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Predictors of new-onset decline in kidney function in a general middle-European population

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Abstract

Background. Limited epidemiological data are available on predictors of new-onset kidney disease.

Methods. In this longitudinal cohort study, 17 375 apparently healthy volunteers of the general Viennese population (46.4% women, age range 20–84 years, men 20–89 years) performed a baseline examination at some time within the study period (1990–2005) and completed a median of two follow-up examinations [interquartile range (IQR) 1 to 4]; the median follow-up period was 7 years (IQR 4 to 11). The outcome of interest was the development of kidney disease, defined as a decrease of the glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 at the follow-up examinations [calculated by the abbreviated modification of diet in renal disease (MDRD) equation]. Logistic generalized estimating equations were used to analyse the relationship between the covariates and the outcome variable.

Results. The following parameters [odds ratios (OR) with 95% confidence intervals] predicted new-onset kidney disease: Age (increase by 5 years), OR = 1.36 (1.34–1.40); National Kidney Foundation-chronic kidney disease (NKF-CKD) stage 1 with proteinuria (+), OR = 1.39 (1.10–1.75); NKF-CKD stage 1 with proteinuria (≥++), OR = 2.07 (1.11–3.87); NKF-CKD stage 2 with proteinuria (+), OR = 2.71 (2.10–3.51); NKF-CKD stage 2 with proteinuria (≥++), OR = 3.80 (2.29–6.31); body mass index, OR = 1.04 (1.02–1.06); current-smoker, OR = 1.20 (1.01–1.43); performing no sports, OR = 1.57 (1.27–1.95); uric acid (increase by 2 mg/dl), OR = 1.69 (1.59–1.80); HDL-cholesterol (decrease by 10 mg/dl), OR = 1.12 (1.07–1.17); hypertension stage 1, OR = 1.35 (1.08–1.67); hypertension stage 2, OR = 2.01 (1.62–2.51); diabetes mellitus, OR = 1.44 (1.07–1.93).

Conclusions. Cardiovascular risk factors as well as NKF-CKD stages 1 and 2 and proteinuria, the more the higher and an entirely novel finding, performing no sports, predicted new-onset kidney disease.

Keywords: Caucasian middle-European population; epidemiology; estimated glomerular filtration rate; new-onset kidney disease; predictors

Introduction

The incidence of end-stage renal disease (ESRD), and concomitantly the number of patients on renal replacement therapy, are increasing steadily [1–3]. Established cardiovascular risk factors are associated with ESRD, hypertension and diabetes being the leading causes [1–3].

The majority of epidemiologic studies related only individual risk factors to renal dysfunction and associated kidney disease: age [4], diabetes mellitus [5,6], hypertension [7,8], obesity [9,10], dyslipidaemia [11,12] and smoking [13–15]. Recent experimental and epidemiological evidence suggests a role of uric acid not only as a marker of reduced kidney function and an independent cardiovascular risk factor [16], but also as a risk factor for the development and progression of renal disease [17–19]. As is generally known, proteinuria has long been recognized as an important risk factor for progression of renal disease as well as an independent risk factor for cardiovascular morbidity and mortality [20–23].

Moreover, there is a bulk of evidence showing the beneficial effects of endurance and/or strength exercise training in

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patients with chronic diseases: improvement of blood pressure control [24,25], lipid profiles [26,27], glycosylated haemoglobin [26–28] and control of body weight [26]. In fact, little is known concerning the effect of physical exercise on risk factors for the development or progression of kidney disease [25,29,30].

The vast majority of studies concerning risk factors of kidney disease investigated patients who subsequently developed ESRD [31]. Only a few studies focused on earlier stages of kidney disease with the belief that early interventions might delay or prevent the progression to ESRD [32]. This is all the more important because a majority of adults with moderate kidney disease have coronary heart disease or risk equivalents [33].

The aim of this longitudinal cohort study was to identify risk factors at an earlier stage of kidney disease within an apparently healthy general adult Viennese population, i.e. representing a general Caucasian middle-European population, using an integral multivariable approach.

