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Renal function in familial longevity: the Leiden Longevity Study

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ABSTRACT

Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that determine the age-related decline in renal function of normal subjects. In the Leiden Longevity Study, middle-aged offspring of non-agenarian siblings and their partners as environmentally matched controls were included. Information was collected on lifestyle, medical history, medication use, and a non-fasting blood sample was drawn. Renal function (estimated glomerular filtration rate, eGFR) was assessed with the Chronic Kidney Disease epidemiology collaboration (CKD-EPI) formula. Linear mixed models were used to account for familial dependencies within the offspring and all analyses were stratified by sex. eGFR was similar between female offspring and female controls (0.44 ml/min/1.73 m^2 (SE 0.72) difference, p = 0.54, age-adjusted). Male offspring had a higher eGFR compared to male controls (1.78 ml/min/1.73 m^2 (SE 0.78) difference, p = 0.022, age-adjusted), and further adjustments for various characteristics did not materially change this difference. Among men with a history of hypertension, or myocardial infarction and/or stroke, offspring had a higher eGFR compared to controls (4.74 ml/min/1.73 m^2 (SE 1.53) difference, p = 0.002, age-adjusted, and 6.21 ml/min/1.73 m^2 (SE 2.85) difference, p = 0.033, age-adjusted, respectively). Middle-aged men, but not women, with a propensity for longevity have better renal function compared to environmentally matched controls, especially among those with a history of cardiovascular disease.

1. Introduction

Longevity is a complex phenotype that results from genetic factors, environment (including lifestyle), chance, and the interaction between these factors. Studies designed to identify genetic determinants for familial longevity have shown that centenarians (Evert et al., 2003) and their offspring (Atzmon et al., 2004; Terry et al., 2003), and offspring of familial non-agenarians (Westendorp et al., 2009) have a lower prevalence of diabetes mellitus, hypertension, and cardiovascular disease, including myocardial infarction. Furthermore, insulin sensitivity is preserved in centenarians (Paolisso et al., 1996) and offspring of nonagenarians have better glucose tolerance (Rozing et al., 2010) and better peripheral insulin sensitivity (Wijsman et al., 2011) than environmentally matched controls. These observations indicate that offspring of long-lived subjects have a better metabolic profile. Moreover, most parameters associated with longevity differ between men and women.

Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that influence the decline in renal function of normal subjects. With increasing age, renal function decreases with approximately 0.4 ml/min/1.73 m^2/year from the age of 18 years onwards (Wetzels et al., 2007). This age-related decline is higher in patients with cardiovascular disease and diabetes mellitus, which are two important risk factors for the decline in renal function (Kronborg et al., 2008). Risk factors for these comorbidities, such as body mass index (BMI), blood pressure, inflammation, glucose metabolism, and lipid metabolism, also independently accelerate renal function decline (Halbesma et al., 2008; Kronborg et al., 2008). Treatment of patients with renal insufficiency mainly focuses on these modifiable renal risk factors (Anon, 2002).

The Leiden Longevity Study was designed to identify genetic determinants of familial longevity (Schoenmaker et al., 2006; Westendorp et al., 2009). In this study, nonagenarian siblings and their offspring, who are genetically enriched for longevity, were included. The offspring

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and the controls, partners of the offspring who are environmentally matched, were used to assess whether at middle-age familial factors related to longevity (genetic or early environmental) influence renal function.

2. Methods

2.1. Study design and participants

In the Leiden Longevity Study 421 families were included, with at least two alive long-lived siblings of 89 years or older for men and 91 years or older for women and with identical Dutch parents. A more detailed description of the study design has been provided elsewhere (Schoenmaker et al., 2006; Westendorp et al., 2009). For 1671 of the offspring of these families and 744 partners of these offspring, all Caucasian, non-fasting blood serum samples were drawn at baseline. Additional information was collected on self-reported lifestyle, information on medical history from the participants' general practitioners and information on medication use from the participants' pharmacies. The Medical Ethical Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all subjects.

