Age and cystatin C in healthy adults: a collaborative study

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Abstract

Background. Kidney function declines with age, but a substantial portion of this decline has been attributed to the higher prevalence of risk factors for kidney disease at older ages. The effect of age on kidney function has not been well described in a healthy population across a wide age spectrum.

Methods. The authors pooled individual-level cross-sectional data from 18 253 persons aged 28–100 years in four studies: the Cardiovascular Health Study; the Health, Aging and Body Composition Study; the Multi-Ethnic Study of Atherosclerosis and the Prevention of Renal and Vascular End-Stage Disease cohort. Kidney function was measured by cystatin C. Clinical risk factors for kidney disease included diabetes, hypertension, obesity, smoking, coronary heart disease, cerebrovascular disease, peripheral arterial disease and heart failure.

Results. Across the age range, there was a strong, non-linear association of age with cystatin C concentration. This association was substantial, even among participants free of clinical risk factors for kidney disease; mean cystatin C levels were 46% higher in participants 80 and older compared with those <40 years (1.06 versus 0.72 mg/L, P < 0.001). Participants with one or more risk factors had higher
cystatin C concentrations for a given age, and the age association was slightly stronger ($\hat{P} < 0.001$ for age and risk factor interaction).

**Conclusions.** There is a strong, non-linear association of age with kidney function, even in healthy individuals. An important area for research will be to investigate the mechanisms that lead to deterioration of kidney function in apparently healthy persons.

**Keywords:** ageing; chronic kidney disease; cystatin C; epidemiology

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**Introduction**

Kidney disease disproportionately affects older persons; the incidence of end-stage renal disease increases with age and the majority of subjects who initiate renal replacement therapy are over 60 years of age [1,2]. Although the strong association between age and kidney function is well established [3], it is unclear what portion of this decline is due to the higher prevalence of risk factors for kidney disease at older ages, such as hypertension, diabetes and vascular disease [4]. The inclusion of persons with these comorbid conditions in prior descriptive studies of kidney function may have inaccurately attributed the risk factor-related decline in kidney function to ageing [5]. A greater understanding of age-related decline in kidney function in a clinically healthy population will inform studies aimed at prevention of kidney disease and its related morbidity in the elderly.

Adding to the complexity of describing age-associated changes in kidney function has been the use of creatinine-based measures in most prior epidemiologic studies. Serum creatinine concentrations are influenced by several factors other than glomerular filtration rate (GFR) including sex, body composition, activity, dietary intake and health status [6]. Older persons may have normal serum creatinine concentrations, despite the presence of kidney dysfunction [7]. Cystatin C is an alternative measure of kidney function that is a better estimate of GFR compared with serum creatinine in the elderly [8–10]. The present study combined cross-sectional data from four studies: the Cardiovascular Health Study (CHS); the Health, Aging and Body Composition Study (Health ABC); the Multi-Ethnic Study of Atherosclerosis (MESA) and the Prevention of Renal and Vascular End-Stage Disease cohort (PREVEND).

The recent availability of cystatin C measurements in several large studies has afforded the opportunity to characterize cystatin C concentrations in ~18 000 individuals aged 28–100 years. The goal of this study was to examine cystatin C concentrations across adulthood to characterize the association of age with kidney function in a healthy population and to compare this association to that in persons with clinical risk factors for kidney disease.

**Subjects and methods**

**Study population**

The CHS aimed to evaluate risk factors for the development and progression of cardiovascular disease in the elderly [11]. The study recruited persons from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania in 1989–1990 for the original cohort and 1992–1993 for a supplementary enrolment period designed to increase the number of African American participants. To be considered eligible for the study, persons had to meet the following criteria: (1) age ≥65 years; (2) not institutionalized; (3) expected to remain in the current community for 3 years or longer; (4) not under active treatment for cancer; and (5) able to give informed consent without requiring a proxy respondent.

