Rapid Kidney Function Decline and Mortality Risk in Older Adults

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Background: Impaired kidney function is associated with increased mortality risk in older adults. It remains unknown, however, whether longitudinal declines in kidney function are independently associated with increased cardiovascular and all-cause mortality in older adults.

Methods: The Cardiovascular Health Study evaluated a cohort of community-dwelling older adults enrolled from 1989 to 1993 in 4 US communities with follow-up through 2005. Among 4380 participants, the slope of annual decline in estimated glomerular filtration rate (eGFR) was estimated using both serum creatinine (eGFRcreat) and cystatin C (eGFRcys) rates, which were measured at baseline, year 3, and year 7 of follow-up. Rapid decline in eGFR was defined as a loss greater than 3 mL/min/1.73 m² per year, and cardiovascular and all-cause mortality were assessed over a mean of 9.9 years of follow-up.

Results: Mean (SD) levels of creatinine and cystatin C were 0.93 (0.30) mg/dL and 1.03 (0.25) mg/L, respectively; mean (SD) eGFRcreat and eGFRcys were 79 (23) mL/min/1.73 m² and 79 (19) mL/min/1.73 m², respectively. Individuals with rapid decline measured by eGFRcreat (n=714; 16%) had increased risk of cardiovascular (adjusted hazard ratio [AHR], 1.70; 95% confidence interval [CI], 1.40-2.06) and all-cause (AHR, 1.73; 95% CI, 1.54-1.94) mortality. Individuals with rapid decline measured by eGFRcys (n=1083; 25%) also had increased risk of cardiovascular (AHR, 1.53; 95% CI, 1.29-1.80) and all-cause (AHR, 1.53; 95% CI, 1.38-1.69) mortality. The association of rapid decline in eGFR with elevated mortality risk did not differ across subgroups based on baseline kidney function, age, sex, race, or prevalent coronary heart disease.

Conclusion: Rapid decline in eGFR is associated with an increased risk of cardiovascular and all-cause mortality in older adults, independent of baseline eGFR and other demographic variables.

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Based on these observations, we hypothesized that elderly participants in the CHS with the greatest declines in eGFR over the 7 years of follow-up would be at elevated risk for cardiovascular and all-cause mortality, and that cystatin C–based estimates of GFR (eGFR_{cys}) decline would be a more powerful predictor of mortality risk than eGFR_{creat}.

METHODS

STUDY POPULATION

The CHS is a longitudinal study of community dwelling older adults designed to evaluate risk factors for cardiovascular disease. The design of this study has been described previously.12 In brief, participants 65 years or older were recruited from Medicare eligibility lists in 4 US communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania). An initial 3201 participants were recruited between 1989 and 1990. Blood samples were drawn from these individuals in the 1989-1990 period (baseline), the 1992-1993 period (year 3), and 1996-1997 (year 7). An additional 687 black participants were added to the study in 1992-1993; these individuals had blood samples drawn in 1992-1993 (year 3) and 1996-1997 (year 7). In total, 4380 of the 5888 participants in CHS had at least 2 blood samples from these visits available for measurement of cystatin C and serum creatinine levels and thus met criteria for inclusion in this analysis.

All participants provided written informed consent, and the institutional review boards of the University of California, San Francisco, University of Washington, Seattle, and University of Pittsburgh, Pittsburgh, Pennsylvania approved the study.

MEASUREMENT OF CYSTATIN C AND CREATININE

Frozen serum samples stored at −70°C from the visits at baseline, year 3, and year 7 were available for measurement of cystatin C levels. Cystatin C levels were measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, now Siemens Healthcare Diagnostics Inc, Deerfield, Illinois) with a nephelometer (BNII, Siemens Healthcare Diagnostics Inc). Previous work has shown this assay to be stable through several freeze–thaw cycles.13 For measurement of cystatin C levels, intra-assay coefficients of variation (CVs) ranged from 2.0% to 2.8%, and interassay CVs ranged from 2.3% to 3.1%. The 1992-1993 blood samples for cystatin C were assayed first in 2003. Subsequently, the 1989-1990 and 1996-1997 levels were assayed in 2006. Cystatin C levels were measured immediately after the visits for measurement of cystatin C and serum creatinine levels.

