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Dual Sensory Impairment and Cognitive Impairment in the Korean Longitudinal Elderly Cohort

Gihwan Byeon, MD,* Gyu Han Oh, MD,* Jin Hyeong Jhoo, MD, PhD, Jae-Won Jang, MD, PhD, Jong Bin Bae, MD, Ji Won Han, MD, PhD, Tae Hui Kim, MD, Kyung Phil Kwak, MD, PhD, Bong Jo Kim, MD, PhD, Shin Gyeom Kim, MD, Jeong Lan Kim, MD, PhD, Seok Woo Moon, MD, PhD, Joon Hyuk Park, MD, PhD, Seung-Ho Ryu, MD, PhD, Jong Chul Youn, MD, PhD, Dong Woo Lee, MD, PhD, Seok Bum Lee, MD, PhD, Jung Jae Lee, MD, PhD, Dong Young Lee, MD, PhD, and Ki Woong Kim, MD, PhD

Correspondence
Dr. Jhoo
jhoojh@kangwon.ac.kr

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Abstract

Objective

To investigate the effects of single sensory impairment (SSI; visual or auditory) or dual sensory impairment (DSI; visual and auditory) on dementia and longitudinal changes of neuropsychological test scores.

Methods

In this nationwide, prospective, community-based elderly cohort study, KLOSCAD (the Korean Longitudinal Study on Cognitive Aging and Dementia), 6,520 elderly individuals (58–101 years) representing the general population were included. We defined visual and auditory sensory impairment via self-report questionnaire: 932 had normal sensory function, 2,957 had an SSI, and 2,631 had a DSI. Demographic and clinical variables including cognitive outcomes were evaluated every 2 years over 6 years. Through logistic regression, Cox regression, and linear mixed model analysis, the relationship between SSI or DSI and dementia prevalence, dementia incidence, and change in neuropsychological scores were evaluated.

Results

At baseline, DSI was significantly associated with increased dementia prevalence compared to normal sensory function (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.17–4.02), but SSI was not (OR 1.27, 95% CI 0.66–2.41). During the 6-year follow-up, the incidence of dementia was significantly higher in the DSI group than in the normal sensory function group (hazard ratio 1.9, 95% CI 1.04–3.46) and neuropsychological scores significantly decreased (β −0.87, 95% CI [−1.17 to −0.58]).

Conclusions

Our results suggest that coexisting visual and hearing impairments facilitate dementia prevalence, dementia incidence, and cognitive decline, but visual or hearing impairment alone do not. Visual and hearing impairment may lead to dementia or cognitive decline independent of Alzheimer pathology.

*These authors contributed equally to this work.

From the Departments of Psychiatry (G.B., J.H.J.) and Neurology (J.-W.J.), Kangwon National University Hospital, Chuncheon; Public Health Medical Service (G.H.O.) and Department of Neuropsychiatry (D.Y.L.), Seoul National University Hospital; Department of Neuropsychiatry (J.B.B., J.W.H., K.W.K.), Seoul National University Bundang Hospital, Seongnam; Department of Psychiatry (T.H.K.), Yonsei University Wonju Severance Christian Hospital; Department of Psychiatry (K.P.K.), Dongguk University Gyeonju Hospital; Department of Psychiatry (B.J.K.), Gyeongsang National University School of Medicine, Jinju; Department of Neuropsychiatry (S.G.K.), Soonchunhyang University Bucheon Hospital; Department of Psychiatry, School of Medicine (J.L.K.), Chungnam National University, Daejeon; Department of Psychiatry, School of Medicine (S.W.M., S.-H.R.), Konkuk University, Konkuk University Chungju Hospital; Department of Neuropsychiatry (J.H.P.), Jeju National University Hospital; Department of Neuropsychiatry (J.C.Y.), Kyunggi Provincial Hospital for the Elderly, Yongin; Department of Neuropsychiatry (D.W.L.), Inje University Sanggye Paik Hospital, Seoul; Department of Psychiatry (S.B.L., J.J.L.), Dankook University Hospital, Cheonan; and Department of Psychiatry, College of Medicine (D.Y.L., K.W.K.), and Department of Brain and Cognitive Science, College of Natural Sciences (K.W.K.), Seoul, Korea.

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Glossary

AD = Alzheimer disease; **BMI** = body mass index; **CERAD TS** = Consortium to Establish a Registry for Alzheimer's Disease Total Score; **CERAD-K** = Korean version of the Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **CIRS** = Cumulative Illness Rating Scale; **DSI** = dual sensory impairment; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **GDS-KR** = Korean version of the Geriatric Depression Scale; **HR** = hazard ratio; **KLOSCAD** = Korean Longitudinal Study on Cognitive Aging and Dementia; **LMM** = linear mixed-effects model; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MOS-SSS** = Medical Outcomes Study Social Support Survey; **OR** = odds ratio; **SSI** = single sensory impairment.

