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Prevalence of renal impairment and its association with cardiovascular risk factors in a general population: results of the Swiss SAPALDIA study

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Abstract

Background. Impaired renal function is evolving as an independent marker of the risk of cardiovascular morbidity and mortality. Little is known about the prevalence of impaired renal function and its relationship to cardiovascular risk factors in the Swiss general population.

Methods. SAPALDIA comprises a random sample of the Swiss population established in 1991, originally to investigate the health effects of long-term exposure to air pollution. Participants were reassessed in 2002/3 and blood measurements were obtained ($n = 6317$). Renal function was estimated using the Cockcroft–Gault equation and the modified MDRD (four-component) equation incorporating age, race, gender and serum creatinine level.

Results. The estimated prevalence of impaired renal function [estimated glomerular filtration rate <60 ml/min/1.73 m^2] differed substantially between men and women, particularly at higher ages, and amounted to 13% [95% confidence interval (CI) 10–16%] and 36% (95% CI 32–40%) in men and women, respectively, of 65 years or older. Smoking, obesity, blood lipid levels, high systolic blood pressure and hyperuricaemia were all more common in men when compared with women. These cardiovascular risk factors were also associated independently with creatinine in both women and men. Women were less likely to receive cardiovascular drugs, in particular angiotensin-converting enzyme inhibitors and β-blockers, when compared with men of the same age.

Conclusion. Moderate renal impairment seems to be prevalent in the general population, with an apparent excess in females which is not explained by conventional cardiovascular risk factors. The unexpected finding questions the validity of the prediction equations, in particular in females.

Keywords: cardiovascular risk; cross-sectional survey; diabetes; general population; prevalence; renal impairment

Introduction

Impaired renal function is evolving as a predictor of cardiovascular morbidity and mortality, independently of other traditional risk factors, such as hypertension, hypercholesterolaemia, overweight, smoking and diabetes [1,2], which are frequently found in patients with renal disease [1]. Hence, in terms of planning and targeting preventive measures for cardiovascular disease in the general population, it is important to estimate which proportion of the population of a country is affected by moderate to severe renal impairment.

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The best known large-scale population-based epidemiological assessments that have systematically tried to estimate the prevalence of cardiovascular risk factors and impaired renal function are PREVEND in The Netherlands [3] and NHANES III [Third National Health and Nutrition Examination Survey (1988–1994)] in the USA [4]. However, in most European populations, the prevalence of moderate to severe renal impairment is unknown.

The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) enrolled a random population sample at the baseline assessment in 1991 and measured a range of cardiovascular blood markers at the first follow-up assessment of the cohort in 2002. We therefore had the opportunity to obtain a crude estimate of the prevalence of moderate to severe renal impairment. Further, we investigated the association between renal impairment and cardiovascular risk factors in the Swiss population. However, in this cross-sectional assessment, we are unable to hypothesize on the direction of the effect between cardiovascular risk factors and serum creatinine measurements.

Subjects and methods

SAPALDIA 2

The SAPALDIA was originally designed to investigate the effects of air pollutants on respiratory health (including lung function, development of symptoms and disease) in a random sample of the adult population of Switzerland [5,6]. The original study consisted of 9651 adults as described elsewhere [5]. The extensive health examinations included a detailed assessment of personal risk factors of respiratory health over the course of 1 year (1991). Of the surviving 9368 participants, 93% ($n = 8715$) could be traced between 2001 and 2003, and were re-contacted for SAPALDIA 2 [6]. Both surveys were an extensive version of the European respiratory health survey [7] and comprised interviews and examinations by trained fieldworkers. In the second survey, there was additionally a collection of blood specimens and blood pressure measurements [6].

Ethical approval for SAPALDIA 2 was given by the central ethics committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the eight examination areas. The consent information provided to participants described the health examination, the blood measurements and information on data protection. Subjects could either give global consent (for all health examinations) or agree to each investigation separately.

The detailed assessment of the representativeness of this cross-sectional assessment of the original cohort can be found in Ackermann-Liebrich *et al.* [6]. Briefly, subjects who agreed to have their blood analysed were similar to those who did not participate in the follow-up study except that a considerable proportion of smokers (28%) had quit smoking. However, the overall distributions of age, sex and body mass index (BMI) were still comparable with those of the general Swiss population, including weight gain over 10 years.

Interviews, blood pressure measurements and serum creatinine measurements

The interview included various questions including smoking habits, presence of diabetes and physical activity. Details of present and past medication use were obtained for all participants and were verified by checking the actual prescription drug packets.

Systolic and diastolic blood pressures were measured after the participant had sat quietly for at least 10 min. Pressures were measured twice with an interval of at least 3 min using an automatic OMRON 705 CP (Tokyo, Japan). The results reported here derive from the average of both measurements. Weight and height were measured in a standardized fashion. Blood samples were taken from all 6327 subjects who had consented to the general blood marker analyses. Blood samples were processed and stored in a standardized fashion according to the SAPALDIA protocol [6]. All laboratory measurements were carried out in the laboratory of the University Hospital Zurich on batches of on average 100 samples. Serum creatinine was measured using the Jaffé reaction (Roche) and calibrated to the Roche enzymatic gold standard reference. This calibration will yield slightly lower serum creatinine measurements than the Cleveland Clinic Jaffé reaction [8].

