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Association Between Cystatin C and 20-Year Cumulative Incidence of Hearing Impairment in the Epidemiology of Hearing Loss Study

Carla R. Schubert, MS; Adam J. Paulsen, MS; David M. Nondahl, MS; Dayna S. Dalton, MS; Mary E. Fischer, PhD; Barbara E. K. Klein, MD; Ronald Klein, MD; Ted S. Tweed, MA; Karen J. Cruickshanks, PhD

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IMPORTANCE Hearing impairment (HI) is one of the most common conditions affecting older adults. Identification of factors associated with the development of HI may lead to ways to reduce the incidence of this condition.

OBJECTIVE To investigate the association between cystatin C, both as an independent biomarker and as a marker of kidney function, and the 20-year incidence of HI.

DESIGN, SETTING, AND PARTICIPANTS Data were obtained from the Epidemiology of Hearing Loss Study (EHLS), a longitudinal, population-based study in Beaver Dam, Wisconsin. Baseline examinations began in 1993 and continued through 1995, and participants were examined approximately every 5 years, with the most recent examination phase completed in 2015. The EHLS participants with serum cystatin C concentration data and without HI at the baseline examination were included in this study.

MAIN OUTCOMES AND MEASURES Participants without HI were followed up for incident HI (pure-tone average of hearing thresholds at 0.5, 1, 2, and 4 kHz >25 dB hearing level in either ear) for 20 years. Cystatin C was analyzed as a biomarker (concentration) and used to determine estimated glomerular filtration rate ($eGFR_{CysC}$). Discrete-time Cox proportional hazards regression models were used to analyze the association between cystatin C concentration and $eGFR_{CysC}$ and the 20-year cumulative incidence of HI.

RESULTS There were 863 participants aged 48 to 86 years with cystatin C data and without HI at baseline. Of these, 599 (69.4%) were women. In models adjusted for age and sex, cystatin C was associated with an increased risk of developing HI (hazard ratio [HR], 1.20; 95% CI, 1.07-1.34 per 0.2-mg/L increase in cystatin C concentration), but the estimate was attenuated after further adjusting for educational level, current smoking, waist circumference, and glycated hemoglobin (HR, 1.11; 95% CI, 0.98-1.27 per 0.2-mg/L increase in cystatin C concentration). Low $eGFR_{CysC}$ was significantly associated with the 20-year cumulative incidence of HI in both the age- and sex-adjusted model (HR, 1.70; 95% CI, 1.16-2.48; <60 vs ≥60 mL/min/1.73 m^2) and the multivariable-adjusted model (HR, 1.50; 95% CI, 1.02-2.22; <60 vs ≥60 mL/min/1.73 m^2).

CONCLUSIONS AND RELEVANCE Reduced kidney function as estimated using cystatin C, but not cystatin C alone, was associated with the 20-year cumulative incidence of HI, suggesting that some age-related HI may occur in conjunction with or as the result of reduced kidney function.

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Author Affiliations: Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison (Schubert, Paulsen, Nondahl, Dalton, Fischer, B. E. K. Klein, R. Klein, Tweed, Cruickshanks); Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin, Madison (Cruickshanks).

Corresponding Author: Carla R. Schubert, MS, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison, 610 Walnut St, Room 1087 WARF, Madison, WI 53726-2336 (schubert@episense.wisc.edu).

Hearing impairment (HI) is one of the most common conditions in older adults, and incidence rates increase significantly with age.[1] In a population-based study of middle-aged and older adults, the overall 15-year cumulative incidence of HI was 39%, 75%, and 93% among those aged 48-59, 60-69, and 70-79 years, respectively.[2] Sensorineural HI is primarily responsible for the decrease in hearing ability seen with age.[1] Loss of hair cells, a reduced ability of the cochlea to amplify and transmit incoming signals, and impaired neural transmission and central processing are all thought to contribute to the development of HI with age.[2-4] Risk factors associated with the incidence of HI in older adults include smoking, adiposity, and hyperglycemia.[2]

