Longitudinal Associations Between Visual Impairment and Cognitive Functioning
The Salisbury Eye Evaluation Study

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IMPORTANCE Worsening vision and declining cognitive functioning are common conditions among elderly individuals. Understanding the association between them could be beneficial in mitigating age-related cognitive changes.

OBJECTIVE To evaluate the longitudinal associations between visual impairment and cognitive function over time in a population-based study of older US adults.

DESIGN, SETTING, AND PARTICIPANTS Prospective longitudinal population-based study of older adults in the greater Salisbury area in Maryland. Overall, 2520 community-residing adults aged 65 to 84 years were assessed at baseline between September 1993 and August 1995 (round 1) and 2 (round 2), 6 (round 3), and 8 (round 4) years later.

MAIN OUTCOMES AND MEASURES Visual acuity (VA) was measured using Early Treatment Diabetic Retinopathy Study charts, and cognitive status was assessed using the Mini-Mental State Examination (MMSE).

RESULTS Of 2520 individuals, the mean (SD) age was 73.5 (5.1) years, 1458 (58%) were women, and 666 (26%) were black. There were 2240 (89%), 1504 (61%), and 1250 (50%) participants in the second, third, and fourth round of study, respectively, with more than half of the loss being due to death. Both VA and MMSE score worsened over time. The mean biannual decline of VA was 0.022 logMAR (approximately 1 line during 8 years; 95% CI, 0.018-0.026), and the mean biannual worsening of MMSE score was −0.59 (95% CI, −0.64 to −0.54; both P < .001). Worse baseline VA was associated with worse baseline MMSE score (r = −0.226; 95% CI, −0.291 to −0.16; P < .001). The rate of worsening VA was associated with the rate of declining MMSE score (r = −0.139; 95% CI, −0.261 to −0.017; P = .03). Cross-lagged models indicated VA in the previous round was associated with MMSE score in the subsequent round (β = −0.995, P < .001), and MMSE score in the previous round was associated with VA in the following round (β = −0.003, P < .001). However, the standardized effect size of VA on MMSE score (β = −0.074; SE, 0.015; P < .001) is larger relative to the reverse effect (β = −0.038; SE, 0.013; P < .001), demonstrating VA is likely the driving force in these dynamic associations.

CONCLUSIONS AND RELEVANCE In a population-based sample of older US adults, visual impairment measured at distance is associated with declining cognitive function both cross-sectionally and longitudinally over time with worsening vision having a stronger association with declining cognition than the reverse. Worsening vision in older adults may be adversely associated with future cognitive functioning. Maintaining good vision may be an important interventional strategy for mitigating age-related cognitive declines.
A n estimated 5.4 million US individuals 71 years or older have cognitive impairment without dementia. Cognitive impairment is associated with decreased quality of life, increased disability and dependency on others, increased health care costs, and early mortality. Visual impairment is another serious concern among elderly individuals and affects more than 2.9 million US adults. Visual impairment has significant negative effects on physical and psychosocial health and represents a comorbidity that increases the risk of disability in persons with cognitive impairment. The prevalence of blindness and visual impairment increased rapidly with age among all racial and ethnic groups, particularly among persons older than 75 years. The burden of visual impairment and cognitive impairment will increase dramatically during the coming decades owing to aging of the US population.

The Mini-Mental State Examination (MMSE) is used to screen for dementia and to estimate the severity and progression of cognitive impairment throughout time. The full version of MMSE includes 30 questions and examines linguistic, computational, memory, concentration, and orientation functions. The MMSE for the visually impaired (MMSE-blind) is performed by omitting 8 items that require vision.

A cross-sectional association between visual impairment and poor cognitive functioning has been reported by several studies, including a 2017 study using large nationally representative samples of US adults. The few studies using longitudinal data to investigate the association between visual acuity (VA) and MMSE score neither have population-representative data nor use multiple waves of longitudinal data. The results of these studies are inconsistent. Our work extends prior research through investigating the longitudinal association between VA and MMSE score and evaluating how the 2 factors are associated with each other over time. Using 4 waves of data from the Salisbury Eye Evaluation (SEE) study, the purpose of this study was to describe the VA and MMSE score trajectories occurring throughout time among aging adults and to estimate the associations among the trajectories. We also examined the longitudinal reciprocal association between VA and MMSE score and assessed the driving factors in the dynamic association using cross-lagged models.