2.2. Renal function

Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease epidemiology collaboration (CKD-EPI) formula (Levey et al., 2009), the Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 2000), and creatinine clearance (ml/min) was estimated with the Cockcroft Gault (CG) formula (Cockcroft and Gault, 1976). The CKD-EPI and MDRD formula use sex, age, black race, and serum creatinine to estimate GFR (eGFR, ml/min/1.73 m^2). The exact formulas are as follows: CKD-EPI; female with creatinine (mg/dl) ≤ 0.7, $144 \times (\text{creatinine (mg/dl)} / 0.7)^{-0.329} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); female with creatinine (mg/dl) >0.7, $144 \times (\text{creatinine (mg/dl)} / 0.7)^{-1.209} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); male with creatinine (mg/dl) ≤ 0.9, $141 \times (\text{creatinine (mg/dl)} / 0.9)^{-0.411} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American); male with creatinine (mg/dl) >0.9, $141 \times (\text{creatinine (mg/dl)} / 0.9)^{-1.209} \times 0.993^{\text{age (years)}}$ ($\times 1.159$ if African-American), and MDRD: $186 \times \text{creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203}$ ($\times 0.742$ if female) ($\times 1.210$ if African-American). Compared with these formulas, the CG formula includes body weight and excludes black race; (140 − age (years)) × body weight (kg)/creatinine (mg/dl) × 72 ($\times 0.85$ if female). To compare the CG estimate with the other two estimates, we normalized it per 1.73 m^2 of body surface area (BSA) using the formula of Du Bois and Du Bois (1916); $\text{BSA} = (\text{body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}) \times 0.007184$.

2.3. Blood parameters

Creatinine levels were measured in a non-fasting blood sample by Kinetic Alkaline Picrate methodology. Glucose, high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL)-cholesterol, and triglyceride levels were measured on a Hitachi Modular P 800 (Roche, Almere, The Netherlands).

2.4. Statistical analyses

Continuous data are given as mean ± standard deviation (SD) and dichotomous data are given as percentages (%). hsCRP and triglyceride levels were logarithmically transformed prior to analyses and geometric means with their SD are reported for these transformed variables. Independent *t*-tests were used to assess differences in continuous data between offspring and controls and for dichotomous data chi-square tests were used.

As primary outcome we used the eGFR calculated with the CKD-EPI formula. This formula has the highest accuracy in patients with an eGFR above 60 ml/min/1.73 m^2 (Michels et al., 2010). Because renal function declines with increasing age (Xu et al., 2010) and effects related to longevity often differ between women and men, first the mean (standard error (SE)) eGFR was calculated, stratified by sex, offspring/control status, and age group (<55, 55–59, 60–64, and ≥65 years). Second, differences in eGFR between offspring and controls (ΔeGFR), stratified by sex, were assessed with linear mixed models to adjust for the correlation of sibling relationship. Furthermore, an interaction term between age continuously and offspring/control status was included in the model to assess whether the difference in eGFR between offspring and controls changes with increasing age. Thereafter, ΔeGFR was further adjusted for age, medical history (diagnosis) of hypertension, cardiovascular disease (myocardial infarction and stroke), or diabetes mellitus, antihypertensive medication, glucose lowering medication, glucose, hsCRP, HDL-cholesterol, and triglyceride levels, smoking (current smoker), and BMI. We made separate models instead of gradually more complex models during adjustment, as many subjects were excluded from the final model because of missing values for one or more of the variables. Finally, we stratified the analyses by the presence of hypertension (having a diagnosis of hypertension in medical history and/or using antihypertensive medication) and by the presence of myocardial infarction or stroke.

GFR was also estimated with the MDRD and CG formula and as a sensitivity analysis we repeated all analyses with these two measurements. Furthermore, we investigated whether associations remained when analyses were repeated in subjects without evidence of renal insufficiency as indicated by an eGFR >60 ml/min/1.73 m^2. As a final sensitivity analysis we imputed all missing values with multiple imputation (using 5 repetitions). This is a recommended technique where missing data for a subject are imputed by a value that is predicted by other known characteristics of this subject (e.g. demographic, anthropometric, and clinical characteristics) (Donders et al., 2006; van Buuren et al., 1999). All characteristics illustrated in Table 1 were included in the model. Statistical analyses were done with PASW/SPSS version 20. P-Values smaller than 0.05 were considered statistically significant.