Kidney function also decreases as people age, and smoking, obesity, and diabetes are known risk factors for chronic kidney disease (CKD).[5,6] Blood levels of endogenous filtration markers are most often used to assess and monitor kidney function. One of these markers is cystatin C (CysC), which is a protein of low molecular mass that is produced by most nucleated cells.[7] Cystatin C is freely filtered by the glomerular membrane and almost completely reabsorbed and degraded by the proximal tubules, making it a robust indicator of kidney function when used to determine estimated glomerular filtration rate (eGFR).[7,8] Aside from its use as a glomerular filtration marker, CysC concentration has been associated with many age-related conditions, including the incidence of exudative age-related macular degeneration,[9] increase in risk of incident cognitive impairment,[10] functional decline,[11] unsuccessful aging,[12] arterial stiffness,[13] and cardiovascular outcomes including incident cardiovascular disease (CVD) and mortality.[14,15] Although many of these conditions are also associated with reduced kidney function, in some of these studies, associations were observed even when analyses were limited to individuals with normal eGFR or without CKD.[9,10,12,14]

Physiologically, as a cysteine protease inhibitor, CysC has a prominent role in the inhibition of several cysteine cathepsins.[16,17] It is possible that CysC may be associated with aging and pathological conditions through its role as a regulator of cysteine cathepsins because disruptions in homeostasis and increases in cysteine cathepsins have been associated with neurological disorders, cardiovascular and inflammatory diseases, and cancer.[16,17] Together these findings suggest that, in addition to being a biomarker of kidney function, CysC may be a biomarker of other pathophysiological changes that occur with age.

Whether CysC is associated with the development of HI is unknown. Few if any studies have evaluated CysC and HI, and most studies of the link between kidney function and hearing have focused on populations with genetic abnormalities or advanced kidney disease. Earlier studies that have been conducted in general adult populations have been cross sectional.[18,19] This study investigates the association between CysC, both as an independent biomarker and as a marker of kidney function, and the 20-year incidence of HI in the Epidemiology of Hearing Loss Study (EHLS).

Key Points

Question What is the association between cystatin C, both as an independent biomarker and as a marker of kidney function, and the 20-year incidence of hearing impairment in middle-aged and older adults?

Findings In this longitudinal, population-based study of 863 participants in the Epidemiology of Hearing Loss Study aged 48 to 86 years at baseline, reduced kidney function as estimated using cystatin C, but not cystatin C alone, was associated with an increased risk of developing hearing impairment during 20 years of follow-up.

Meaning Some age-related hearing impairment may occur in conjunction with or as the result of reduced kidney function.

Methods

Study Population

The EHLS is a longitudinal, population-based study of sensory health and aging (1993-present).[1,2,20,21] Participants were eligible for the EHLS if they were residents of Beaver Dam, Wisconsin, were aged 43 to 84 years during the period 1987-1988, and participated in the Beaver Dam Eye Study (1988-1990).[20,22] The baseline EHLS examinations took place from 1993 to 1995, concurrent with the Beaver Dam Eye Study 5-year follow-up, and EHLS follow-up examinations occurred approximately every 5 years thereafter (1998-2000, 2003-2005, 2009-2010, and 2014-2016).[1,2,20-22] Those who were 75 years or older at baseline had an additional examination at 2½ years (during the period 1995-1997). The EHLS was approved by the Health Sciences Institutional Review Board of the University of Wisconsin, Madison. All participants provided written informed consent before each examination, and all study protocols were performed in accordance with the tenets of the Declaration of Helsinki.[23]

Hearing Evaluation

Participants' hearing was tested using pure-tone audiometry measuring air and bone conduction following the same standardized protocol at each examination.[1,2,20,21] Hearing tests were conducted using clinical audiometers and TDH-50 headphones (Telephonics Dynamic Headphones 50; Telephonics) or ER-3A insert earphones (EARtone 3A; Etymotic Research Inc) in sound-treated booths following the guidelines of the American Speech-Language-Hearing Association.[24] Participants who were unable to come to the clinic site were examined in their homes or group facilities and were tested with a portable audiometer and insert earphones. Audiometers were calibrated every 6 months, and sound levels were taken monthly in the clinic booths and at the time of examination for those tested off-site to ensure that American National Standards Institutes standards were met.[25,26] Pure-tone air-conduction hearing thresholds were measured at 0.5, 1, 2, 3, 4, 6, and 8 kHz, and the pure-tone average was calculated for hearing thresholds at 0.5, 1, 2, and 4 kHz.[1,2,20,21]