Subjects and methods

Study design and population

It is common practice for the adult Viennese population to have the opportunity to perform yearly preventative medical checkups, due to invitations being issued by the health insurance companies. These examinations are usually performed by general practitioners.

Within the ongoing Vienna Health Screening Project, the general adult population of Vienna is invited by the Department of Health Prevention since 1990 to yearly extensive (study protocol) preventive medical checkups. Within this project, invitations are sent out by letter to e.g. companies, educational, social, governmental and non-governmental institutions (52.3% of all invitations were randomly selected using the Viennese company register file) as well as to households (47.7% of all invitations were randomly selected using the Austrian register of residents file) with the aim of obtaining a representative Viennese study cohort. In 1990, 6000 invitation letters were sent out to volunteers to participate in the study and subsequently 3000 letters were sent out every year until 2004. Overall 48 000 invitation letters were sent out; 38.0% volunteers accepted the study offer. Participants who performed the baseline examination were reminded annually by a letter to attend follow-up examinations. Until 2005, 18 239 apparently healthy volunteers (46.4% women, age range 20–84 years, men 20–89 years) performed the baseline examination at some time within the study period. Due to the study protocol, no preset time intervals for the follow-up examinations were demanded imperatively. Participants who attended at least one follow-up examination were included in the analysis, even if the patients died afterwards. In order to investigate predictors at an earlier stage of kidney disease, 329 participants with a baseline GFR <60 ml/min/1.73 m^2 [calculated by the simplified modification of diet in renal disease (MDRD) equation] were excluded, as well as 534 participants who did not attend any follow-up examination (i.e. dropouts).

The institutional review board at the Department of Health Prevention, Vienna, Austria, approved the study. All participants gave informed consent according to the Helsinki declaration.

Assessments of risk factors

Assessment of medical history and physical examination was performed by specially trained general practitioners (GPs) with respect to the study protocol. Height (cm) and weight (kg) were measured by study nurses. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Smoking status was defined as no-smoking, current-smoking or ex-smoking at baseline. Sports habits were classified as potentially preventive for health if the amount of endurance exercise exceeded 15 min per training unit and/or resistance exercise was performed due to a training protocol; furthermore physical exercise had to be performed continuously $\geq$2 times/week [34]. Blood pressure measurements were done according to the currently used guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7 [35]); two measurements of systolic and diastolic blood pressure were performed by the study nurses within a time interval of at least 15 min, and additionally one measurement was assessed by a GP. The arithmetic mean of the three measurements was used for statistical analysis. Evaluation of hypertension was performed using the JNC7 classification; normal blood pressure: systolic $<$120 mmHg and diastolic $<$80 mmHg; prehypertension: systolic $=$ 120–139 mmHg or diastolic $=$ 80–89 mmHg; hypertension stage 1: systolic $=$ 140–159 mmHg or diastolic $=$ 90–99 mmHg; hypertension stage 2: systolic $\geq$160 mmHg or diastolic $\geq$100 mmHg. Blood testing of fasting serum parameters included creatinine (mg/dl), glucose (mg/dl), uric acid (mg/dl), total cholesterol (mg/dl), HDL-cholesterol (mg/dl), LDL-cholesterol (mg/dl) and triglycerides (mg/dl). Participants with a fasting glucose level of 126 mg/dl or higher were defined as diabetic. Impaired fasting glucose was defined as a fasting glucose level between 100 and 125 mg/dl in the absence of diabetes [36]. Dipstick proteinuria was measured semi-quantitatively. Chronic kidney disease was classified using the National Kidney Foundation-chronic kidney disease (NKF-CKD) classification [37].

Measurements and definitions

Kidney function was estimated by GFR [38–40], which was calculated by the simplified MDRD equation [38]: GFR (ml/min/1.73 m^2) $= 186.3 \times$ serum creatinine$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ (0.742 if female). Since the MDRD formula is sensitive to the creatinine assay methodology [42], the following correction formula was necessary (due to our creatinine assay methodology used) to convert measured creatinine to 'MDRD creatinine': MDRD creatinine (mg/dl) $= -0.215 + 1.08 \times$ measured creatinine [43].