PREDICTOR VARIABLES: CHANGE IN eGFR_{CREAT} AND eGFR_{CYS}

To compare changes in kidney function as measured by eGFR_{creat} and eGFR_{cys}, we used estimating equations to transform each measurement into a GFR estimate. To determine eGFR_{cys}, we used an equation derived from a pooling of cohorts that used iohexol–mate clearance as the criterion standard (eGFR_{cys} = 76.7 × cystatin C^{−1.18}).14 While several different equations have been proposed for eGFR_{cys}, this equation is based on the largest cohort of subjects derived from multiple data sources that all used nephelometric methods for cystatin C evaluation. We indirectly calibrated the measured serum creatinine level in the CHS cohort to the Cleveland Clinic Laboratory using NHANES III data, as described previously.15,16 To determine eGFR_{creat}, we used the 4-variable equation of the Modification of Diet in Renal Disease Study Group17 (eGFR_{creat} = 186.3 × serum creatinine^{−1.154} × age^{−0.203} × 1.212 [if black] × 0.742 [if female]).

Rates of change were calculated using the 2 or 3 available cystatin C and creatinine measurements. Annualized change in eGFR was calculated using a least-squares regression slope. We examined the association of change in eGFR with mortality risk on a continuous scale by creating cubic spline plots of the middle 95% of eGFR_{cys} change vs mortality. The 25% of the cohort with the largest decline in eGFR_{cys} corresponded approximately to an annual loss of 3 mL/min/1.73 m^2; we used this as a cutoff value for “rapid decline,” representing a magnitude of change that is 3 times the rate previously described in studies of normal aging, and that was beyond the range of noise in measurement.18

OUTCOME VARIABLES: CARDIOVASCULAR MORTALITY AND ALL-CAUSE MORTALITY

Events that occurred after at least 2 completed measures of cystatin C and creatinine levels were included. Events were ascertained by annual examinations and interim 6-month telephone interviews through June 30, 2005, with a median follow-up time of 9.9 years (maximum follow-up of 11.1 years). The methods of ascertaining and adjudicating events have been described previously.19 Cardiovascular mortality was defined as death from coronary heart disease, heart failure, peripheral vascular disease, or cerebrovascular disease. Medical records, death certificates, obituary review, household contacts, and the Centers for Medicare and Medicaid Services health care utilization database were used to determine vital status. Through these methods, outcome measures were obtained in 100% of participants.

COVARIATES

We chose covariates as potential confounding factors based on their biological plausibility or based on prior studies. The following covariates were examined: (1) baseline cystatin C and creatinine levels; (2) demographic variables (age, sex, and race); (3) cardiovascular risk factors (body mass index and weight, hypertension defined by history and use of antihypertensive agents, or an average of 3 blood pressure measurements ≥140/90 mm Hg; diabetes mellitus defined by the use of insulin or an oral hypoglycemic agent or a fasting serum glucose level ≥126 mg/dL; [to convert glucose to millimoles per liter, multiply by 0.0555]; levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides; (4) novel cardiovascular risk factors (C-reactive protein, fibrinogen, and hemoglobin concentrations); (5) subclinical vascular disease indicators (atrial fibrillation and left ventricular hypertrophy by electrocardiography, ankle–arm index, and carotid intima–media thickness); and (6) occurrence of cardiovascular disease (coronary artery disease, stroke, transient ischemic attack, and congestive heart failure) prior to the last cystatin C or creatinine level measurement. For the multivariate models, blood pressure was included using both a categorical variable and systolic and diastolic blood pressure readings at the time of the first measurement of cystatin C and creatinine.