CysC Measurement

Blood samples were collected at the time of the baseline examination (1993-1995) and stored at −80°C until they were tested in 2007. Serum CysC concentration was measured at the University of Minnesota, Minneapolis, with use of a nephelometer (Dade Behring BN 100; Siemens). Interassay precision was 1.72 mg/L (coefficient of variation, 6.4%) and 0.78 mg/L (coefficient of variation, 5.2%) at 2 control levels.[9]

Covariates

Information on demographic factors, medical history, occupation, and behavioral factors was collected via an interviewer-administered questionnaire at the baseline examination. Factors considered in this study included educational level (<16 vs ≥16 years), occupation (professional or managerial vs rest), occupational noise exposure,[2] smoking status (current, past, or never), history of heavy alcohol consumption (ever drinking ≥4 drinks per day on average), exercise (at least once per week long enough to work up a sweat), and self-reported history of physician-diagnosed kidney disease, cardiovascular disease (angina, stroke, or myocardial infarction), or thyroid disease.[2] Blood pressure, height, weight, and waist circumference were measured. Blood pressure was measured following the Hypertension Detection and Follow-up Program protocol.[27] Hypertension was defined as a physician diagnosis of hypertension with current use of antihypertensive medication, a measured systolic blood pressure greater than or equal to 140 mm Hg, or a measured diastolic blood pressure greater than or equal to 90 mm Hg. The percentage of glycated hemoglobin (GHb) in whole blood was measured using the affinity chromatography method (Isolab, Inc) on nonfasting blood samples obtained at the time of baseline examination. Diabetes was defined as a physician diagnosis of diabetes, a suspected diagnosis of diabetes with current treatment, or a measured GHb level greater than 8% (to convert to a proportion of total hemoglobin, multiply by 0.01).[2]

Statistical Analysis

All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc). Included in these analyses were participants with CysC data and without HI (pure-tone average hearing level ≤25 dB) in both ears at baseline. Incidence of HI was defined as a measured pure-tone average hearing level greater than 25 dB in either ear at any follow-up examination.

The CysC concentration was analyzed both continuously (per 0.2-mg/L increase) and dichotomously comparing the highest quintile (Q5, ≥1.04 mg/L) vs all others (Q1-Q4, <1.04 mg/L). An eGFR was calculated using CysC ($eGFR_{CysC}$) in the CKD Epidemiology Collaboration formula (for CysC ≤ 0.8 mg/L, $133 \times (CysC/0.8)^{-0.499} \times 0.996^{age}$ [× 0.932 if female]) or for CysC > 0.8 mg/L, $133 \times (CysC/0.8)^{-1.328} \times 0.996^{age}$ [× 0.932 if female]).[28] Estimated GFR_{CysC} was analyzed both as a continuous measure (per 20-mL/min/1.73 m^2 decrease) and as a dichotomous variable where eGFR < 60 mL/min/173 m^2 was defined as decreased function. This cut point was selected because it is considered to indicate moderately decreased function and the diagnostic threshold for CKD.[29] By comparison, an eGFR of more than 90 mL/min/173 m^2 is considered to indicate normal function, 60 to 89 mL/min/173 m^2 to indicate mildly decreased function, <30 mL/min/173 m^2 to indicate severely decreased function, and <15 mL/min/173 m^2 to indicate kidney failure.[29]

Kaplan-Meier survival estimates were used to calculate 20-year cumulative incidence of HI. Cox discrete-time proportional hazards analyses were used to model the associations between CysC and $eGFR_{CysC}$ at baseline and the 20-year cumulative incidence of HI. Associations were first evaluated in models adjusted for age and sex and then in multivariable models that investigated these associations after adjustment for risk factors associated with the 15-year cumulative incidence of HI (age, sex, educational level, waist circumference, current smoking, and GHb >12%) and other potential confounders.[2] It has been reported that thyroid function can affect the production of CysC[30]; therefore, sensitivity analyses were run on all final models after removing participants who reported a history of any thyroid disease.

