Examining the utility of cystatin C as a confirmatory test of chronic kidney disease across the age range in middle-aged and older community-dwelling adults

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ABSTRACT

Background Cystatin C has been proposed as a confirmatory test of chronic kidney disease (CKD). This is most applicable to older individuals with CKD, the majority of whom have a creatinine-based estimated glomerular filtration rate (eGFR) of 45–59 mL/min/1.73 m² (CKD stage 3a). We sought to examine the utility of cystatin C as a confirmatory test of CKD across the age range in the general population of older adults.

Methods Cross-sectional analysis of 5386 participants from The Irish Longitudinal Study on Ageing, a cluster-sampled national cohort of community-dwelling adults aged ≥50 years. Cystatin C and creatinine were measured simultaneously using standardised assays. Using generalised additive models, we modelled the distributions of creatinine and cystatin C per year of age from four distributional parameters: location, dispersion, skewness, kurtosis. Among participants with CKD stage 3a, we estimated the predicted probability of cystatin C eGFR <60 mL/min/1.73 m² ('confirmed CKD') as a function of age.

Results Median age was 62 years, 53% were female and median cystatin C eGFR was 80 mL/min/1.73 m². We observed progressive variability in cystatin C with increasing age. Compared with creatinine, cystatin C levels rose sharply beyond the age of 65. Among participants with CKD stage 3a (n=463), the predicted probability of 'confirmed CKD' increased steadily with age, from 15% at age 50 to 80% at age 80.

Conclusions The clinical utility of cystatin C may be maximised in middle-aged individuals, in whom the distribution of cystatin C is less variable than older adults, and the pretest probability of confirming CKD is lower.

INTRODUCTION

The risk-based paradigm for the diagnosis and classification of chronic kidney disease (CKD)¹ suggests a steep age gradient in the prevalence of CKD.^{2,3} Among older individuals with CKD, the majority have modest reductions in estimated glomerular filtration rate (eGFR), in the range of 45–59 mL/min/1.73 m² (CKD stage 3a). While a proportion of this group is at increased risk of end-stage kidney disease (ESKD) and cardiovascular events,⁴ many more older adults are left with a diagnosis that carries an uncertain clinical significance.⁵ Furthermore, creatinine is a suboptimal kidney biomarker in this demographic due to variable generation of creatinine in the setting of declining muscle mass,

evidenced by U-shaped associations with mortality.⁶ The need for better risk-stratification within this heterogeneous older population with mild CKD has fuelled interest in alternative kidney biomarkers that are not influenced by nutrition or muscle mass. One such candidate biomarker is cystatin C, a small (13 kDa) molecule released by all nucleated cells and freely filtered at the glomerulus.

Early studies showed that the reciprocal of cystatin C had consistently better correlation with measured GFR than the reciprocal of creatinine.⁷ More recently, equations have been developed to estimate GFR from cystatin C (eGFR_{cys}). Whereas adjusting for non-GFR determinants of creatinine generation (age, gender and race) greatly improves the correlation between creatinine-based eGFR (eGFR_{creat}) and measured GFR, the same adjustments for cystatin C only minimally improve its performance as a predictor of measured GFR. The net result is that using eGFR_{cys} rather than eGFR_{creat} appears to produce little or no additional gain.⁸ GFR estimating equations using the combination of creatinine and cystatin C have demonstrated greater precision than equations using either filtration marker alone, including in older adults⁹; however, this is balanced against the higher cost and limited availability of cystatin C assays.¹⁰

Where cystatin C outperforms creatinine in risk prediction. Recent landmark studies have demonstrated that reclassification of CKD using cystatin C can substantially alter an individual's risk profile for major clinical end points.^{6,11} For these reasons, cystatin C has entered Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines as a confirmatory test of CKD. Recommendation 1.4.3.5 'suggests measuring cystatin C in adults with eGFR_{creat} 45–59 mL/min/1.73 m² who do not have markers of kidney damage, if confirmation of CKD is required (2C). If eGFR_{cys} is also <60 mL/min/1.73 m², the diagnosis of CKD is confirmed. If eGFR_{cys} is ≥60 mL/min/1.73 m², the diagnosis of CKD is not confirmed'.

