Family History of Myocardial Infarction Increases Risk of Renal Dysfunction in Middle Age.

Christensson, Anders; Melander, Olle; Fjellstedt, Erik; Ohlson Andersson, Maria

Published in:
American Journal of Nephrology

DOI:
10.1159/000358259

2014

Family history of myocardial infarction increases risk of renal dysfunction in middle age

Anders Christensson, MD, PhD[1], Olle Melander, MD, PhD[2], Erik Fjellstedt, MD, PhD[1], Maria Ohlson-Andersson, MD, PhD[2]

[1]Dept of Nephrology and Transplantation, [2]Dept of Internal Medicine

Skåne University Hospital

Lund University

Malmö, Sweden

Running head: Myocardial infarction and renal dysfunction

Conflict of interest statement: No conflict of interest was declared.

Key words: Chronic kidney disease, glomerular filtration rate, heredity, myocardial infarction

Word count: 4076

Correspondence to:

Anders Christensson, MD, PhD, Assoc prof

Dept of Nephrology and Transplantation

Skåne University Hospital, Lund University,

20502 Malmö, Sweden

Phone: +46-40-333755, +46-706-293038

Fax: +46-40-337335

e-mail: anders.christensson@med.lu.se

Abstract

Background/Aims: Chronic kidney disease is common in the general population and may lead to end-stage renal disease, most frequent among males. Familial clustering of kidney diseases has been observed. We aimed to study a potential association between family history of myocardial infarction and renal dysfunction.

Methods: We studied 22 297 males and 10 828 females, aged 33-60 years, from a population-based cohort study. Estimated glomerular filtration rate (eGFR) was assessed by the CKD-EPI creatinine equation. Every participant filled in a self-administered questionnaire including family history. Heredity for myocardial infarction was defined as mother or father having had myocardial infarction and/or died from myocardial infarction, and/or brother or sister having had myocardial infarction. Binary logistic regression and multiple linear regression were used in the analyses.

Results: Multiple linear regression revealed a significantly increased risk of renal dysfunction in those with a positive heredity for myocardial infarction (the whole cohort p=0.01, men p= 0.000, women p=0.169). Binary logistic regression showed that males with heredity for myocardial infarction with a mean age of 43 years have a two times higher risk (p=0.02) of belonging to the group with GFR less than 45 mL/min/1.73m^2 compared to those without heredity. For the whole cohort the increased risk was 1.6 times (p=0.07). There was no significant association for females (p=0.88).

Conclusion: These findings demonstrate that a familiar burden of myocardial infarction is associated with renal dysfunction, in men, already in middle age. Genetic variants may underlie predisposition to CKD in those with heredity for myocardial infarction.

Introduction

Chronic kidney disease (CKD) is common and more than 10% of the western population is affected [1]. A minority leads to end stage renal disease (ESRD) and 60-65% of these are males [2, 3]. The reason for this male dominance has largely remained elusive. In earlier stages of CKD there is no male predominance over females [3, 4]. Primary disorder of the heart or kidney often results in secondary dysfunction or injury of the other organ. This interaction is termed cardiorenal syndrome (CRS) [5-8]. Another pathophysiological explanation is concurrent development of both both renal and cardiac dysfunction due to atherosclerosis [9].

In many CKD patients arteriosclerosis seems to be a major pathogenic mechanism in the setting of diabetes mellitus and hypertension [10]. However, susceptibility to CKD varies considerably among individuals with known risk factors which suggests a role for genetic factors other than those that influence high blood pressure and hyperglycemia. This has been shown from animal models [11] and suggested from human studies by the disproportionate burden of ESRD among afroamerican individuals that may not be explained by greater prevalence of hypertension or diabetes mellitus [12, 13]. Therefore, it will be interesting to identify genes that transfer susceptibility to CKD. Several studies have shown a genetic predisposition for CKD among individuals. Satko et al reviewed data on familial clustering of CKD and recommended the use of "family history" as a surrogate marker for risk of future nephropathy until kidney failure genes are identified [14]. Lei et al demonstrated that severe renal failure clustered within families independent of high blood pressure and diabetes *per se*, suggesting the presence of nephropathy susceptibility genes [15].

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There has been efforts to identify genetic causes to cardiac diseases in patients with CKD [16-18]. However, there are fewer reports about genetic factors causing CKD in patients with cardiac diseases or heredity for cardiac diseases.