3. Results

Of the 1671 included offspring and 744 included controls, 1300 offspring and 596 controls had a creatinine measurement as well as information on medical history and medication use. The population characteristics in Table 1 show that 695 (53%) of the offspring were female and 342 (57%) of the controls were female ($p = 0.144$). The female offspring were older than the female controls (mean ± SD; 59.3 ± 6.5 versus 56.9 ± 6.9 years, $p < 0.001$). The age difference between male offspring and male controls was smaller (mean ± SD; 59.3 ± 6.5 versus 60.9 ± 6.9 years, $p = 0.001$). Independent of age differences, offspring were less likely to have hypertension, myocardial infarction, and diabetes mellitus compared to controls. A difference in the prevalence of myocardial infarction was only present in men, 4% versus 8% ($p = 0.024$), and the difference in prevalence of diabetes mellitus was most pronounced in men, 5% versus 11% ($p = 0.005$). In both males and females, glucose and triglyceride levels were lower in offspring compared to controls.

Fig. 1A and B show the mean eGFR for female and male offspring and controls, stratified by age. Estimated GFR was similar between female offspring and female controls (75.5 ml/min/1.73 m^2 (SE 0.52) vs. 76.8 ml/min/1.73 m^2 (SE 0.69), $p = 0.090$) but higher in male offspring (82.7 ml/min/1.73 m^2 (SE 0.53)) than in male controls (79.6 ml/min/1.73 m^2 (SE 0.77)) ($p < 0.001$). In female offspring, with increasing age eGFR decreased 0.78 ml/min/1.73 m^2/year (SE 0.06, $p < 0.001$) and in female controls this was 0.73 ml/min/1.73 m^2/year (SE 0.08, $p < 0.001$) (p-value for interaction = 0.63). In male offspring, with increasing age eGFR decreased 0.79 ml/min/1.73 m^2/year (SE 0.07, $p < 0.001$) and in male controls this was 0.86 ml/min/1.73 m^2/year

Table 1
Characteristics for the total study population stratified by sex.

	Women			Men		
	Offspring (n = 695)	Control (n = 342)	p-value	Offspring (n = 605)	Control (n = 254)	p-value
Age (years)	59.3 ± 6.5	56.9 ± 6.9	<0.001	59.3 ± 6.5	60.9 ± 6.9	0.001
Smoking, n (%)[a]	75 (12)	45 (15)	0.26	76 (15)	37 (16)	0.68
BMI (kg/m^2)[a]	25.1 ± 4.0	25.3 ± 3.7	0.37	25.7 ± 2.9	25.9 ± 3.3	0.54
Hypertension	182 (27)	114 (34)	0.013[f]	164 (28)	84 (34)	0.10
Diagnosis in medical history, n (%)[b]	158 (23)	93 (28)	0.094	136 (23)	68 (27)	0.20
Antihypertensive medication, n (%)[c]	118 (17)	78 (23)	0.024[f]	96 (16)	58 (23)	0.015
Myocardial infarction, n (%)[b]	6 (1)	4 (1)	0.62	23 (4)	19 (8)	0.024[f]
Stroke, n (%)[b]	12 (2)	9 (3)	0.32	32 (5)	7 (3)	0.10
Diabetes mellitus	26 (4)	20 (6)	0.11	31 (5)	26 (11)	0.005[f]
Diagnosis in medical history, n (%)[b]	26 (4)	19 (6)	0.16	31 (5)	26 (11)	0.005[f]
Glucose lowering medication, n (%)[d]	10 (1)	9 (3)	0.17	12 (2)	13 (5)	0.013[f]
Glucose (mmol/l)[e]	5.7 ± 1.2	6.0 ± 1.5	0.003[f]	5.9 ± 1.4	6.3 ± 2.0	0.008[f]
hsCRP (mg/l)[e]	1.41 ± 2.95	1.52 ± 3.01	0.31	1.34 ± 2.85	1.32 ± 2.82	0.79
HDL-cholesterol (mmol/l)[e]	1.59 ± 0.45	1.56 ± 0.48	0.27	1.27 ± 0.36	1.22 ± 0.36	0.050
Triglycerides (mmol/l)[e]	1.39 ± 1.66	1.49 ± 1.72	0.048[f]	1.72 ± 1.71	1.83 ± 1.71	0.11