ANALYTIC METHODS

All covariates were compared between participants with and without rapid decline in kidney function defined by eGFR_{cys}, and separately by eGFR_{creat}. χ^2 tests were used for discrete variables, and t tests for continuous variables.
Interactions between baseline level of kidney function and change in kidney function were evaluated, and stratified analyses were performed by baseline kidney function using low, medium, and high cystatin C categories (<1.0 mg/L, 1.0-1.28 mg/L, ≥1.29 mg/L), and by the presence of CKD (eGFRcreat < 60 mL/min/1.73 m²). In addition, because of concern about regression to the mean, we considered 2 separate models: one that did not adjust for baseline eGFR, and a second model that adjusted for mean eGFR.

We examined the association of rapid decline based on the association of eGFRcre and eGFRcreat within subgroups based on age, sex, race, and coronary heart disease. Finally, we evaluated these associations within the subgroup of participants who were at low risk, defined as the absence of diabetes, hypertension, or cardiovascular disease at baseline, and compared the association with those participants with 1 or more of these risk conditions. The purpose of this subgroup analysis was to evaluate whether decline in kidney function is associated with mortality risk even in a relatively low-risk subgroup.16

Cox proportional hazards models were used to evaluate the association of each measure of kidney function decline with the 2 mortality endpoints. Covariate selection was conducted as in previous reports from CHS using cystatin C.11

Briefly, candidate variables were evaluated as determinants of each outcome in univariate analyses. Those that were significant were entered into multivariate proportional hazards models. Variables were selected for inclusion in the final adjusted models based on whether they changed the primary predictor’s coefficient (change in eGFRcre) by 5% or more. Variables that met this definition of confounding were retained.

We constructed separate models for eGFRcre and eGFRcreat, but with identical covariates. We presented hazard ratios (HRs) for those with rapid decline defined by change in eGFRcre and eGFRcreat. In addition, we compared mortality risk among participants who had rapid decline by eGFRcreat only, eGFRcre only, neither, or both using unadjusted and multivariate-adjusted proportional hazards models.

Table 1. Characteristics of Patients With Rapid Decline in eGFRcre and/or eGFRcreat vs Those Without This Rapid Declinea

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; eGFRcre, eGFR by creatinine measurement; eGFRcre, eGFR by cystatin C measurement; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TIA, transient ischemic attack.

1SI conversion factors: To convert all types of cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; CRP to nanomoles per liter, multiply by 9.524.

2Unless otherwise indicated, data are reported as mean (SD) values or number (percentage) of patients and represent baseline characteristics.

3Data are reported as median (interquartile range).

4No baseline diabetes mellitus, hypertension, or CVD.

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Analyses were performed using S-Plus (release 6.1; Insightful Inc, Seattle, Washington) and SPSS statistical software (release 14.0.2; SPSS Inc, Chicago, Illinois).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The 4380 individuals with 2 or 3 measurements of cystatin C and creatinine levels were younger, more likely to be female, and had substantially fewer cardiovascular risk factors, better baseline kidney function, and less cardiovascular disease at baseline than those with 0 or 1 measurement of cystatin C level. Mortality prior to the third clinical visit accounted for 51% of those who had 0 or 1 measurement of cystatin C, and loss to follow-up accounted for 4%.

Among the 4380 participants with 2 or 3 measurements of cystatin C, mean (SD) age was 72 (5) years; 9% of the cohort had diabetes mellitus at baseline, and 21% had prevalent cardiovascular disease. Mean (SD) baseline creatinine and cystatin C levels were 0.93 (0.30) mg/dL and 1.03 (0.25) mg/L, respectively (to convert creatinine and cystatin C levels were 0.01 (0.07) mg/dL and 0.03 (0.06) mg/L and −0.4 (3.6) mL/min/1.73 m² and −1.8 (2.6) mL/min/1.73 m², respectively.