**Methods**

**Study Population**

The SEE study is a population-based prospective cohort study of age-related eye diseases and functional impact in community-residing individuals, conducted from September 1993 to July 2003. Details of the SEE study have been previously described. Briefly, the sample was selected from the Health Care Financing Administration Medicare eligibility list and included individuals between ages 65 and 84 years as of July 1, 1993, living in Salisbury, Maryland. The sample included 100% of black residents and a random age-stratified sample of 58% of white residents. At baseline, eligible participants had to score higher than 17 on the MMSE and be able to travel to the clinic for a complete examination. At follow-up visits, there were no restrictions. There were 2520 participants in the initial cohort (round 1), who were reassessed 2 (round 2), 6 (round 3), and 8 (round 4) years later. There were 2240 second-round participants (89%) (October 1995 to August 1997), 1504 third-round participants (61%) (June 1999 to May 2001), and 1250 fourth-round participants (50%) (June 2001 to July 2003) with more than half of the loss between rounds being due to death. Written informed consent was obtained in accordance to the Declaration of Helsinki and the Joint Community of Clinical Investigation at Johns Hopkins University. The University of Miami institutional review board approved this study.

**Visual Acuity**

Presenting VA was assessed under normal luminance using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Lighthouse illuminated box). The Early Treatment Diabetic Retinopathy Study chart refraction was performed on participants with 20/32 visual acuity or worse using a forced-choice procedure. Presenting binocular distance VA was converted to logMAR with a higher score indicating worse VA.

**Mini-Mental State Examination**

The MMSE consists of 11 simple tasks grouped into 7 cognitive domains: orientation to time, orientation to place, registration of 3 words, attention and calculation, recall of 3 words, language, and visual construction. A possible score of 30 was used to provide an assessment of an individual’s cognitive performance based on direct observation of completion of tasks. If a participant could not see, the items requiring sight were omitted, and the maximum score was adjusted and prorated to be comparable with 30. Lower MMSE score indicated poor cognitive function. Participants were tested with their usual eyewear. Visual acuity and MMSE scores were measured at baseline and at each of the follow-up rounds: 2, 6, and 8 years later.

**Covariates**

The following variables were included as controls in the full models: age in years, sex (female vs male), race (black vs white), and education level (less than high school, high school graduate, and above high school). All covariates were measured at the baseline assessment.

**Statistical Analysis**

**Latent Growth Models**

Growth curve trajectory models were first estimated for MMSE scores and VA separately. The models allow for individual dif-
ferences in trajectories through random effects. The growth curve best described the MMSE score and VA trajectories included the fixed and random effect of intercept and slope of time. These models provided the following for each outcome: (1) average level at baseline (the intercept); (2) average biannual change between baseline and the last assessment (the slope); (3) interindividual variation in baseline levels (random intercept); and (4) interindividual variation in changes over time (random slope).

Next, the VA and MMSE score trajectory models were combined into 1 model and estimated simultaneously to assess the association between the 2 trajectories. Figure 1 depicts the paths of this model. The parameters estimated include the correlations between the baseline values, the correlations between baseline values and slopes, and the correlations between the slopes. The model equations were estimated simultaneously while controlling for age, sex, race, and education.

Cross-lagged Models
The latent growth model does not determine whether the association of changes in VA and MMSE score were due to VA being associated with MMSE score or the reverse. Therefore, we examined the longitudinal reciprocal association between VA and MMSE score using cross-lagged models. The cross-lagged model estimated how MMSE scores and VA are associated with each other after conditioning on their stability through an autoregressive path (ie, after the prior level of MMSE scores and VA were accounted for). In Figure 2, VA at each time was regressed on VA at the prior time and MMSE at the prior time. Similarly, MMSE score at each time was regressed on MMSE score and VA of the prior time. Visual acuity and MMSE score measured at the same time were allowed to correlate. These series of regression equations were estimated simultaneously while controlling for age, sex, race, and education in each regression equation.

To achieve a more parsimonious cross-lagged model, we examined paths for equality over time and when they were equal, these paths were constrained to be equal across time. Comparison of nested models was conducted using a Wald test and a cutoff of .05. We tested the path equality for the lagged effects of VA and MMSE score, the crossed effects between VA and MMSE score, as well as confounding effect of age, sex, race, and education. Model constraints are illustrated in Figure 2; paths that were constrained equal were drawn with the same color and marked with the same letter. All models were evaluated using model fit statistics including the Comparative Fit Index and Tucker-Lewis Index for which values above 0.90 indicate good fit and values above 0.95 indicate excellent fit. The root mean square error of approximation was also used for which values less than 0.05 indicate excellent fit. We included all study participants in the analysis whether or not they had missing items. Maximum Likelihood Robust for missing data estimation was used to obtain estimates in the presence of missing data.26 We used a sandwich estimator for the standard errors that is robust to nonnormality.27 Analyses were
conducted using SAS, version 9.3 (SAS Institute Inc) and Mplus 7.31 software packages (Muthén & Muthén).