The suggested use of cystatin C is thus not to confirm an individual's GFR, but rather to inform their risk profile. It is unclear whether this reclassification of risk solely reflects the role of cystatin C as a filtration marker, or whether other factors governing cystatin C production may be confounding the observed risk relationships between cystatin C and clinical outcomes. These potential non-GFR determinants of cystatin C, which include

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adiposity¹² and inflammation,¹³ are also age-related. The distribution of cystatin C could therefore vary with increasing age, which could in turn influence its utility as a discriminator of risk at older ages. This question is most pertinent among community-dwelling older adults, in whom the KDIGO guideline is likely to be most applicable. To examine this question, we compared the distributions of creatinine and cystatin C per year of age in a large sample of middle-aged and older adults, and subsequently estimated the predicted probability of 'confirmed CKD' as a function of age in the subgroup with CKD stage 3a.

METHODS

Participants

This was a cross-sectional analysis from wave 1 (June 2009 to June 2011) of The Irish Longitudinal Study on Ageing (TILDA), a cluster-sampled cohort of older adults resident in the community. Each member of the Irish population aged ≥ 50 years had an equal probability of being invited to participate. The study design has been described in detail elsewhere.^{14 15} A total of 8175 participants (62% household response rate) were recruited at wave 1. Participants were interviewed in their home by way of a computer-assisted personal interview (CAPI). Each participant was subsequently invited to have a comprehensive health assessment in the research centre or a modified assessment in their home.¹⁶ All participants provided informed written consent. Ethical approval for the TILDA study was granted by the Research Ethics Committee of Trinity College Dublin and all experimental procedures were adherent with the Declaration of Helsinki.

Health variables

The CAPI captured information on age, gender, smoking history and self-reported physician-diagnosed conditions. Medication use was recorded during the interview and cross-checked with medication labels. Glycated haemoglobin (HbA1c) was measured from frozen buffy coat samples.¹⁷ We defined diabetes mellitus as one or more of a self-reported physician's diagnosis; receiving insulin or oral hypoglycaemic medications; HbA1c level ≥ 48 mmol/mol. We defined hypertension as a self-reported physician's diagnosis of hypertension and/or receiving antihypertensive medication. We defined cardiovascular disease as the number (zero, one, two or more) of self-reported physician-diagnosed conditions: angina, heart failure, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack or stroke. Body mass index and waist circumference were measured at the health assessment. Blood pressure (BP) was measured by a nurse according to a standard protocol using a digital automated BP monitor (Omron M10-IT, Omron, Kyoto, Japan) and recorded as the average of two seated measurements.

Measurement of kidney biomarkers

At wave 1, a 25 mL venous blood sample was collected from each consenting participant. Samples were transported to a central laboratory in temperature-controlled shipping boxes where they were centrifuged, aliquoted into cryovials and stored at -80°C . Cystatin C and creatinine were measured simultaneously from frozen plasma. Cystatin C was measured using a second-generation particle-enhanced immunoturbidimetric assay (Roche Tina-quant) on a Roche Cobas 701 analyser, traceable to the European reference standard material (ERM-DA471/IFCC) for cystatin C.¹⁸ Creatinine was measured using an enzymatic method traceable to isotope-dilution mass spectrometry (Roche

Creatinine plus V.2, Roche Diagnostics, Basel, Switzerland). GFR was estimated in each participant from the Chronic Kidney Disease Epidemiology equations for creatinine¹⁹ or cystatin C.⁸ As the sample was all Caucasian, the race variable was not applied to GFR estimates.

STATISTICAL ANALYSIS

Analyses were performed using R²⁰ and Stata V.14.1 (StataCorp, College Station, Texas, USA). Continuous variables are presented as mean (SD) or median (IQR) as appropriate. Categorical variables are presented as count (percentage). The distributions of creatinine and cystatin C were modelled using the Box-Cox Power Exponential (BCPE) distribution. The BCPE includes four parameters: location (μ), dispersion (σ), skewness (ν) and kurtosis (τ), providing a flexible model for skewed and heavy-tailed outcomes whose values are greater than zero.²¹ An identity (linear) link was used for the μ and ν BCPE distributional parameters as functions of age and sex, whereas a log-link was used for the σ and τ parameters. This ensured values always greater than zero for the latter two. Natural cubic splines were used to model the cystatin C BCPE distribution as a function of age, with five knots for the μ BCPE parameter and two knots for the other three BCPE parameters. All BCPE parameters, as functions of age, were stratified by sex. Natural cubic splines were used to model the creatinine BCPE distribution as a function of age, with three knots for the μ BCPE parameter, zero knots for the σ BCPE parameter (first order polynomial) and two knots for the other two BCPE parameters. The ν and τ BCPE parameters, as functions of age, were stratified by sex.

