Central Auditory Dysfunction as a Harbinger of Alzheimer Dementia

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Objective: To confirm that central auditory dysfunction (CAD) may be a precursor to the onset of Alzheimer dementia (AD).

Design: Cohort study.

Setting: Research study center.

Participants: Two hundred seventy-four volunteers from a dementia surveillance cohort were followed up for as long as 4 years after undergoing complete audiometric assessment. Twenty-one received a consensus diagnosis of AD after a hearing test.

Intervention: The following 3 central auditory tests were performed: the Dichotic Sentence Identification, the Dichotic Digits, and the Synthetic Sentence Identification With Ipsilateral Competing Message.

Main Outcome Measures: A new diagnosis of AD using the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association criteria at a consensus conference.

Results: The mean scores on each CAD test were significantly poorer in the incident dementia group. Cox proportional hazards models with age as the time scale were used to estimate the hazard ratio for incident dementia based on CAD test results. After adjusting for educational level, the hazard ratio for incident dementia in people with severe CAD based on a Dichotic Sentence Identification in free report mode of less than 50% was 9.9 (95% confidence interval, 3.6-26.7).

Conclusions: Central auditory dysfunction is a precursor to AD. We recommend evaluation with CAD tests in older adults who report hearing difficulty. Those with severe CAD should receive a modified rehabilitation program and be considered for referral for neurologic evaluation.


The growing prevalence and high virulence of Alzheimer dementia (AD) has created a serious public health problem. Early detection of AD is a logical strategy for emerging treatments aimed at limiting the progression of the disorder. However, given the insidious onset of AD, it is difficult to distinguish the normal cognitive decline of aging from pathologic dysfunction in the early stages of AD. Therefore, we sought to determine whether central auditory dysfunction (CAD) is an early manifestation of AD and whether use of CAD testing for older people with hearing concerns might have future utility in the earlier recognition of cognitive disorders such as AD.

Central auditory dysfunction is suspected when people have difficulty understanding speech in the presence of background noise, a common problem for older adults. Most people with age-related CAD can converse reasonably well in quiet but do poorly in noise, the so-called cocktail party effect, which is also referred to by the terms central presbycusis and age-related processing disorder.

Central auditory dysfunction impedes communication and confounds conventional auditory rehabilitation in proportion to its severity. The pathophysiology of CAD is not fully understood, but dichotic listening paradigms have been widely used to study interhemispheric interaction and callosal function. A number of studies, such as the early work by Grady et al and Grimes and colleagues, reported that the inability of patients with AD to divide attention in dichotic performance tasks was related to anterior temporal lobe atrophy and reduced glucose metabolism. More recent research further implicated involvement of parietal and frontal areas, which influence attention processing, and a variety of executive function activities, such as planning and initiation of activities.

Extracting auditory signals in noise or competing signals, as in CAD testing, requires substantial attentional and behavioral processing resources, and we theorize that the neuro-
degneration of the different cortical areas affected by dementia may affect CAD test results before other cognitive screening test results become abnormal.

Prevalence of CAD increases with age and is common in people diagnosed with AD. Central auditory dysfunction is also more prevalent in older people with mild memory impairment compared with cognitively normal older people. These findings suggest that CAD demonstrated by speech-in-noise testing or competing speech is a sign of subtle cognitive dysfunction. Given the dramatic worldwide increase in AD and the finding that many people have subtle cognitive dysfunction years before a diagnosis of AD, efforts aimed at early identification and at-risk status are appropriate. A logical question is whether tests of CAD have a potential role in evaluation of possible cognitive decline in elderly people with hearing complaints. This question has direct clinical relevance because tests for CAD using competing speech are widely available, easy to administer in a short time, and already in use for planning auditory rehabilitation.