Estimation of renal function and markers of the metabolic syndrome complex

All the following analyses were restricted to the sample with available serum creatinine measurements ($n = 6317$). Renal function was estimated using the modified MDRD (four-component) equation incorporating age, sex, serum creatinine level and an adjustment for African descent. The formula reads:

$$\begin{aligned}&\text{eGFR (MDRD)}\\&\quad = 186 \times [(\text{serum creatinine in mg/dl})^{(-1.154)}]\\&\qquad \times [\text{age}^{(-0.203)}]\end{aligned}$$

multiplied by a correction factor of 0.742 if the participant was female [9,10]. This was a Caucasian population. Because of the enzymatic calibration method of measuring serum creatinine, the estimated glomerular filtration rate (eGFR) using the MDRD equation is ~5% higher than it should be based on the MDRD study [8]. Hence, we might slightly overestimate renal function throughout our study.

An alternative estimator of renal function was the Cockcroft–Gault equation, calculated as:

$$\begin{aligned}&\text{eGFR (Cockcroft} - \text{Gault)}\\&\quad = [140 - \text{age (years)}] \times \text{weight (kg)}\\&\qquad \times 1.23/\text{serum creatinine (}\mu\text{mol/l)}\end{aligned}$$

multiplied by a correction factor of 0.85 if the participant was female [11,12]. A correction for body surface area (BSA) was carried out by correcting the eGFR (Cockcroft–Gault) according to Du Bois [13] where $\text{BSA} = \text{weight (kg)}^{0.425} \times \text{height (m)}^{0.725} \times 0.202$.

These measures of eGFR were categorized according to NKF KDOQI into below and above stage 3 renal disease ($<60\,\text{ml/min/1.73}\,\text{m}^2$) [12].

A third, very crude estimator of renal function was 100/[serum creatinine (mg/dl)] [12]. Of note is that both equations

above contain an inverse of serum creatinine, so that this estimator is approximately proportional to both MDRD and Cockcroft–Gault eGFRs.

Variables belonging to the metabolic syndrome complex [triglycerides and high-density lipoprotein (HDL) cholesterol] were categorized according to ATP III guidelines, where applicable [14]. Since blood glucose and blood lipids were not always measured after 12 h fasting, we decided not to apply the ATP III categorization to blood glucose and low-density lipoprotein (LDL) cholesterol. A haemoglobin A1c measurement was obtained only in participants with blood glucose values >6.1 mmol/l. Age groups were categorized for tabulation into those <55, 55–65 and >65 years of age. Medication history was coded in a standardized fashion according to ATC codes [15]. In particular, we used the ATC definition for cardiovascular drugs (antihypertensive medication as well as lipid-lowering therapy) and its categorization for diuretics and angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs). Medication history of drugs was used as an indirect marker of preceding or underlying medical, in particular cardiovascular, problems.

Statistical analysis

We performed simple tabulations of proportions according to gender and age. For initial baseline analyses, Kruskal–Wallis tests and F tests as well as χ^2 tests or Fisher's exact tests were carried out to determine the significance, when necessary.

In models using eGFR based on Cockcroft–Gault and MDRD equations, associations between age, sex and eGFR will exist by default, which in the presence of random error might distort the findings [16]. Therefore, we ran two different linear regression models with two different outcomes. The first used eGFR was based on the MDRD equation and it was therefore easier to interpret the outcome variable. The second used the estimator based on the inverse of serum creatinine as a conceptual crude measurement of renal function. In contrast to the raw serum creatinine measurements, both the inverse of serum creatinine and the MDRD eGFR were approximately normally distributed.

Age at the time of the blood collection, BMI, C-reactive protein (CRP) and blood pressure measurements were entered as continuous variables, centred on norm values (i.e. CRP = 0, systolic blood pressure 125 mmHg, diastolic blood pressure 80 mmHg) or their mean (i.e. age). Cholesterol, HDL and triglyceride measurements were centred on their mean. LDL was omitted because it had been derived from the latter measurements by calculation. The number of ever prescribed drugs was entered as a score variable, and physical activity as a categorical variable. The medication categories cardiovascular drugs, ACE inhibitors/ARBs and diuretics were each coded as binary variables. Smoking habits in 2001/2 at the time of blood measurements were categorized as current, past and non-smokers. The variable diabetes was binary, containing information on self-reported presence of the disease. Because of several non-linear associations, polynomial regression analysis was used to find the best order of transformation of exposure variables. In the case of BMI and age, this was a quadratic association.

We used the transformed exposure variables and additionally entered variables in a stepwise fashion into our linear regression model while examining the confounding effects between different variables during the model building process. A final model tested specifically for interactions between predicting variables and gender as well as diabetes using Wald tests. The gender-specific interactions were significant for both MDRD-based models as well as the inverse of serum creatinine (for both outcomes: $P < 0.001$ in the overall test of all interaction terms). The interaction terms with diabetes were not significant either for the MDRD or for the inverse of serum creatinine (overall Wald tests for interaction: $P = 0.102$ and $P = 0.101$, respectively). Variables, unless they were *a priori* confounders such as diabetes or age, were omitted from the final model if they did not reach statistical significance ($P = 0.05$) in at least one gender group. For easier interpretability, results are reported using the categorical associations for age and BMI using the gender-specific models. Investigation of outliers revealed those individuals with high CRP and urate; however, these had no influence on the size or direction of the final results. Analyses were carried out with Stata version 8 [17].