Measurements, calibration, standardization and validation of serum chemistry parameters were performed in a

single laboratory throughout the 16-year study period according to good laboratory practice guidelines. Glucose, creatinine, cholesterol, HDL-cholesterol and triglycerides were measured on the Hitachi 917® clinical chemistry analyzer using systemic reagents from Roche® Inc. LDL-cholesterol was measured using Friedewald's formula; inter-assay coefficient of variation (CV) was 2.4%. Glucose was measured by the hexokinase method (Gluco-quant®); intra-assay CV was 1.0% and inter-assay CV was 1.7%. Creatinine was measured by means of the kinetic Jaffé method; intra-assay CV was 0.7% and inter-assay CV was 2.3%. Cholesterol was measured by an enzymatic method (Cholesterol CHOD-PAP®); intra-assay CV was 0.8% and inter-assay CV was 1.7%. HDL-cholesterol was measured as a direct quantitative determination by an enzymatic assay (HDL-C-plus second generation); intra-assay CV was 0.8% and inter-assay CV was 1.8%. Triglycerides were measured by an enzymatic method (Triglycerides GPO-PAP®); intra-assay CV was 1.5% and inter-assay CV was 1.8%. Uric acid was measured by an enzymatic method (UA-plus®); intra-assay CV was 0.5% and inter-assay CV was 0.8%. Dipstick proteinuria was measured semi-quantitatively by a Combour-test®.

Statistical analysis

The outcome of interest (i.e. the dependent variable) was the development of kidney disease defined as a decrease of GFR <60 ml/min/1.73 m^2 (i.e. NKF-CKD stage 3) at a follow-up examination. Covariates included age, sex, NKF-CKD stages 1 and 2, dipstick proteinuria (+) and (≥++), NKF-CKD stage 1 with proteinuria (+), NKF-CKD stage 1 with proteinuria (≥++), NKF-CKD stage 2 with proteinuria (+), NKF-CKD stage 2 with proteinuria (≥++), BMI, BMI categories, sports, current-smokers, ex-smokers, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, uric acid, fasting serum glucose, systolic blood pressure, diastolic blood pressure, JNC7 blood pressure categories [35] and modified diagnosis of diabetes mellitus categories [36]. Logistic generalized estimating equations (GEEs) were used to analyse the relationship between the covariates and the outcome variable, a method taking into account the dependence between repeated measurements within the same individual at different follow-up periods [44]. Since there was an significant correlation between the outcome variables on the same person and as the strength of these within-participant correlations decreased with increasing time between the subsequent examinations, an autoregressive correlation structure was used for the GEE models. First, all covariates, i.e. predictors, were univariably analysed after adjusting for age considering the known association of this parameter with GFR [4,38] and sex, taking into account the sex-related differences as shown in the baseline data (Table 1). Subsequently, a multivariable GEE model was performed with respect to statistical significance resulting from the univariable analyses. Since visual data inspection showed a rather nonlinear relationship between blood pressure as well as blood glucose and the odds for developing new-onset kidney disease, only the respective categorical terms were used for multivariable analysis. In addition, the study cohort is very similar, classified by the factors NKF-CKD stages as well as by the semi-quantitative amount of proteinuria. In order to avoid explaining the same statistical variation, only the combination of NKF-CKD stages with the proteinuria groups was included in the multivariable model. Covariates were retained if Wald tests gave a $P < 0.05$.

All continuous data are presented as means ± standard deviations (SD). Categorical data are presented as percentages. A two-tailed $P < 0.05$ was considered to indicate statistical significance for the univariable analyses. All data analysis was done in the R environment for statistical computing, version 2.4 [45], using the 'geepack library', version 1.0–10 [46].