The Health ABC study was designed to examine the relation between age-related changes of health and body composition and incident functional limitations in initially well-functioning black and white adults aged 70–79 years. Each of the two study sites, Pittsburgh, PA and Memphis, TN, recruited participants from a list of Medicare beneficiaries between April 1997 and June 1998. Inclusion criteria were (1) reported ability to walk one-quarter mile, climb ten steps and perform basic activities of daily living without difficulty; (2) absence of life-threatening illness; and (3) plan to remain in the geographic area for at least 3 years.

MESA is a cohort of men and women, aged 45–84 years, and free of clinical cardiovascular disease at baseline, designed to examine progression from subclinical to clinical cardiovascular disease in adults [12]. The cohort is ~38% white, 28% African American, 23% Hispanic and 11% Asian (of Chinese descent). Participants were recruited from six field centers (New York, NY; Baltimore, MD; Chicago, IL; Los Angeles, CA; Minneapolis/St Paul, MN and Winston Salem, NC) with a variety of population-based approaches from 2000 to 2002.

The PREVEND study is a prospective cohort that includes inhabitants aged 28–75 of the city of Groningen, The Netherlands in 1997–1998. The study was designed to investigate the natural course of urinary albumin excretion and its impact on renal and cardiovascular disease; for this purpose, the PREVEND cohort was enriched for subjects with higher concentrations of albuminuria. However, the present study includes only a sub-sample that is representative of the general population of Groningen; these methods have been previously described [13,14].

The present study and parent studies have been approved by all relevant institutional review boards.

**Kidney function**

Three of the four studies (CHS, Heath ABC and MESA) had cystatin C measured by the same protocol and laborator of the University of Vermont, and the PREVEND study used the same method at a different site. Cystatin-C was measured in all studies by a BNII nephelometer (Dade Behring Inc., Deerfield, IL) that utilizes a particle-enhanced immunonephelometric assay (N Latex Cystatin-C) [15]. The assay range is 0.195–7.330 mg/L, with the reference range for young, healthy individuals estimated as 0.53–0.95 mg/L (cystatin C in mg/L may be converted to nmol/L by multiplying by 74.9). Intra-assay coefficients of variation (CVs) range from 2.0 to 2.8% and inter-assay CVs range from 2.3 to 3.1%. Samples were measured from frozen plasma (CHS and Health ABC) or serum (MESA and PREVEND) and stored at −70 °C (CHS, Health ABC, MESA) or −20 °C (PREVEND). Studies have shown that cystatin C is stable when frozen, and can withstand several freeze/thaw cycles [16]. To ensure the comparability of the University of Vermont and PREVEND laboratories, we ran a comparison study of 101 samples. The correlation between the two sets was 0.97, the CV was 6% and the mean difference was 0.055 mg/L, which was not significantly associated with the mean concentration.

We calculated estimated GFR (eGFR) based on the cystatin C equation (eGFR = cystatin C $^{-1.10} \times 76.7$) developed by the CKD-EPI group [17].

**Other variables**

Age, sex and race were determined by self-report. Participants were considered healthy if they were free of clinical risk factors for kidney disease including diabetes [self-reported history or fasting glucose ≥126 mg/dL or oral glucose tolerance test ≥200 mg/dL (glucose in mg/dL may be converted to mmol/L by multiplying 0.055)], hypertension (self-reported history or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), obesity (body mass index ≥30 kg/m²), smoking (former or current), coronary heart disease (history of coronary heart disease, myocardial infarction, coronary arterial bypass graft, angioplasty, angina), cerebrovascular disease (history of stroke, transient ischaemic attack, carotid endarterectomy), peripheral arterial disease (history of revascularization, claudication) and heart failure. Plasma glucose values in PREVEND were
transformed to whole blood values using an internally validated correction factor [18,19]. We limited our definition of clinical risk factors for kidney disease to those conditions that were potentially modifiable or preventable and could be identified in a clinical setting.

