = 0.04). The difference in progression rates between both groups was, overall, weak, and adjusting for baseline eGFR (potentially mediator in the association) abrogated any group difference.

In subgroup analyses (Figure 3), the adjusted annual decline in eGFR was, in general, greater in individuals with parental history of CVD versus those without. In particular, the association of parental history of CVD with faster eGFR decline reached statistical significance in women and in individuals older than 45 years or with eGFR less than 90 mL/min/1.73 m².

DISCUSSION

In this observational study, we found that premature parental history of CVD was consistently associated with lower eGFR and higher odds of decreased eGFR in the offspring. Furthermore, parental history of CVD was associated in crude analysis with a faster rate of decline in eGFR. To the best of our knowledge, this is the first study to suggest that the interplay between cardiac and kidney diseases expands to a cross-generational level.

Although definitions of familial CVD history vary, it is well established that the association between family history and offspring CVD is strongest with earlier age of presentation of CVD in the family member (premature family history) and this is classically established before the age of 50 years.²⁵ Whereas there is probably a greater genetic component with premature CVD events, increased contribution of environmental factors and behaviors that are less heritable might account for late CVD events. Evidence suggests that premature CVD may carry genetic susceptibility for developing traditional risk conditions in the offspring, such as obesity, hypertension, diabetes and dyslipidemia.^{12,26,27} Remarkably, these CVD risk factors have also been proposed as risk factors of occurrence and progression of CKD.^{28–32} Such findings would be in line with the attenuation in odds for decreased eGFR that we observed after explorative adjustment in our study. In addition, increasing evidence associates familial aggregation of premature CVD with novel markers of inflammation and endothelial dysfunction,^{13,14} which have also been proposed as predictors of decreased kidney function.^{33,34} Recent genome-wide association studies have identified risk single-nucleotide polymorphisms for CVD³⁵ and for kidney function and CKD.³⁶ However, except for the *SH2B3* locus, which may partly explain the overlap

between genetic polymorphisms underpinning CVD and CKD phenotypes, evidence is still sparse.^{35,37} Apart from genetic traits, environmental exposures shared within a family may also, to some extent, mediate the association between parental history of CVD and offspring eGFR. Specifically, the potential role of cigarette smoking, sedentary lifestyle, and unhealthy diet in the pathogenesis of CKD may be analogous to the role of these factors in the pathogenesis of CVD.^{38–40} However, the substantial residual OR observed even after multivariable adjustment for these risk factors in our study may suggest additional mechanisms for familial aggregation of decreased eGFR.

In the present study, the link between parental history of CVD and presence of decreased eGFR held constant, regardless of adjustment for confounders. Since it has been suggested that the deterioration of kidney function varies between sexes and races,^{41–43} and that kidney function trajectory changes with ageing,⁴⁴ further research investigating possible synergic effects of these genetic and exposure-time proxies, *i.e.* sex-, race-, and age-parental CVD interactions, on the risk of decreased eGFR is necessary. Decreased kidney function is becoming a global disease burden⁴⁵ that affects approximately 8% of the general population in the United States.⁴⁶ Associated complications include CVD, kidney disease progression, acute kidney injury, cognitive decline, anemia, bone and mineral disorders, fractures, and other conditions. Importantly, even within the normal range (>60 mL/min/1.73 m²), reduced eGFR is independently associated with higher risk of end-stage renal disease (ESRD), total and cardiovascular mortality.^{47,48} One recent meta-analysis suggests that the risk gradient for cardiovascular mortality linearly increases with decreasing eGFR below 75 mL/min/1.73 m².⁴⁷

However, kidney function progression may be more important than CKD stage *per se*.⁴⁹ Thus, the analysis of eGFR decline in our study becomes particularly interesting. Although the difference of absolute decline rate of eGFR observed for individuals with parental CVD (0.06 mL/min/1.73 m² more per year) seems mild, it represents a 15% increase in the rate of decline. Such a difference could well be an underestimation because of the nature of our screening program, whereby participants motivated to adopt a healthy lifestyle were more likely to attend follow-up examinations (selection bias). In this analysis, we report that the association between parental CVD history and eGFR decline was largely (if not entirely) attenuated after adjustment for baseline eGFR. We do not consider, *a priori*, eGFR as a confounder, given that parental CVD history antecedes to the offspring's eGFR. Rather, baseline eGFR may be a consequence of family history, and thus a causal mediator. Nevertheless, the difference in baseline eGFR between the two groups might also imply some residual confounding, and justified altogether the construction of this exploratory adjustment.