In a previous study of the Framingham dementia cohort, severe CAD, based on very low scores (<50% correct) on the Synthetic Sentence Identification With Ipsilateral Competing Message (SSI-ICM) test, was found to presage an incident dementia diagnosis by 3 to 12 years with a risk ratio of 9 to 12. The present study was conducted to confirm these findings in a different population and to determine whether the results of other competing speech tests are also associated with incipient dementia. Thus, we ascertained the presence and degree of CAD in a cohort of older individuals with and without mild memory impairment but no clinical diagnosis of dementia and followed their cognitive status for 4 years. We tested 3 hypotheses:

1. Older people with CAD are more likely to experience the onset of dementia than people without CAD, controlling for age and educational level.
2. In older people with mild, amnestic, single-domain cognitive impairment but no other manifestations of dementia, severe CAD is more prevalent than in people with normal cognitive status.
3. Results of competing speech tests with a dichotic presentation (Dichotic Sentence Identification [DSI]) is more likely to be associated with an increased risk of dementia diagnosis in the follow-up period than are tests involving dichotic digits (Dichotic Digits Test [DDT]) or unilateral competing speech paradigms (SSI-ICM).

METHODS

PARTICIPANTS

Participants were enrolled in the Adult Changes in Thought (ACT) Study, a population-based longitudinal study of aging and dementia that began in 1994. The ACT Study was designed to determine the incidence of Alzheimer disease, other types of dementia, and cognitive impairment and to determine risk factors for these conditions. The details of the ACT Study have been described previously.

The present report is a longitudinal study of the 313 members of the ACT cohort who participated in hearing testing. For the current analysis of incident dementia, 17 subjects with a dementia diagnosis at the time of the hearing test were excluded. In addition, 22 cognitively normal people who dropped out of the ACT Study without a follow-up visit for cognitive assessment after the hearing test were also excluded. These exclusions resulted in an analysis sample of 274 participants. At the time of the hearing test, 54 participants (19.7%) were judged as memory impaired without dementia on the basis of a Cognitive Abilities Screening Instrument (CASI) total score of 86 or less or a total CASI score of 90 or less with a CASI memory subscale score of 10 or less and a team consensus diagnosis confirming that no dementia was present. The ACT Study does not assess subjects as having mild cognitive impairment, but this memory-impaired group likely includes persons in that category. Details regarding group classification procedures can be found in the 2008 study by Gates et al.

Informed consent was obtained for all participants with the use of forms and procedures approved by the Human Studies Committee of the University of Washington and the institutional review board of the Group Health Cooperative.

COGNITIVE SCREENING

The CASI consists of 25 items that cover 9 cognitive domains (attention, mental manipulation, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, and abstraction and judgment). Total scores range from 0 to 100, with higher scores indicating better cognitive performance. After the baseline examination, follow-up examinations that include CASI screening are conducted biennially in the ACT Study to identify incident cases of dementia and AD. Participants scoring 87 or higher on the CASI are considered dementia free.

All participants were administered the CASI at the ACT Study baseline examination and at each biennial evaluation. Persons scoring no more than 86 on the CASI were referred for a standardized clinical and neuropsychological evaluation that was reviewed at a consensus diagnosis meeting attended by a geriatric physician (E.B.L.), neurologist, research nurse, and neuropsychologist (S.M.M.). Dementia diagnosis was based on criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Participants with dementia who met National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable Alzheimer disease at the consensus conference were considered AD cases. The date of dementia onset is defined by convention as the date halfway between the ACT Study visit that triggers the dementia evaluation and the most recent prior ACT Study visit.

HEARING TESTING

Peripheral Auditory Tests

The status of the peripheral auditory system was assessed using standard clinical equipment and spaces. Conventional tympanometry, pure-tone behavioral thresholds, and word recognition scores were obtained with equipment that met American National Standards Institute S3.6-1996 specifications. Additional details can be found in Gates et al. Participants were required to have word recognition scores at a high but comfortable presentation level (which was 90 dB hearing level for most participants) in quiet of 72% correct or better to be included in the study.