For each biomarker, the optimal model for each BCPE distribution was sought using the Generalised Additive Model for Location Shape and Scale (GAMLSS) package in R.²² Based on the fitted BCPE models, plots were produced of the predicted 5th, 25th, 50th, 75th and 95th centiles of the target population as continuous curves across the age range (50–85 years) for males and females for creatinine and cystatin C. All models incorporated an inverse probability weight to reduce bias from (1) non-response at the initial recruitment stage and (2) non-participation in the health assessment and/or inability to provide a blood sample. A detailed description of the weighting method is provided in a supplementary file. SEs and CIs accounted for the two-stage clustered sampling of participants (households within geographical regions and individuals within households).

We estimated the likelihood of $\text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$ as a function of age in the subgroup of participants with CKD stage 3a defined by $\text{eGFR}_{\text{creat}} 45\text{--}59 \text{ mL/min/1.73 m}^2$ ($n=463$). Probability estimates by year of age, stratified by sex, were obtained using the postestimation *margins* command in Stata.

RESULTS

Characteristics of the study population

A total of 5386 participants had a measurement of creatinine and cystatin C at wave 1 (online supplementary figure 1). Within this group, the majority of assessments were performed at the health centre, but a substantial number of participants (650, 12%) had a modified assessment in their home. Characteristics of the study population, overall and by gender, are provided in table 1. The median (IQR) age of the cohort was 62 (55–69) years and 53.5% of participants were female. One-quarter of the participants ($n=1291$) were aged 70 years or over. Median (IQR) eGFR_{cys} and eGFR_{cr} were 80 (67–93) mL/min/1.73 m² and 82 (69–92) mL/min/1.73 m², respectively.

Table 1 Characteristics of study participants

	Total (n=5386)	Men (n=2505)	Women (n=2881)
Age, median (IQR)	62 (55–69)	62 (56–69)	61 (55–69)
Age category, n (%)			
50–64 years	3265 (60.6)	1468 (58.6)	1797 (62.4)
65–74 years	1428 (26.6)	718 (28.7)	710 (24.6)
≥75 years	693 (12.9)	319 (12.7)	374 (13.0)
Smoking, n (%)			
Current	841 (15.6)	395 (15.8)	446 (15.5)
Former	2112 (39.2)	1178 (47.0)	934 (32.4)
Never	2433 (45.2)	932 (37.2)	1501 (52.1)
BMI (kg/m ²), median (IQR)	28.1 (25.3–31.3)	28.7 (26.2–31.5)	27.5 (24.6–31.0)
Waist (cm), mean (SD)	95.3 (13.8)	101.6 (11.9)	89.9 (13.0)
Diabetes, n (%)	442 (8.3)	264 (10.6)	178 (6.2)
Hypertension, n (%)	2295 (42.6)	1145 (45.7)	1150 (39.9)
SBP (mm Hg), mean (SD)	135.6 (19.8)	139.2 (18.6)	132.4 (20.3)
DBP (mm Hg), mean (SD)	82.3 (11.2)	83.4 (11.2)	81.4 (11.1)
CV conditions, n (%)			
None	4797 (89.1)	2128 (85.0)	2669 (92.6)
One	430 (8.0)	264 (10.5)	166 (5.8)
Two or more	159 (3.0)	113 (4.5)	46 (1.6)
Creatinine eGFR, median (IQR)	82 (69–92)	82 (70–92)	81 (69–93)
Cystatin C eGFR, median (IQR)	80 (67–93)	81 (68–94)	79 (66–92)

Data were missing for waist circumference (n=21), BMI (n=14), diabetes (n=52), blood pressure (n=30).

BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Distributions of creatinine and cystatin C with age

The relationship between creatinine and age is illustrated by way of plots of the predicted population limits in [figure 1](#) for male and female participants. The trajectory of this slope was relatively flat. In both sexes, there was evidence of greater dispersion in the distribution of creatinine with advancing age. This change in the distribution pattern with age appeared to be more prominent in women. In contrast to creatinine, the relationship between cystatin C and age was strongly positive and non-linear ([figure 2](#)), particularly beyond the age of approximately 65 years in both sexes. The distribution of cystatin C changed markedly with advancing age, such that an individual aged 80 years had a strikingly different distribution to that of an individual aged 50 years. As well as increasing median levels with age, older participants demonstrated progressively greater variability in cystatin C levels (see online supplementary figure 2).

Cystatin C as a confirmatory test of CKD

A total of 463 participants had CKD stage 3a defined by $\text{eGFR}_{\text{creat}} < 45\text{--}59\text{ mL/min/1.73 m}^2$. The predicted probability of $\text{eGFR}_{\text{cys}} < 60\text{ mL/min/1.73 m}^2$ in this subgroup of participants increased steadily with age ([figure 3](#)). For example, the probability (95% CI) of $\text{eGFR}_{\text{cys}} < 60\text{ mL/min/1.73 m}^2$ for an individual aged 50, 60, 70 and 80 years was 0.15 (0.08 to 0.22), 0.34 (0.27 to 0.41), 0.60 (0.55 to 0.65) and 0.81 (0.76 to 0.86), respectively. This pattern of increasing probability with age was consistent in men and women.

[Table 2](#) compares the clinical characteristics of participants (all CKD stage 3a) with confirmed and unconfirmed CKD, overall and within age categories (50–64, 65–74 and ≥75 years). Overall, participants with confirmed CKD (n=278, 60%) had a higher prevalence of diabetes (17% vs 8%), cardiovascular disease (27%

vs 17%) and hypertension (76% vs 52%). Differences in mean waist circumference between confirmed and unconfirmed CKD were most marked in the oldest age category (99 vs 89 cm), whereas differences in mean BP between the groups were most marked in the youngest age category (137/87 vs 132/82 mm Hg in confirmed vs unconfirmed CKD). Among 173 participants aged ≥75 years with CKD stage 3a, only 25 (14%) were reclassified as not having CKD after testing with cystatin C. In contrast, among 113 participants aged 50–64 years, a higher proportion (n=74, 65%) were reclassified as not having CKD, in keeping with a lower burden of cardiovascular risk factors in this group. Online supplementary table 1 shows the reclassification of all $\text{eGFR}_{\text{creat}}$ stages using eGFR_{cys} . Among participants with $\text{eGFR}_{\text{creat}} 60\text{--}89\text{ mL/min/1.73 m}^2$ (n=3027), 363 (12%) were reclassified to an $\text{eGFR}_{\text{cys}} < 60\text{ mL/min/1.73 m}^2$. Those reclassified had a higher cardiovascular risk profile (online supplementary table 2), consistent with data showing higher risk of adverse outcomes in this group.⁶

DISCUSSION

The findings of this study were threefold: (1) we observed progressive variability in the distribution of filtration markers with increasing age, which was more pronounced for cystatin C than creatinine; (2) beyond the age of approximately 65 years there was a sharp curvilinear increase in cystatin C levels with age in both men and women, which was not observed with creatinine; (3) in the subgroup with CKD stage 3a, the predicted probability of $\text{eGFR}_{\text{cys}} < 60\text{ mL/min/1.73 m}^2$ ('confirmed CKD') increased steadily with age. Taken together, these findings suggest that cystatin C performs better as a confirmatory test of CKD in middle-aged adults, while providing little additional diagnostic information in those over 75 years of age.

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Figure 1 Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for creatinine ($\mu\text{mol/L}$) per year of age between 50 and 85 years in men and women superimposed on scatter plots (grey dots) of the observed relationship between creatinine and age. The side panels illustrate the modelled distribution of creatinine at specific ages (50, 60, 70 and 80 years) for men and women, respectively.