Continuous variables are illustrated as mean ± standard deviation (SD) and as geometric mean ± SD for the logarithmically transformed variables high sensitivity C-reactive protein (hsCRP) and triglyceride levels. The p-value was obtained with an independent t-test, for continuous variables, or with a chi-square test.

[a] Smoking and body mass index (BMI) were available for 1654 and 1657 subjects respectively.

[b] Percentage of subjects with a diagnosis of this co-morbidity present in their medical history. Hypertension, myocardial infarction, stroke, and diabetes mellitus were available for 1856, 1886, 1890, and 1864 subjects respectively.

[c] All types of antihypertensive medication.

[d] Insulin and other blood glucose lowering medication.

[e] Glucose, hsCRP, high density lipoprotein (HDL)-cholesterol, and triglyceride levels were available for 1884, 1889, 1895, and 1895 subjects respectively.

[f] P-value remained significant after adjustment for age.

(SE 0.09, $p < 0.001$) (p-value for interaction = 0.53). These results and the results in Fig. 1A and B indicate that at any age the eGFR difference between offspring and controls, in both women and men, was similar.

Table 2 shows the difference in eGFR between offspring and controls, stratified by sex and adjusted for various characteristics. Female offspring had a similar eGFR compared to female controls (−1.32 ml/min/1.73 m^2 (SE 0.78), $p = 0.090$). After adjustment for age, history of hypertension, myocardial infarction, stroke, and diabetes mellitus, the difference remained unaltered (0.13 ml/min/1.73 m^2 (SE 0.75), $p = 0.86$). Male offspring had a significant higher crude eGFR compared to male controls (3.05 ml/min/1.73 m^2 (SE 0.87), $p < 0.001$). After adjustment for age, the point estimate in men changed to 1.78 ml/min/1.73 m^2 (SE 0.78, $p = 0.022$). Further adjustment for history of hypertension, myocardial infarction, stroke, and diabetes mellitus did not affect the observed difference in men (1.83 ml/min/1.73 m^2 (SE 0.80), $p = 0.022$). Adjustment for medication use, blood parameters or lifestyle factors slightly attenuated the difference in men (1.63 (SE 0.77), $p = 0.035$; 1.54 (SE 0.78), $p = 0.048$; and 1.73 (SE 0.83), $p = 0.036$, respectively).

Table 3 shows the age-adjusted difference in eGFR between offspring and controls stratified by sex and additionally stratified by the presence of hypertension and the presence of myocardial infarction or stroke. In women there was no difference between offspring and controls in any of the strata. In men with hypertension, offspring had a higher eGFR compared to controls (4.74 ml/min/1.73 m^2 (SE 1.53), $p = 0.002$, age-adjusted). Moreover, in men with a previous history of myocardial infarction or stroke, offspring had a higher eGFR compared to controls (6.21 ml/min/1.73 m^2 (SE 2.85), $p = 0.033$, age-adjusted).