The aim of the present study was to evaluate a potential relationship between heredity for MI and development of renal dysfunction in middle-aged persons. This was achieved in a population based cohort comprising more than 33 000 individuals. To the best of our knowledge, no studies of the association between heredity for MI and renal function impairment have been reported.

Material and Method

Patients

The Malmö Preventive Project (MPP) is a population based cross-sectional screening and intervention programme designed to study the risk of cardiovascular disease, hypertension, and metabolic syndrome [24]. Every inhabitant in each selected age group living in Malmö was invited to participate in this broad health-screening program, which enrolled subjects from 1974 to 1992. Participation across each age group was high (average 71.2%) [24]. The database consists of 33 346 individuals, 22 361 males and 10 985 females. Every participant filled in a self-administered questionnaire on medical and personal history including life style and hereditary factors. Men were recruited largely between 1974 and 1982, while women were recruited between 1977-1979 and again between 1983-1992. Additionally, men and women of different ages were targeted at different time points during recruitment, resulting in different mean ages (Table 1). A detailed description of the recruitment and screening protocol has been published previously [24, 25]. Females were significantly older (6 years) than males, 49.7 years and 43.7, respectively, at inclusion.

In the present study 219 individuals were excluded since it was not possible to calculate eGFR due to lack of data. Thus 33 127 individuals (22 299 males and 10 828 females) were included in the investigation. Two men were excluded due to eGFR > 300 mL/min/1.73m^2, leaving 33 125 for further analysis (22 297 men and 10 828 women) (Table 1).

Measurements

Serum creatinine was drawn at inclusion and analyzed using a kinetic alkaline picrate assay with stable normal range throughout the whole inclusion period. There were no

methodological changes during the study time. The values for serum creatinine (Jaffé method) were calibrated to fit enzymatic methods and the same as used for calibrating to IDMS level. Fasting serum cholesterol, trigycerides and blood glucose were measured according to standard procedures at the Department of Clinical Chemistry, Skåne University Hospital Malmö, Sweden.

Estimates of GFR

GFR was estimated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula for creatinine. CKD-EPI GFR = 141 x $\min(Scr/k, 1)^{a}$ x $\max(Scr/k, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1 [26]. Adjustment for race was not necessary in this homogenous cohort of people of Caucasian race. Estimated GFR (eGFR) was also calculated according to the following two equations: a) Cockroft-Gault (CG) creatinine clearance (mL/min) = (140-age) x weight x 1.23 / S-creatinine (x 0.85 if female) [27]. CG was adjusted for body surface area (BSA) of 1.73m^2 (CG/BSA). BSA was calculated according to the duBois and duBois formula [28] b) Four-variable (or abbreviated) MDRD. GFR (mL/min/1.73 m^2) = 175 x (S-creatinine / 88.4) $^{-1.154}$ x age $^{-0.203}$ (x 0.742 if female) [29, 30] Adjustment for black (1.212) was not necessary in this homogenous cohort of people of Caucasian race. If not stated otherwise CKD-EPI was the primary eGFR method used throughout this study.

Heredity for MI

The definition of heredity for MI was a positive answer in the self-administered questionnaire regarding; mother or father having had MI and/or mother or father having had MI before the

age of 60 years and/or mother or father died from MI and/or brother or sister having had MI. If one of these questions was answered positively it was considered that heredity for cardiovascular disease was present.

Previous MI

History of MI was based on registry data from medical records and the National Inpatient Registry. ICD code ICD10=I21, ICD9=410 was used.

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Blood pressure

High blood pressure was considered present if diastolic blood pressure was >90 mm Hg, or systolic blood pressure was >140 mm Hg or if there was a positive answer in the self-reported questionnaire; are you prescribed antihypertensive medicine.

Diabetes

The definition of diabetes was a positive answer in the self-reported questionnaire regarding; do you have diabetes, are you prescribed antidiabetic drugs or if fasting B-glucose was >6 mmol/L (which corresponds to fasting plasma glucose ≥7.0 mmol/L).

Statistics

The cohort showed a normal distribution of the parameters analyzed (data not shown). Therefore, parametric methods were used in the statistical calculations, such as Student t-test, linear regression, binary logistic regression and estimates of correlation. Binary logistic regression analyses (entermethod) and multiple linear regression were used to identify the most important risk factors responsible for eGFR among heredity, previous MI, hypertension, diabetes, BMI, cholesterol, smoking and age. All variables were entered in the same model.