**Statistical analysis**

Baseline characteristics of participants were summarized across study populations. To characterize the shape of the relationship between age and cystatin C, we plotted the variables using a locally weighted regression (Stata function–lowess) in persons with and without risk factors for kidney disease. We next calculated the age-specific mean and standard deviations (SD) of cystatin C by decade of age (<40, 40–50, 50–60, 60–70, 70–80, >80 + years). These analyses were repeated in sex strata among persons free of risk factors for kidney disease. Clinical risk factor, sex and race interaction terms with age were tested based on linear regression models in healthy participants. To account for the non-linearity of the age and cystatin C relationship, age was modelled as the best-fit polynomial function including up to a fifth order term, based on a data-adaptive learning algorithm [20].

To compare the distribution of cystatin C across the age spectrum, we plotted the kernel density estimates (R function–density) of cystatin C concentrations by decade of age among participants without risk factors for kidney disease. We used a smoothing bandwidth of 1.5 times the SD of the smoothing kernel.

As a complementary analysis, we calculated the prevalence and standard error of eGFR <60 ml/min/1.73m² (cystatin C >1.24 mg/L) by decade of age.

To estimate the period (calendar year) and birth cohort (birth year) effects on cystatin C concentrations, we restricted the age range to the overlap present across all four studies, 69–75 years (n = 6053). We included age, study and birth year or period year in a linear regression model with cystatin C as the outcome. We also examined if there were systematic differences in cystatin C concentration by study (CHS, Health ABC, MESA and PREVEND). We included age, sex, race and study indicator variables in a linear regression model with cystatin C as the outcome. We restricted this analysis to persons free of clinical risk factors for kidney disease to account for differences in the risk factors across the studies.

All analyses were conducted using Stata 9.0 (StataCorp., College Station, TX) and R (The R Foundation, Vienna, Austria).

**Results**

CHS and Health ABC included older aged participants, MESA included both middle and older aged persons and PREVEND sampled individuals across adulthood (Table 1). All of the cohorts were more than half female. CHS, Health ABC and MESA included black participants, whereas only 1% of PREVEND participants were self-indentified as black. PREVEND participants had a lower prevalence of obesity and diabetes, and lower mean blood glucose. Systolic blood pressure levels were higher in the two older cohorts, whereas diastolic blood pressure levels were similar across the cohorts. The prevalence of coronary heart disease, cerebrovascular disease, peripheral arterial disease and heart failure varied across the cohorts; by design, MESA participants were free of these conditions. The participants without clinical risk factors for kidney disease comprised 36% of the participants under 40 years, 25% of 40–49 year olds, 20% of 50–59 year olds, 13% of 60–69 year olds, 11% of 70–79 year olds and 10% of those over 80 years.

Across the age range, we observed a strong, non-linear association of age with cystatin C concentrations in participants with and without clinical risk factors for kidney disease (Figure 1). The rate of increase in cystatin C concentrations appeared to accelerate with age particularly among persons with clinical risk factors for kidney disease compared to those with no risk factors.