The prevalence of dementia is increasing with society's aging. East Asia is a rapidly aging area.[1] Hearing and visual impairments are also common in the elderly, and can coexist in the same individual, leading to a dual sensory impairment (DSI).[2-5] There are several studies on whether sensory impairments, including vision and hearing impairments, constitute a risk factor for dementia or cognitive decline.[6-8] However, studies on DSI are relatively rare and have produced conflicting results.[9,10] Most studies had relatively small samples, were cross-sectional in design, and used inconsistent outcome variables (different diagnostic criteria for dementia) and simple screening tests (e.g., Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment).[11] Moreover, they did not assess dementia incidence or change in neuropsychological scores. They were mainly conducted in Western countries; hence, most focused on White races. Large-scale studies on the association between DSI and cognitive impairment in Asian patients are lacking.

We aimed to determine the effect of visual or hearing impairments on dementia baseline prevalence, dementia incidence, and cognitive decline during follow-up by implementing a retrospective analysis of data from a large-scale elderly prospective community cohort study in Korea. We examined whether the *APOE* genotype interacts with sensory impairments to cause cognitive dysfunction. Lastly, we attempted to determine whether sensory impairments had a more significant effect on Alzheimer-related dementia development than on dementia in general.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board of Seoul National University Bundang Hospital (IRB number B-0912-089-010) and written informed consent was obtained from each participant or caregiver after receiving a complete explanation of the study.

Participants

This study was conducted as part of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), a nationwide, prospective, community-based elderly cohort study, which aimed to evaluate cognitive aging and dementia in community-dwelling elderly Koreans aged ≥60 years. In order to construct a representative cohort of elderly Koreans, we randomly sampled 30 villages and towns from 13 districts across South Korea. In October 2010, we randomly selected 10% of residents aged ≥60 years in urban areas and 20% in rural areas using residential rosters. Finally, 12,694 elderly individuals were sampled, and 6,818 (53.7%) participated in the baseline KLOSCAD assessment. Between November 2012 and October 2014, initial baseline evaluations were conducted and subsequent follow-ups were performed biennially. In this study, we included data until the third follow-up. Among the participants of the baseline evaluation (n = 6,818), we excluded 318 participants who did not self-report visual and hearing evaluations.[12] The number of participants at each wave and attrition are presented in figure 1.

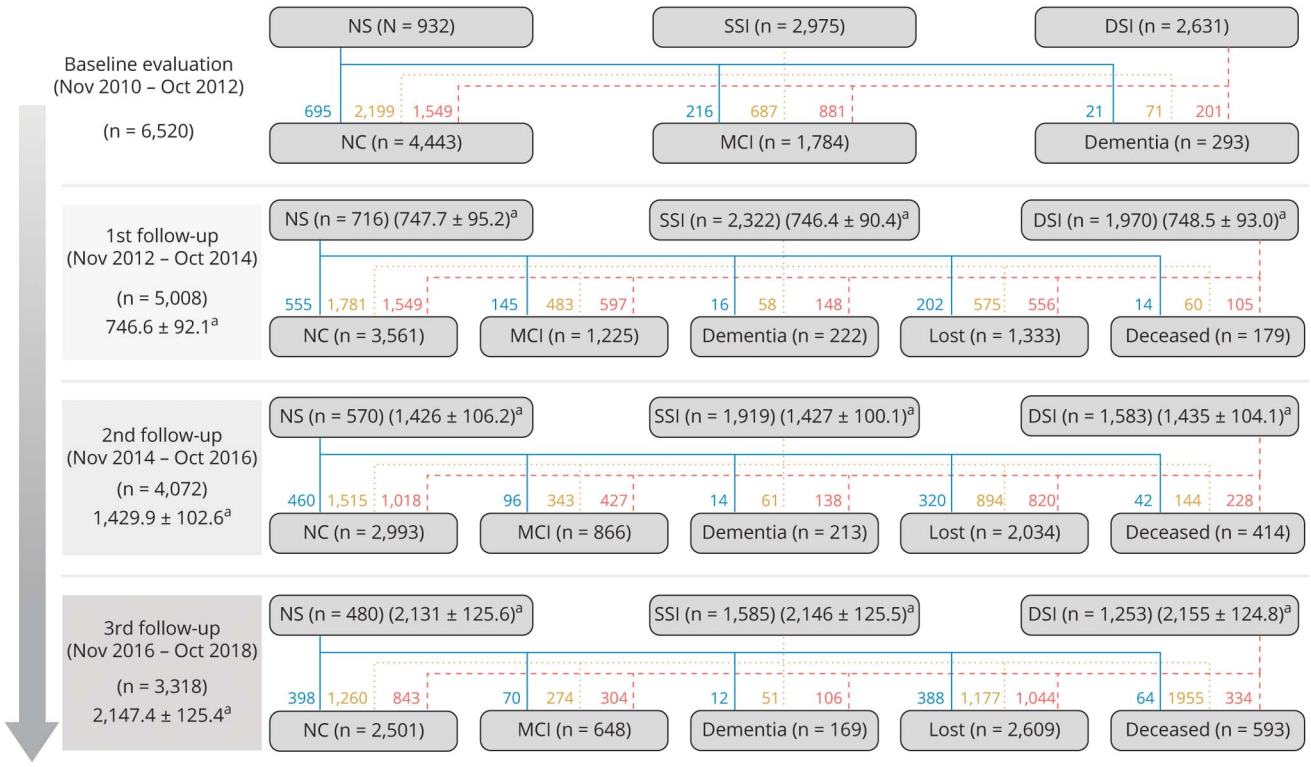
Measures

KLOSCAD participants were evaluated with clinical and laboratory assessments, including *APOE* genotyping, and with neurocognitive tests. Detailed information regarding each assessment is provided below.

