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Male sex and vascular risk factors affect cystatin C-derived renal function in older people without diabetes or overt vascular disease

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Abstract

Background/objectives: to explore the effect of ageing on renal function with cystatin C as the marker of glomerular filtration rate (GFR) in the general population without vascular disease or diabetes.

Design: a cross-sectional analysis of a healthy subset from the Good Aging in Skåne-cohort study representative of the Swedish general population.

Subjects: 1252 participants without vascular disease and diabetes (43.9% men) of whom 203 were over 80 years old were included from the original cohort of 2931.

Methods: plasma cystatin C and plasma creatinine were used as markers for GFR. Estimated GFR (eGFR) was calculated with three chronic kidney disease epidemiology collaboration (CKD-EPI) formulas involving cystatin C, creatinine or both.

Results: the median for plasma cystatin C was 0.93 mg/l (60–69 years old), 1.04 (70–79 years old) and 1.24 (80+ years old). The difference in mg/l between the 5th and 95th percentile was 0.46, 0.62 and 0.90 for these age groups. Male sex increased the age effect on plasma cystatin C levels with 0.004 mg/l/year ($P = 0.03$), adjusted for vascular risk factors. Smoking, lower HDL and higher diastolic blood pressure were associated with higher cystatin C levels. 54.7% (CKD-EPI creatinine) to 73.9% (CKD-EPI cystatin C) of the 80+ had an eGFR < 60 ml/min/1.73 m².

Conclusion: non-diabetics without overt vascular disease exhibit an age related but heterogeneous decline in renal function. The ageing effect is more pronounced in men. At least half of healthy 80+ years old could be expected to have at least CKD Stage 3 with eGFR < 60 ml/min/1.73 m².

Keywords: *cystatin C, ageing, kidney function, sex, epidemiology*

Introduction

It is established that kidney function is reduced with age, but since there is a co-variation with vascular disease, the precise ageing effect is uncertain. There are studies strongly supporting the hypothesis that a decline in kidney function is related to normal senescence [1, 2]. In the indigenous people of Kuna, who have no known vascular disease, there is an age-related decrease in glomerular filtration rate (GFR) as measured by inulin clearance [1]. In a subset of healthy participants aged 29–100 years from four cohort studies, there was a strong correlation between age and increasing cystatin C [2]. On the other hand, in the well-known Baltimore Longitudinal study of Ageing, where creatinine clearance was the measure of GFR and healthy participants were followed for up to 14 years, 36% showed no decline in creatinine clearance [3].

If there is an ageing effect on renal function in the absence of disease, there is little evidence as to what factors influence it. A sex effect has been proposed and rejected [4, 5]. Smoking seems a natural culprit, and it has indeed been shown that it induces microalbuminuria and that it deteriorates kidney function in those with CKD [6], and there are indications that it also increases the risk of CKD in the general population [7]. Blood lipid levels, physical activity, BMI and blood pressure have all been investigated for their correlation with kidney dysfunction and evidence has been found [7–9]. Vascular risk factors causing atherosclerosis are thus likely to account for an important part of the decline in renal function with age, whereas the influence of sex is less certain.

An age-associated decline in renal function has been interpreted to be linear as well as accelerating [2, 10, 11].

Another debate is whether or not there is an epidemic of chronic kidney disease (CKD). There is an escalating proportion of the population with CKD defined by estimated GFR (eGFR) <60 ml/min/1.73 m² [12]. Nevertheless, it is uncertain whether an eGFR below this limit is always due to disease or if a normal ageing process can lead to such low filtration.

In a large population study, it is usually not feasible to use true clearance methods since it is invasive. However, eGFR will never become more than an estimate and has weaknesses particularly in older people due to changes in body composition. Therefore, finding suitable formulas for all ages, body compositions, with or without chronic disease has not been possible. Cystatin C has arisen as a strong alternative, especially in older people since it is not dependent on muscle mass [13].