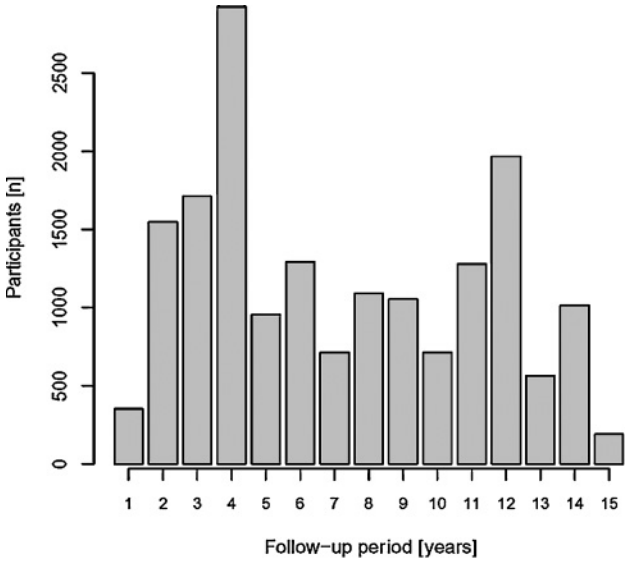

Fig. 1. Until 2005, 17 375 apparently healthy volunteers (46.4% women, age range 20–84 years, men 20–89 years) performed a baseline examination at some time within the study period and completed a median of two follow-up examinations [interquartile range (IQR) 1 to 4]. The median follow-up period was 7 years (IQR 4 to 11) and the mean follow-up period was 7.2 ± 3.9 years. Altogether, a total of 17 375 baseline examinations and 59 142 follow-up examinations were used for analysis.

Results

A total of 17 375 volunteers (46.4% women, age range 20–84 years, men 20–89 years) were assessed longitudinally. They performed the baseline examination and completed a median of two follow-up examinations (IQR 1 to 4), i.e. a total of 59 142 follow-up examinations. The median follow-up period was 7 years (IQR 4 to 11); the mean follow-up period was 7.2 ± 3.9 years (Figure 1). Participants who dropped out did not show systematic differences in their baseline characteristics compared to the total cohort. Overall 190 participants died within the study period.

Baseline characteristics of participants are shown in Table 1. According to the NKF-CKD classification [37], at baseline 91.4% of the participants (women and men) were classified as apparently free of kidney disease, and 8.6% of the volunteers were classified into NKF-CKD stages 1 ($n = 841$; 4.8%) or 2 ($n = 648$; 3.8%). A total of 329 participants were excluded at baseline, because

Table 1. Baseline characteristics of participants stratified by sex

Total population $n = 17\,375$ (100%)	Men $n = 9315$ (53.6%)	Woman $n = 8060$ (46.4%)
Age (years)	41.6 ± 11.4	42.2 ± 12.0
GFR (ml/min/1.73 m^2)	95.5 ± 15.6	92.1 ± 11.3
NKF-CKD stages [37]		
Apparently healthy (%)	91.0	91.8
Stage 1 (%)	5.7	3.9
Stage 2 (%)	3.3	4.3
Proteinuria (dipstick)		
Ø (%)	91.0	91.8
+ (%)	8.3	7.3
≥++ (%)	0.7	0.9
Body mass index (kg/m^2)	25.3 ± 3.1	23.7 ± 3.8
Body mass index categories (%)		
BMI (kg/m^2) < 25	52.4	69.9
25 ≤ BMI (kg/m^2) < 30	40.1	23.2
BMI (kg/m^2) ≥ 30	7.5	6.9
Sports if performed (%)	16.3	15.0
Smoking		
Current-smoker (%)	30.3	31.7
Ex-smoker (%)	18.5	12.2
Non-smoker (%)	51.2	56.1
Total cholesterol (mg/dL)	221.2 ± 41.8	219.5 ± 40.5
LDL (mg/dL)	143.1 ± 37.5	132.5 ± 36.9
HDL (mg/dL)	52.3 ± 13.4	67.1 ± 20.2
Triglycerides (mg/dL)	129 ± 71.0	101.4 ± 50.1
Uric acid (mg/dL)	6.0 ± 1.2	4.3 ± 1.0
Systolic blood pressure (mmHg)	132.3 ± 15.6	124.0 ± 16.8
Diastolic blood pressure (mmHg)	82.0 ± 9.4	78.1 ± 9.6
Fasting serum glucose (mg/dL)	88.7 ± 14.6	84.4 ± 12.8
Blood pressure groups [34]		
Normal (%)	15.8	38.4
Prehypertension (%)	49.1	41.3
Stage 1 (%)	27.0	15.0
Stage 2 (%)	8.1	5.3
Blood glucose groups [35]		
Normal (%)	86.3	93.5
Impaired fasting glucose (%)	12.6	5.9
Diabetes mellitus (%)	1.1	0.6

Data are mean ± standard deviations or percentages. Abbreviations: GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NKF-CKD, National Kidney Foundation—chronic kidney disease.