Cystatin C has consistently been shown to be a stronger predictor of hard adverse outcomes than creatinine, including in an older adult population.^{23 24} Conversely, a 'normal' cystatin C level predicts a favourable outcome.¹¹ The potential for cystatin C to stratify risk in this way was demonstrated in a large meta-analysis of both general population and CKD cohorts.⁶ Individuals whose CKD was not confirmed by cystatin C had a substantially lower risk profile for ESKD, cardiovascular and all-cause mortality. Given that the majority of older

adults with CKD fall into the G3a category (eGFR 45–59 mL/min/1.73 m²), and their risk of ESKD is low due to competing mortality,²⁵ it was hoped that additional testing with cystatin C could remove a large proportion of low-risk older adults from that category and reclassify them as not having CKD. It is evident from our findings, however, that such reclassification is not uniform across age. In the subpopulation of adults aged 75 years and over, we estimate that for every seven adults tested, only one will be reclassified as not having CKD. This

Figure 2 Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for cystatin C (mg/L) per year of age between 50 and 85 years in men and women superimposed on scatter plots (grey dots) of the observed relationship between cystatin C and age. The side panels illustrate the modelled distribution of cystatin C at specific ages (50, 60, 70 and 80 years) for men and women, respectively.

testing comes at a cost, both to the healthcare provider in terms of time and the expense of the additional assay, and to the individual patients who must undergo extra blood draws. Examining the distribution of cardiovascular risk factors in confirmed versus unconfirmed CKD suggests that the pretest probability of confirming CKD in those over 75 years could be further refined by consideration of these risk factors, for example, waist circumference.

Our findings are in keeping with an analysis from the REasons for Geographical And Racial Differences in Stroke (REGARDS) study.²⁶ The authors examined the reclassification of CKD using cystatin C within three age categories (<65, 65–79, ≥80 years) and found that CKD was confirmed in almost all participants aged 80 years and over. The REGARDS cohort is a US population sample with over-representation of black participants, and the authors did not stratify their results by race. The present

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Figure 3 Predicted probability of cystatin C estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² per year of age (left panel), and stratified by gender (right panel), among participants with chronic kidney disease (CKD) stage 3a (creatinine eGFR 45–59 mL/min/1.73 m², n=463).

analysis provides more granular and population-representative data regarding the relationship between cystatin C and age, including the probability of confirming CKD by continuous age, in a homogeneous European sample. Our data suggest that the clinical utility and cost-effectiveness of measuring cystatin C may be maximised in middle-aged adults, in whom the distribution of cystatin C is less variable, and the predicted probability of eGFR_{cys} <60 mL/min/1.73 m² is lower. For example, two-thirds of community-dwelling adults aged 50–64 years would be reclassified as not having CKD after cystatin C testing, potentially resulting in fewer investigations and fewer referrals to nephrology services.

The differences we observed in the relative distributions of cystatin C and creatinine with age were striking. Few studies have interrogated the relationship between cystatin C and age. A pooled analysis of individual-level data from four different cohorts demonstrated a non-linear relationship between cystatin C and age using a locally weighted smoothed regression plot, even in the absence of traditional CKD risk factors.²⁷ The authors compared the distribution of cystatin C (untransformed) by decade of age using kernel density estimates and showed increasing mean and variance with each ascending decade in this clinically heterogeneous sample. Data from a subsample of the third national health and nutrition examination survey (NHANES III) showed that median cystatin C levels began to rise beyond the age of 40 years in both sexes.²⁸ The distribution of the inverse of cystatin C was modelled across age, which did not facilitate interpretation of

variability with age. In the present analysis, we adopted a flexible approach to model the shape of the distributions of cystatin C and creatinine across age and stratified by sex. With four parameters that can vary, as opposed to two in a normal distribution, the BCPE distribution has greater scope to model any observed data. This methodology has been applied to other health measures in the TILDA cohort, for example, the generation of normative data for older community-dwelling adults in tests of physical performance and cognition.²⁹

Our study has a number of limitations. Creatinine and cystatin C were measured at a single time point. We did not measure GFR in the sample; however, GFR is rarely measured in clinical practice, and the KDIGO guideline refers to estimated GFR only. The guideline is suggested for individuals without evidence of kidney damage such as albuminuria; however, we did not measure urinary albumin in tandem with the plasma biomarkers. Some of our health variables were self-reported physician-diagnosed conditions, which are subject to measurement error. These limitations are balanced by several strengths. The TILDA sample is large and enriched for the target population for the KDIGO guideline, that is, community-based individuals with mild-to-moderate reductions in kidney function. Our study population included 1291 participants (24% of the cohort) who were aged 70 years or over. Health assessments were performed in the home for older and frailer participants who could not attend the research centre. Both creatinine and cystatin C were measured simultaneously in a central laboratory using standardised assays for both filtration markers. A key strength of our study is the household-level sampling of participants which, along with application of an inverse probability weight, facilitated the generation of robust data for cystatin C and creatinine that are representative of the target population.