Clinical and Laboratory Assessments

Demographic information (age, sex, education level, income, body mass index [BMI], exercise time, alcohol consumption, caffeine consumption, and cigarette smoking) was obtained from all participants and dichotomized or categorized according to existing evidence[13-16] to insert them into the regression model as covariates (table 1). Education and income were categorized so that the distributions had equal numbers of individuals. Regarding education, the following 5 categories were offered: "Did not attend any school/Graduated from elementary school/Graduated from middle school/Graduated from high school/Was enrolled in a university or superior school." Income was divided according to the total household monthly income. Low income corresponded to <845 dollars; the intermediate group, 845 < x < 2,535 dollars; and the high group, >2,535 dollars. Comorbid illness and chronic illness burden[17] were evaluated with the Cumulative Illness Rating Scale (CIRS). We subtracted the score of "eyes, ears, nose, and throat" and of "psychiatric illness" from the total CIRS score to avoid redundancy in the evaluation. We evaluated depression with the Korean version of the Geriatric Depression Scale (GDS-KR). According to a prior validation study, in participants >80 years, >15 points were dichotomized as depression and <15 points as no depression. In participants <80 years, >16

Figure 1 Number of Participants and Follow-up Length of the Cohort at Each Wave



After baseline evaluation, 3 follow-up waves were implemented at intervals of about 2 years. The period in parentheses indicates the period in which the evaluation was conducted. n indicates the number of participants for each group. [a]The follow-up period (days) from the baseline at the time the evaluation was performed in each wave for each group (mean ± SD). DSI = dual sensory impairment; MCI = mild cognitive impairment; NC = normal cognition; NS = normal sensory; SSI = single sensory impairment.

points were dichotomized as depression and <16 points as no depression.[18] The overall social support of the patient was evaluated using the total Medical Outcomes Study Social Support Survey (MOS-SSS) score as a continuous variable.[19] *APOE* genotyping was tested in participants who consented to genetic testing.

Neurocognitive Tests

We assessed the participants' cognitive function using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K). The CERAD-K consists of the following subitems: J1, Verbal fluency test; J2, Boston Naming Test; J3, MMSE for Dementia Screening; J4, Word list memory test; J5, Constructional praxis test; J6, Word list recall test; J7, Word list recognition test; J8, Constructional recall test; and J9 A/B, Trail-Making Test A and B.[20,21] The CERAD total score (TS) was calculated by summing J1–J7 to evaluate overall cognitive domains, according to a previous study.[22]

Clinical Diagnosis

To diagnose cognitive disorders, geriatric neuropsychiatrists specialized in dementia research conducted a face-to-face standardized diagnostic interview including physical and neurologic examinations using the CERAD-K Packet Clinical Assessment Battery.[20] According to the principle of the Clinical Dementia Rating, severity of dementia was evaluated considering premorbid function of the participant.[23] Dementia was diagnosed according to DSM-IV diagnostic criteria.[24] Only participants with activities of daily living impairment due to cognitive decline such as memory, orientation, and judgment were judged as having dementia, and deterioration due to physical disability and depression were excluded.[23,24] This evaluation result was confirmed by a consensus panel conference formed by a geriatric psychiatrist, clinical psychologist, and a nurse. The dementia subtype was determined according to the following established diagnostic criteria: Alzheimer disease (AD) according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[25]; and vascular dementia according to the criteria of the National Institute of Neurologic Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences Neurocognitive tests.[26] The diagnosis of mild cognitive impairment (MCI) was according to the Consensus Criteria from the International Working Group on MCI.[27]

Assessment of Auditory and Visual Function

Participants were asked to self-evaluate their hearing. "Normal" was 0, "Reduced but able to communicate without using a hearing aid" was 1, "Reduced so that communication is possible only using hearing aids" was 2, "Difficulty communicating even when hearing aid is used" was coded as 3, and "I can't hear at

all" was coded as 4. In the case of visual function, "Normal" was 0, "Reduced, but able to view newspaper or television without wearing glasses or lenses" was 1, "Reduced, so that I can view newspaper or television only with glasses or lenses" was 2, "Reduced. As a result, I can't view newspaper or television even if I wear glasses or lenses" was 3, and "I can't see at all" was 4. In this study, 0 was defined as "normal" and 1, 2, 3, and 4 were defined as "sensory impairment." The group with normal visual and hearing function was classified as normal sensory function, the group with visual only or auditory only impairments was classified as single sensory impairment (SSI), and the group with both visual and hearing impairments was classified as DSI.