309 volunteers were classified into NKF-CKD stage 3, 6 into NKF-CKD stage 4 and 14 into NKF-CKD stage 5, respectively.

BMI was about 7% higher in men compared to women. Systolic and diastolic blood pressure were about 9% higher in men compared to women, fasting serum glucose was about 5% higher and uric acid was about 40% higher, HDL-cholesterol was about 20% lower and triglycerides were about 30% higher in men as well. Proteinuria, smoking status and sports performance showed only slight differences in women versus men.

Logistic GEEs for individual predictors were performed after adjusting for age and sex. The outcome of interest was the development of kidney disease defined as a decrease of GFR <60 ml/min/1.73 m^2 at the follow-up examinations. Each individual's last follow-up examination was used for a detailed description of the gradual progression of CKD (Table 2). Overall, 268 (1.5%) participants developed NKF-CKD stage 3; 8 (0.05%) participants NKF-CKD stage 4 and 12 (0.07%) participants NKF-CKD stage 5 at the last follow-up examination.

Results are presented as odds ratios (OR) with a 95% confidence interval (CI) for all individual predictors as shown in Table 3.

Subsequently, a multivariable GEE model was performed with respect to statistical significance resulting from the univariable analyses of the individual predictors as shown in Table 4.

Discussion

In a large apparently healthy adult Viennese cohort showing baseline characteristics very similar to data from respective Viennese community-based studies [47–49], established cardiovascular risk factors predicted the development of new-onset kidney disease. This is the first study on this issue performed within a general middle-European population using an integral multivariable approach that focused on an earlier stage of kidney disease with the belief that early interventions might delay or prevent sequelae.

Table 2. Progression of CKD and decline in eGFR during the whole study period

Progression of CKD	(%)	Mean GFR (ml/min/1.73 m^2)	Mean GFR decline (ml/min/1.73 m^2)	Mean GFR decline (%)
(a) Apparently free of kidney disease (AFKD) at the baseline examination ($n = 15\,886$)[a]				
CKD-stage 1	753 (4.7)	92	3	3
CKD-stage 2	307 (1.9)	71	16	18
CKD-stage 3	210 (1.3)	55	22	29
CKD-stage 4	3 (0.02)	24	49	67
CKD-stage 5	2 (0.01)	13	56	81
(b) Chronic kidney disease (CKD)-stage 1 at the baseline examination ($n = 841$)[b]				
CKD-stage 2	42 (5.0)	68	28	29
CKD-stage 3	21 (2.5)	52	39	43
CKD-stage 4	1 (0.1)	26	66	71
CKD-stage 5	3 (0.4)	14	76	84
(c) Chronic kidney disease (CKD)-stage 2 at the baseline examination ($n = 648$)[c]				
CKD-stage 3	37 (5.7)	49	14	22
CKD-stage 4	4 (0.6)	23	38	62
CKD-stage 5	7 (1.1)	13	48	78

[a]Mean GFR = 94 ± 12 ml/min/1.73 m^2 at the baseline examination and 86 ± 13 ml/min/1.73 m^2 at the last follow-up examination for participants who remained AFKD.
[b]Mean GFR = 92 ± 3 ml/min/1.73 m^2 at baseline examination and 84 ± 7 ml/min/1.73 m^2 at the last follow-up examination for participants who remained in CKD-stage 1.
[c]Mean GFR = 65 ± 6 ml/min/1.73 m^2 at the baseline examination and 63 ± 9 ml/min/1.73 m^2 at the last follow-up examination for participants who remained in CKD-stage 2.
Each individual's baseline examination and the last follow-up examinations were chosen for calculation of the estimated glomerular filtration rate (eGFR) using the simplified modification of diet in renal disease (MDRD) equation [38]. Classification of chronic kidney disease (CKD) was done using the National Kidney Foundation-CKD stages [37].