In conclusion, we observed substantial non-linearity in cystatin C distribution as a function of age in a large cohort of community-dwelling older adults. The predicted probability of 'confirmed CKD' using cystatin C increased steadily with age, approaching 80% at age 80 years. Our findings suggest that the usefulness of cystatin C as a confirmatory test of CKD may not be uniform across age. Among older community-dwelling adults, the diagnostic yield of additional testing with cystatin C may be small relative to the extra cost and burden involved. While cystatin C clearly has a role in clinical risk-stratification of CKD, more work is needed to further our understanding of this biomarker and its clinical utility in the general population of older adults. Specifically, future studies should investigate the cost-effectiveness and acceptability of using cystatin C as a confirmatory test of CKD irrespective of age.

Table 2 Characteristics of participants with chronic kidney disease stage 3a, confirmed or unconfirmed by cystatin C testing

	All (n=463)		50–64 years (n=113)		65–74 years (n=177)		≥75 years (n=173)	
	Confirmed (278, 60%)	Unconfirmed (185, 40%)	Confirmed (39, 35%)	Unconfirmed (74, 65%)	Confirmed (91, 51%)	Unconfirmed (86, 49%)	Confirmed (148, 86%)	Unconfirmed (25, 14%)
Male, n (%)	121 (43.5)	76 (41.1)	12 (30.8)	28 (37.8)	41 (45.1)	38 (44.2)	68 (46.0)	10 (40)
Waist (cm)	99.7 (13.9)	96.2 (12.8)	98.5 (14.4)	96.9 (11.4)	101.6 (13.8)	97.5 (12.9)	98.7 (13.8)	89.4 (14.6)
Diabetes, n (%)	47 (17.0)	14 (7.7)	7 (18.0)	2 (2.7)	19 (20.9)	10 (11.8)	21 (14.3)	2 (8.0)
CVD, n (%)	76 (27.3)	31 (16.8)	5 (12.8)	8 (10.8)	24 (26.4)	16 (18.6)	47 (31.8)	7 (28.0)
HTN, n (%)	212 (76.3)	96 (51.9)	30 (76.9)	31 (41.9)	69 (75.8)	52 (60.5)	113 (76.4)	13 (52.0)
SBP (mm Hg)	140.0 (21.4)	135.2 (20.9)	136.6 (21.6)	131.9 (20.3)	133.9 (22.0)	134.9 (21.2)	144.7 (19.9)	145.9 (19.1)
DBP (mm Hg)	80.7 (11.9)	80.0 (11.1)	87.4 (11.3)	81.6 (12.0)	79.0 (11.0)	78.9 (10.9)	79.9 (12.0)	78.7 (8.4)

Numbers expressed as mean (SD) unless otherwise stated.

CVD, cardiovascular disease (yes/no); DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure.

What is already known on this subject

- Current guidelines suggest using cystatin C to confirm or refute the presence of chronic kidney disease, based on differential risk of hard outcomes arising from that reclassification.
- Several studies have identified non-renal determinants of cystatin C, which may be contributing to the risk of clinical outcomes.
- These factors such as adiposity and inflammation also accrue with age, and could therefore influence the usefulness of cystatin C as a confirmatory test at older ages.

What this study adds

- This study provides population-representative data regarding the distribution of cystatin C as a function of age in a national cohort of Irish community-dwelling adults aged ≥ 50 years, showing a sharp rise after the age of approximately 65 years.
- We demonstrate that the predicted probability of confirming chronic kidney disease with cystatin C increases steadily with age, reaching 80% at the age of 80 years.
- The utility of cystatin C may be more cost-effective in middle-aged adults (50–64 years), two-thirds of whom would be reclassified as not having chronic kidney disease, potentially reducing the burden on healthcare resources.

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Competing interests None declared.

Ethics approval Research Ethics Committee of Trinity College Dublin.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The anonymised TILDA dataset is publicly available to researchers who meet the criteria for access, at no monetary cost, from the Irish Social Science Data Archive (ISSDA) at University College Dublin (<http://www.ucd.ie/issda/data/tilda/>) and the Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan (<http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315>).

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