In the light of these uncertainties, we decided to study a representative group of non-diabetic older people without vascular disease to (i) explore the variations in plasma

concentrations of cystatin C, (ii) study the effect of ageing on the level of plasma cystatin C, identify a possible impact of sex and evaluate whether smoking, physical inactivity and other atherosclerotic risk factors also affect the kidney function of those without known vascular manifestations, (iii) estimate the proportion that would be diagnosed as having CKD with the prevailing criterion.

This is, to our knowledge, the first time cystatin C has been studied in a large population of healthy older people originating from one cohort.

Methods

Study design and population

The original population of the Good Aging in Skåne (GÅS), part of the Swedish National Study on Aging and Care (SNAC), includes 2,931 participants aged 60–93 years old from 9 age cohorts, randomised from the municipality registers with a participation rate of 60%. The study has been described elsewhere in detail [14] and creatinine and cystatin C has been studied for the whole cohort [15].

In 116 participants, laboratory values were missing and were therefore excluded. Participants were also excluded on the following criteria to achieve a healthy subgroup: history of diabetes, hypertension, myocardial infarction; signs of myocardial infarction on EKG; NYHA Class 1–4; angina pectoris; coronary bypass surgery; PTCA/PCI; cerebral infarction; TIA; aortic aneurysm; intermittent claudication; renal artery stenosis; ischaemic kidney disease; glomerulonephritis; tubular disease; kidney malformations and medical treatments that could be assumed to treat these conditions specifically. The diagnoses were deduced from medical examination, history and medical records. Medication was self-reported. Thus, the study population was 1,252 participants.

Potential factors that could influence the GFR in this healthy study population were identified by the authors as age, sex, smoking, physical inactivity, known dyslipidaemia, total cholesterol, HDL, BMI and in-office blood pressure. Results are presented for three age groups: 60–69 years (young age group), 70–79 years (intermediate age group) and 80+ years (oldest age group).

Measurements and definitions

Hypertension was defined as having a clinical diagnosis of hypertension from medical records or medical history or use of antihypertensive drugs (ATC C02, C08 and C09).

Smoking habits were categorised as current/former smoker or never smoker. Physical inactivity was defined as sedentary or less than 2 h weekly of walking, easy gardening and household work.

Laboratory measurements

Plasma cystatin C was as one batch measured by a fully automated particle-enhanced immunoturbidimetric assay [16] at Lund University Hospital, Laboratory Medicine using the Hitachi Modular P analysis system and reagents from DAKO (Dako A/S, Glostrup, Denmark). The total analytical imprecision was 2.1% (with concentration of 1.0 mg/l in control sample) and 1.7% (with concentration of 4.0 mg/l in control sample). Normal reference range: 0.63–1.44 mg/l (>50 years) [17]. Hereafter plasma cystatin C level will be referred to as cystatin C.

Plasma creatinine was measured using a creatininase-based procedure on the Hitachi Modular P analysis system (Roche, Basel, Switzerland, application 652) at Lund University Hospital, Laboratory Medicine. The method is calibrated to IDMS levels. The total analytical imprecision was 3.0% (with a concentration of 60 µmol/l in control sample) and 1.4% (with a concentration of 578 µmol/l in control sample). Normal reference range: 60–100 µmol/l for men and 50–90 µmol/l for women. Hereafter plasma creatinine level will be referred to as creatinine.

Cholesterol and HDL were measured by conventional methods at Lund University Hospital, Laboratory Medicine.

Estimated GFR and CKD

Three formulas from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) were used to calculate eGFR [18]. CKD-EPI creatinine = $141 \times \min(\text{Scr}/k, 1)^a \times \max(\text{Scr}/k, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if female) $\times 1.159$ (if black), 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. CKD-EPI cystatin C = $133 \times \min(\text{Scys}/0.8, 1)^{-0.499} \times \max(\text{Scys}/0.8, 1)^{-0.328} \times 0.996^{\text{age}} \times 0.932$ (if female), min indicates the minimum of Scys/0.8 or 1, and max indicates the maximum of Scys/0.8 or 1. CKD-EPI creatinine–cystatin C = $135 \times \min(\text{Scr}/\kappa, 1)^a \times \max(\text{Scr}/\kappa, 1)^{-0.601} \times \min(\text{Scys}/0.8, 1)^{-0.375} \times \max(\text{Scys}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} \times 0.969$ (if female) $\times 1.08$ (if black), κ is 0.7 for females and 0.9 for males, a is -0.248 for females and -0.207 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. Scr is serum/plasma creatinine and Scys is serum/plasma cystatin C.

eGFR was categorised in CKD stages according to Kidney Disease Outcomes Quality Initiative guidelines [19].