Therefore the predictors of the multivariable model are subsequently discussed in detail (Table 4).

First, the relation between age and GFR is well known and due to the physiological process of ageing [4,38,50], the 80% higher odds concerning female sex were unexpected. This was an issue to investigate in more detail, since the prevalence of ESRD is not higher in women compared to men in Austria [3]. A plausible mathematical explanation to this finding could be that sex appears in the numerator of the MDRD equation, which results in lower GFR values for women. In order to untie this finding, we replicated the approach of Fox *et al*. [32], who used the fifth sex-specific percentile of the baseline GFR as the cut-off limit at the follow-up examinations of their study sample to define new-onset kidney disease: the mean baseline GFR at the fifth percentile (i.e. cut-off limit at the follow-up examinations) was 67 ml/min/1.73 m^2 for women and 73 ml/min/1.73 m^2 for men. Consequently, the resulting age-adjusted sex-specific OR (if female) for developing new-onset kidney disease was 0.88 (0.82 to 0.93), which confirms the results of the Framingham study [32]. In fact, little is known concerning the impact of sex on new-onset kidney disease: Domrongkitchaiporn *et al*. [51] did not include the terms age and sex in the statistical analysis because of the presence of both variables in the MDRD formula; Yamagata *et al*. [50] performed a sex-stratified analysis. So far, we suggest that the impact of sex on new-onset kidney disease should be interpreted retentively, especially when different cut-off limits for the classification of CKD were used.

As expected, NKF-CKD stages 1 and 2 (which by definition refers to the existence of initial CKD at baseline), and the more the higher proteinuria, were revealed as the major predictors for progression of CKD [20,21,32,50].

Little is known regarding the effect of physical exercise on risk factors for the development or progression of kidney disease [25,29,30]. It seems plausible that the well-examined beneficial effects of endurance and/or resistance exercise in chronic disease (e.g. reduction of blood pressure, insulin resistance and BMI, improvement of the serum lipid profile) should play their role in chronic kidney disease as well. Indeed, as an entirely novel finding, participants who did not perform sports showed 57% higher odds for developing new-onset kidney disease.

Current-smoking at baseline induced 20% higher odds for the development of new-onset kidney disease compared to non-smoking [32,50]. The mechanisms of smoking-induced renal damage are only partly understood; probably they comprise haemodynamic (e.g. increase in blood pressure and presumably intraglomerular pressure) and chronic effects (e.g. endothelial cell dysfunction) [14].

Remarkably, uric acid at baseline was associated with 69% higher odds (with an increase of 2 mg/dl) to develop new-onset kidney disease. Recent experimental and epidemiological evidence suggests a role of uric acid not only as a marker of reduced kidney function [52] and an independent cardiovascular risk factor [16], but also as a risk factor for the development of renal disease [17–19]. Additionally, independent nephrotoxic effects of elevated uric acid are described, e.g. entry of uric acid into both endothelial

Table 3. Individual predictors of developing chronic kidney disease (defined as a GFR <60 ml/min/1.73 m^2)