Auditory Evoked Potential Test Battery

To control for the functional status of the ascending auditory pathways and primary auditory cortex, auditory brainstem re-
Table 1. Baseline Demographic Characteristics by Performance on the DSI<sup>a</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DSI Score &lt;50%</th>
<th>DSI Score ≥50%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=44)</td>
<td>(n=230)</td>
<td>(N=274)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (38.6)</td>
<td>85 (37.0)</td>
<td>102 (37.2)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (61.4)</td>
<td>145 (63.0)</td>
<td>172 (62.8)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>85.3 (5.6)</td>
<td>78.9 (4.8)</td>
<td>78.9 (5.2)</td>
</tr>
<tr>
<td>Educational level&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤High school</td>
<td>18 (40.9)</td>
<td>52 (22.7)</td>
<td>70 (25.6)</td>
</tr>
<tr>
<td>Some college</td>
<td>13 (29.5)</td>
<td>56 (24.5)</td>
<td>69 (25.3)</td>
</tr>
<tr>
<td>College graduate</td>
<td>13 (29.5)</td>
<td>121 (52.8)</td>
<td>134 (49.1)</td>
</tr>
<tr>
<td>Difficulty hearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (29.5)</td>
<td>105 (45.7)</td>
<td>118 (43.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>31 (70.5)</td>
<td>125 (54.3)</td>
<td>156 (56.9)</td>
</tr>
<tr>
<td>Ever used a hearing aid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36 (81.8)</td>
<td>206 (89.6)</td>
<td>242 (88.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (18.2)</td>
<td>24 (10.4)</td>
<td>32 (11.7)</td>
</tr>
<tr>
<td>Pure-tone average, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better ear</td>
<td>27.8 (8.5)</td>
<td>22.7 (8.7)</td>
<td>23.5 (8.9)</td>
</tr>
<tr>
<td>Worse ear</td>
<td>33.2 (8.5)</td>
<td>26.9 (9.4)</td>
<td>27.9 (9.5)</td>
</tr>
<tr>
<td>Word recognition score, worse ear, %&lt;sup&gt;c&lt;/sup&gt;</td>
<td>42 (95.5)</td>
<td>225 (97.8)</td>
<td>267 (97.4)</td>
</tr>
<tr>
<td>≥80</td>
<td>2 (4.5)</td>
<td>5 (2.2)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Baseline CASI score, mean (SD)</td>
<td>88.8 (5.4)</td>
<td>95.6 (3.9)</td>
<td>94.5 (4.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CASI, Cognitive Abilities Screening Instrument; DSI, Dichotic Sentence Identification.
<sup>a</sup>Unless otherwise indicated, data are expressed as number (percentage) of subjects. Percentages have been rounded and might not total 100.
<sup>b</sup>One person with a DSI score of 50% or higher did not report educational level.
<sup>c</sup>Word recognition score was calculated for each ear. If all numbers were recognized correctly, a score of 100% (50×2) was given. The participant reported all digits heard for each presentation and a percentage-correct score was calculated for each ear.

Central Auditory Processing Tests

The 3 behavioral central auditory tests were the SSI-ICM, the DSI in the free mode, and the DDT. The sequence of test presentation was randomized to prevent an order effect. Recorded materials on compact disc used for the tests were obtained from Auditec of St Louis (Maplewood, Missouri). The poorer score across ears was used in the present analyses.

Synthetic Sentence Identification With Ipsilateral Competing Message. The SSI-ICM requires the listener to select which one of 10 nonsense sentences was presented against a background of an interesting narrative presented by the same talker in the same ear. A practice presentation of 1 to 3 lists was completed with a +10 dB signal to noise ratio. For the actual test, the stimulus was at 0 dB signal to noise ratio at the same presentation level. Up to 30 presentations may be necessary to reach an asymptote.<sup>11,12</sup> Only 1 list of 10 sentences was presented for participants scoring 90% or better, and 2 lists were presented if the score was 80% or better; otherwise, 3 lists were presented. This strategy was used for the training and the actual test. Because raw SSI-ICM scores are known to decrease with age and hearing level, we used a presentation level 50 dB above the mean pure-tone threshold (at 0.5, 1.0, and 2.0 kHz) and inserted earphones to enhance high-frequency audibility and avoid collapsing ear canals. To obtain optimal performance from the participants, pauses between presentations were taken as needed for slow responders. Correct identification of 80% or more of presentations is considered normal.