Those with decline of eGFRcys, of greater than 3 mL/min/1.73 m² per year were older and more likely to have hypertension, diabetes mellitus, and cardiovascular disease at baseline than those with smaller interval changes (Table 1). First occurrences of cardiovascular disease (coronary heart disease, stroke, transient ischemic attack, or congestive heart failure) between the 1989-1990 (baseline) and 1996-1997 (year 7) testings were more common in the group with rapid decline in eGFRcys. Similar relationships were seen between those with and without rapid decline in eGFRcreat (Table 1).

CARDIOVASCULAR AND ALL-CAUSE MORTALITY

Of the 4380 individuals in the study group, 2219 died during the follow-up period (51%), 834 from cardiovascular causes (19%). The relationship between change in eGFR and mortality during follow-up is depicted in Figure 1, with the vertical line marking the cut point for rapid decline (3 mL/min/1.73 m² per year). When eGFRcreat was used as the measure of rapid decline, 1083 individuals had rapid decline (25%). The percentages of participants with all-cause and cardiovascular mortality were 63% and 26%, respectively, among persons with rapid decline, and 47% and 17%, respectively, among participants without rapid decline. After multivariate adjustment, rapid decline by eGFRcys remained associated with a greater than 50% increase in all-cause mortality and cardiovascular mortality (Table 2). Using eGFRcreat, we found that 714 individuals had rapid decline (16%); after multivariate adjustment, rapid decline by eGFRcys was associated with a greater than 70% increase in all-cause mortality and cardiovascular mortality. Models that did not adjust for baseline eGFR yielded similar HRs in adjusted analysis, with a 50% increase in all-cause cardiovascular mortality using eGFRcys and a 60% increase in both outcomes using eGFRcreat. The HRs were, in fact, slightly higher after adjustment for average eGFR across all available measurements (80% increased hazard of all-

![Figure 1. Association of kidney function decline by cystatin C–based estimated glomerular filtration rate (eGFRcys) with all-cause mortality (spline analysis, with top and bottom 2.5% removed).](image)

![Image](https://example.com/image.png)

**Table 2. Association of Rapid Kidney Function Decline as Measured by eGFRcys and eGFRcreat With All-Cause and CVD Mortality**

<table>
<thead>
<tr>
<th>eGFR Change</th>
<th>All-Cause Mortality</th>
<th>CVD Mortality</th>
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<td></td>
<td>Unadjusted Demo Adjusted</td>
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<td></td>
<td>Unadjusted Demo Adjusted</td>
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<td>eGFRcreat ≤3 mL/min/1.73 m²/y (n=3297)</td>
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<td>1 [Reference]</td>
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<tr>
<td>eGFRcreat &gt;3 mL/min/1.73 m²/y (n=1083)</td>
<td>1.69 (1.54-1.87)</td>
<td>1.57 (1.42-1.73)</td>
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<tr>
<td>eGFRcys ≤3 mL/min/1.73 m²/y (n=3666)</td>
<td>1.53 (1.42-1.69)</td>
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<tr>
<td>eGFRcys &gt;3 mL/min/1.73 m²/y (n=714)</td>
<td>1.75 (1.56-1.95)</td>
<td>1.80 (1.61-2.02)</td>
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Abbreviations: CVD, cardiovascular disease; Demo, demographically; eGFR, estimated glomerular filtration rate; eGFRcreat, eGFR by creatinine concentration; eGFRcys, eGFR by cystine C concentration; IMT, intimal-medial thickness.

*All data are reported as hazard ratios (95% confidence intervals).
*Adjusted for baseline cystatin C or creatinine level, age, sex, and race.
*Adjusted for baseline cystatin C or creatinine level, age, sex, race, weight change, diabetes mellitus, systolic blood pressure, diastolic blood pressure, hypertension, medications, ankle-arm index, common carotid IMT, and internal carotid IMT.
*Adjusted for baseline cystatin C or creatinine level, age, sex, race, weight change, diabetes mellitus, systolic blood pressure, diastolic blood pressure, hypertension, medications, ankle-arm index, common carotid IMT, internal carotid IMT, electrocardiogram, left ventricular hypertrophy, and prevalent congestive heart failure.
cause or cardiovascular mortality using eGFR_cys, and >90% increased hazard using eGFR_creat).