Results

The characteristics of participants by gender and age are displayed in Table 1. On average and compared with women, men had higher systolic and diastolic blood pressures, triglycerides, glucose, urate and serum creatinine as well as lower levels of HDL cholesterol. BMIs and total cholesterol levels were higher for men than for women, except in the age group above 65 years, with women having a tendency to obesity. Interestingly, CRP levels were higher in women compared with men. When stratified according to ATC III recommendations for the prevention of cardiovascular disease, men presented more frequently than women with hypertriglyceridaemia, low HDL cholesterol, smoking and diabetes mellitus. Comparison of physical activity patterns between the sexes revealed more physical activity leading to sweating in men compared with women across all ages. Women were more likely to have taken at least one medication at ages above 55 years. However, the main bulk of the ever prescribed medication were cardiovascular drugs, particularly in men, increasing across age groups. ACE inhibitors and ARBs, as well as β-blockers, were prescribed more often to men than to women. In summary, the cardiovascular profile was more favourable for women than for men, except for the presence of higher CRP levels and a higher prevalence of obesity in the older age groups.

Mean creatinine was higher for men than for women and increased slightly with age (Table 1, Figure 1). Nevertheless, in all age strata, the median eGFR was lower in women than in men, especially in the older age groups. Both Figures 1B and 2A show that the major bulk of the distributions of eGFR <60 ml/min/1.73 m^2 within each age and sex category lie between 30 and 60 ml/min/1.73 m^2, with the boxes and capped lines not extending below the 30 ml/min/1.73 m^2 line and the proportion of individuals with an eGFR <45 ml/min/1.73 m^2 being much smaller. This is especially the case for women, whereas severe outliers occurred more often for men.

Table 1. Characteristics of participants by gender and age group

Characteristics (unit)	Men								Women								*P*-value for men *vs* women by age
	Total ($n=3100$)		<55 years ($n=1751$)		55–65 years ($n=901$)		>65 years ($n=448$)		Total ($n=3217$)		<55 years ($n=1813$)		55–65 years ($n=877$)		>65 years ($n=527$)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	51.8	11.4	43.3	7.4	59.7	2.8	68.6	2.2	52.5	11.4	44.1	7.2	59.8	2.9	68.8	2.2	0.0629
SBP (mmHg)	132.3	17.8	127.7	14.8	136.4	18.7	141.3	20.5	120.8	19.1	114.0	15.8	126.4	18.0	135.9	20.0	<0.001
DBP (mmHg)	82.5	10.7	81.2	10.3	84.5	10.8	83.3	11.2	76.8	10.4	74.7	10.1	79.4h	10.2	80.4	10.2	<0.001