Results

There were 1681 participants aged 48 to 86 years at baseline who were at risk for HI; of these, 863 had CysC data. Among these 863 participants, 599 (69.4%) were women. The participants with CysC data were slightly older than participants without CysC data (mean [SD] age, 62 [8.8] vs 59 [7.9] years), but there were no differences in sex, educational level, smoking history, waist circumference, or GHb level. The 20-year cumulative incidence of HI was 75% among those at risk for HI who had CysC data. The CysC concentrations ranged from 0.37 to 2.32 mg/L, with a mean (SD) of 0.91 (0.20) mg/L. Only 17 participants (2.0%) at risk for HI self-reported a history of kidney disease; among those, the mean CysC concentration was 0.91 mg/L (range, 0.60-1.29 mg/L). The overall mean $eGFR_{cysC}$ at baseline was 86.1 mL/min/1.73 m^2 (range, 22.6-148.5 mL/min/1.73 m^2) and was lower among those who developed HI during follow-up than those who did not (mean [SD], 83.5 [19.1] vs 90.1 [18.5] mL/min/1.73 m^2) (**Table 1**). There were 83 participants (9.6%) with an eGFR consistent with CKD ($eGFR_{cysC}$ < 60 mL/min/1.73 m^2) at baseline; of these, 63 developed HI during follow-up (Table 1).

CysC and 20-Year Cumulative Incidence of HI

The CysC concentration was associated with an increased risk of developing HI in a model adjusted for age and sex (hazard ratio [HR], 1.20; 95% CI, 1.07-1.34 per 0.2-mg/L increase in CysC concentration) (**Table 2**) but was not associated in a model further adjusted for educational level, current smoking, waist circumference, and GHb greater than 12% (HR, 1.11; 95% CI, 0.98-1.27 per 0.2-mg/L increase in CysC concentration). In models comparing participants with the highest CysC concentrations (Q5) with all others (Q1-Q4), there were no significant associations between high concentration of CysC and the development of HI in models adjusted for age and sex or more fully adjusted models (Table 2).

Table 1. Characteristics of 863 Participants in EHLS by 20-Year Cumulative Incidence of Hearing Impairment Among Those With Cystatin C Data at Baseline

Characteristic	Incident Hearing Impairment, No. (%) or Mean (SD)		Age-Adjusted and Sex-Adjusted HR (95% CI)
	Yes (n = 531)	No (n = 332)	
Women	342 (64.4)	257 (77.4)	1 [Reference]
Men	189 (35.6)	75 (22.6)	2.16 (1.72-2.73)[a]
Educational level <16 y	427 (80.4)	269 (81.0)	1.11 (0.85-1.46)
Occupation in production/manufacturing/farming	146 (28.7)	65 (20.6)	1.24 (0.96-1.59)
Occupational noise exposure in current job	43 (8.1)	36 (10.8)	1.06 (0.73-1.55)
Current smoking	66 (12.5)	48 (14.5)	1.26 (0.91-1.73)
History of heavy alcohol consumption[b]	100 (18.9)	40 (12.1)	1.23 (0.91-1.66)
Exercise at least once a week	219 (41.2)	148 (44.6)	0.86 (0.69-1.06)
$eGFR_{CysC}$ < 60 mL/min/1.73 m^2	63 (11.9)	20 (6.0)	1.70 (1.16-2.48)
History of kidney disease	9 (1.7)	8 (2.4)	0.97 (0.43-2.21)
History of CVD	45 (8.5)	18 (5.5)	1.26 (0.82-1.95)
Hypertension	269 (51.0)	144 (43.8)	1.22 (0.98-1.52)
Diabetes	46 (8.7)	23 (6.9)	1.46 (0.98-2.19)
Age, y	63.8 (8.7)	59.1 (8.2)	1.84 (1.70-1.98)[c]
Cystatin C concentration, mg/L	0.93 (0.20)	0.87 (0.18)	1.20 (1.07-1.34)[d]
$eGFR_{CysC}$, mL/min/1.73 m^2	83.5 (19.1)	90.1 (18.5)	1.21 (1.06-1.38)[e]
Waist circumference, cm	93.7 (15.5)	89.2 (16.5)	1.15 (1.07-1.24)[f]
GHb concentration, %	6.3 (1.4)	6.2 (1.2)	1.19 (1.09-1.30)