Statistical Analysis

To compare baseline demographic and clinical characteristics among sensory groups, analysis of variance was performed for continuous variables and Pearson χ^2 test for categorical variables. Multiple logistic regression analysis was performed to examine the effect of sensory impairment on baseline dementia prevalence. Next, to examine the effect of baseline sensory impairment on dementia incidence during the follow-up period (first–third follow-up; about 6 years), Cox hazard regression was implemented excluding participants with dementia at baseline. Finally, we examined longitudinal cognitive decline (during the follow-up period) using linear mixed-effects models (LMM). In this analysis, we also excluded participants with dementia at baseline evaluation because our main purpose was to analyze whether sensory impairment predicted subsequent cognitive decline. We evaluated the association between baseline sensory impairment and cognitive decline (change in CERAD TS during follow-up period) with "time from baseline" × "group (normal sensory function/SSI/DSI)" interaction in a LMM.

In the above analyses, 3 models were set according to covariates. When implementing logistic and Cox analyses, in model 1, demographic variables (age, sex, education, income) were adjusted for; in model 2, comorbid disease and lifestyle variables (CIRS, BMI, alcohol consumption, smoking, exercise) were added to the covariates of model 1; and in model 3, depression (GDS) and social support (MOS-SSS) were additionally inserted as covariates. Regarding LMM analysis, baseline diagnoses, which included normal cognition (reference) and MCI, were added as covariates to adjust for the effect of an existing cognitive impairment. Other covariates were inserted in the same order as in the logistic and Cox regression analyses. Because depression and social support could have a mediating effect attenuating the association between sensory impairment and cognitive impairment, our main interest was in model 2.

When categorical variables were inserted as independent variables in the analytic models, the reference value was assigned as follows. For sensory impairment group, "normal sensory group," for sex, "female," for education, "not attending any school," for income, "lower," for BMI, "normal," for alcohol consumption, "non problematic drinking," for smoking, "never," for caffeine consumption, "not excessive," for exercise, ">150," and for depression, "no depression."

Furthermore, in order to investigate whether visual only impairment and auditory only impairment influenced cognitive function differently, we further divided the groups into normal sensory function, auditory only impairment, visual only impairment, and DSI, and repeated the above analyses.

As a sensitivity analysis, a LMM analysis was performed excluding not only dementia but also MCI at baseline to reject the occurrence of visual or hearing impairment in people with underlying cognitive decline.

Moreover, to overcome the weakness that the independent variable in this study was produced by self-report questionnaire, we conducted another supplementary analysis. Among CIRS, using the presence or absence of eye and ear disease such as "cataract, glaucoma, macular degeneration, and hearing loss" specifically coded in the category of "eyes, ears, nose, and throat," we classified them into "nondiagnosed"/"single disease (eye or ear disease alone)"/"dual disease (both eye and ear disease)" groups and performed the above analysis. We present the results only for model 2.

To examine the interaction effect between *APOE* genotype and sensory impairment, we first implemented a generalized estimating equation model analysis adding the interaction term between *APOE* ε4 positivity and sensory group with the same covariates as the above model. If the interaction term was statistically significant, to confirm whether the *APOE* genotype interacts with the sensory impairment in causing cognitive decline, a logistic regression, LMM, and Cox regression analysis were conducted according to *APOE* ε4 positivity (whether or not there is an *APOE* ε4 allele). Due to the small number of participants with *APOE* genotype results, the statistical power was expected to be weak. Therefore, model 1, with a relatively small number of covariates, was employed. Second, logistic and Cox hazard regression analyses were performed by limiting the dependent variables to AD dementia in order to test whether sensory impairment had distinctive effects on the development of AD relative to other dementia types. As the number of dementia subtype events was smaller than the total and the statistical power decreased, only models 1 and 2 were presented.

We performed all statistical analyses using R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). All tests were 2 sided with $\alpha = 0.05$ and we report 95% confidence intervals (CIs).

Data Availability

The datasets used or analyzed in this study are available from Ki Woong Kim on reasonable request.

Results

Baseline Characteristics

Among the 6,520 participants included at baseline, 932 were in the normal sensory group, 2,957 in the SSI group, and 2,631 in

the DSI group. Among the 3 groups, dementia was more prevalent in the DSI group (n = 201, 7.6%; table 1). The age of all cohort participants ranged from 58 to 101 years.

Their baseline characteristics are shown in table 1. In the DSI group, compared to the other groups, men were more prevalent, and participants were older, had lower educational background, lower income, more comorbid diseases, a higher rate of depression, less social support, drank more alcohol, smoked more, and exercised less. These variables were later added as covariates in the analytical model.