Weight (kg)	81.8	12.6	81.4	12.9	82.7	12.1	81.9	12.9	66.8	12.9	65.6	13.0	68.1	13.0	69.4	13.2	0.001
BMI (kg/m^2)	26.6	3.8	26.0	3.8	27.3	3.6	27.6	3.7	25.2	4.8	24.3	4.7	26.0	4.7	27.1	4.9	<0.001
Total cholesterol (mmol/l)	6	1.1	6.0	1.1	6.1	1.1	6.0	1.1	6	1.1	5.8	1.1	6.4	1.1	6.5	1.1	<0.001
HDL-cholesterol (mmol/l)	1.3	0.4	1.3	0.4	1.3	0.4	1.3	0.3	1.7	0.4	1.7	0.4	1.7	0.5	1.6	(0.5)	0.027
Triglycerides (mmol/l)*	1.8	1.2–2.7	1.6	1.1–2.5	1.9	1.3–2.9	1.9	1.4–2.8	1.3	0.9–1.9	1.1	0.8–1.6	1.5	1.1–2.2	1.7	1.2–2.4	<0.001
BG (mmol/l)	5.8	1.8	5.5	1.2	6.1	2.5	6.1	1.8	5.4	1.2	5.2	1.1	5.6	1.2	5.8	1.5	<0.001
Creatinine (μmol/l)*	94	87–101	93	87–100	94	87–103	96	88–104	81	75–87	80	74–86	81	76–88	83	76–90	<0.001
eGFR ($ml/min/1.73\,m^2$)	78.9	11.5	82.4	10.4	75.6	10.8	72.3	12.2	69.3	10.4	72.6	9.9	66.2	8.8	63.0	9.9	<0.001
Urate (mmol/l)	363	8.9	355.9	75.8	370.1	81.2	376.0	83.1	269.7	68.3	251.8	58.7	282.9	67.4	309.5	77.9	<0.001
hsCRP (mg/l)*	1	(0.5–2.1)	0.8	0.4–1.7	1.2	0.6–2.4	1.4	0.7–3.1	1.1	0.5–2.6	0.8	0.4–2.0	1.4	0.7–3.0	1.8	0.9–3.9	<0.001
Median no. of medications used (IQR)*	0	0–1	0	0–0	0	0–2	1	0–3	0	0–2	0	0–1	1	0–3	1	0–3	<0.001
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Obese[a]	501	16.2	217	12.4	183	20.3	101	22.6	490	15.3	189	10.4	169	19.4	132	25.2	0.1538
Low HDL cholesterol[b]	543	17.5	302	17.3	170	18.9	71	15.9	625	19.4	310	17.1	193	22.0	122	23.2	0.03
Hypertriglyceridaemia[c]	1636	52.8	850	48.5	523	58.1	263	58.7	1044	32.5	419	23.1	367	41.9	258	49.0	<0.001
High blood pressure[d]	1482	49.2	686	40.2	524	59.8	272	63.1	906	29.3	302	17.2	335	39.6	269	54.2	<0.001
Active smokers[e]	841	27.2	529	30.9	227	25.2	85	19.0	722	22.5	497	27.5	174	19.9	51	9.7	<0.001
Diabetes	144	4.7	28	1.6	75	8.3	41	9.2	72	2.2	14	0.8	26	3.0	32	6.1	<0.001
HbA1c >6.5%	146	4.7	32	1.8	71	7.9	43	9.6	75	2.3	19	1.1	18	2.1	38	7.2	0.007
Physical activity leading to sweating[f]																	<0.001
Never	731	23.9	324	18.8	253	28.3	154	34.8	1080	34.1	501	28.1	330	38.3	249	47.8	
Once per week	1159	37.9	672	39.0	337	37.7	150	33.9	1129	35.7	690	38.7	282	32.7	157	30.1	
Several times per week	1170	38.2	727	42.2	305	34.1	138	31.2	955	30.2	590	33.1	250	29.0	115	22.1	
At least one medication ever taken	1323	42.7	487	27.8	516	57.3	320	71.4	1736	54.0	721	39.8	594	67.7	421	79.9	<0.001
% cardiovascular medications[g]	737	55.7	177	36.3	335	64.9	225	70.3	649	37.4	159	22.1	242	40.7	248	58.9	<0.001
% ACE inhibitors/ARBs[g]	314	23.7	65	13.4	147	28.5	102	31.9	253	14.6	50	6.9	81	13.6	122	29.0	<0.001
% β-Blockers[g]	297	22.5	65	13.4	144	27.9	88	27.5	249	14.3	47	6.5	101	17.0	101	24.0	<0.001
% Diuretics[g]	67	5.1	9	1.9	29	5.6	29	9.1	100	5.8	18	2.5	32	5.4	50	11.9	0.303