Several limitations of our study should be acknowledged. Firstly, the ACLS cohort is predominantly white and middle-to-high socioeconomic status, and although stratified analysis by race shows consistent results, low sample sizes in these subgroups may limit the study power and the generalizability of our findings. Secondly, we relied on self-reported parental history, however this is a method widely used in previous studies of this kind. A negative parental history report has been suggested as more accurate,^{21,22} but we do not envisage that false-positive reporting has an impact on the relationships investigated.

Thirdly, kidney function in our study was not directly measured. Nonetheless, eGFR is a more likely screening tool in the community and the CKD-EPI creatinine equation performs fine in general population studies.²³ In addition, information on albuminuria was not available in ACLS, which is another key characteristic of CKD. Fourthly, the lack of data on covariates such as markers of inflammation and endothelial function prevents us from exploring other possible causal pathways. Nevertheless, the exposure, *i.e.* parental history of premature CVD, is largely a genetic marker and thus exempted from being confounded by measured and unmeasured offspring phenotypes. A final limitation is that approximately 70% of ACLS participants did not attend a second examination. We tried to overcome this with the use of random-coefficient models²⁴ and the sensitivity analysis to support the robustness of our findings. All in all, changes in the rate of eGFR loss in our study should be interpreted cautiously and await confirmation in independent cohorts.

To conclude, we found in this cohort study that parental history of premature CVD was associated with lower eGFR, higher odd of decreased eGFR, and a nominally faster rate of decline in eGFR in the offspring. Our findings may imply a previously unrecognized cross-generational link between the heart and the kidneys and, more importantly, may shed light on CKD risk discrimination in the community. The concept that ascertainment of parental history aids risk prediction for primary prevention is in concert with the major nephrology, cardiology and hypertension guidelines.^{3,4,10,11} Should future studies confirm an additional prognostic value (over and above traditional risk factors) for parental CVD history in prediction of incident ESRD, such easily queried information may assist clinicians and patients in the evaluation of CKD risk and treatment decisions. Even though parental history is not modifiable, it has been shown that individuals who are more aware of their parents' medical illnesses may be able to estimate their risk for disease more accurately and perhaps be more motivated to follow a healthy lifestyle or adjust their risk factors.²¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank the Cooper Clinic physicians and technicians for collecting the baseline data, and staff at the Cooper Institute for data entry and data management.

Support: This work is supported by the National Science Foundation for Young Scholars of China [81402737 to X.H.]; the Swedish Research Council [to J.J.C.]; National Institutes of Health grants [AG06945, HL62508, and DK088195]; and the Spanish Ministry of Economy and Competitiveness [RYC-2010-05957 and RYC-2011-09011 to J.R.R. and F.B.O.]. The funders of this study did not have any role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

REFERENCES

1. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome. *J Am Coll Cardiol.* 2008 Nov; 52(19):1527–1539. [PubMed: 19007588]
2. Hatamizadeh P, Fonarow GC, Budoff MJ, Darabian S, Kovesdy CP, Kalantar-Zadeh K. Cardiorenal syndrome: pathophysiology and potential targets for clinical management. *Nat Rev Nephrol.* 2013 Feb; 9(2):99–111. [PubMed: 23247571]