The number of participants and follow-up length (days) at each wave are presented in figure 1. At the final third follow-up, about 51% (3,818/6,520) of baseline participants completed the evaluation. When comparing the baseline characteristics of the group who completed the third follow-up evaluation (n = 3,318) with the group who dropped out or died (loss group) during the follow-up period (n = 3,202), patients in the loss group were older (71.7 ± 7.6 vs 68.8 ± 6.0, $p < 0.001$), had less education ("not attending school and only elementary school": 53.7% vs 44.2%, $p < 0.001$), and were more likely to have a lower income (41.4% vs 34.8%, $p < 0.001$). In addition, patients in the loss group were more frequently diagnosed with dementia (7.4% vs 1.7%, $p < 0.001$), more frequently diagnosed with depression (22.9% vs 20.1%, $p = 0.009$), and have a lower MOS-SSS score (69.5 ± 24.3 vs 71.2 ± 22.8, $p = 0.004$). However, sex (female: 56.2% vs 57.7%, $p = 0.219$) and CIRS score (4.1 ± 2.6 vs 3.9 ± 2.5, $p = 0.058$) were not significantly different between the "loss" and "completed" groups.

Association Between Sensory Impairments and Baseline Dementia Prevalence

At baseline, the number of individuals with dementia was 343. Logistic regression analysis revealed, according to models 1 and 2, that DSI was significantly associated with high baseline dementia prevalence (model 1: odds ratio [OR] 1.74, 95% CI 1.07–2.84; model 2: OR 2.17, 95% CI 1.17–4.02), but that SSI was not. However, in model 3, this relationship was no longer statistically significant (model 3: OR 1.81, 95% CI 0.94–3.49). The covariates included in model 3, depression and MOS-SSS, significantly increased (OR 2.98) or lowered (OR 0.99) the probability of dementia, respectively (table 2).

Association Between Sensory Impairments and Dementia Incidence During Follow-up

The total number of individuals who developed dementia during the 6-year follow-up period was 245. In the Cox regression analysis of dementia incidence from baseline, DSI significantly increased the incidence of dementia in models 1 (hazard ratio [HR] 2.19, 95% CI 1.25–3.81) and 2 (HR 1.9, 95% CI 1.04–3.46), while SSI did not. This relationship was no longer significant in model 3 (HR 1.79, 95% CI 0.98–3.28; table 3).

Association Between Sensory Impairments and Change in Neuropsychological Test Scores During Follow-up

In LMM analysis with CERAD TS as outcome variable, after follow-up, the overall CERAD TS score increased (β 0.65, 95% CI 0.40–0.91, $p < 0.001$). There was a statistically significant time interaction with DSI in all models (1, 2, and 3; model 1: β −0.8, 95% CI = −1.08 to −0.51, $p < 0.001$; model 2: β −0.87, 95% CI = −1.17 to −0.57, $p < 0.001$; model 3: β −0.86, 95% CI −1.16 to −0.56, $p < 0.001$), but not with SSI. These results imply that the neurocognitive scores of the DSI group significantly decreased during follow-up compared to the other groups (normal sensory group, SSI group; table 4 and figure 2).

Association Between Sensory Impairment and Cognitive Impairment (Division Into 4 Groups)

To determine the specific effects of visual and hearing impairments on dementia and cognitive decline, the same analysis was performed with a further division of the groups into normal sensory, hearing impairment alone, visual impairment alone, and both visual and hearing impairment (DSI) groups. The results indicated a significant effect of DSI on dementia baseline prevalence, dementia incidence, and cognitive decline. But no significant effects of visual (OR 1.27, 95% CI 0.67–2.44; HR 1.23, 95% CI 0.66–2.30; β −0.12, 95% CI −0.41 to 0.16, $p = 0.397$) or of hearing impairment alone (OR 1.15, 95% CI 0.35–3.79; HR 0.93, 95% CI 0.26–3.30; β −0.38, 95% CI −1.01 to 0.26, $p = 0.245$) were observed.

Sensitivity Analysis

When LMM analysis was performed excluding baseline MCI, the DSI × follow-up period interaction was statistically significant (model 2: β −0.88, 95% CI −1.21 to −0.55, $p < 0.001$), which was not the case for SSI (model 2: β −0.04, 95% CI −0.35 to 0.27, $p = 0.786$).

Association Between Specific Eye or Ear Disease in CIRS and Prevalence and Incidence of Dementia and Cognitive Decline

In the analysis, single disease (OR 0.97, 95% CI 0.71–1.32, $p = 0.846$) and dual disease (OR 0.75, 95% CI 0.31–1.60, $p = 0.487$) did not have a significant effect on the prevalence of dementia. Dual disease (HR 1.95, 95% CI 1.05–3.64, $p = 0.034$) but not single disease (HR 0.95, 95% CI 0.71–1.29; HR 1.23, $p = 0.757$) had a significant effect on the incidence of dementia. Both single disease (β −0.5, 95% CI −0.71 to 0.29 $p < 0.001$) and dual disease (β −1.12, 95% CI −0.71 to −0.29 $p = 0.004$) had significant interaction effects with period on CERAD TS, while the effect size of dual disease was larger.