*Median and interquartile range are given instead of mean (SD); comparisons were carried out using the Kruskal–Wallis test.
SBP, systolic blood pressure; DBP, diastolic blood pressure (212 blood pressure measurements missing); BMI, body mass index (20 missing); BG, blood glucose; HbA1c, haemoglobin A1c (measured on 1230 subjects with an elevated blood glucose); eGFR, estimated glomerular filtration rate (measured by the MDRD equation; hsCRP, high sensitive C-reactive protein; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
[a]BMI $>30\,kg/m^2$.
[b]HDL <1.0 mmo/l in men and <1.3 mmol/l in women.
[c]Triglycerides ≥1.7 mmol/l.
[d]Blood pressure ≥135/85.
[e]Nine values missing.
[f]Ninety-three values missing.
[g]Percentage of medication categories calculated for those who ever took at least one medication.

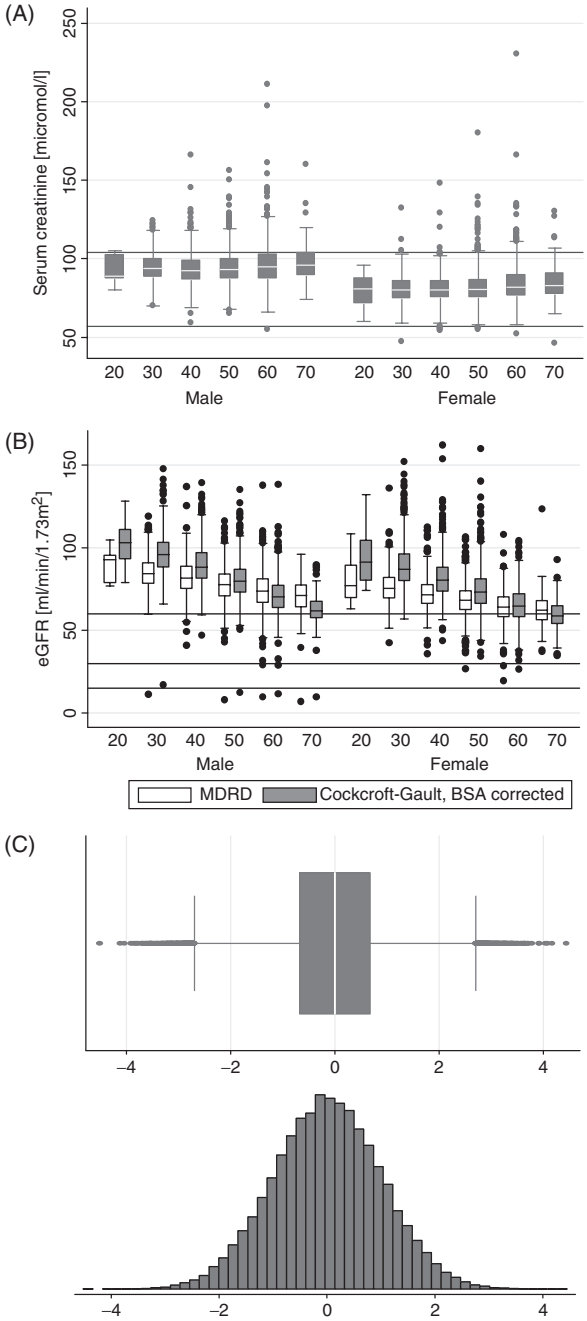

Fig. 1. (**A**) Box-plot of creatinine (*y*-axis) stratified by gender and age groups (in years) (*x*-axis). The four male dialysis patients with values of creatinine >400 µmol/l are omitted in order to display the rest of the distribution on a larger scale. Horizontal lines indicate abnormally low or high creatinine values (57 and 104 µmol/l). Age category 20 denotes individuals from 20 up to 29 years, age category 30 those aged 30–39, etc., up to age category 70 which encompasses those aged 70 and above. (**B**) Box-plot of MDRD and Cockcroft–Gault eGFR (*y*-axis) stratified by gender and age groups (in years) (*x*-axis). Horizontal lines indicate NKF KDOQI categories of <60 ml/min/1.73 m^2 (stage 3, moderately impaired GFR), <30 ml/min/1.73 m^2 (stage 4, severe impairment) and <15 ml/min/1.73 m^2 (stage 5, kidney failure). (**C**) Conceptual display of a histogram and a corresponding box-plot to facilitate interpretation of (A) and (B). Boxes represent 25–75 percentiles of the distribution, with medians denoted by the middle lines within the boxes. Upper and lower adjacent values (2.5–97.5 percentiles) are indicated with capped lines; outside values are denoted by circles or squares.

Overall, women were found to present more frequently than men with stage 3 renal impairment according to NKF KDOQI, i.e. with an eGFR of <60 ml/min/1.73 m^2 (see Figure 2). This was observed independently of whether the MDRD or the Cockcroft–Gault formula was used (Figures 1 and 2). Using the MDRD equation, we estimated the following prevalences for men and women, respectively: at ages below 55 years, 1.1% [95% confidence interval (CI) 0.6–1.6%] and 7.9% (95% CI 6.7–9.2%); at ages between 55 and 65 years, 7.1% (95% CI: 5.4–8.8%) and 23.5% (95% CI 20.7–26.3%); and at ages above 65 years, 12.9% (95% CI 9.8–16.1%) and 35.9% (95% CI 31.8–40.0%).

In Figure 2, we see that the black columns for the Cockcroft–Gault are higher than the white columns for the MDRD-estimated proportions; fewer individuals presented with impaired renal function if estimated by MDRD as compared with Cockcroft–Gault. It follows that distributions of prediction from the two formulae only partially overlapped. In Figure 2B, the light grey columns show the proportions of patients categorized as <60 ml/min/1.73 m^2 by either of the equations, while the dark grey columns show the proportions of those <60 ml/min/1.73 m^2 according to both equations at the same time. The four patients who were dialysis dependent were appropriately categorized by all prediction formulae correctly into the low eGFR category.

However, according to Figure 2B, divergences between women and men in terms of their prevalence of eGFR <60 ml/min/1.73 m^2 in age groups above 40 years is not explained by discrepancies between MDRD and Cockcroft–Gault equations. We still observe a 2- to 4-fold increase of estimated moderately impaired renal function in women as compared with men.

In a next step, relationships between cardiovascular risk factors and creatinine measurements were investigated. The results of the fitted associations are given in Tables 2 and 3. We used both MDRD and the inverse of creatinine estimator as a conceptual crude measurement of renal function (for details, see Subjects and methods). Because for both outcomes overall interactions between predictors and gender were found, we present the absolute effects of predictors separately using gender-specific models. Because diabetic patients have a substantially different cardiovascular risk profile, diabetes was included as a predictor, without however reaching statistical significance in any of the models. Physical activity was retained in the model, possibly because of its association with muscle mass which is only inappropriately captured by BMI. Older individuals had lower eGFR and inverse serum creatinine values corresponding to more impaired renal function. The effect of age group on inverse serum creatinine was flatter than for the MDRD-based regressions because the inverse of serum creatinine incorporates the effect of age both on muscle and on kidney function and creatinine handling. For men, there was a U-shaped relationship between eGFR and BMI, while for women there was a more J-shaped association. There was a positive significant association