3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002 Feb; 39(2 Suppl 1):S1–S266. [PubMed: 11904577]
4. Chapter 1: Definition and classification of CKD. *Kidney inter., Suppl.* 2013; 3(1):19–62.
5. Lloyd-Jones DM, Nam BH, D'Agostino RB, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults - A prospective study of parents and offspring. *JAMA.* 2004 May; 291(18):2204–2211. [PubMed: 15138242]
6. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association Between Family History and Coronary Heart Disease Death Across Long-Term Follow-Up in Men The Cooper Center Longitudinal Study. *Circulation.* 2012 Jun; 125(25):3092–3098. [PubMed: 22623718]
7. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. *J Am Soc Nephrol.* 1998 Jul; 9(7):1270–1276. [PubMed: 9644638]
8. O'Dea DF, Murphy SW, Hefferton D, Parfrey PS. Higher risk for renal failure in first-degree relatives of white patients with end-stage renal disease: a population-based study. *Am J Kidney Dis.* 1998 Nov; 32(5):794–801. [PubMed: 9820449]
9. Christensson A, Melander O, Fjellstedt E, Ohlson-Andersson M. Family History of Myocardial Infarction Increases Risk of Renal Dysfunction in Middle Age. *American journal of nephrology.* 2014 Jan 30; 39(2):85–91. [PubMed: 24481112]
10. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002 Dec 17; 106(25):3143–3421. [PubMed: 12485966]
11. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003 Dec; 42(6):1206–1252. [PubMed: 14656957]
12. De Backer G, De Henauw S, Sans S, et al. A comparison of lifestyle, genetic, bioclinical and biochemical variables of offspring with and without family histories of premature coronary heart disease: the experience of the European Atherosclerosis Research Studies. *Journal of cardiovascular risk.* 1999 Jun; 6(3):183–188. [PubMed: 10463146]
13. Margaglione M, Cappucci G, Colaizzo D, Vecchione G, Grandone E, Di Minno G. C-reactive protein in offspring is associated with the occurrence of myocardial infarction in first-degree relatives. *Arterioscler Thromb Vasc Biol.* 2000 Jan; 20(1):198–203. [PubMed: 10634818]
14. Clarkson P, Celermajer DS, Powe AJ, Donald AE, Henry RM, Deanfield JE. Endothelium-dependent dilatation is impaired in young healthy subjects with a family history of premature coronary disease. *Circulation.* 1997 Nov 18; 96(10):3378–3383. [PubMed: 9396430]
15. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA.* 1989 Nov 3; 262(17):2395–2401. [PubMed: 2795824]
16. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation.* 2011 Dec 6; 124(23):2483–2490. [PubMed: 22144631]
17. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr.* 1999 Mar; 69(3):373–380. [PubMed: 10075319]
18. Jackson AS, Pollock ML. Generalized equations for predicting body density of men. *Br J Nutr.* 1978 Nov; 40(3):497–504. [PubMed: 718832]
19. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009 May 5; 150(9):604–612. [PubMed: 19414839]
20. Rabe-Hesketh, S.; Skrondal, A. *Multilevel and Longitudinal Modeling Using Stata.* 2nd ed. College Station, TX: Stata Press; 2008.
21. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med.* 2004 Mar 16; 140(6):434–440. [PubMed: 15023709]