Overall, and among participants with and without clinical risk factors, the mean cystatin C concentration was higher in each ascending decade of life, with an accelerated effect (Table 2). In persons less than 40 years, the mean cystatin C was only about 6% higher (0.04 mg/L) among those with clinical risk factors for kidney disease, but this difference increased with age to 16% (0.17 mg/L) in participants over 80 years. These differences in cystatin C concentrations between participants with and without clinical risk factors in any decade were substantially smaller than the differences between the youngest (<40 years) and oldest (≥80 years) age groups [62% (0.47 mg/L) in participants with clinical risk factors and 47% (0.34 mg/L) in participants without]. The association of age with cystatin C
Table 2. Mean cystatin C concentrations by decade of age among participants with and without clinical risk factors for kidney disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Risk factors</th>
<th>Cystatin C (mg/L) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 (n = 911)</td>
<td>All (n = 2846)</td>
<td>0.72 (0.17)</td>
</tr>
<tr>
<td>40–49 (n = 1831)</td>
<td>(n = 584)</td>
<td>0.76 (0.21)</td>
</tr>
<tr>
<td>50–59 (n = 2677)</td>
<td>(n = 1369)</td>
<td>0.78 (0.16)</td>
</tr>
<tr>
<td>60–69 (n = 4564)</td>
<td>(n = 2135)</td>
<td>0.84 (0.17)</td>
</tr>
<tr>
<td>70–79 (n = 7367)</td>
<td>(n = 3950)</td>
<td>0.95 (0.28)</td>
</tr>
<tr>
<td>80+ (n = 903)</td>
<td>(n = 6556)</td>
<td>1.05 (0.34)</td>
</tr>
<tr>
<td>&lt;40 (n = 911)</td>
<td>Men (n = 1049)</td>
<td>0.76 (0.21)</td>
</tr>
<tr>
<td>40–49 (n = 1831)</td>
<td>(n = 131)</td>
<td>0.80 (0.17)</td>
</tr>
<tr>
<td>50–59 (n = 2677)</td>
<td>(n = 210)</td>
<td>0.83 (0.11)</td>
</tr>
<tr>
<td>60–69 (n = 4564)</td>
<td>(n = 197)</td>
<td>0.87 (0.13)</td>
</tr>
<tr>
<td>70–79 (n = 7367)</td>
<td>(n = 268)</td>
<td>0.99 (0.20)</td>
</tr>
<tr>
<td>80+ (n = 903)</td>
<td>(n = 268)</td>
<td>1.08 (0.17)</td>
</tr>
<tr>
<td>&lt;40 (n = 911)</td>
<td>Women (n = 1797)</td>
<td>0.69 (0.14)</td>
</tr>
<tr>
<td>40–49 (n = 1831)</td>
<td>(n = 196)</td>
<td>0.70 (0.16)</td>
</tr>
<tr>
<td>50–59 (n = 2677)</td>
<td>(n = 252)</td>
<td>0.76 (0.14)</td>
</tr>
<tr>
<td>60–69 (n = 4564)</td>
<td>(n = 332)</td>
<td>0.84 (0.15)</td>
</tr>
<tr>
<td>70–79 (n = 7367)</td>
<td>(n = 417)</td>
<td>0.94 (0.19)</td>
</tr>
<tr>
<td>80+ (n = 903)</td>
<td>(n = 543)</td>
<td>1.05 (0.21)</td>
</tr>
</tbody>
</table>

*P*-value for trend across decades <0.001 for all groups.
†P*-value for age and risk factor interaction <0.001.
‡P*-value for age and sex interaction = 0.03.

Fig. 1. Smoothed plot of age and cystatin C across the age range among participants with and without clinical risk factors for kidney disease. Clinical risk factors included diabetes, hypertension, obesity, smoking, coronary heart disease, cerebrovascular disease, peripheral arterial disease and heart failure.

The prevalence was similar in those with and without risk factors under 60 years, but in participants over 60 years, the presence of clinical risk factors was associated with an over 2-fold risk of eGFR <60 ml/min/1.73 m² (14% versus 5%).

Fig. 2. The plot illustrates the distribution of cystatin C concentrations by decade of age in participants without risk factors for kidney disease. The mean and variance are greater with each ascending decade of age.

Cohort and period effects were not significant when included in a model with age (P = 0.27 for both). There were small study effects of the Health ABC cohort and CHS cohorts compared with PREVEND and MESA. After adjustment for age, sex and race, both CHS and Health ABC cystatin C concentrations were 0.05 mg/L higher compared with PREVEND (P < 0.001 for both) among participants without clinical risk factors for kidney disease. MESA cystatin C concentrations were 0.02 mg/L higher compared with PREVEND, although this difference did not reach statistical significance (P = 0.08).
Discussion

We observed a strong, non-linear association of age with cystatin C concentrations even in participants without clinical risk factors for kidney disease. These results suggest that kidney function worsens considerably with age, even among apparently healthy persons. If validated, these findings could impact our understanding of ageing of the kidney. Unknown risk factors or subclinical levels of known risk factors likely have significant deleterious effects on kidney function. Furthermore, some decline in kidney function in older persons may represent usual ageing.