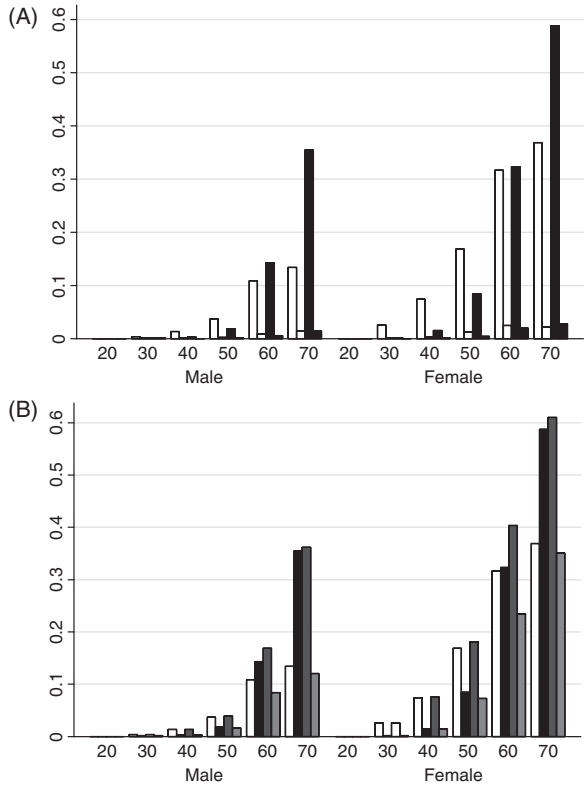

Fig. 2. (A) Prevalence (*y*-axis) of eGFR <60 ml/min/1.73 m^2 and <45 ml/min/1.73 m^2, stratified by gender and age groups (in years) (*x*-axis). Tall white boxes represent the proportion who were estimated to be <60 ml/min/1.73 m^2, and the shorter boxes those <45 ml/min/1.73 m^2 according to MDRD; tall black boxes show those proportions <60 ml/min/1.73 m^2 according to the body surface-adjusted Cockcroft–Gault equation, and the shorter ones those <45 ml/min/1.73 m^2. Age category 20 denotes individuals from 20 up to 29 years, age category 30 those aged 30–39, etc., up to age category 70 which encompasses those aged 70 and above. **(B)** Comparison of formulae estimating the prevalence (*y*-axis) of eGFR <60 ml/min/1.73 m^2, stratified by gender and age groups (in years) (*x*-axis). White boxes represent proportions according to MDRD, black boxes those according to the body surface-adjusted Cockcroft–Gault equation (equivalent to the tall boxes in A). Light grey boxes display the proportions within each age/gender stratum who, according to at least one of the formulae, would be have moderate renal impairment, dark grey boxes those who would be <60 ml/min/1.73 m^2 according to both equations at the same time.

with current smoking, a negative relationship with serum lipid markers, as well as a negative relationship with serum urate levels. Serum urate levels, diuretic medication and the number of substances taken were confounding each other—the most parsimonious model was the one with serum urate and number of substances ever taken.

A subgroup analysis in those individuals who took at least one medication was conducted to evaluate the effect of the medication subgroup. In men, none of the subgroups had a significant impact on renal impairment above the information carried in the sum total of medications ever taken. In women, there was some confounding between cardiovascular medication and sum total of medications taken on inverse creatinine, with a borderline effect for ACE inhibitors ($P = 0.062$), and a significant effect for diuretics in the MDRD model ($P = 0.012$). However, in the full sample, there was overall only borderline evidence for a differential relationship between the sexes by type of medication if adjusted for serum urate (inverse creatinine, *P*-values for interaction >0.1; MDRD, *P*-value for interaction = 0.082 for diuretics; other *P*-values for interaction >0.1; results not shown).

It is of note that the HDL level did not reach statistical significance in either sex and therefore was excluded from the model. Isolated systolic blood pressure increases were significantly associated with eGFR measures. Diastolic blood pressure did not reach the level of statistical significance and was omitted from the model. The relationship between CRP and renal function differed by sex (*P*-value for interaction = 0.001), with women having a positive association, and men a negative association. The associations remained of similar size and significance when outliers, such as high CRP levels, were excluded from the model.

Discussion

This is to our knowledge the first population-based cross-sectional assessment of the prevalence of renal impairment and cardiovascular risk factors in Switzerland. In general, the cardiovascular risk profile seemed more favourable for women than for men. However, in the Swiss population, moderate to severe renal impairment, as defined by NKF KDOQI, seemed to be more common in women, particularly in the older age groups.

NKF KDOQI guidelines recommend the use of serum creatinine-based predictions of eGFR, preferably MDRD and Cockcroft–Gault equations, to target specifically patients with renal impairment with an eGFR <60 ml/min/1.73 m^2 for further cardiovascular assessment [12], and NHANES III has used MDRD for estimation of the prevalence of renal impairment in the general population [4]. Because of the enzymatic calibration of the serum creatinine assays, we might have overestimated the eGFR by ~5% using the MDRD equation [8]. Because this is an assessment of the general population, the measurement error introduced by non-creatinine chromogen substances can be believed to be fairly low and to not bias our results. This study was limited in not having urinary measurements, and the presence of proteinuria could have been an important indicator for the effective presence of an active kidney disease. However, according to the KDOQI guidelines, the availability of additional spot urine measurements to quantify proteinuria/microalbuminuria is particularly important when classifying subjects in stages 1 and 2 as having chronic kidney disease [12]. This study focused on more severe impairment.

The prevalence of moderate to severe renal disease might be estimated from creatinine measurements by general practitioners' or hospital laboratories.