Dichotic Sentence Identification. The DSI uses 6 of the same sentences as the SSI-ICM but presents 1 sentence to each ear simultaneously. The sentences were presented at 30 dB above the pure-tone average in each ear, and the participant was asked to select from a printed list which 2 sentences were heard. Filer et al<sup>11</sup> showed that the test is resistant to the effects of senoneural hearing loss until the degree of loss exceeds 50 dB. The DSI was administered as outlined by Jerger and Martin<sup>15</sup> in the free report mode. Five presentations were used if the score was 100%; otherwise, another 5 sentences per ear were administered (20 sentences in total). In adults, the right ear scores are normally higher than the left ear scores, presumably owing to age-related corpus callosum dysfunction.<sup>15</sup> Normal scores are 80% or higher in adults.

Dichotic Digits Test. The DDT is a widely used dichotic test to screen for CAD.<sup>16</sup> The DDT was given at 50 dB above the pure-tone average for each ear. After practice sessions were completed, 25 sets of double-digit pairs were presented for a total of 50 digits per ear. The participant reported all digits heard for each presentation and a percentage-correct score was calculated for each ear. If all numbers were recognized correctly, a score of 100% (50×2) was given. The participant reported all digits heard for each presentation, and a percentage-correct score was calculated for each ear. The DDT is relatively easy to administer and is not greatly affected by mild to moderate hearing loss.<sup>14</sup> The score is commonly abnormal in people with probable AD.<sup>17</sup> Normal scores for adults are 90% or higher.<sup>18</sup>

STATISTICAL METHODS

The behavioral CAD tests were scored on the left and right ears of each study participant. For each CAD test, the current analysis used the poorer of the 2 scores from the left and right ears. Mann-Whitney rank sum tests were used to evaluate differences in the peripheral audiometric measures between participants with a dementia diagnosis during follow-up compared with those without a dementia diagnosis. Cox proportional hazards models with age as the time scale were used to estimate the hazard ratio for incident all-cause dementia and AD associated with moderate or severe CAD. In analyses with AD as the outcome, follow-up time for participants with a dementia diagnosis of a type other than AD was censored at the dementia diagnosis date. Patients without a dementia diagnosis were censored at the date of their last ACT Study visit. Regression models were adjusted for education level. We used commercially available software (STATA, version 11 for Windows; StataCorp LP, College Station, Texas) for data analysis.

Table 1 shows the demographic characteristics of the study population. Of 274 participants, 37.2% were male, and nearly half (49.1%) were college graduates. The mean age was 79.6 (range, 71-96) years. More than half (56.9%) said they had a hearing problem, but only 11.7% had ever used a hearing aid. The word recognition score was normal (80% correct or better) in at least 1 ear for all par-
Participants and from 72% to 80% in the poorer ear in 7 participants (2.6%). Twenty-three participants had a positive consensus dementia diagnosis resulting from a follow-up ACT assessment at 10 to 48 months (mean, 26.4 months) after the hearing test. The mean time from the hearing test to dementia onset for the incident cases was 14 months. Of the 23 all-cause dementia diagnoses, 21 (91%) also met the NINCDS-ADRDA criteria for possible or probable AD. Eighteen of the incident dementia cases were from participants with memory impairment at the time of the hearing test, and 5 were from the cognitively normal group. These 5 participants received their dementia diagnosis at 4, 9, 19, 21, and 24 months after the hearing test.