The strong association of age with higher cystatin C concentrations among apparently healthy persons raises the question of what causes age-related declines in kidney function. The ageing of the kidney may represent cumulative exposure to subclinical levels of risk factors and microvascular disease that could affect kidney function without crossing the threshold of clinical disease [21]. In addition to risk factor exposure, there are biological processes that encompass ageing [4]. One possibility is that age-associated loss of kidney function is due to a progressive loss of nephron units and a decline or alteration in cellular function over time. As kidney function declines, there is increased stress on the remaining nephrons, which likely leads to an acceleration in their decline [22]. It has also been hypothesized that lower energy expenditure impacts GFR, which may influence kidney function in older adults [23–25]. Finally, laboratory studies have observed a number of biochemical decrements in ageing kidney cells, including fewer mitochondria, lower enzyme concentrations and ATPase activity, decreased sodium transport and oxygen consumption and lower tubular transport [26].

The hypothesis that some kidney function decline represents usual ageing is consistent with studies that have described normal age-related declines in function in other physiologic domains. Cardiac output, maximum oxygen consumption, muscle strength, lung function, immune function, metabolic rate and some hormone concentrations are all observed to decline with age, even in healthy elderly [27]. In the current study, we identified healthy study participants as those free of clinical risk factors for kidney disease: non-smoker, not obese, and no history of diabetes, hypertension, cardiovascular disease or heart failure. Restriction of the healthy subpopulation to persons without subclinical disease may have further attenuated the age effect. However, a more rigorous definition of risk factors may be a difficult target goal for health in the general population, as in the present study, healthy persons were only about 10% of those over 70 years of age.

Our findings are consistent with prior studies of ageing of the kidneys, although some included persons with comorbid conditions known to affect kidney function [5] [4]. In one of the earliest cross-sectional reports, Davies and Shock described a non-linear decrease in GFR after 40 years; however, the study included persons with comorbid diseases. In another seminal report, Wesson illustrated the progressive decline of GFR with age by combination of data from 27 cross-sectional studies [28]. However, persons with comorbidities were included and the data were sparse on persons over age 60. Investigators from the Baltimore longitudinal studies of ageing were among the first to longitudinally study kidney function in a healthy subpopulation, with follow-up time up to 24 years. Consistent with our findings, they reported a progressive linear decline in creatinine clearance among 548 individuals free of diabetes, coronary heart disease, abnormal urinalysis or cerebrovascular disease [29]. In addition, a recently published study on cystatin C concentrations in the USA reported a strong and independent association of age with cystatin C concentrations in persons over 60 years, even after adjustment for chronic health conditions [30]. Our study used a stricter definition of healthy compared to prior studies and it represents the largest collaborative effort to describe the age-related change in cystatin C concentrations.

Several studies have reported that cystatin C is a better marker for measured GFR compared with creatinine [8]. To increase the interpretability of cystatin C concentration into a clinically meaningful metric, researchers have developed equations to transform cystatin C into estimated GFR [17]. These equations can be used to estimate kidney function, but they were developed in a relatively young population with established chronic kidney disease and have not yet been validated in the general population. The mean cystatin C in the largest equation study, conducted by the CKD-EPI group, was 1.8 (SD = 0.8) mg/L (17), whereas the mean cystatin C level in the present study was 0.95 (0.30) mg/L. Application of a regression equation outside of the range of cystatin C values in which it was developed may introduce bias into the estimates; therefore, we chose to present untransformed cystatin C instead of eGFR for the majority of analyses. Because the cystatin C eGFR analysis is a cut-point analysis (equivalent to the prevalence of cystatin C > 1.24 mg/L), the validity of the equation in the present study population is not essential to make inferences.