Abbreviations: CVD, cardiovascular disease; $eGFR_{CysC}$, estimated glomerular filtration rate calculated using cystatin C; EHLS, Epidemiology of Hearing Loss Study; GHb, glycated hemoglobin; HR, hazard ratio.

SI conversion factor: To convert GHb to a proportion of total hemoglobin, multiply by 0.01.

[a] Adjusted for age.

[b] Defined as 4 or more drinks per day.

[c] Per 5-year increase in age; adjusted for sex.

[d] Per 0.2-mg/L increase in cystatin C concentration.

[e] Per 20-mL/min decrease in $eGFR_{CysC}$.

[f] Per 10-cm increase in waist circumference.

$eGFR_{CysC}$ and 20-Year Cumulative Incidence of HI

In a model adjusted for age and sex, the risk of developing HI significantly increased with each 20-mL/min decrease in $eGFR_{CysC}$ (HR, 1.21; 95% CI, 1.06-1.38 per 20-mL/min decrease), but the estimate was attenuated in the multivariable-adjusted model (HR, 1.11; 95% CI, 0.96-1.28 per 20-mL/min decrease). However, a low $eGFR_{CysC}$ consistent with CKD ($eGFR_{CysC}$ < 60 mL/min/1.73 m^2) was associated with an increased risk of developing HI in both the model adjusted for age and sex (HR, 1.70; 95% CI, 1.16-2.48) and multivariable-adjusted models (HR, 1.50; 95% CI, 1.02-2.22). Results were similar in sensitivity analyses that excluded participants with thyroid disease.

Discussion

In this longitudinal study of middle-aged and older adults, we evaluated the association of CysC concentration and $eGFR_{CysC}$ with the 20-year cumulative incidence of HI. Participants with lower $eGFR_{CysC}$ consistent with moderate or worse CKD were at an increased risk of developing HI in the following 20 years compared with those with better kidney function at baseline. Although a higher concentration of CysC was associated with HI in a model adjusted for age and sex, there was not a significant association with HI in the more fully adjusted model. These findings suggest that reduced kidney function is associated with an increased risk of developing HI but that CysC concentrations alone are not.

We believe our study is one of the first to find an association between reduced kidney function and increased risk of developing HI in a general adult population with normal hearing at baseline. Two earlier population studies have reported associations between moderate CKD and HI, but those studies were cross-sectional and therefore not able to ascertain the temporal sequence of the association between kidney function and HI.[18,19]

Although traditionally serum creatinine levels have been used clinically to calculate eGFR, more recently $eGFR_{CysC}$ has been found to have some advantages over creatinine-calculated eGFR, and current guidelines recommend using $eGFR_{CysC}$ to confirm CKD in those with reduced creatinine-calculated eGFR without albminuria.[8,29,31] Creatinine levels can be affected by several factors other than GFR, such as muscle mass and diet, which can reduce the accuracy of creatinine-based eGFR and of risk prediction in some populations, especially the elderly population.[8,29,31] Cystatin C levels are less affected than creatinine levels by muscle mass and diet, and $eGFR_{CysC}$ has been reported to be more accurate for risk prediction of some outcomes than creatinine-calculated eGFR.[8,29,31] Because serum CysC levels may be affected by factors other than GFR, such as obesity, smoking, and thyroid disease, we performed sensitivity analyses in our study that excluded those individuals who reported any thyroid disease and adjusted for smoking and adiposity in the final multivariable models.