Variable	Parameter evaluation	Odds ratio (95% CI)	*P*-value
Age (years)	↑ by 5 years	1.49 (1.45–1.53)	<0.0001
Sex	If female	2.05 (2.04–2.06)	<0.0001
NKF-CKD stages [37]	Stage comparisons versus apparently healthy		
Stage 1		1.89 (1.23–2.93)	0.0041
Stage 2		3.03 (2.41–3.81)	<0.0001
Proteinuria (dipstick)			
+	Both versus	1.70 (1.34–2.11)	<0.0001
≥++	no proteinuria	2.69 (2.33–3.11)	<0.0001
CKD Stages with proteinuria (±)			
Stage 1 (+)	Stage comparisons versus apparently healthy	1.37 (1.09–1.72)	0.0073
Stage 1 (≥++)		2.19 (1.79–2.68)	<0.0001
Stage 2 (+)		2.39 (1.89–3.03)	<0.0001
Stage 2 (≥++)		4.14 (2.27–7.58)	<0.0001
Body mass index (kg/m^2)	↑ by 1 kg/m^2	1.02 (1.01–1.03)	0.0003
25 ≤ BMI (kg/m^2) < 30 BMI (kg/m^2) ≥ 30	Group comparison versus BMI (kg/m^2) <25	1.05 (0.91–1.21)	0.5043
		1.19 (1.02–1.40)	0.0261
Sports	if no	1.31 (1.06–1.62)	0.0117
Smoking			
Current-smoker	Both versus non-smokers	1.25 (1.04–1.49)	0.0152
Ex-smoker		1.07 (0.90–1.29)	0.4371
Total cholesterol (mg/dl)	↑ by 10 mg/dl	1.02 (1.00–1.03)	0.0536
LDL (mg/dl)	↑ by 10 mg/dl	1.03 (1.01–1.04)	0.0171
HDL (mg/dl)	↓ by 10 mg/dl	1.12 (1.08–1.17)	<0.0001
Triglycerides (mg/dl)	↑ by 10 mg/dl	1.03 (0.99–1.01)	0.6709
Uric acid (mg/dl)	↑ by 2 mg/dl	1.51 (1.34–1.69)	<0.0001
Systolic blood pressure (mmHg)	↑ by 10 mmHg	1.07 (1.03–1.11)	0.0006
Diastolic blood pressure (mmHg)	↑ by 10 mmHg	1.05 (1.00–1.08)	0.0481
Fasting serum glucose (mg/dl)	↑ by 10 mg/dl	1.04 (1.00–1.10)	0.0698
Blood pressure groups [35]	Group comparisons versus normotension	1.11 (0.89–1.31)	0.3483
		1.42 (1.01–2.02)	0.0455
Prehypertension		2.26 (1.41–3.62)	0.0007
Hypertension stage 1			
Hypertension stage 2			
Blood glucose groups [36]	Both groups versus glucose <100 mg/dl	1.17 (0.94–1.46)	0.1552
Impaired fasting glucose diabetes mellitus		1.82 (1.15–2.87)	0.0099

All predictors are age adjusted and sex adjusted, except for age, which is sex adjusted, and sex, which is age adjusted. Abbreviations: GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NKF-CKD, National Kidney Foundation—chronic kidney disease.

Table 4. Multivariable predictors of developing chronic kidney disease (defined as a GFR < 60 ml/min/1.73 m^2)

Variable	Parameter evaluation	Odds ratio (95% CI)	*P*-value
Age (years)	↑ by 5 years	1.36 (1.34–1.40)	<0.0001
Sex	If female	1.80 (1.56–2.06)	<0.0001
CKD stages with proteinuria(±)			
Stage 1 (+)	Stage comparisons versus apparently healthy	1.39 (1.10–1.75)	0.0061
Stage 1 (≥++)		2.07 (1.11–3.87)	0.0228
Stage 2 (+)		2.71 (2.10–3.51)	<0.0001
Stage 2 (≥++)		3.80 (2.29–6.31)	<0.0001
Body mass index (kg/m^2)	↑ by 1 kg/m^2	1.04 (1.02–1.06)	0.0002
Current-smoker	If yes	1.20 (1.01–1.43)	0.0377
Sports	If no	1.57 (1.27–1.95)	<0.0001
Uric acid (mg/dl)	↑ by 2 mg/dl	1.69 (1.59–1.80)	<0.0001
HDL (mg/dl)	↓ 10 mg/dl	1.12 (1.07–1.17)	<0.0001
Blood pressure groups [35]	Both groups versus normotension		
Hypertension stage 1		1.35 (1.08–1.67)	0.0064
Hypertension stage 2		2.01 (1.62–2.51)	<0.0001
Diabetes mellitus [36]	versus glucose <100 mg/dl	1.44 (1.07–1.93)	0.0147

Multivariable general estimating equations model performed with respect to statistical significance resulting from the univariable analyses (Table 3). Covariates were retained if Wald tests gave a $P < 0.05$.

and vascular smooth muscle cells, resulting in local inhibition of endothelial nitric oxide levels, stimulation of vascular smooth muscle cell proliferation and stimulation of vasoactive and inflammatory mediators [16,53]. An evaluation of the role of uric acid as a potential risk factor would require a single-factor analysis using a confounder model from an epidemiological point of view. Yet this was not the primary aim of our study.