Table 2 gives the mean scores for each of the 3 CAD tests and the percentage of participants with moderately abnormal (<80% correct) and severely abnormal (<50% correct) results, stratified by dementia status during follow-up. On each hearing measure evaluated, the incident dementia group performed worse than the nondemented group, and the differences were statistically significant. On average, the nondemented group scored approximately 75% correct across all 3 tests. The success across tests was more varied for the incident dementia group, with mean scores of 55% for the SSI-ICM and 58% for the DDT. The incident dementia group scored particularly poorly on the DSI, with a mean score of 37%. The proportion of participants scoring below the threshold for severe abnormality ranged between 8.8% (DDT) and 19.1% (SSI-ICM) among the nondemented participants. Among the incident dementia group, nearly two-thirds (65.2%) scored in the severely abnormal range on the DSI.

The results from the Cox proportional hazards models are summarized in Table 3. Because only 2 of the incident dementia cases were non-AD, the regression results for all-cause dementia and AD were similar. Only the results for the outcome of incident AD are presented herein. The adjusted hazard ratio for severe CAD (<50%) based on the DSI was 9.9 (95% confidence interval [CI], 3.6-26.7). Moderate impairment (<80%) on the DSI was also associated with increased risk of AD diagnosis, with an estimated hazard ratio of 6.8 (95% CI, 1.9-24.1). Moderate impairment on the DDT was also associated with increased risk of AD, but a score of less than 50% was not a significant predictor. The SSI-ICM results were not significant predictors at either level.

### COMMENT

This is the second report showing an increased risk of a subsequent diagnosis of AD in older people with severe CAD. The present study showed that severe CAD as measured by the DSI in free report mode strongly and significantly predicted the risk of a subsequent diagnosis of AD up to 3 years later. The bulk of the incident dementia cases (80.3%) were in the original memory-impaired group (based on the CASI test results), and many of these may have had early dementia at the time of auditory testing if they had undergone evaluation. Nonetheless, the association of severe CAD and early dementia remains.

Given that more than 1 million older people undergo auditory evaluation annually as part of the rehabilitation of age-related hearing loss, adding the DSI to that evaluation would be likely to (1) establish or not establish the need for a modified aural rehabilitation program, (2) identify people at risk for cognitive dysfunction, and (3) generate appropriate referrals at little extra cost or time.

Determining the presence of CAD with the use of behavioral tests that include dichotic competing speech paradigms has established value in selecting appropriate auditory rehabilitation measures for people with presbycusis. In some cases, unilateral hearing aid fitting might be more appropriate than the customary binaural approach. In addition, computer-based auditory training exercises are becoming widely available and may be useful in enhancing speech comprehension.

The present study extends the utility of CAD testing in the detection of older people at risk for cognitive decline. Elderly people with very poor scores (<50%) on the dichotic competing speech tests but with normal or near-normal speech recognition in quiet may have cognitive decline as a factor. Future research might include a larger study to determine how frequently these findings occur and what the longer-term outcomes may be; eventually, strategies aimed to target interventions on this population should be evaluated. We believe that it is already reasonable to consider such cases for referral for neurologic assessment.

If CAD indeed predicts the risk of a later dementia diagnosis, tests for CAD would be more useful in the evaluation of elderly persons who report hearing difficulty than they are at present. Tests for CAD are currently used for people who have difficulty understanding speech in noise while wearing hearing aids. If our results are confirmed by future studies, the case could be made for the widespread use of the tests to screen for CAD as a cause of hearing difficulty and a risk factor for possible incipient
dementia and, thus, as an indication for neuropsychological evaluation. Although this approach would identify only a fraction of the total at-risk population, this fraction could undergo evaluation for dementia sooner than the remainder of the population. Such a strategy would generate an enriched population for studies of new treatments designed to alter the course of the disease at an early stage.

**STRENGTHS OF STUDY**

The value of a prospective cohort approach is well known. The auditory study was an addition to the original ACT Study and benefited from the experience of the study scientists. Auditory testing was viewed by the cohort members as a popular addition. The cohort members were familiar with the cognitive testing methods and easily adapted to the auditory test paradigms. Early identification of people at risk for AD will become increasingly important, especially if new, more effective treatments to delay the progression of AD are developed. Given that 1 million hearing aid evaluations of adults are performed annually in the United States and that about 15% of these adults may have CAD, it is entirely plausible that central auditory testing could provide a useful screen for risk of preclinical AD. Additional study will be required to test that presumption.