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We analysed the cohort from dichotomised groups at two different GFR cut-off values, 60 mL/min/1.73 m^2 and 45 mL/min/1.73 m^2, respectively. The cohort was analysed as a whole but also separately for men and women. The statistical analyses were performed with SPSS program version 21.0 (IBM Corp, Armonk, NY, USA). P-values less than 0.05 were considered to be statistically significant.

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Results

Baseline data

Baseline data are presented separately for males and females in Tables 2 a-b. GFR was normally distributed over a relatively wide range. The distribution pattern was identical for males and females (not shown). Mean eGFR for the whole cohort was 85.1 mL/min/1.73 m^2 (SD ± 14.3) with CKD-EPI, 81.7 mL/min/1.73 m^2 (SD ± 15.0) with MDRD and 87.2 mL/min/1.73 m^2 (SD ± 15.9) with CG/BSA. Our data from CKD-EPI show that 931 (2.8%) of the whole cohort demonstrates eGFR <60 mL/min/1.73 m^2. Corresponding figures are 354 (1.6%) for males and 577 (5.4%) for females, respectively. In the whole cohort 22.6 % had high blood pressure, 23.5 % among the males and 20.7% among the females, respectively. Diabetes mellitus was present among males at a rate of 5.4% and females of 4.7%. The amount of smokers in the study was 44 %, 49 % of the males and 35 % of the females, respectively (Table 1). Mean age among the men with positive heredity for MI was 43.9 years compared to 43.7 years for all men in the cohort. Corresponding ages for women with positive heredity for MI was 49.3 years compared to 49.7 years for all women in the cohort.

Binary logistic regression

Heredity for MI

We performed binary logistic regression from dichotomised groups. At a cut-off at GFR 45 mL/min/1.73 m^2 we found a significant odds ratio (OR) for men (2.06, p=0.025) if heredity was present (Table 3b). This means that a man with positive heredity for MI at the age of 43 years has a 2.1 times higher risk of belonging to the group with GFR less than 45 mL/min/1.73m^2 compared to a 43 years old man without heredity for MI. For women and the whole cohort the OR did not reach statistical significance (OR 0.93, p=0.88 and OR 1.6, p=0.071, respectively) (Tables 3a and c).

At a cut-off at 60 mL/min/1.73 m^2 the OR was 1.22 (p=0.053) for males if heredity for MI was present. For females and the whole cohort the OR was not significant (Table 4). We performed the same analyses with the MDRD formula and found similar significances (not shown).

Previous MI

In the whole cohort previous MI more than sevenfolded (OR 7.47, p=0.001) the risk of being in the group with GFR less than 45 mL/min/1.73m^2. For males the risk was nearly ten-folded (OR 9.2, p<0,001) but was not significant for women (Table 3). In the whole cohort previous MI more than double-folded (OR 2.0, p=0.030) the risk of being in the group with GFR less than 60 mL/min/1.73m^2 . For males the OR was 2.1 (p=0.046) but for women this was not significant (Table 4).

Hypertension

Hypertension was a significant risk factor for both males and females with OR of 2.38 (p=0.012) and 2.50 (p=0.046), respectively. For the whole cohort the OR was 2.5 (p=0.001) at a cut-off at 45 mL/min/1.73 m^2 (Table 3a). This was also significant for a cut-off at 60 mL/min/1.73 m^2, however less pronounced, (Table 4a).

Diabetes mellitus

If diabetes mellitus was present there was a double-folded (OR 2.22, p=0.036) risk of belonging to the group with GFR less than 45 mL/min/1.73m^2 for the whole cohort, but no significant data for males and females, respectively (Table 3). Diabetes mellitus was close to significant as a risk factor of belonging to the group with GFR less than 60 mL/min/1.73 m^2

(OR 1.3, p=0.058) for the whole cohort and significant for males (OR 1.48, p=0.040) but not for females (OR 1.16, p=0.41) (Table 4).

Hypercholesterolemia

Serum cholesterol was a significant risk factor in both males and females in the group with GFR below 60 mL/min/1.73m^2 compared to above 60 mL/min/1.73m^2 (Table 4).