The sensitivity analysis with GFR estimated with the MDRD or CG formula as outcome showed similar crude and adjusted results. Repeating the analyses in subjects with eGFR >60 ml/min/1.73 m^2 (offspring n = 1220, controls n = 556) resulted in similar differences in eGFR in female offspring compared to female controls (0.10 ml/min/1.73 m^2 (SE 0.66), $p = 0.87$, age-adjusted), and in male offspring compared to male controls (1.59 ml/min/1.73 m^2 (SE 0.71), $p = 0.026$, age-adjusted). Multiple imputation of missing data resulted in a similar eGFR in female offspring compared to female controls (−0.01 ml/min/1.73 m^2 (SE 0.72), $p = 0.99$) and a non-significant higher eGFR in male offspring compared to male controls (1.39 ml/min/1.73 m^2 (SE 0.78, $p = 0.073$). In men with hypertension eGFR was significantly higher in offspring compared with controls (4.30 ml/min/1.73 m^2 (SE = 1.57), $p = 0.006$) after multiple imputation and in men with a history of myocardial infarction or stroke this was 6.70 ml/min/1.73 m^2 (SE = 3.06, $p = 0.029$).

4. Discussion

Our aim was to investigate whether subjects with a familial propensity for longevity have better renal function compared to control subjects. We found that in the male but not in the female sex, middle-aged individuals with a propensity for longevity had a better renal function compared to environmentally matched controls. This renal function difference in men was predominately present in subjects with hypertension or cardiovascular disease.

In our study three findings dependent on sex were present. First, we found that at middle-age, women had a lower renal function compared to men. This is in line with several other studies (Coresh et al., 2003; Halbesma et al., 2008; Wetzels et al., 2007), showing a lower eGFR in women throughout life, and in line with the correction factor for women used in the CKD-EPI (Levey et al., 2009), MDRD (Levey et al., 2000), and CG formula (Cockcroft and Gault, 1976). Second, in men the age-associated decrease in eGFR was slightly stronger than in women. This difference may suggest that men are biologically older than women at a similar calendar age, which is in line with the evidence that men live five to ten years shorter than women (Mathers et al., 2004). Third, women had less cardiovascular disease and diabetes mellitus than men. This is in line with the fact that men develop co-morbidities, such as cardiovascular disease (Lloyd-Jones et al., 2010) or diabetes mellitus (Danaei et al., 2009), at an earlier age in life than women.

In men, a difference in renal function between longevity-prone subjects and environmentally matched controls was observed. This difference may be explained by the lower prevalence of (sub)clinical hypertension and cardiovascular disease in men from long-lived families, which probably reflects a lower degree of atherosclerosis. Atherosclerosis is an inflammatory process in which inflammation has an important role in each phase of the process. Inflammation is involved in fat accumulation in the vessel wall, maturation of the vascular lesion,