Statistical analysis

To assess the combined effect of age and the factors sex, smoking and physical activity on cystatin C, a multivariate regression analysis was performed with adjustment for main effects: age, sex, smoking, physical activity, in-office systolic and diastolic blood pressure, BMI, total cholesterol, HDL, lipid-lowering treatment as well as interaction effects between age and sex, smoking and physical activity (Table 3). *P*-values corresponding to age and interaction terms involving age

were adjusted for multiple testing using Bonferroni correction. A *P*-value of <0.05 was considered statistically significant. Analyses were conducted using the statistical software SAS 9.2, Cary, NC.

Ethical considerations

The study was approved by the regional ethics committee at Lund University (LU 744-00). All subjects provided written consent to participate.

Results

Baseline characteristics are shown in Table 1. The proportion of women, never smokers, physically inactive, higher in-office blood pressure and lower BMI increased with age. Average cholesterol and HDL levels were roughly similar across the age groups. Males were more likely to be classified as smokers particularly in the older age groups and had lower total cholesterol. Among the oldest participants, 73.9% (CKD-EPI cystatin C) versus 54.7% (CKD-EPI creatinine) reach below the 60 ml/min/1.73 m² limit and 3.9% versus 3.4% below the 30 ml/min/1.73 m² limit (see Supplementary data are available in *Age and Ageing* online, Appendix for further detail).

Cystatin C values

The median for cystatin C rose from 0.93 mg/l among the 60–69 years old to 1.24 in the oldest group. The difference between the youngest and the intermediate group was 0.11 compared with 0.20 which was the difference between the intermediate and oldest age group. Cystatin C was similar for men and women among the youngest and oldest age groups. Women in the intermediate group had a lower median cystatin C than men. The difference in mg/l between the 5th and the 95th percentile was 0.46, 0.62 and 0.90 for the three age groups in order (see Table 2 for details).

The effect of age and sex on cystatin C

The outcome of a multiple regression analysis is displayed in Table 3. The age effect on cystatin C was strong, with an estimated rise of 0.015 mg/l/year. A higher independent cystatin C value was associated with smoking, a higher diastolic blood pressure, being female, and a lower HDL level. Being male increased the age effect with 0.004 ml/min/1.73 m²/year, adjusted for vascular risk factors. No significant additional ageing effect was seen for smoking and physical inactivity.

It has been suggested that the relationship between cystatin C and age is non-linear. To take this into account, a similar analysis was performed where the relationship between age and cystatin C was described via a cubic spline function. The additional ageing effect with male sex remained significant as well as the effect of HDL.

Table 1. Baseline characteristics of the general non-diabetic 'GÅS'-population without vascular manifestations stratified by age groups