**Results**

There were 2520 study participants at baseline, of whom 1458 (58%) were women, 1854 (74%) were white, and 666 (26%) were black (Table 1). The mean (SD) age at the baseline was 73.5 (5.1) years. The percent of participants who had MMSE scores indicating cognitive impairment (<24) increased from 11% (276 of 2520) at baseline to 20.6% (257 of 1250) in the fourth round. Visual acuity value (logMAR) also increased over time indicating worsening of vision.

The mean baseline level (intercept) of VA was 0.04 logMAR (approximate Snellen equivalent 20/25) (SE, 0.004; P < .001). The average biannual worsening over time (slope) of VA was 0.022 logMAR (95% CI, 0.018-0.026; P < .001). The annual declines in VA were 0.011 logMAR, which is an annual loss of less than 1 letter on the ETDRS acuity chart or close to 1 line over 8 years (Table 2). The baseline average (intercept) of MMSE score was 27.3 (95% CI, 27.2-27.4; P < .001), 3 points higher than the cutoff value of 24 for cognitive impairment, indicating this aged population had normal cognitive functioning on average initially. The slope of MMSE score loss was −0.59 (95% CI, −0.64 to −0.54; P < .001). There were significant individual differences in intercept and slope for MMSE score and VA trajectory as indicated by statistically significant variances of intercept and slope for both trajectories (Table 2). The simultaneous equations in Figure 1 show paths that were statistically significant (drawn with solid lines), with dotted lines indicating nonsignificant paths. The overall model fit of the simultaneous equation model was very good (Comparative Fit Index, 0.967; Tucker-Lewis Index, 0.948; root mean square error of approximation, 0.044). We found worse baseline VA significantly associated with worse baseline MMSE score, indicating a cross-sectional association between VA and MMSE score (r = −0.226; 95% CI, −0.29 to −0.16; P < .001) (eTable 1 in the Supplement). The rate of worsening VA was associated with the rate of declining MMSE score as shown by more positively sloped VA trajectories that were significantly associated with more negatively sloped trajectories of MMSE score (r = −0.139; 95% CI, −0.261 to −0.017; P = .03). Visual acuity level at baseline was not associated with changes in VA over time in this community-residing older population (r = −0.096; SE, 0.062; P = .12). However, the starting value of MMSE score was associated with MMSE score rate of change, as indicated by a statistically significant association between MMSE score intercept and MMSE score slope (r = 0.17; 95% CI, 0.01-0.32; P < .05).

Age was statistically significant in associating with all 4 estimated parameters, namely MMSE score intercept, MMSE score slope, VA intercept, and VA slope. Sex, race, and educa-

**Table 1. Demographic Characteristic, VA, and MMSE Score of the Study Population at Each Round**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Round 1 (n = 2520)</th>
<th>Round 2 (n = 2240)</th>
<th>Round 3 (n = 1504)</th>
<th>Round 4 (n = 1250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>73.5 (5.1)</td>
<td>75.2 (5.0)</td>
<td>78.2 (4.7)</td>
<td>79.8 (4.6)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>1062 (42)</td>
<td>927 (41)</td>
<td>618 (41)</td>
<td>501 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>1458 (58)</td>
<td>1313 (59)</td>
<td>886 (59)</td>
<td>749 (60)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td>1854 (74)</td>
<td>1660 (74)</td>
<td>1135 (75)</td>
<td>956 (76)</td>
</tr>
<tr>
<td>Black</td>
<td>666 (26)</td>
<td>580 (26)</td>
<td>369 (25)</td>
<td>294 (24)</td>
</tr>
<tr>
<td>Education, No. (%)</td>
<td>1299 (52)</td>
<td>1131 (51)</td>
<td>723 (48)</td>
<td>597 (48)</td>
</tr>
<tr>
<td>&lt;High school</td>
<td>514 (20)</td>
<td>454 (20)</td>
<td>314 (21)</td>
<td>259 (20)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>707 (28)</td>
<td>655 (30)</td>
<td>467 (31)</td>
<td>394 (32)</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>27.16 (2.6)</td>
<td>27.21 (2.8)</td>
<td>25.73 (3.6)</td>
<td>25.66 (3.7)</td>
</tr>
<tr>
<td>% MMSE score &lt;24</td>
<td>11.0</td>
<td>11.4</td>
<td>19.8</td>
<td>20.6</td>
</tr>
<tr>
<td>Average presenting logMAR VA (approximate Snellen equivalent)</td>
<td>0.035 (20/50)</td>
<td>0.068 (20/100)</td>
<td>0.088 (20/160)</td>
<td>0.076 (20/125)</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE, Mini-Mental State Examination; VA, visual acuity.