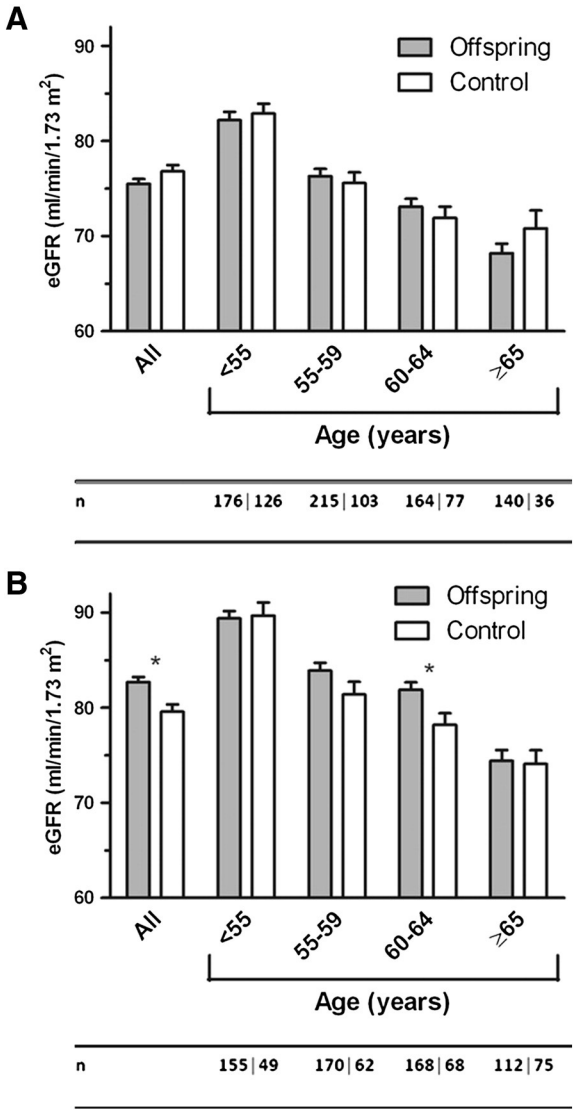

Fig. 1. Mean estimated glomerular filtration rate for offspring and controls stratified by sex and age. For each age category (x-axis) in women (A) and men (B) the crude mean (bar) and standard error (error bar) of the glomerular filtration rate (GFR) estimated with the Chronic Kidney Disease epidemiology collaboration formula (y-axis) is presented for both offspring and controls (legend). *P-value for eGFR difference between offspring and controls is <0.05. P-values were obtained from linear mixed models adjusted for sibling relationship. For female offspring and controls the range (25%–75%) for age was 49.8–53.5 and 47.4–53.2 years respectively in the lowest age category (<55 years) and 66.4–70.2 and 65.6–69.1 years respectively in the highest age category (≥65 years). For men these ranges were 49.4–54.0, 49.2–53.3, 66.2–69.6, and 66.7–70.1 years respectively.

and eventually ruptures of the atherosclerotic plaque leading to myocardial infarction or stroke (Blake and Ridker, 2002; Nabel, 2003). Longevity-prone men may better handle inflammatory stress and thereby have less atherosclerosis and a later onset of inflammatory diseases, such as myocardial infarction and stroke. This better handling of inflammatory stress may furthermore reduce the negative consequences of inflammatory diseases, such as fibrosis of heart and renal tissue (Vlassara et al., 2009). Our finding of a larger eGFR difference in male offspring compared to male controls with a previous history of myocardial infarction or stroke compared to male subjects without such a history may support this. However, our data showed that hsCRP levels were similar between male offspring and controls, but hsCRP may not be a good indicator for these inflammatory processes.

In women we observed no difference in renal function between offspring and controls, and this could explain why Lai et al. (Lai et al., 2012), who did not stratify their results by sex, found no difference in renal function between offspring and controls. There are two possible reasons to explain the absence of a difference. First, the prevalence of atherosclerotic disease in women aged 60–70 years is much lower than in men in the same age category. Moreover, the difference between male offspring and male controls was mainly observed in men with hypertension or cardiovascular disease. Although, we found no statistical significant difference in women, we did find a trend in women with a myocardial infarction or stroke in their medical history (eGFR difference of 6.98 ml/min/1.73 m^2 (SE 5.46), $p = 0.21$). Second, the absence of a difference in renal function between women from long-lived families and controls might be explained by the effect of sex hormones. Sex hormones have immuno-modulating actions often resulting in a more anti-inflammatory state (Villablanca et al., 2010). The genes involved in longevity leading to a better handling of inflammatory stress and less atherosclerosis may then play a less important role. Furthermore, our findings might suggest that the anti-inflammatory effects of sex hormones are less effective once myocardial infarction or stroke has developed. However, the exact pro- and anti-inflammatory actions of sex hormones need to be elucidated.

There are some limitations to our study. First, baseline information on medical history and medication use were not available for all offspring and controls. However, it is unlikely that this selection of subjects has led to biased results, because these data were only missing when the subjects' general practitioner or pharmacy did not respond, which likely was a random process. Indeed, our results suggest that our data is not missing selectively, because when we used multiple imputation, which is a valid method to handle missing data, results were similar to our complete case analysis and the estimates in the subjects with hypertension or cardiovascular disease remain significant. Second, for our main analysis, GFR was estimated with the CKD-EPI formula. A problem with the CKD-EPI formula is that it sometimes overestimates the real GFR in patients with a low renal function (<60 ml/min/1.73 m^2) and patients with a low BMI (<18.5 kg/m^2) (Michels et al., 2010; van den Brand et al., 2011). However, only a small proportion of subjects fell in these categories and with the other two formulas, the MDRD and CG formula, we found similar results. Besides this, for each subject only one eGFR measurement was available, making it not possible to relate longevity to renal function decline. Third, we could not adjust for all established risk factors for decline in renal function, such as hemoglobin and calcium/phosphate levels, because this information was lacking. Fourth, survival bias and the low number of subjects (especially controls) in the highest age category are possible causes for not finding an eGFR difference between male offspring and controls aged 65 years or older. Power problems could have also influenced results in other strata. Fifth, the age of our study population may be too young for detecting overall renal function differences between offspring and controls, because too few people have developed hypertension, myocardial infarction, or stroke.