Interaction and Subgroup Analysis According to *APOE* ε4 Positivity

Among baseline participants, the number of individuals with *APOE* genotype results was 5,211. The number of *APOE* ε4 positive individuals was 1,202 and that of *APOE* ε4 negative

Table 1 Demographic Characteristics of Participants at Baseline

Variables	Normal sensory (n = 932)	SSI (n = 2,957)	DSI (n = 2,631)	*p* Value
Diagnosis				
Normal cognition	695 (74.6)	2,199 (74.4)	1,549 (58.9)	<0.001
Mild cognitive impairment	216 (23.2)	687 (23.2)	881 (33.5)	
Dementia	21 (2.3)	71 (2.4)	201 (7.6)	
Alzheimer dementia[a]	14 (66.7)	51 (71.8)	145 (72.1)	
Age, y	68.3 ± 6.1	68.8 ± 6.2	72.6 ± 7.4	<0.001
Sex				
Female	487 (52.3)	1,673 (56.6)	1,549 (58.9)	0.002
Male	444 (47.7)	1,282 (43.4)	1,079 (41.1)	
Education				
Not attending any school	113 (12.1)	320 (10.8)	569 (21.6)	<0.001
Under elementary school	296 (31.8)	972 (32.9)	917 (34.9)	
Under middle school	161 (17.3)	429 (14.5)	368 (14.0)	
Under high school	176 (18.9)	629 (21.3)	412 (15.7)	
Upper university	186 (20.0)	607 (20.5)	365 (13.9)	
Income				
Lower	327 (35.3)	982 (33.3)	1,160 (44.4)	<0.001
Intermediate	440 (47.5)	1,310 (44.4)	1,026 (39.2)	
High	159 (17.2)	656 (22.3)	429 (16.4)	
***APOE* genotype**[b]				
***APOE* ε4 positive**	147 (18.8)	577 (24.5)	474 (23.4)	0.005
***APOE* ε4 negative**	633 (81.2)	1,776 (75.5)	1,555 (76.6)	
Modified CIRS	3.5 ± 2.4	3.9 ± 2.5	4.3 ± 2.6	<0.001
BMI				
Underweight	24 (2.8)	58 (2.1)	80 (3.4)	0.068
Normal	275 (32.4)	938 (33.5)	822 (34.5)	
Overweight	237 (27.9)	781 (27.9)	670 (28.1)	
Obese	314 (36.9)	1,027 (36.6)	813 (34.1)	
Alcohol				
Nonproblematic drinking	816 (88.0)	2,542 (86.1)	2,333 (89.2)	0.002
Problematic drinking	111 (12.0)	410 (13.9)	282 (10.8)	
Smoking				
Never	638 (70.0)	2,060 (70.2)	1,821 (70.1)	0.003
Ex	140 (15.4)	542 (18.5)	503 (19.4)	
Current	133 (14.6)	334 (11.4)	273 (10.5)	
Caffeine				
Non excessive caffeine	900 (96.9)	2,869 (97.2)	2,547 (97.2)	0.86
Excessive caffeine	29 (3.1)	83 (2.8)	73 (2.8)	

Continued

Table 1 Demographic Characteristics of Participants at Baseline *(continued)*

Variables	Normal sensory (n = 932)	SSI (n = 2,957)	DSI (n = 2,631)	*p* Value
Exercise				
Upper 150	91 (9.9)	263 (9.0)	149 (5.7)	<0.001
Lower 150	831 (90.1)	2,673 (91.0)	2,449 (94.3)	
Depression				
No depression	769 (85.2)	2,341 (81.5)	1,803 (72.7)	<0.001
Depression	134 (14.8)	530 (18.5)	678 (27.3)	
MOS-SSS	73.0 ± 23.2	72.9 ± 22.8	66.5 ± 24.0	<0.001

Abbreviations: BMI = body mass index; CIRS = Cumulative Illness Rating Scale; DSI = dual sensory impairment; MOS-SSS = Medical Outcomes Study Social Support Survey; SSI = single sensory impairment.
Values are n (%) or mean ± SD.
[a] Proportion of Alzheimer disease among all dementia in each sensory group.
[b] *APOE* genotype was presented in subsamples (n = 5,211).

individuals 4,009. When we implemented the interaction analysis, the interaction term between *APOE* ε4 positivity and the sensory impairment group was not statistically significant with respect to prevalence (SSI: OR 0.38, 95% CI 0.11–1.37, $p = 0.131$; DSI: OR 0.48, 95% CI 0.15–1.57, $p = 0.207$), incidence (SSI: HR 0.46, 95% CI 0.11–1.85, $p = 0.271$; DSI: HR 0.42, 95% CI 0.11–1.61, $p = 0.205$), and cognitive decline (SSI × period: β −0.34, 95% CI −1.09 to 0.41, $p = 0.372$; DSI × period: β 0.21, 95% CI −0.56 to 0.98, $p = 0.594$). When looking into the result of descriptive statistics on *APOE* genotype, the difference in the incidence of dementia between the sensory groups was remarkable in the *APOE* ε4-negative group (normal sensory: 1.2%, SSI: 2.4%, DSI: 6.0%) compared to the positive group (normal sensory: 3.4%, SSI: 3.1%, DSI: 7.2%), so we assumed that sensory impairment might be differently associated with cognitive impairment according to *APOE* genotype status. *APOE* genotype is known not only to increase dementia (or AD) risk itself but also by interacting with multiple risk factors such as sex, vascular risk factors, and education.[28-30] For this reason, although not statistically significant in the interaction analysis, a subgroup analysis was performed. In the negative