**Table 2. Intercept and Slope Estimates of MMSE and Visual Acuity Trajectories**

<table>
<thead>
<tr>
<th>Models</th>
<th>Intercept</th>
<th>SE</th>
<th>Intercept Variance</th>
<th>SE</th>
<th>Slope</th>
<th>SE</th>
<th>Slope Variance</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trajectory of MMSE score</td>
<td>27.3*</td>
<td>0.05</td>
<td>4.21*</td>
<td>0.24</td>
<td>−0.59*</td>
<td>0.023</td>
<td>0.37*</td>
<td>0.05</td>
</tr>
<tr>
<td>Trajectory of visual acuity (logMAR)</td>
<td>0.04*</td>
<td>0.004</td>
<td>0.038*</td>
<td>0.004</td>
<td>0.022*</td>
<td>0.002</td>
<td>0.002*</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.

* P < .001.
Longitudinal Associations Between Visual Impairment and Cognitive Functioning

In this population-based study, we investigated the association between VA and MMSE score and extended the finding on the association between VA and cognitive functioning from cross-sectional to longitudinal, which allowed us to determine the influence of one on the change in the other. Our study demonstrates VA is associated with cognitive status not only cross-sectionally in older adults, but more importantly, VA and cognitive functioning are associated longitudinally (ie, they are changing together). Notably, our results suggest that VA has a substantially larger influence on subsequent change in MMSE score than the other way around.

Based on our latent growth model results, over the course of this 8-year study, an older adult with the mean VA decline of approximately 1 line on the ETDRS chart would have an associated decline in MMSE score of 0.83 point. An older person experiencing larger VA declines (ie, loss of about 2 lines over 8 years on the ETDRS chart) would experience an associated decline of 2.5 points on the MMSE.

This older population had normal mean cognitive functioning at the beginning of the study (MMSE score, >17 and mean MMSE score, 27.3); therefore, the possibility of older adults not being able to perform the VA test well owing to poor cognitive ability was small. Comparing the effect of VA at the beginning of the study on cognitive function 2 years later vs the reverse, we found that the standardized regression coefficient of VA to MMSE score was almost twice that of MMSE score to VA (−0.074 vs −0.038, both P < .001). This indicated the influence of VA on MMSE score was stronger than the reverse during the first round of the study. This pattern of bidirectional association with VA having a stronger influence on MMSE score was observed again in the following rounds (−0.059 vs −0.035 for round 2 and −0.065 vs −0.047 for round 3, all P < .001). This demonstrated VA is likely the dominant factor of the dynamic associations between VA and MMSE score. To our knowledge, this is the first time this dependency has been shown.

As a sensitivity analysis, we repeated the analyses using MMSE-blind, which omits the 8 items that require vision, for all participants including those with normal vision. The latent growth curve model results indicate VA and MMSE-blind score remain significantly associated cross-sectionally (r = −0.12; 95% CI, −0.19 to −0.05; P < .01); longitudinally the correlation between the rate of change of VA and MMSE-blind score becomes borderline significant (r = −0.1; 95% CI, −0.21 to 0.01; P = .07). The cross-lagged model findings remain significant (all P < .01). Thus, the conclusion that VA exerts a substantially larger influence on subsequent change in MMSE score than the reciprocal is unchanged.

Discussion

In this population-based study, we investigated the association between VA and MMSE score and extended the finding on the association between VA and cognitive functioning from cross-sectional to longitudinal, which allowed us to determine the influence of one on the change in the other. Our study demonstrates VA is associated with cognitive status not only cross-sectionally in older adults, but more importantly, VA and cognitive functioning are associated longitudinally (ie, they are changing together). Notably, our results suggest that VA has a substantially larger influence on subsequent change in MMSE score than the other way around.