Table 2. Final model for the relationship between MDRD and cardiovascular markers in men and women

	Unit	Men			Women		
		Estimate	95% CI	*P*-value	Estimate	95% CI	*P*-value
Baseline*	ml/min/1.73 m^2	85.64	83.97 to 87.31	<0.001	71.19	69.60 to 72.78	<0.001
Effect of age*	40–49 years	−2.59	−3.72 to −1.45	<0.001	−3.69	−4.71 to −2.68	<0.001
	50–59 years	−6.27	−7.40 to −5.14	<0.001	−6.47	−7.53 to −5.41	<0.001
	60–69 years	−9.17	−10.42 to −7.92	<0.001	−9.57	−10.77 to −8.36	<0.001
	≥70 years	−12.79	−14.82 to −10.77	<0.001	−10.67	−12.42 to −8.91	<0.001
BMI	<20 kg/m^2	1.06	−1.71 to 3.83	0.452	−0.36	−1.46 to 0.75	0.526
	25–29.9 kg/m^2	−0.62	−1.48 to 0.23	0.155	0.23	−0.57 to 1.02	0.575
	30–34.9 kg/m^2	0.77	−0.51 to 2.05	0.24	2.19	1.03 to 3.35	<0.001
	≥35 kg/m^2	3.26	0.96 to 5.56	0.005	3.59	1.77 to 5.42	<0.001
Smoking	Former	1.23	0.34 to 2.12	0.007	0.23	−0.54 to 1.01	0.554
	Current	3.57	2.65 to 4.50	<0.001	1.91	1.10 to 2.73	<0.001
Presence of diabetes	*vs* absent	1.07	−0.79 to 2.92	0.261	0.48	−1.74 to 2.71	0.67
CRP	1 mg/l increase	−0.06	−0.14 to 0.02	0.162	0.21	0.12 to 0.30	<0.001
Triglycerides	1 mmol/l increase	−0.56	−0.83 to −0.28	<0.001	−0.02	−0.41 to 0.36	0.911
Cholesterol	1 mmol/l increase	−0.63	−0.98 to −0.27	0.001	−0.71	−1.02 to −0.39	<0.001
Blood pressure	Systolic 10 mmHg increase	0.05	−0.18 to 0.28	0.655	0.23	0.04 to 0.43	0.02
Urate levels	1 mmol/l increase	−0.03	−0.04 to −0.03	<0.001	−0.05	−0.05 to −0.04	<0.001
Medication	per substance increase	−0.42	−0.67 to −0.18	0.001	−0.27	−0.45 to −0.08	0.006
Physical activity leading to sweating	Once/week *vs* never	−1.18	−2.19 to −0.17	0.022	−0.77	−1.57 to 0.03	0.06
	Several times/week *vs* never	−1.43	−2.47 to −0.39	0.007	−0.74	−1.60 to 0.12	0.092

A baseline individual for both men and women is a person with BMI between 20 and 24.9 kg/m^2, an age of 30–39 years, mean cholesterol, HDL and triglyceride levels, CRP of zero, non-smoking and non-diabetic and with a blood pressure of 125/80 mmHg, and a urate <350 μmol/l.
*Adjusted for all other variables displayed and area of residence.

Table 3. Final model for the relationship between inverse creatinine and cardiovascular markers in men and women

	Unit	Men			Women		
		Estimate	95% CI	*P*-value	Estimate	95% CI	*P*-value
Baseline*	100/creatinine (dl/mg)	95.12	93.37 to 96.87	<0.001	104.89	102.72 to 107.07	<0.001
Effect of age*	40–49 years	1.78	0.59 to 2.98	0.003	0.24	−1.15 to 1.63	0.735
	50–59 years	1.31	0.13 to 2.50	0.029	0.13	−1.32 to 1.58	0.861
	60–69 years	0.69	−0.62 to 2.01	0.302	−1.26	−2.91 to 0.38	0.132
	≥70 years	−1.69	−3.82 to 0.43	0.118	−1.24	−3.64 to 1.16	0.311
BMI	<20 kg/m^2	1.09	−1.81 to 3.99	0.46	−0.36	−1.87 to 1.15	0.64
	25–29.9 kg/m^2	−0.55	−1.44 to 0.35	0.233	0.31	−0.78 to 1.39	0.58
	30–34.9 kg/m^2	0.93	−0.42 to 2.27	0.178	3.00	1.41 to 4.58	<0.001
	≥35 kg/m^2	3.62	1.22 to 6.03	0.003	4.78	2.28 to 7.27	<0.001
Smoking	Former	1.43	0.50 to 2.37	0.003	0.37	−0.70 to 1.43	0.5
	Current	3.75	2.78 to 4.73	<0.001	2.62	1.51 to 3.73	<0.001
Presence of diabetes	*vs* absent	1.18	−0.77 to 3.13	0.235	0.82	−2.23 to 3.86	0.6
CRP	1 mg/l increase	−0.07	−0.15 to 0.02	0.119	0.28	0.16 to 0.40	<0.001
Triglycerides	1 mmol/l increase	−0.60	−0.89 to −0.31	<0.001	−0.09	−0.62 to 0.44	0.747
Cholesterol	1 mmol/l increase	−0.60	−0.98 to −0.23	0.001	−0.88	−1.31 to −0.45	<0.001
Blood pressure	Systolic 10 mmHg increase	0.08	−0.16 to 0.32	0.517	0.41	0.14 to 0.68	0.003
Urate levels	1 mmol/l increase	−0.03	−0.04 to −0.03	<0.001	−0.07	−0.07 to −0.06	<0.001
Medication	Per substance increase	−0.43	−0.69 to −0.17	0.001	−0.34	−0.59 to −0.08	0.011
Physical activity leading to sweating	Once/week *vs* never	−1.14	−2.20 to −0.08	0.035	−1.15	−2.24 to −0.05	0.041
	Several times/week *vs* never	−1.53	−2.62 to −0.44	0.006	−1.10	−2.28 to 0.08	0.067

A baseline individual for both men and women is a person with BMI between 20 and 24.9 kg/m^2, an age of 30–39 years, mean cholesterol, HDL and triglyceride levels, CRP of zero, non-smoking and non-diabetic and with a blood pressure of 125/80 mmHg, and a urate <350 μmol/l.
*Adjusted for all other variables displayed and area of residence.