22. Wilson BJ, Qureshi N, Santaguida P, et al. Systematic review: family history in risk assessment for common diseases. *Ann Intern Med.* 2009 Dec 15; 151(12):878–885. [PubMed: 19884616]
23. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med.* 2012 Jun 5; 156(11):785–795. W-270, W-271, W-272, W-273, W-274, W-275, W-276, W-277, W-278. [PubMed: 22312131]
24. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med.* 1997 Oct 30; 16(20):2349–2380. [PubMed: 9351170]
25. Sivapalaratnam S, Boekholdt SM, Trip MD, et al. Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study. *Heart.* 2010 Dec; 96(24):1985–1989. [PubMed: 20962344]
26. Becker DM, Yook RM, Moy TF, Blumenthal RS, Becker LC. Markedly high prevalence of coronary risk factors in apparently healthy African-American and white siblings of persons with premature coronary heart disease. *Am J Cardiol.* 1998 Nov 1; 82(9):1046–1051. [PubMed: 9817479]
27. Allen JK, Blumenthal RS. Risk factors in the offspring of women with premature coronary heart disease. *Am Heart J.* 1998 Mar; 135(3):428–434. [PubMed: 9506328]
28. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int.* 2008 Jan; 73(1):19–33. [PubMed: 17928825]
29. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med.* 1996 Jan 4; 334(1):13–18. [PubMed: 7494564]
30. Brancati FL, Whelton PK, Randall BL, Neaton JD, Stamler J, Klag MJ. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. *JAMA.* 1997 Dec 17; 278(23):2069–2074. [PubMed: 9403420]
31. Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients. *Kidney Int Suppl.* 2005 Dec;(99):S87–S93. [PubMed: 16336584]
32. Hsu CC, Kao WH, Coresh J, et al. Apolipoprotein E and progression of chronic kidney disease. *JAMA.* 2005 Jun 15; 293(23):2892–2899. [PubMed: 15956634]
33. Kronenberg F. Emerging risk factors and markers of chronic kidney disease progression. *Nat Rev Nephrol.* 2009 Dec; 5(12):677–689. [PubMed: 19935815]
34. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int.* 2011 Oct; 80(8):806–821. [PubMed: 21697815]
35. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature.* 2011 Oct 6; 478(7367):103–109. [PubMed: 21909115]
36. Kottgen A, Pattaro C, Boger CA, et al. New loci associated with kidney function and chronic kidney disease. *Nat Genet.* 2010 May; 42(5):376–384. [PubMed: 20383146]
37. Olden M, Teumer A, Bochud M, et al. Overlap between common genetic polymorphisms underpinning kidney traits and cardiovascular disease phenotypes: the CKDGen consortium. *Am J Kidney Dis.* 2013 Jun; 61(6):889–898. [PubMed: 23474010]
38. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients--absence of evidence or evidence of absence? *Clin J Am Soc Nephrol.* 2008 Jan; 3(1):226–236. [PubMed: 18003763]
39. Johansen KL, Painter P. Exercise in individuals with CKD. *Am J Kidney Dis.* 2012 Jan; 59(1):126–134. [PubMed: 22113127]
40. Howden EJ, Leano R, Petchey W, Coombes JS, Isbel NM, Marwick TH. Effects of Exercise and Lifestyle Intervention on Cardiovascular Function in CKD. *Clin J Am Soc Nephrol.* 2013 Sep; 8(9):1494–1501. [PubMed: 23970136]
41. Silbiger SR, Neugarten J. The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis.* 1995 Apr; 25(4):515–533. [PubMed: 7702046]
42. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol.* 2000 Feb; 11(2):319–329. [PubMed: 10665939]

43. Muntner P, Newsome B, Kramer H, et al. Racial differences in the incidence of chronic kidney disease. *Clin J Am Soc Nephrol*. 2012 Jan; 7(1):101–107. [PubMed: 22076879]
44. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007 Oct; 18(10):2758–2765. [PubMed: 17855638]
45. Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med*. 2013 Aug 1; 369(5):448–457. [PubMed: 23902484]
46. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007 Nov 7; 298(17):2038–2047. [PubMed: 17986697]
47. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010 Jun 12; 375(9731):2073–2081. [PubMed: 20483451]
48. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012 Dec 12; 308(22):2349–2360. [PubMed: 23111824]
49. Rosansky SJ. Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. *American journal of nephrology*. 2012; 36(1):1–10. [PubMed: 22699366]

Figure 1.

Flowchart describing the inclusion and exclusion of participants.

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CVD, cardiovascular disease.

Figure 2.

Comparison of mean eGFR between individuals with and without parental cardiovascular disease history, stratified by sex, ethnicity, age categories, and presence of diabetes mellitus, hypertension, and hypercholesterolemia - By two-way analysis of variance, differences between individuals with and without parental cardiovascular disease history were statistically significant (all P values <0.001). No significant interaction of parental cardiovascular disease history with sex, age categories, ethnicity, or the presence of diabetes mellitus, hypertension, or hypercholesterolemia was observed (all P values for interaction >0.40). Black bars represent individuals with parental cardiovascular disease history. White bars represent individuals without parental cardiovascular disease history. Error bars represent standard errors.

Abbreviations: DM, diabetes mellitus; HTN, hypertension.

Figure 3.

Annual change of eGFR in study participants with and without parental cardiovascular disease history - Dots and horizontal bars represent the estimates and 95% confidence intervals of age (every 1-year increment) assessed by random-coefficient models adjusted for sex and ethnicity. Participant's age was introduced as random-effect of the models. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

Table 1

Differences in baseline characteristics between participants with and without history of parental CVD.