While a longitudinal study design is preferred in studies of ageing, few studies have measured kidney function across decades of follow-up. Instead, cross-sectional designs have been used in most studies of ageing and kidney
function [28,29,31], as in other studies of age trajectories of growth and decline [32–34]. The primary limitation of cross-sectional data is that each observation includes not only an age effect, but also period and cohort effects [35], which can lead to discordant results from cross-sectional and longitudinal studies. However, if the period and cohort effects are small, the effect of age can be accurately estimated. Our findings suggest that the period and cohort effects were insignificant in the study population.

Our study has limitations that should be considered when interpreting the findings. Primarily, none of the included studies measured GFR; therefore, we cannot measure the extent to which cystatin C concentrations are influenced by factors other than GFR. In addition, the relation of cystatin C with GFR has not been well studied in a population of older adults with near normal kidney function. By the use of cross-sectional data, we are unable to characterize definitively the period or birth cohort effects, although there was little evidence of period or birth cohort effects among participants in the age range that overlapped across the four cohorts (69–75 years). Selection bias is a potential limitation of our study; however, since age and poor kidney function are both associated with an increased risk of mortality, this would most likely bias the age association towards null. In addition, the present study did not include historical data on the severity of risk factors over the life course or information on medication use. Finally, there may be some misclassification of risk factor status.

In conclusion, cystatin C concentrations increase substantially with age, even in the absence of clinical risk factors for kidney disease. Studies aimed at prevention of kidney disease should consider that some age-related decline in kidney function is likely, even in healthy individuals. An important area for research will be to investigate the mechanisms that lead to deterioration in function in apparently healthy persons. Future studies should also examine the extent to which treatment of clinical risk factors may prevent the progression to kidney disease and its related adverse consequences. To that end, accurate assessment of kidney function is important for the clinical care of elderly persons who are disproportionately affected by kidney disease.

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Conflict of interest statement. None declared.

References

Gender & menopausal status determine the association of MS & CKD


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Clinical implication of metabolic syndrome on chronic kidney disease depends on gender and menopausal status: results from the Korean National Health and Nutrition Examination Survey

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Abstract

Background. The prevalence of chronic kidney disease (CKD) has been increasing throughout the world over the last decade. Metabolic syndrome (MS) has been known to be an independent risk factor of CKD. However, both renal and metabolic diseases are experienced differently in men and women, and clinical implication of MS on CKD may be different according to gender.

Methods. To understand the association between MS and CKD, we performed a cross-sectional study in non-institutionalized civilians using the data of the Korean National Health and Nutrition Examination Survey. Of 37 769 participants, 5091 were available for the analysis of the prevalence of CKD (defined as dipstick proteinuria or a reduced GFR < 60 ml/min/1.73 m²).

Results. The prevalence of CKD was 8.9% (7.4% in men, 4.7% in premenopausal women and 20.1% in postmenopausal women) and MS was seen in 26.2% (24.9% in men, 13.9% in premenopausal women and 52% in postmenopausal women). The prevalence of CKD increased with ageing, in particular after sharply after the age of 50 in both genders. MS was a significant determinant of CKD; however, sub-analysis revealed that MS was a risk factor for CKD only in men under the age of 60 and in postmenopausal women. Neither MS per se nor individual components of MS were associated with CKD in men over the age of 60 and in premenopausal women.

Conclusion. Differential effect of MS on CKD according to age and gender in our study may provide a clue to define the subject in need for more attention for the treatment of MS in terms of the development of CKD.

Keywords: chronic kidney disease; gender difference; metabolic syndrome

Introduction

The number of chronic kidney disease (CKD) patients has been increasing throughout the world over the last decade and is expected to continue growing [1,2]. A rise in the