Apart from the problem of standardization of serum creatinine measurements across different laboratories, such data only include patients who need a general practitioner or need to attend hospital, and therefore may represent a subgroup with a greater risk for renal disease than the general population and overestimate the prevalence of renal disease. Our study is examining a healthy general population. However, we cannot rule out that some of those who did not agree to assessment ($n = 2388$, 27.4%) were systematically more ill than those who did agree to the blood measurements. There was a slightly greater proportion of women and ex-smokers in our sample, which highlights a possible participation bias. Furthermore, the blood measurements were obtained 10 years after the original recruitment of participants into the study, with 283 having died.

Despite these shortcomings of our data, there are several reasons to take our findings seriously. First of all, the use of sex- and age-stratified prevalence estimates takes age and sex imbalances into account.

Secondly, the prevalence obtained for smoking, obesity and indicators of the metabolic syndrome associated with cardiovascular disease was in accordance with other surveys of cardiovascular risk factors in the general population across Europe and as observed in PREVEND [3,4,18–20]. The associations between cardiovascular risk factors and serum creatinine were in line with PREVEND, with smoking and high systolic blood pressure being more strongly related to microalbuminuria in the general population whereas their effect went in both directions for eGFR [3]. This would fit our findings of an increase in eGFR possibly related to hyperfiltration due to smoking and high systolic blood pressure [21]. Elevated CRP levels are known to be associated both with hyperfiltration and with diminished filtration depending on BMI. CRP also seems to modify the relationship between microalbuminuria and hypertension [22]. We are unable to investigate this further.

Lastly, the prevalence of renal impairment in men was similar to that observed in NHANES III and PREVEND [3,4,22]. However, we observed an exceptionally high prevalence for moderate to severe renal impairment estimates in women.

A survivor bias in favour of women is unlikely to explain the large differences between sexes, particularly for age groups 50–69, because over a period of 11 years only 283 had died. Even if these included all males with renal impairment, these are not sufficient to fill the gap in observed prevalence of renal impairment between men and women.

It is very unlikely that the calibration explains the major sex differences found in this study, because all batches were analysed together. Several patients, and particularly older female patients, could just have had some functional reversible kidney impairment due, for example, to diuretic intake, a voluntary fluid restriction before the examination or a regular intake of analgesics. In both women and men, creatinine was associated with medication history, being an indirect marker of co-morbidities, as described previously [3]. Men had more cardiovascular drug prescriptions, including β-blockers and ACE inhibitors/ARBs. This is in line with the higher prevalence of hypertension and other risk factors in men compared with women. We found that medication had a larger absolute effect on eGFR in men than in women, while for serum urate the effects were comparable. Hence, it is unlikely that functional reversible renal impairment explains the differences in prevalence of renal impairment.

It remains a possibility that the correction factors for female sex in both MDRD and Cockcroft–Gault formulae are incorrect. This might explain to some extent the substantial differences in estimated renal function between women and men. The Cockcroft–Gault equation was developed to estimate creatinine clearance in young healthy men and is known to overestimate GFRs when renal function is severely impaired [11]. On the other hand, MDRD is inaccurate in healthy slim young individuals. However, the performance of MDRD increases if GFR is <60 ml/min/1.73 m^2 and at older ages [4,9,10,23,24], and recent European validation studies support some but not such large errors in correction factors between men and women [16,23]. The slightly different relationships of cardiovascular risk factors with both inverse creatinine and eGFR could indicate that post-menopausal women might even have a different pattern of declining renal function with age than captured by those formulae.

Many recent estimates obtained by epidemiological assessments of the cardiovascular risk associated with renal function rely on estimations based on MDRD or Cockcroft–Gault [1]. Therefore, even if these formulae are not a reflection of the eGFR itself, these are still transformations of serum creatinine that—even for eGFRs between 30 and 60 ml/min/1.73 m^2—seem to be highly associated with cardiovascular risk in both sexes. Hence, despite the problems mentioned, our estimates seem robust, in view of the overestimation of eGFR together with a possible survivor and responder bias, even slightly optimistic picture of the current situation of cardiovascular risk factors in Switzerland, with women at older ages possibly at higher risk for cardiovascular disease than estimated previously by conventional risk factors.

Potential factors that could be ameliorated in the older age groups are more physical activity and weight reduction. Smoking, in particular in the young groups, is a further problem, and is currently targeted by the Swiss Health Authorities.

In conclusion, cardiovascular risk and impaired renal function might be underappreciated in women in Switzerland. However, there remains some doubt about the validity of prediction equations, in particular in females. In view of the ageing population and

because of the estimated high prevalence of moderate to severe renal impairment in the general Swiss population, the findings of this cross-sectional study are particularly important and require further detailed assessments.

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