| Demographics | | | | | | |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Age groups (years) | 60–69 | 70–79 | ≥80 | All | | |
| Number of participants | 834 | 215 | 203 | 1,252 | | |
| Sex <i>n</i> of males (%) | 390 (46.8) | 88 (40.9) | 71 (35.0) | 546 (43.9) | | |
| Age years mean (SD) | 63.0 (3.0) | 74.5 (3.0) | 85.2 (3.9) | 68.5 (9.1) | | |
| Males | 62.9 (3.0) | 74.4 (3.0) | 85.0 (3.8) | 67.6 (8.5) | | |
| Females | 63.0 (3.0) | 74.6 (3.0) | 85.4 (3.9) | 69.3 (9.4) | | |
| Physical inactivity <i>n</i> (%) | 93 (11.3) | 27 (12.8) | 50 (26.3) | 170 (13.9) | | |
| Males | 57 (14.8) | 9 (10.4) | 16 (23.2) | 82 (15.2) | | |
| Females | 36 (8.2) | 18 (14.4) | 34 (28.1) | 88 (12.9) | | |
| Smoking <i>n</i> (%) | 541 (64.9) | 97 (45.1) | 82 (40.4) | 720 (57.5) | | |
| Males | 270 (69.2) | 53 (60.2) | 47 (66.2) | 370 (67.4) | | |
| Females | 271 (61.0) | 44 (34.6) | 35 (26.5) | 350 (49.8) | | |
| Total cholesterol ^b (mmol/l) mean (SD) | 6.09 (0.99) | 6.03 (1.18) | 6.03 (1.17) | 6.07 (1.05) | | |
| Males | 5.92 (0.98) | 5.50 (1.18) | 5.41 (0.93) | 5.79 (1.02) | | |
| Females | 6.24 (0.98) | 6.38 (1.04) | 6.35 (1.15) | 6.28 (1.03) | | |
| HDL ^c (mmol/l) mean (SD) | 1.44 (0.44) | 1.50 (0.51) | 1.51 (0.48) | 1.46 (0.46) | | |
| Males | 1.26 (0.36) | 1.28 (0.40) | 1.30 (0.37) | 1.27 (0.36) | | |
| Females | 1.59 (0.44) | 1.66 (0.52) | 1.62 (0.50) | 1.61 (0.47) | | |
| Lipid-lowering medication <i>n</i> (%) | 62 (7.4) | 12 (5.6) | 4 (2.0) | 78 (6.2) | | |
| Males | 31 (7.9) | 3 (3.4) | 2 (2.8) | 36 (6.6) | | |
| Females | 31 (7.0) | 9 (7.1) | 2 (1.5) | 42 (6.0) | | |
| Weight | 76.9 (14.9) | 72.7 (11.5) | 67.4 (12.0) | 74.6 (14.4) | | |
| Males | 84.6 (13.8) | 80.5 (10.1) | 75.1 (11.1) | 82.7 (13.4) | | |
| Females | 70.2 (12.4) | 67.3 (9.1) | 63.2 (10.5) | 68.4 (11.8) | | |
| BMI (kg/m ²) mean (SD) | 26.1 (4.1) | 25.2 (3.2) | 23.9 (3.4) | 25.6 (4.0) | | |
| Males | 26.6 (3.7) | 25.5 (2.7) | 24.2 (3.1) | 26.1 (3.6) | | |
| Females | 25.7 (4.4) | 25.1 (3.5) | 23.8 (3.6) | 25.2 (4.2) | | |
| Blood pressure ^a (mmHg) mean (SD) | 140/84 (20/10) | 151/82 (21/10) | 153/80 (24/11) | 144/83 (22/11) | | |
| Males | 141/85 (20/11) | 150/82 (20/11) | 148/79 (26/11) | 145/82 (22/10) | | |
| Females | 140/82 (20/10) | 151/82 (22/10) | 156/80 (23/12) | 145/83 (22/11) | | |
| Measurements of kidney function | | | | | | |
| Age (years) | 60–69 | 70–79 | ≥80 | All | | |
| Cystatin C ^e (mg/l) mean (SD) | 0.93 (0.15) | 1.09 (0.33) | 1.28 (0.27) | 1.01 (0.25) | | |
| Males | 0.93 (0.15) | 1.17 (0.47) | 1.29 (0.25) | 1.02 (0.28) | | |
| Females | 0.93 (0.14) | 1.03 (0.17) | 1.27 (0.28) | 1.01 (0.22) | | |
| Creatinine ^d (μM) mean (SD) | 80.9 (14.7) | 84.1 (21.8) | 88.3 (20.0) | 82.7 (17.2) | | |
| Males | 89.5 (14.2) | 95.91 (26.1) | 100.0 (21.3) | 91.9 (18.0) | | |
| Females | 73.4 (10.4) | 75.8 (13.0) | 82.1 (16.2) | 75.5 (12.6) | | |
| CKD-EPI creatinine equation (ml/min/1.73 m ²) mean (SD) | 78.1 (13.8) | 67.3 (14.0) | 57.5 (15.4) | 72.9 (16.1) | | |
| Males | 80.4 (14.4) | 67.5 (15.8) | 59.9 (16.8) | 75.7 (16.8) | | |
| Females | 76.0 (13.0) | 67.1 (12.6) | 56.2 (14.4) | 70.7 (15.3) | | |
| CKD-EPI cystatin C equation (ml/min/1.73 m ²) mean (SD) | 83.0 (15.2) | 67.1 (15.0) | 51.6 (13.6) | 75.2 (19.1) | | |
| Males | 86.3 (15.9) | 65.3 (16.5) | 52.7 (12.8) | 78.6 (20.1) | | |
| Females | 80.2 (14.0) | 68.3 (13.7) | 51.1 (14.0) | 72.6 (17.9) | | |
| CKD-EPI creatinine–cystatin C equation (ml/min/1.73 m ²) mean (SD) | 80.7 (12.5) | 68.1 (13.0) | 55.3 (12.3) | 74.4 (15.8) | | |
| Males | 83.7 (13.0) | 67.8 (14.6) | 57.1 (12.0) | 77.7 (16.4) | | |
| Females | 78.1 (11.5) | 68.3 (11.8) | 54.3 (12.4) | 71.9 (14.9) | | |
| Prevalence of CKD Stages 3–5 ^f and 4–5 ^g | | | | | | |
| Age groups (years) | 60–69 | 70–79 | ≥80 | | | |
| | CKD-EPI cystatin C | CKD-EPI creatinine | CKD-EPI cystatin C | CKD-EPI creatinine | CKD-EPI cystatin C | CKD-EPI creatinine |
| CKD 3–5 <i>n</i> (%) | 49 (5.9) | 72 (8.6) | 62 (28.8) | 62 (28.8) | 150 (73.9) | 111 (54.7) |
| Males | 21 (5.4) | 27 (6.9) | 27 (30.7) | 22 (25) | 49 (69.0) | 33 (46.5) |
| Females | 28 (6.3) | 45 (10.1) | 35 (27.6) | 40 (31.5) | 101 (76.5) | 78 (59.1) |