Although our study indicates that reduced kidney function preceded the development of HI, it cannot establish causality. Nonetheless, reduced kidney function leads to a wide range of systemic effects, and theoretically there are biological mechanisms through which reduced kidney function could affect hearing. Some level of uremic symptoms can occur in individuals with an eGFR less than or equal to 60 mL/min/1.73 m^2, which is 50% of the GFR of a healthy young adult and

is the cut point used in our study.[29,32] Uremia has been reported to inhibit sodium-potassium adenosine triphosphatase, which is essential in the cochlea for regulating potassium and maintaining the endocochlear potential.[32-34] Effects of uremia can also include insulin resistance and increased systemic inflammation and oxidative stress[32,33]; some of these factors have also been associated with hearing loss.[2,35,36]

Alternatively, anatomical and physiological similarities between the cochlea and the kidney have been well documented, and therefore a common cause for kidney and hearing dysfunction is also possible.[33,34] Chronic kidney disease is a well-known risk factor for CVD, but CVD may also lead to CKD.[37,38] In the Cardiovascular Health Study, clinical and subclinical CVD were associated with a more rapid decrease in kidney function in elderly individuals, possibly due to atherosclerosis of renal arteries.[39] Traditional CVD risk factors, such as smoking, diabetes, and adiposity[2] and subclinical atherosclerosis,[40] are also associated with the incidence of HI, which suggests that microvascular damage may be a common link between kidney dysfunction and HI.[33,41]

The lack of an association between CysC concentration and HI was unexpected in the context of earlier studies of aging. The CysC concentration has been shown to increase with age in healthy adults[42,43] and has been associated with macular degeneration, CVD, cognitive impairment, and unsuccessful aging.[9,10,12,14] These earlier findings suggested that CysC concentration had the potential to also have an association with HI; however, in this study, CysC concentration was not significantly associated with HI after adjusting for educational level, current smoking, adiposity, and poor glycemic control.

Strengths and Limitations

Strengths of this study include the prospective design with a 20-year follow-up period and the standardized, objective measurement of hearing function and CysC concentration at baseline. Limitations of the study include that only 1 measure of CysC concentration was obtained at baseline, which limited our ability to adjust for changes in kidney function that may have occurred over the follow-up period. Although our study found an increased risk of developing HI among those individuals with reduced kidney function, it cannot quantify the magnitude of the effect of reduced kidney function on hearing function. Thyroid disease was self-reported, and undiagnosed thyroid disease or other unknown conditions could have affected CysC concentrations.

Table 2. Multivariable Models of Cystatin C, $eGFR_{CysC}$, and 20-Year Cumulative Incidence of Hearing Impairment

Variable	20-y Incidence of Hearing Impairment, HR (95% CI)	
	Model Adjusted for Age and Sex	Multivariable-Adjusted Model[a]
Cystatin C concentration		
Per 0.2-mg/L increase	1.20 (1.07-1.34)	1.11 (0.98-1.27)
Quintile 5 vs 1-4	1.22 (0.92-1.61)	1.05 (0.79-1.41)
$eGFR_{CysC}$, mL/min/1.73 m^2		
Per 20-mL/min decrease	1.21 (1.06-1.38)	1.11 (0.96-1.28)
<60 vs ≥60	1.70 (1.16-2.48)	1.50 (1.02-2.22)

Abbreviations: $eGFR_{CysC}$, estimated glomerular filtration rate calculated using cystatin C; HR, hazard ratio.

[a] Adjusted for age, sex, educational level, current smoking, waist circumference, and glycated hemoglobin concentration greater than 12% (to convert to a proportion of total hemoglobin, multiply by 0.01).

Conclusions

As an independent biomarker, CysC concentration was not significantly associated with the incidence of HI, but reduced kidney function was associated with an increased risk of developing HI in middle-aged and older adults during 20 years of follow-up. These findings suggest some age-related hearing loss may occur in conjunction with or as the result of reduced kidney function, and clinicians should be aware that patients with reduced kidney function may be more likely to develop HI.

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Study concept and design: Schubert, Dalton, Fischer, Cruickshanks.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Schubert, Paulsen, Nondahl, Fischer.
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