Multiple linear regression

When analyzing the same parameters, as included in binary logistic regression, with multiple linear regression we found that heredity for MI revealed a significant association to decreased renal function with a regression coefficient (B) of -0.790 (p=0.000) for men and significant for the whole cohort (B= -0.441, p=0.010) (Table 5). There was no significant association between heredity for MI and decreased renal function among women (B=0.53, p=0.169). We performed the same analysis with MDRD as dependent variable and found similar results (not shown).

Age

Estimated GFR (CKD-EPI) was significantly decreased by 0.716 mL/min/1.73 m^2 per year in the whole cohort (p=0.000). It was also highly significant (p=0.000) for both men and women, B= -0.699 and -0.669 mL/min/1.73 m^2 per year, respectively.

Discussion

This study shows an association between family history of MI and renal dysfunction in middle age. Men, already at the age of the 40s, have a double folded risk of belonging to the group with GFR less than 45 mL/min/1.73m^2, if presenting a positive heredity for MI. We found no increased risk for the female cohort. These findings may reveal a familiar cause of CKD.

Although CKD has been recognised as a risk factor for MI, genetic factors for predisposition to MI in individuals with CKD have remained largely unknown. In a Japanese study by Fujimako et al. 1,339 Japanese individuals with CKD the genotypes for 248 polymorphisms of 181 candidate genes were determined and showed association to MI in individuals with CKD [18].

However, knowledge about the association between heredity for cardiovascular diseases and CKD are so far limited. Our cohort with a questionnaire about heredity data and a high attendance rate made it possible to examine middle-aged persons regarding associations between heredity for MI and CKD. Studying relatively young persons means that other factors developing over the life time of a person have less influence of the results. The importance of our findings is that the observations were seen already in relatively young persons. These findings mean that a familiar factor in males may predispose to belonging to the group with GFR less than 60 mL/min/1.73m^2 at the age of 40 years and that genetic variants may underly predisposition to CKD in men with heredity for MI. Males may be more sensitive for a genetic burden and environmental influence. We found no increased risk for having GFR less than 60 mL/min/1.73m^2 among females with heredity for MI. The female group was 6 years older due to the unique sampling strategy. Our findings may be one clue to the different prevalence of ESRD among males and females.

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One common pathogenic mechanism for CKD and MI is vascular disease, eg atherosclerosis. Myocardial infarction is a multifactorial and polygenic disease, and is strongly influenced by a genetic component [19]. Recent genome-wide association studies (GWAS) have implicated various candidate genes underlying predisposition to MI, but the genes that confer susceptibility to this condition remain to be identified [20-23]. Thus, persons with heredity for MI are prone to develop atherosclerosis and subsequent CKD. However, the incidence of CKD varies among individuals with common risk factors and suggests a role for genetic factors other than those that affect high blood pressure and hyperglycemia [12, 13]. Our findings are in accordance with these observations. We hypothesize that the difference between men and women concerning incidence of ESRD may be due to genetic factors. Because of multifactorial causes of CKD the described genetic difference between the sexes does not affect the prevalence of earlier stages of CKD. One hypothesis is that many factors predispose to the early and less severe CKD stages but that the genetic factor may have a greater influence on the severe cases of CKD leading to ESRD. This may explain the big difference in sex distribution of ESRD, rendering two thirds men and one third women. In earlier stages there is a more balanced sex distribution.

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Another interesting aspect, though not new, is the finding that previous MI nearly tenfolded the risk of being in the group with GFR less than 45 mL/min/1.73m^2 for males. The increase in risk was also seen with the cut-off at 60 mLmin/1.73m^2. This emphasizes the strong association between cardiac diseases and CKD. This is important as it demonstrates that this large, representative cohort is highly informative in reference to the association between cardiac disease and impaired kidney function. The representativeness of this cohort in this aspect has previously been shown where we demonstrated a significantly increased risk of

cardiovascular events after 28 years follow-up among both men and women with moderately impaired renal function at baseline [7]. The common pathophysiological pathway for our results may be the development of vascular disease due to atherosclerotic mechanisms affecting both the heart and the kidneys.

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The strength of this study is the large cohort of individuals who took part in a representative population based screening programme. The project invited entire birth-cohorts identified through the local population registry and reached a high attendance rate of about 70%. We used several formulas for eGFR to secure the results (not shown). However, all results presented are based on the CKD-EPI formula which is recognised to be one of the most accurate formulas for persons with normal to moderately impaired renal function. We found the same results regarding association between heredity for MI and renal dysfunction in young men with the CG/BSA formula and MDRD formula (not shown). The observed association was confirmed both from binary logistic regression and multiple linear regression.