Continued

Table 1. Continued

| Demographics | | | | | | |
|----------------------|---------|---------|---------|---------|---------|---------|
| Age groups (years) | 60–69 | 70–79 | ≥80 | All | | |
| CKD 4–5 <i>n</i> (%) | 0 (0.0) | 2 (0.2) | 2 (0.9) | 3 (1.4) | 8 (3.9) | 7 (3.4) |
| Males | 0 (0.0) | 1 (0.3) | 2 (2.3) | 3 (3.4) | 2 (2.8) | 3 (4.2) |
| Females | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 6 (4.6) | 4 (3.0) |

Missing data: 4 (0.3%) no weight, 52 (4.2%) no BMI, 94 (7.6%) no cholesterol, 96 (7.7%) no HDL, 4 (0.3%) no diastolic blood pressure, 3 (0.2%) no systolic blood pressure.

^aBlood pressure is systolic blood pressure/diastolic blood pressure. Normal range.

^bCholesterol (mmol/l): 3.9–7.8.

^cHigh-density lipoprotein (mmol/l): males 0.80–2.1, females 1.0–2.7.

^dCreatinine (μmol/l): males 60–105, females 45–90.

^eCystatin C (mg/l): 0.63–1.44.

^fCKD Stages 3–5 eGFR < 60 ml/min/1.73 m².

^gCKD Stages 4–5 eGFR < 30 ml/min/1.73 m².