We conclude that renal function was higher in middle-aged men with a propensity for longevity compared to environmentally matched controls. This renal function difference in men was predominately present in subjects with hypertension or cardiovascular disease. A possible explanation for the observed effect is the presence of a different handling of inflammation and atherosclerosis in subjects with a familial propensity for longevity.

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Table 2
Difference in estimated glomerular filtration rate between offspring and controls stratified by sex.

	Women[a]				Men[b]			
	n	ΔeGFR	SE	p-value	n	ΔeGFR	SE	p-value
Crude	1037	−1.32	0.78	0.090	859	3.05	0.87	<0.001
+1: age	1037	0.44	0.72	0.54	859	1.78	0.78	0.022
+2: age, HT, MI, stroke, DM	998	0.13	0.75	0.86	822	1.83	0.80	0.022
+3: age, antihypertensive and glucose lowering medication	1037	0.23	0.72	0.74	859	1.63	0.77	0.035
+4: age, glucose, hsCRP, triglycerides, HDL-cholesterol	1026	0.11	0.73	0.87	851	1.54	0.78	0.048
+5: age, smoking, BMI	898	0.36	0.77	0.64	747	1.73	0.83	0.036
+1, 2, 3, 4, 5	858	−0.11	0.80	0.89	707	1.46	0.85	0.088

Δ estimated glomerular filtration rate (eGFR) is the difference in eGFR, estimated with the Chronic Kidney Disease epidemiology collaboration formula, between offspring and controls assessed with a linear mixed model. A positive number means that eGFR is higher in offspring compared to controls. The crude ΔeGFR was adjusted for sibling relationship. We additionally adjusted for age and the main risk factors for decline in renal function: diagnosis of hypertension (HT), myocardial infarction (MI), stroke, or diabetes mellitus (DM) in medical history, antihypertensive and glucose lowering medication, glucose, high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL)-cholesterol, and triglyceride levels, and smoking and body mass index (BMI). hsCRP and triglyceride levels were logarithmically transformed.

[a] Offspring n = 695 and control n = 342.

[b] Offspring n = 605 and control n = 254.

Table 3
Difference in age-adjusted estimated glomerular filtration rate between offspring and controls stratified by sex and presence of hypertension or cardiovascular disease.

	Women					Men				
	Offspring n	Control n	ΔeGFR	SE	p-value	Offspring n	Control n	ΔeGFR	SE	p-value
Hypertension[a]										
No	504	221	0.27	0.86	0.75	423	166	0.35	0.88	0.69
Yes	182	114	0.22	1.41	0.87	164	84	4.74	1.53	0.002
Myocardial infarction/stroke										
No	676	325	0.00	0.73	0.99	552	229	1.30	0.80	0.10
Yes	15	13	6.98	5.46	0.21	49	25	6.21	2.85	0.033

Δ estimated glomerular filtration rate (eGFR) is the difference in eGFR, estimated with the Chronic Kidney Disease epidemiology collaboration formula, between offspring and controls assessed with a linear mixed model. A positive number means that eGFR is higher in offspring compared to controls. We adjusted for sibling relationship and age.

[a] Defined as either having a diagnosis of hypertension in medical history and/or using antihypertensive medication.

Conflict of interest

M.C.M.d.G, N.H., F.W.D., C.A.W., D.v.H., A.B.M., S.P.M., P.E.S., R.G.J.W., and A.J.M.d.C have nothing to declare.

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