	Parental CVD* (n=3,339)	No Parental CVD (n=9,902)	P
Female sex	861 (25.8)	2,590 (26.2)	0.7
Age (y)	50.4 ± 9.3	47.9 ± 9.9	<0.001
Ethnicity			0.1
White	3,193 (95.7)	9,419 (95.1)	
Black	48 (1.4)	125 (1.3)	
Hispanic	48 (1.4)	212 (2.1)	
Asian	27 (0.8)	76 (0.8)	
Other	23 (0.7)	70 (0.7)	
BMI (kg/m ²)	26.5 ± 4.2	26.4 ± 4.2	0.02
Waist circumference (cm)	90.5 ± 13.8	89.3 ± 13.5	<0.001
Fat body mass (%)	24.3 ± 6.2	23.4 ± 6.2	<0.001
Current smoker	344 (10.3)	1,091 (11.0)	0.3
Heavy drinker [†]	439 (13.2)	1,178 (11.9)	0.06
Physical inactivity [‡]	665 (19.9)	1,766 (17.8)	0.008
Diabetes [§]	152 (4.6)	373 (3.8)	0.05
Hypertension [§]	1,214 (36.4)	2,930 (29.6)	<0.001
Hypercholesterolemia [§]	1,199 (35.9)	2,701 (27.3)	<0.001
Fasting glucose (mg/dL)	101 ± 18	98 ± 14	<0.001
Systolic BP (mmHg)	123 ± 15	121 ± 15	<0.001
Diastolic BP (mmHg)	82 ± 10	81 ± 10	<0.001
Triglycerides (mg/dL)	110 [77–159]	104 [74–151]	<0.001
Total cholesterol (mg/dL)	203 ± 37	197 ± 36	<0.001
HDL cholesterol (mg/dL)	52 ± 16	52 ± 16	0.8
eGFR (mL/min/1.73 m ²)	69.4 ± 12.9	74.8 ± 14.2	<0.001
Decreased eGFR ^{††}	802 (24.0)	1,417 (14.3)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

* Defined as occurrence of heart attacks, coronary disease, angioplasty, or stroke before age of 50 years in either father or mother.

[†] Defined as alcohol drinks >14 and >7 per week for men and women, respectively.

[‡] Defined as no leisure-time physical activity during past three months.

[§] Defined as history of physician diagnosis, measured phenotypes that met clinical thresholds for a specific condition, or, when appropriate, combination of both methods.

^{††} Defined as eGFR < 60 mL/min/1.73m².

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Association between parental CVD history and presence of decreased eGFR

Logistic regression models	OR (95% CI)
Model 1: Crude	1.89 (1.72–2.09)
Model 2: Sex and ethnicity-adjusted	1.89 (1.72–2.08)
Model 3: Model 2 + age	1.68 (1.52–1.86)
Model 4: Model 3 + smoking status, heavy drinking, and physical inactivity	1.68 (1.52–1.86)
Model 5: Model 3 + BMI, percentage of fat mass, systolic BP, fasting glucose, triglycerides, total cholesterol, and diabetes	1.60 (1.43–1.79)

Note: Decreased eGFR defined as $< 60 \text{ mL/min/1.73 m}^2$. For all models, $P < 0.001$.

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; CI, confidence interval; OR, odds ratio.

Table 3

Annual eGFR change in study participants with and without parental CVD history.

Linear mixed models	Parental CVD (n=2838)	No parental CVD (n=9313)	P
Model 1: Crude	−0.48 (−0.52 to −0.43)	−0.42 (−0.45 to −0.40)	0.04
Model 2: Sex and ethnicity-adjusted	−0.47 (−0.51 to −0.42)	−0.41 (−0.44 to −0.39)	0.06
Model 3: Model 2 + baseline eGFR	−0.05 (−0.07 to −0.03)	−0.04 (−0.05 to −0.03)	0.2

Note: Values are given as annual change in eGFR (95% confidence interval) in mL/min/1.73 m². Random-coefficient models with an unstructured covariance matrix were used for the analyses. The models were fitted by maximum likelihood estimation. Participant's age was introduced as random-effect of the models.

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.