Table 2. Age- and sex-specific cystatin C-values (mg/l) in percentiles for the general non-diabetic ‘GÅS’-population without vascular manifestations (*n* = 1,252)

| Age groups (years) | Min–max | p5 | p25 | p50 | p75 | p95 |
|--------------------|-----------|------|------|------|------|------|
| 60–69 | 0.48–1.83 | 0.72 | 0.84 | 0.93 | 1.01 | 1.18 |
| Males | 0.48–1.62 | 0.72 | 0.84 | 0.92 | 1.01 | 1.21 |
| Females | 0.49–1.83 | 0.71 | 0.84 | 0.93 | 1.00 | 1.16 |
| 70–79 | 0.67–4.83 | 0.81 | 0.93 | 1.04 | 1.16 | 1.43 |
| Males | 0.71–4.83 | 0.85 | 0.98 | 1.10 | 1.20 | 1.74 |
| Females | 0.67–1.76 | 0.79 | 0.91 | 1.02 | 1.12 | 1.32 |
| ≥80 | 0.78–2.44 | 0.93 | 1.09 | 1.24 | 1.40 | 1.83 |
| Males | 0.91–2.00 | 0.98 | 1.09 | 1.26 | 1.45 | 1.85 |
| Females | 0.78–2.44 | 0.85 | 1.08 | 1.23 | 1.38 | 1.83 |

Discussion

This study particularly focuses on the non-diabetic general older population without vascular manifestations and points to a decline in kidney function with age that is more pronounced in men.

The ageing effect observed in population studies is explained by several structural changes seen in the ageing kidney: loss of renal mass, arterial sclerosis, arteriolar hyalinosis, loss of tubules, interstitial fibrosis and increasing glomerulosclerosis [20].

Even though male sex is associated with lower cystatin C levels, there is an additional ageing effect in men. The sex effect on GFR has been debated and results are diverse. Odden *et al.* showed the opposite sex-dependent ageing effect on cystatin C levels in their population of healthy participants aged 28–100 years old, although the additional ageing effect in their study was clinically insignificant and as far as we understand not corrected for multiple testing as in the present study [2]. In addition, to our knowledge, this study is the first in which cystatin C is analysed in a large number of healthy persons older than 80 years originating from one general population study with one standardised study protocol and standardised laboratory methods.

Although the effect of sex on GFR has been quite extensively researched for younger adults, there are much less data on the sex-specific effects of ageing. In a meta-analysis, male sex was associated with a more rapid rate of progression in CKD [21]. Berg confirmed this in healthy potential kidney donors and showed a significant decrease in men with age compared with females, but this was done in a group aged 20–50 years [5]. A slower decline in kidney function in women is explained by higher levels of oestrogen and lower levels of androgens [22]. The suggested mechanisms are that women have a more robust nitric oxide system [23], lower renin–angiotensin–system activity [24] and in the ageing women increased levels of metalloproteases preventing matrix expansion in the kidney [25].

Our data confirm previous findings that in the healthier older people, HDL seems to have a protective effect on renal function. [8, 26].

Smoking is related to a decline in kidney function in this population. However, when smoking interacts with the ageing effect, we cannot see a significant additional ageing effect of smoking. This might be due to our broad definition of smoking that includes all the people who have ever smoked. It could also be due to the fact that the smokers that have had vascular incidents are excluded by definition or survival bias.

The increase in cystatin C nearly doubled comparing the young and intermediate age groups with the intermediate and oldest age groups, which may indicate an accelerating ageing effect. This corresponds to previous findings [2, 11]. However, in the study of the whole GÅS cohort including subjects with diabetes and vascular manifestations, this phenomenon was not obvious. One explanation might be that the ageing effect is diluted by vascular disease in the non-selected material [15]. Forthcoming longitudinal studies on subjects without vascular manifestations and risk factors may reveal a possible accelerating ageing effect on renal function.

The ageing effect—whether accelerating or not—seems to be highly individual since the intra-age-group difference between the 5th and 95th percentile almost doubled from

Table 3. Association of age, sex and atherosclerotic risk factors with cystatin C (mg/l) in the general non-diabetic 'GÅS'-population without vascular manifestations ($n = 1,252$)