We examined the association of rapid kidney function decline with each mortality outcome within subgroups defined by baseline kidney function (as defined by an eGFR_creat <60 mL/min/1.73 m² and by initial level of cystatin C), age, sex, race, and baseline coronary heart disease (Figure 2). The point estimates were similar and statistically significant within each subgroup in Figure 2. When results were stratified by baseline CKD, rapid decline was associated with similar increases in risk for all-cause and cardiovascular mortality. There were no significant interactions between rapid kidney function decline by eGFR_cys or eGFR_creat and age (dichotomized at the median), race, sex, or baseline kidney function with either mortality end point. Furthermore, among participants who were free of diabetes mellitus, hypertension, and cardiovascular disease at baseline (n=1918), similar associations were seen between rapid decline in eGFR and risk of all-cause mortality: for rapid decline by eGFR_cys, the adjusted HR was 1.56 (95% confidence interval, 1.32-1.84); for rapid decline by eGFR_creat, the adjusted HR was 1.83 (95% confidence interval, 1.51-2.21). These HRs were not different compared with the subgroup with at least 1 of these comorbidities at baseline (Figure 2).

COMPARISON BETWEEN eGFR_CYS AND eGFR_CREAT LOSS

The group of participants with rapid decline by both eGFR_creat and eGFR_cys had all-cause and cardiovascular mortality rates nearly twice those of the group that did not meet either criterion (Table 3). Overall mortality was similar in each group that met only 1 criterion of rapid decline but approximately 50% higher than the rate for the group that met neither criterion.

In this prospective cohort of community dwelling older adults, we observed an association between rapidly declining kidney function (loss of eGFR >3 mL/min/1.73 m² per year) and elevated risk for all-cause and cardiovascular mortality. These associations with elevated risk were observed regardless of the initial eGFR. Rapid decline by either eGFR_creat or eGFR_cys was associated with elevations in mortality risk, and these associations were similar across subgroups of age, sex, race, cardiovascular disease, and baseline risk status.

While CKD is a well-established risk factor for all-cause and cardiovascular mortality, loss of kidney function within a population with relatively well-preserved kidney function has not previously been associated with adverse outcomes. One prior study examined progression to CKD over 13 years of follow-up among a cohort of 281 individuals with hypertension and baseline eGFR higher than 90 mL/min/1.73 m²; the authors noted an association, albeit without controlling for level of baseline eGFR, between progression to CKD and future cardiovascular disease events. It is noteworthy that this was a select population with a known risk factor for progres-
sion, whereas the CHS population was substantially larger, more heterogeneous, and more generalizable to the general population of older adults.

There are several reasons why loss of kidney function may be associated with increased mortality risk. Ongoing decline in kidney function may play a causal role by exacerbating cardiovascular disease risk factors such as hypertension and dyslipidemia or by causing retention of inflammatory solutes leading to oxidative stress and vascular damage. In addition, worsening kidney function may lead to decreased appetite, loss of lean body mass, decreased physical function, and overall frailty.22,23 Alternatively, loss of kidney function may be a marker of global atherosclerotic disease progression, with vascular disease leading to multi-organ dysfunction—including in the kidneys—and predisposing to higher mortality risks.

Rapid decline measured by eGFR <sub>creat</sub> and eGFR <sub>cys</sub> were both associated with adverse outcomes. Overall, eGFR <sub>cys</sub> detected more individuals with decline in kidney function in this cohort than did eGFR <sub>creat</sub>, possibly reflecting that cystatin C is more sensitive to small changes in eGFR.