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### Table 3. Cross-lagged Model Controlled for Age, Sex, Race, and Education

<table>
<thead>
<tr>
<th>Variable</th>
<th>Round 1 to 2a</th>
<th>Round 2 to 3a</th>
<th>Round 3 to 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized β (SE)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA to VA</td>
<td>0.769 (0.019)</td>
<td>0.712 (0.029)</td>
<td>0.825 (0.022)</td>
</tr>
<tr>
<td>MMSE to MMSE</td>
<td>0.511 (0.018)</td>
<td>0.529 (0.022)</td>
<td>0.676 (0.022)</td>
</tr>
<tr>
<td>VA to MMSE</td>
<td>−0.074 (0.015)</td>
<td>−0.059 (0.012)</td>
<td>−0.065 (0.013)</td>
</tr>
<tr>
<td>MMSE to VA</td>
<td>−0.038 (0.014)</td>
<td>−0.035 (0.013)</td>
<td>−0.047 (0.017)</td>
</tr>
<tr>
<td>Unstandardized β (SE)c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA to VA</td>
<td>0.829 (0.023)</td>
<td>0.829 (0.023)</td>
<td>0.829 (0.023)</td>
</tr>
<tr>
<td>MMSE to MMSE</td>
<td>0.55 (0.025)</td>
<td>0.714 (0.03)</td>
<td>0.714 (0.03)</td>
</tr>
<tr>
<td>VA to MMSE</td>
<td>−0.995 (0.201)</td>
<td>−0.995 (0.201)</td>
<td>−0.995 (0.201)</td>
</tr>
<tr>
<td>MMSE to VA</td>
<td>−0.003 (0.001)</td>
<td>−0.003 (0.001)</td>
<td>−0.003 (0.001)</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE, Mini-Mental State Examination; VA, visual acuity.

a All P < .01.
b Raw coefficients β were constrained. Standardized coefficients were different owing to differences in residual variances.

c Raw coefficients β were constrained.

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Our finding on the longitudinal association between visual impairment and cognitive decline is in agreement with other studies. Using latent growth curve modeling, the Australian Longitudinal Study of Aging,29 which measured cognitive function as memory, speed, and verbal ability in older adults, showed a correlation between the levels of sensory (vision and hearing) and cognitive performance and a moderate-sized association between rates of change in memory and vision (r = 0.22). An analysis by the Berlin Aging study30 using similar analytical techniques also found a moderate correlation between cognitive and sensory declines.

Two theories have been proposed to explain the association between visual impairment and cognitive function decline in older adults. The first theory hypothesizes that visual impairment influences cognitive function through affecting activities older adults are involved (the sensory loss consequence theory).16,31 Poor vision reduces older adults’ ability to participate in activities that help to maintain their well-being and leads to decrease in brain stimulation that could become a risk factor for cognitive function decline. The second hypothesis is that VA and cognitive function decline are both the result of a common cause, such as inflammation or degeneration of central nervous function.32,33 While the association between VA and cognitive function likely operates through both pathways, at least to some extent, few studies have formally tested these hypotheses, to our knowledge. The findings from our research indicate that vision has a greater influence on MMSE score than vice versa and suggests that vision is the dominating factor of the vision-cognition association. This result is supportive of the sensory loss consequence theory.

Strengths and Limitations
Our study has several strengths. We used a prospective and population-based sample to observe vision and cognitive functioning of older adults residing in a community setting. Visual acuity was measured clinically, and therefore measurement inaccuracy was reduced. Our work extends prior work on the association between VA and MMSE score through evaluating the association of within-person changes in a structural equation modeling framework. To our knowledge, this is the first analysis to use cross-lagged modeling techniques to investigate the longitudinal association between VA and cognitive functioning. We estimated the bidirectional associations between VA and MMSE score simultaneously and were able to identify the factor that contributed most to the association. Our trajectory models control for unobserved characteristics of individuals that are not changing substantially within the time frame of the study, e.g., genetic heritage, family social supports. These factors are held constant without having to explicitly control for them in the model. This type of analysis provides stronger support for causal associations compared with a cross-sectional association.

The Mini-Mental State Examination is a global measure of cognitive functioning and may not be as specific as other more clinical cognitive measures. This older population was fairly cognitively intact and had little cognitive impairment even by the end of the study. Further work in populations that includes a spectrum of cognitive functioning are needed to fully examine the direction and driver of the vision-cognition association. Additionally, it is possible that participants with visual impairments had difficulty seeing the vision-dependent items for the MMSE. However, adjusted and prorated MMSE scoring was used, as described in the Methods section.

Conclusions
The number of US residents older than 65 years is projected to more than double in the next 40 years, increasing from 40.2 million in 2010 to 88.5 million in 2050.34 Maintaining good cognitive ability is crucial for older adults’ day-to-day functions and an essential component in healthy aging. Understanding the cognitive changes that accompany aging and finding ways to slow down the pace of cognitive decline is critical for maintaining well-being in late life. The longitudinal association between vision and cognitive functioning suggests maintaining good vision may be an important interventional strategy for mitigating age-related cognitive changes. Our findings reinforce the importance of the primary prevention of visual impairment that could be achieved through the prevention of disabling ocular conditions and treatment of correctable visual impairment.

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