**WEAKNESSES OF STUDY**

The underlying premise of this study was that auditory testing might have utility as a screening test for dementia risk. The short span between hearing test and consensus in some cases argues that some participants, particularly those who failed consensus within 6 months of the auditory testing, may have been in an early, albeit undetected stage of dementia at the time of their hearing test. However, none of these people were reported by their family members to be demented in terms of daily activities or worsened memory. Furthermore, the longer duration between test and consensus diagnosis for other subjects is consistent with our earlier findings. Because the transition between normalcy and dementia is usually envisioned as gradual, contemporary thinking suggests a transition zone between the 2 states. From that viewpoint, our CAD testing clearly labeled most of those who received a dementia diagnosis shortly after the auditory testing as being in such a transition. This is analogous to the now popular diagnostic state, mild cognitive impairment. It is not known whether CAD might be a good predictor of mild cognitive impairment in persons who are more likely to experience progression. This is another important area in which more research might be particularly valuable.

Another limitation of this study is the robustness of the results. The small sample size resulted in wide CIs around the estimated effect sizes. However, despite the wide CIs, the results from this study support the findings from our previous study, and the consistency of the results across different study populations (ACT and Framingham) help to build the case for the observed associations.

Given that none of our participants was diagnosed as having dementia at the time of the hearing test, the finding that CAD heralds a dementia diagnosis in a substantial number of cases has real-world implications. In our previous incident dementia cohort study, the SSI-ICM was the only CAD test available. Comparison of the SSI-ICM, DDT, and DSI (Table 2) in the present study indicated...
cates that the DSI has the best predictive power for incident dementia among the 3. In the present study, far greater effort was made to achieve maximum SSI-ICM scores than was possible previously. The modified SSI-ICM paradigm11 may have made the test too easy. The cutoff point at which the CAD test results are imputed to be normal has traditionally been 80% or more correct answers. However, using that score as a cutoff point in this and previous populations contributes to poor specificity of CAD testing in estimating the likelihood for subsequent dementia conversion. As in our previous report, a grossly abnormal score (<50% correct) in the presence of normal or near-normal word recognition scores improves the specificity greatly. When a very low DSI score is used in people with normal or near-normal (>72% correct) word recognition scores in quiet, the sensitivity of the low DSI score to detect incipient dementia is 65% (95% CI, 44%-86%) and the specificity is 88% (84%-92%), with a positive predictive value of 34% (20%-49%) and a negative predictive value of 97% (94%-99%). These findings illustrate the importance of considering the results of CAD testing in elderly individuals as merely indicators for further evaluation rather than as indicative of a definitive dementia diagnosis.

CONCLUSIONS

We recommend that central auditory function be evaluated in senior citizens seeking assistance for hearing difficulty generally and in those specifically reporting difficulty hearing in noise. Patients who have a very poor score (ie, <50% correct) and are not known to be demented should be considered prime candidates for referral and evaluation of cognitive function. In the present study, the DSI in free report mode was the test most likely to uncover a latent cognitive defect. The DDT using less than 80% correct as the cutoff was also associated with a subsequent dementia diagnosis, although it was not as robust as using less than 50% correct as the criterion. The DDT is easier to complete than the DSI or the SSI-ICM, which resulted in fewer people falling into the very low score category.

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Author Contributions: Drs Gates and Larson and Ms Anderson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gates, McCurry, Feeney, and Larson. Acquisition of data: Gates, McCurry, Feeney, and Larson. Analysis and interpretation of data: Gates, Anderson, McCurry, Feeney, and Larson. Drafting of the manuscript: Gates, Anderson, McCurry, and Feeney. Critical revision of the manuscript for important intellectual content: Gates, Anderson, McCurry, and Larson. Statistical analysis: Anderson. Obtained funding: Gates, McCurry, and Larson. Administrative, technical, and material support: Feeney and Larson. Study supervision: Gates and Feeney.

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REFERENCES