One weakness of this study is that the female group was smaller and 6 years older due to the unique sampling strategy. The women were included a decade later than the men. Socio-economic and life style factors differed at this time and may be an explanation for the gender difference. Single measurements of eGFR with creatinine and no available data on urinary albumin-creatinine ratio make it impossible for characterisation into CKD stages. Another weakness may be the validity of the answers of the questions in the self-administered questionnaire on medical and personal history including life style and familiar factors. However, the high attendance rate may counteract this.

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In conclusion, we show an association between heredity for MI and renal dysfunction in middle age. The findings were significant for males and may reveal a familiar factor causing ESRD more frequently in males than in females. However, the genetic mechanisms remain largely unknown and needs further exploration.

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Acknowledgements

This work was supported by grants from the Fulbright Commission, the Swedish Medical Research Council, the Faculty of Medicine at Lund University, Stiftelsen för njursjuka, Research Funds of Region Skåne, and the Research Fund of Skåne University Hospital. Statistical assistance was provided by Henrik Månsson, Jan-Åke Nilsson and Anders Dahlin.

Statement of competing financial interests

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No conflict of interest was declared.

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Tables

Table 1. Patient data at inclusion. Age at inclusion and distribution of screening years for males and females. Number of persons in each GFR-category. Prevalence of hypertension, diabetes mellitus, previous MI, heredity for MI and smoking.

	Men N=22 297	**Women** N=10 828
Age at screening (mean, (SD, range))	43.7 (±6.6, 26.5-61.2)	49.7 (±7.4, 28.2-57.6)
1974-1976	3970 (18%)	0 (0%)
1977-1979	8004 (36%)	2728 (25%)
1980-1982	9347 (42%)	2 (0%)
1983-1984	976 (4%)	2519 (23%)
1985-1992	0 (0%)	5579 (52%)
CKD-EPI <30 (mL/min/1.73m^2)	15	5
30-44 (mL/min/1.73m^2)	24 (0.1%)	17 (0.2%)
45-59 (mL/min/1.73m^2)	315 (1.4%)	555 (5.1%)
60-89 (mL/min/1.73m^2)	12845 (57.6%)	7515 (69.4%)
≥90 (mL/min/1.73m^2)	9098 (40.8%)	2736 (25.3%)
Hypertension	5249 (23.5%)	2246 (20.7%)
Diabetes mellitus	1210 (5.4%)	506 (4.7%)
Previous MI	69 (0.31%)	24 (0.22%)
Heredity for MI	6814 (30.6%)	2693 (24.9%)
Smokers	10926 (49%)	3790 (35%)

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Table 2a.

Baseline data men (n=22 297)

Parameter	min	max	mean	SD
CKD-EPI (mL/min/1.73m^2)	4.37	156	87.26	13.83
MDRD (mL/min/1.73m^2)	5	333	84.02	14.78
CG/BSA (mL/min/1.73m^2)	7.87	274.6	89.18	15.55
BMI	14.3	52	24.7	3.30
Blood pressure systolic (mm Hg)	75	255	127	14.9
Blood pressure diastolic (mm Hg)	50	175	85.5	9.64
S-cholesterol (mmol/L)	2.03	44.23	5.6	1.09
S-triglycerides (mmol/L)	0.10	38.95	1.51	1.05
B-glucose fasting (mmol/L)	2.2	27.8	5.0	0.99
Age at screening (years)	26.5	61.2	43.7	6.6
S-creatinine (µmol/L)	27	1061	93.1	18.87

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Table 2b

Baseline data women (n=10 828)

Parameter	min	max	mean	SD
CKD-EPI (mL/min/1.73m^2)	7.92	141	80.71	14.2
MDRD (mL/min/1.73m^2)	8	265	76.8	14.19
CG/BSA (mL/min/1.73m^2)	11.6	227	83.07	15.76
BMI	13.9	56.3	24.39	4.21
Blood pressure systolic (mm Hg)	75	250	124.6	16.65
Blood pressure diastolic (mm Hg)	45	130	81.6	9.16
S-cholesterol (mmol/L)	2.43	14.55	5.81	1.11
S-triglycerides (mmol/L)	0.18	13.75	1.11	0.604
B-glucose fasting (mmol/L)	2.3	23.7	4.88	0.962
Age at screening (years)	28.2	57.6	49.7	7.40
S-creatinine (µmol/L)	26	505	76.08	12.1