However, participants with only eGFR <sub>creat</sub> rapid decline also had elevated mortality risk, which implies that change in eGFR <sub>cys</sub> has imperfect sensitivity for detecting high-risk individuals. Individuals with rapid decline in kidney function detected by both measures had the highest risk (nearly 10% annual mortality rate), suggesting that the 2 measures may provide complementary risk assessment in older adults.

Although the CHS comprises a community-based, representative sample of older adults in the US, the individuals included in this analysis were selected for having survived long enough to have at least 2 measures of kidney function. These participants were healthier and had better kidney function on average than the full CHS cohort, so their magnitude of decline in kidney function was likely less than would have been observed in the overall cohort. Nevertheless, even in this healthier subgroup, there was substantial variability in kidney function loss over time, and rapid declines of kidney function were strongly associated with mortality risk.

Our study has several limitations. We do not have direct measurements of GFR and therefore cannot assess whether the changes we observed in eGFR by either cystatin C or creatinine are truly reflective of changes in kidney function. Because 85% of the black subjects in this study were added to the cohort after the first measurement of cystatin C and creatinine, most had only 2 measurements of creatinine level; thus, we cannot determine change in eGFR as accurately in this population. Albuminuria was not measured at baseline in CHS, so we cannot comment on the role of this marker of kidney disease in mediating or modifying the relationships we observed. While regression to the mean may have led to misclassification bias, we considered several different statistical adjustments for baseline kidney function to account for this and noted that our results were robust regardless of the method used. Although cystatin C appears to be a very sensitive marker of kidney function, it may be affected by thyroid dysfunction, corticosteroid use, and body composition, and cystatin C measurements may not reflect actual GFR as accurately at the extremes of body mass.24,25 In addition, we cannot determine whether the association of rapid kidney decline with mortality risk is causal or rather a marker of other physiologic processes that impact the kidney and other organs. Despite adjustment in multivariate models for both hypertension and diabetes mellitus, we cannot exclude the possibility of residual confounding from lifetime exposure to these conditions. However, we observed similar associations with increased mortality for the subgroup without hypertension, diabetes mellitus, or cardiovascular disease, suggesting that residual confounding was unlikely to be the primary explanation for our findings.

There are several potential implications of the results. First, decline in kidney function exceeding 3 mL/min/1.73 m<sup>2</sup> per year is independently associated with adverse outcomes. Second, changes in serum creatinine and cystatin C levels appear to provide complementary information in older adults, with the 2 measures capturing overlapping subgroups at increased mortality risk. Third, these findings were robust across multiple subgroups, including level of baseline kidney function. These associations should be confirmed in other cohorts of older adults as well as in other populations at risk for kidney disease progression. Recognition of early loss of eGFR

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<tr>
<th>Rapid Decline by eGFR &lt;sub&gt;creat&lt;/sub&gt;,eGFR &lt;sub&gt;cys&lt;/sub&gt;</th>
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<th>CVD Mortality</th>
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Abbreviations: CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; eGFR <sub>creat</sub>, eGFR by creatinine concentration; eGFR <sub>cys</sub>, eGFR by cystatin C concentration; HR, hazard ratio; IMT, intimal-medial thickness.

<sup>b</sup>Adjusted for baseline cystatin C or creatinine level, age, sex, race, weight change, diabetes mellitus, systolic blood pressure, diastolic blood pressure, hypertension, medications, ankle-arm index, common carotid IMT, and internal carotid IMT.

<sup>a</sup>Adjusted for baseline cystatin C or creatinine level, age, sex, race, weight change, diabetes mellitus, systolic blood pressure, diastolic blood pressure, hypertension, medications, ankle-arm index, common carotid IMT, internal carotid IMT, electrocardiogram, left ventricular hypertrophy, and prevalent congestive heart failure.
may be important as a prognostic tool in older adults regardless of their baseline comorbid conditions.

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