Table 2 Association Between Sensory Impairment and Dementia Prevalence

Predictors	OR	95% CI	*p* Value
Model 1[a]			
SSI[b]	1.13	0.67–1.89	0.652
DSI[b]	1.74	1.07–2.84	0.026
Model 2[c]			
SSI[b]	1.27	0.66–2.41	0.475
DSI[b]	2.17	1.17–4.02	0.014
Model 3[d]			
SSI[b]	1.18	0.60–2.34	0.632
DSI[b]	1.81	0.94–3.49	0.076

Abbreviations: CI = confidence interval; DSI = dual sensory impairment; OR = odds ratio; SSI = single sensory impairment.
[a] Model 1: adjusted for age, sex, education, and income.
[b] Reference: normal sensory.
[c] Model 2: adjusted for age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, and exercise.
[d] Model 3: adjusted for age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, exercise, depression, and Medical Outcomes Study Social Support Survey.

Table 3 Association Between Sensory Impairment and Dementia Incidence

Predictors	HR	95% CI	*p* Value
Model 1[a]			
SSI[b]	1.41	0.79–2.50	0.245
DSI[b]	2.19	1.25–3.81	0.006
Model 2[c]			
SSI[b]	1.21	0.65–2.25	0.549
DSI[b]	1.9	1.04–3.46	0.037
Model 3[d]			
SSI[b]	1.24	0.66–2.31	0.504
DSI[b]	1.79	0.98–3.28	0.058

Abbreviations: CI = confidence interval; DSI = dual sensory impairment; HR = hazard ratio; SSI = single sensory impairment.
[a] Model 1: adjusted for age, sex, education, and income.
[b] Reference: normal sensory.
[c] Model 2: adjusted for age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, and exercise.
[d] Model 3: adjusted for age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, exercise, depression, and Medical Outcomes Study Social Support Survey.

Table 4 Association Between Sensory Impairment and Cognitive Decline

Predictors	β	95% CI	*p* Value
Model 1[a]			
SSI[b] **× period**	−0.09	−0.37 to 0.19	0.521
DSI[b] **× period**	−0.79	−1.08 to −0.51	<0.001
Model 2[c]			
SSI[b] **× period**	−0.14	−0.42 to 0.15	0.353
DSI[b] **× period**	−0.87	−1.17 to −0.57	<0.001
Model 3[d]			
SSI[b] **× period**	−0.14	−0.43 to 0.15	0.339
DSI[b] **× period**	−0.86	−1.16 to −0.56	<0.001

Abbreviations: CI = confidence interval; DSI = dual sensory impairment; SSI = single sensory impairment.
Trajectories of Consortium to Establish a Registry for Alzheimer's Disease Total Score were based on predicted values for linear mixed-effects models group (normal sensory/SSI/DSI) × period interaction, period since baseline, and groups as primary predictors.
[a] Model 1: adjusted for baseline diagnosis, age, sex, education, and income.
[b] Reference: normal sensory.
[c] Model 2: adjusted for baseline diagnosis, age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, and exercise.
[d] Model 3: adjusted for baseline diagnosis, age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, exercise, depression, and Medical Outcomes Study Social Support Survey.

APOE ε4 subgroup, DSI was associated with increased prevalence and incidence of dementia, and with cognitive decline, and the HR and the LMM β slope were statistically significant (OR 1.94, 95% CI 0.90–4.15; HR 2.85, 95% CI 1.23–6.61; β −0.82, 95% CI −1.15 to −0.48). On the other hand, in the positive *APOE* ε4 subgroup, there was no statistical significance in any of the 3 analyses, and the effect size was also relatively small (OR 1.84, HR 1.43, β −0.68, 95% CI −1.37 to 0.01; table 5.