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Table 3.
Odds ratio for dichotomised groups with a cut-off GFR of 45 mLmin/1.73m^2. Estimation from binary logistic regression. GFR was estimated from CKD-EPI. 95% confidence interval (CI). All variables were entered in the same model.

a) All (n=33 125)

	OR	p	95% CI
Heredity for MI	1.61	0.071	0.959, 2.694
Previous MI	7.47	0.001	2.246, 24.874
Hypertension	2.47	0.001	1.449, 4.206
Diabetes	2.22	0.036	1.054, 4.653
BMI	1.02	0.535	0.957, 1.089
Cholesterol	1.24	0.042	1.008, 1.519
Age	1.06	0.006	1.016, 1.099

b) Men (n=22 297)

	OR	p	95% CI
Heredity for MI	2.06	0.025	1.096, 3.872
Previous MI	9.18	0.001	2.608, 32.346
Hypertension	2.38	0.012	1.211, 4.681
Diabetes	2.02	0.159	0.759, 5.347
BMI	0.997	0.959	0.905, 1.099
Cholesterol	1.065	0.671	0,797, 1.423
Age	1.073	0.003	1.024, 1.125

c) Women (n=10 828)

	OR	p	95% CI
Heredity for MI	0.927	0.882	0.340, 2.526
Previous MI	1.120	0.998	0.232, 3.431
Hypertension	2.500	0.046	1.014, 6.163
Diabetes	2.43	0.141	0.747, 7.889
BMI	1.050	0.278	0.962, 1.146
Cholesterol	1.514	0.003	1.151, 1.991
Age	1.009	0.832	0.929, 1.096

Table 4.
Odds ratio for dichotomised groups with a cut-off GFR of 60 mL/min/1.73m^2. Estimation from binary logistic regression. GFR was estimated from CKD-EPI. 95% confidence interval (CI). All variables were entered in the same model.

a) All (n=33 125)

	OR	p	95% CI
Heredity for MI	1.080	0.306	0.932, 1.251
Previous MI	1.967	0.030	1.066, 3.629
Hypertension	1.411	0.000	1.222, 1.629
Diabetes	1.278	0.058	0.992, 1.646
BMI	1.024	0.007	1.007, 1.042
Cholesterol	1.186	0.000	1.119, 1.258
Age	1.161	0.000	1.148, 1.175

b) Men (n=22 297)

	OR	p	95% CI
Heredity for MI	1.219	0.053	0.998, 1.527
Previous MI	2.133	0.046	1.013, 4.493
Hypertension	1.702	0.000	1.354, 2.139
Diabetes	1.478	0.040	1.018, 2.146
BMI	1.044	0.009	1.011, 1.078
Cholesterol	1.202	0.000	1.091, 1.323
Age	1.156	0.000	1.138, 1.174

c) Women (n=10 828)

	OR	p	95% CI
Heredity for MI	1.051	0.622	0.863, 1.279
Previous MI	2.487	0.100	0.840, 7.358
Hypertension	1.368	0.001	1.131, 1.655
Diabetes	1.156	0.410	0.819, 1.633
BMI	1.019	0.062	0.999, 1.040
Cholesterol	1.146	0.001	1.061, 1.238
Age	1.117	0.000	1.093, 1.142

Table 5.
Multiple linear regression analysis. Unstandardized regression coefficients (B) for parameters vs eGFR measured with CKD-EPI. 95% confidence interval (CI). All variables were entered in the model but only heredity and age are shown in the table.

a) All (n= 33 125)

	Coefficient (B)	p	95% CI
Heredity for MI	-0.441	0.010	-0.775, -0.107
Age	-0.716	0.000	-0.739, -0.693

b) Men (n=22 297)

	Coefficient (B)	p	95% CI
Heredity for MI	-0.790	0.000	-1.114, -0.378
Age	-0.699	0.000	-0.738, -0.684

c) Women (n=10 828)

	Coefficient (B)	p	95% CI
Heredity for MI	0.530	0.169	-0.225, 1.285
Age	-0.669	0.000	-0.719, -0.619