| Factor | Estimated effect | 95% CI | P-value | Adjusted P-value (Bonferroni) |
|---|------------------|------------------|---------|-------------------------------|
| Age (mg/l/year) | 0.015 | [0.011, 0.020] | <0.001 | <0.001 |
| Male | -0.245 | [-0.420, 0.069] | 0.006 | |
| Smoking | 0.495 | [0.080, 0.919] | 0.019 | |
| Physical inactivity | -0.088 | [-0.396, 0.220] | 0.574 | |
| Lipid-lowering medication | 0.006 | [-0.036, 0.048] | 0.780 | |
| BMI | -0.000 | [-0.003, 0.003] | 0.983 | |
| Systolic blood pressure | -0.000 | [-0.001, 0.000] | 0.196 | |
| Diastolic blood pressure | 0.002 | [0.000, 0.003] | 0.038 | |
| Total cholesterol | -0.003 | [-0.013, 0.007] | 0.550 | |
| HDL | -0.038 | [-0.063, -0.012] | 0.004 | |
| Age*male (mg/l/year) | 0.004 | [0.001, 0.006] | 0.005 | 0.030 |
| Age*smoking (mg/l/year) | -0.006 | [0.001, 0.012] | 0.029 | 0.173 |
| Age*physical inactivity (mg/l/year) | 0.002 | [-0.002, 0.007] | 0.360 | 2.159 |
| Smoking*physical inactivity (mg/l) | -0.484 | [-0.934, 0.034] | 0.035 | 0.209 |
| Age*smoking*physical inactivity (mg/l/year) | 0.007 | [0.000, 0.013] | 0.041 | 0.245 |

The estimated effect of a factor is expressed in mg/l unless otherwise stated. All models are adjusted for age, sex, smoking, physical inactivity, lipid-lowering medication, BMI; systolic blood pressure, diastolic blood pressure, total cholesterol and HDL. ** denotes interaction.

the youngest to the oldest age group in our study. In early longitudinal studies on ageing and kidney function, it was observed that although most people deteriorated a third did not [3].

At least half of the participants over 80 in this study demonstrated an eGFR < 60 and are thus regarded as having CKD in spite of being relatively healthy. It has been shown, however, that older individuals with deteriorated kidney function have a lower risk than younger of progression to end-stage renal disease [27]. In the whole GÅS cohort, 6.5% (CKD-EPI creatinine) and 18.9% (CKD-EPI cystatin C) of persons >80 years old were classified as CKD Stages 4–5 (severe kidney disease) [15] which correspond with a Belgian cohort of 80+ years [28]. In this healthier subgroup, the prevalence was much lower than 3.9% (CKD-EPI cystatin C) and 3.4% (CKD-EPI creatinine), which could indicate that normal ageing normally does not result in severely reduced kidney function.

Our study has some limitations. We do not use a confirmatory gold standard such as iohexol clearance. At the time for this study, there was no international calibrator for cystatin C which may be a concern when using the different formulas. The problem with the current use of estimation equations is highlighted by the fact that depending on which formula used half (CKD-EPI creatinine) or two thirds (CKD-EPI cystatin C) of the 80 years old in the study fall below the limit of eGFR 60 ml/min. Moreover, albuminuria was not measured, which would complement our measures of kidney dysfunction. The self-reported data could include underreporting of previous smoking. The cystatin C assay was run before the introduction of a calibrator for cystatin C.

The participation rate in GÅS was 60% and visits at home were done to counteract selection bias of the more frail older people. In a study of a healthier subgroup, the participation rate is a smaller problem since there tends to be a

selection bias with the participants being healthier. Inherent confounders to cross-sectional studies include specific birth cohort effects and survivors' bias. In this particular case, survivors' bias would work against the age effect since there is an increased mortality risk with reduced kidney function [29].

In conclusion, this cross-sectional study shows an effect of ageing on cystatin C levels in those without overt vascular disease or diabetes. This ageing effect is more pronounced in men and is also associated with lower HDL, higher diastolic blood pressure and smoking. This tendency has to be confirmed in longitudinal studies. The heterogeneity in plasma concentration of cystatin C seems to become greater with age. Finally, the incidence of severe CKD (eGFR < 30) in those over 80 years old is substantially lower in the healthier subset compared with the whole GÅS cohort.

Key points

- Creatinine is not good enough as a marker for renal function in older people.
- Cystatin C increases with age in older people without known vascular disease and diabetes.
- The decline in renal function measured by cystatin C is more pronounced in men.
- At least half of the healthy 80+ population could be diagnosed with CKD independent of GFR marker.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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