An increase in BMI of 1 kg/m^2 was associated with 4% higher odds for developing incident kidney disease. This is a really weak effect and probably due to the near normal BMI values of our rather young study population. However, obesity was revealed as a relevant risk factor with hazard ratios of 1.42 (men) and 1.56 (women) within a Japanese cohort [50].

The same applies for HDL-cholesterol, which (in this study cohort) was also in the normal range. A decrease of 10 mg/dl showed 12% higher odds for developing new-onset kidney disease, which we considered as a weak effect. Nevertheless, low HDL-cholesterol [54] was shown as a risk factor for the development of renal dysfunction.

Blood pressure at baseline was in the normal and prehypertensive range in ∼70% of the population (Table 1). Visual data inspection showed a rather nonlinear relationship between blood pressure and the odds for developing new-onset kidney disease with only modest increases over the normal and prehypertensive ranges and strong increases for the hypertensive ranges. Therefore, blood pressure groups were used in the multivariable model instead of linear terms for systolic and diastolic blood pressure. As expected, stage 1 hypertension predicted new-onset kidney disease with 35% higher odds and stage 2 with 101% higher odds [8,32,50].

The same visual data inspection with its consequences applies for fasting serum glucose and the diagnosis of diabetes mellitus. In this study cohort, the number of participants having diabetes mellitus were few (Table 1). Nevertheless, having diabetes mellitus predicted the development of new-onset kidney disease with 44% higher odds with a wide CI. Two large epidemiological studies reported considerably higher odds for developing new-onset kidney disease [32,51], both having a remarkably higher prevalence of diabetics within their study cohorts; in contrast, another large study [50] showed hazard ratios of 0.71 (men) and 0.76 (women) for patients having untreated diabetes mellitus (probably showing hyperfiltration) and hazard ratios of 1.20 (men) and 1.12 (women) for patients having treated long-lasting diabetes, respectively.

Strength of the study: this study has the advantage of a large sample of participants apparently healthy at baseline and the use of an integral multivariable approach concerning established and rather novel cardiovascular risk factors. We examined risk factors altogether that led to new-onset kidney disease, where interventions could be efficacious for delaying the continuous progress of the decline in kidney function. Moreover, early interventions could be important since a majority of adults with moderate kidney disease have coronary heart disease or risk equivalents [55].

Limitations of the study: this study may have been subject to a survival bias because participants had to attend follow-up examinations and 534 participants dropped out. Though unlikely (they showed very similar baseline data compared to the study cohort), it is possible that those individuals may have developed more severe risk factors after the baseline examination and could have had rapid disease progression in the interim. This is certainly a limitation and may have led to underestimation of some findings. It is noteworthy that this study population was predominantly middle-aged compared to the general age distribution in Vienna [41]. For that reason, the multivariable analysis was performed for volunteers aged ≤65 years, too. The resulting ORs were very similar to the results from the total cohort. Moreover, using the surrogate parameter the estimated GFR calculated by the MDRD formula to represent the severity of kidney disease is not a gold standard method, but it must be considered the method of choice within large epidemiologic studies, because of its simplicity and low cost. Correction of routine measured creatinine to 'MDRD-creatinine' is mandatory [42] and was performed by the correction formula of Hallan *et al*. [43], who used exactly the same creatinine assay methodology as we did.

In conclusion, cardiovascular risk factors as well as NKF-CKD stages 1 and 2 and proteinuria, the more the higher, predicted the development of new-onset kidney disease. A rather novel finding was the role of uric acid as a predictor in this context; implementation of a confounder model could possibly confirm its role as a risk factor. An entirely novel finding was that performing no sports was revealed as an important predictor of new-onset kidney disease.

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