Subgroup Analysis Limiting Dependent Variables as AD

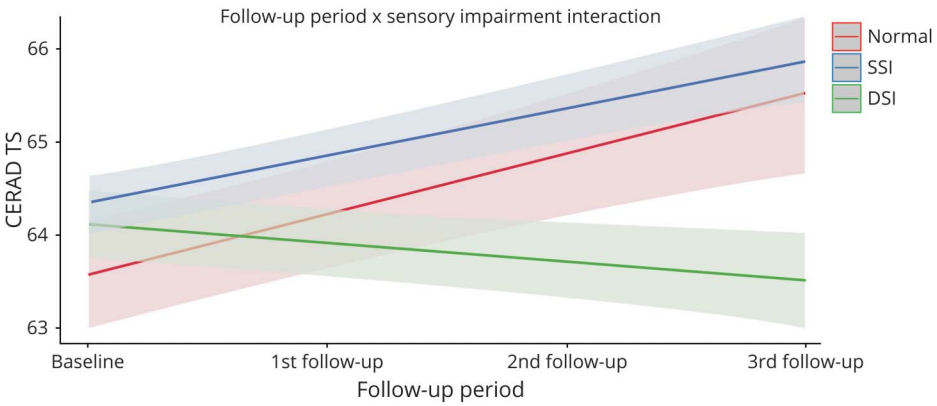
In the analysis that limited the dependent variable to AD, DSI in model 1 was associated with a significant increase in prevalence and incidence of AD. In model 2, the association with AD prevalence was also significant (OR 2.46, 95% CI 1.26–4.80), but there was no statistical significance in the association with incidence of AD (HR 1.65, 95% CI 0.85–3.20).

Discussion

In this study, DSI was associated with baseline prevalence of dementia, incidence of dementia, and cognitive decline over the follow-up period, but the presence of visual impairment or of hearing impairment alone did not show such association. The results of the sensitivity analysis indicated that, even if there was no previous cognitive decline, DSI was associated with a future decline in cognitive function. Regarding subgroup analysis, in the *APOE* ε4-negative group, DSI was associated with dementia prevalence, incidence, and cognitive decline, but this was not the case in the *APOE* ε4-positive group. In the analysis using dementia subtype (AD) as an outcome, only baseline prevalence of AD was significantly higher in the DSI group, but incidence did not significantly increase during follow-up.

In this study, visual only and hearing only impairment did not specifically influence dementia onset or cognitive decline, but there was a significant effect of DSI. This is consistent with findings of previous studies where the presence of DSI increased dementia incidence, but that presence of SSI did not,[9,31] and cognitive performance significantly decreased in DSI but not in SSI.[32] In this study, both an increased prevalence and incidence of dementia and a decrease in neuropsychological test scores due to DSI were demonstrated, which could constitute strong evidence that DSI is a risk factor for dementia.

Figure 2 Linear Mixed Model (LMM) Plot: Association Between Sensory Impairment and Cognitive Decline



LMM analysis included participants with normal cognition and participants with MCI excluding baseline dementia. Groups according to sensory impairment shows associations with estimated trajectories of Consortium to Establish a Registry for Alzheimer's Disease Total Score (CERAD TS) across follow-up. Trajectories were based on predicted values for linear mixed-effects models group (normal sensory/single sensory impairment [SSI]/dual sensory impairment [DSI]) × period interaction, period since baseline, and groups as primary predictors. Models were additionally adjusted for baseline diagnosis, age, sex, education, income, modified Cumulative Illness Rating Scale, body mass index, alcohol, smoking, caffeine, and exercise.

Table 5 Subgroup Analysis According to *APOE* Genotype

	APOE ε4-negative			*APOE* ε4-positive		
Predictors	**OR**	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Logistic regression[a]						
SSI[b]	1.56	0.71 to 3.45	0.271	0.82	0.27 to 2.47	0.728
DSI[b]	1.94	0.90 to 4.15	0.089	1.84	0.67 to 5.06	0.24
Cox regression[a]						
SSI[b]	2.22	0.93 to 5.29	0.073	0.9	0.30 to 2.75	0.855
DSI[b]	2.85	1.23 to 6.61	0.015	1.43	0.49 to 4.16	0.507
Linear mixed model[c]						
SSI[b] × period	0.01	−0.32 to 0.33	0.969	−0.35	−1.02 to 0.31	0.299
DSI[b] × period	−0.82	−1.15 to −0.48	<0.001	−0.68	−1.37 to 0.01	0.054

Abbreviations: CI = confidence interval; DSI = dual sensory impairment; OR = odds ratio; SSI = single sensory impairment.
Models were adjusted for baseline diagnosis, age, sex, education, and income.
[a] Models were adjusted for age, sex, education, and income.
[b] Reference: normal sensory.
[c] Trajectories of Consortium to Establish a Registry for Alzheimer's Disease Total Score were based on predicted values for linear mixed-effects models group (normal sensory/SSI/DSI) × period interaction, period since baseline, and groups as primary predictors.

According to the results of the sensitivity analysis, we can infer that in the clinically cognitively normal group, with or without underlying progressed neurodegeneration, if there is a decrease in sensory function, cognitive function could be expected to decrease.

In this study, CERAD TS increased over time except in the DSI group. This result could be considered to be due to the practice effect of serial neuropsychological tests. According to previous studies, serial neuropsychological tests can increase test scores by a practice effect, particularly noticeable in normal elderly people and patients with MCI.[33] Because only normal elderly people and patients with MCI of baseline participants were included in the LMM analysis, this might have influenced CERAD TS increase by the probability of the practice effect.

In this study, differences in sensory deprivation, neurodegeneration, social isolation, and depression could explain why DSI had a significant effect but SSI did not. Sensory impairments might limit the neural resources needed for cognitive function by increasing the cognitive load. Moreover, sensory impairment could directly affect the brain's structure and function. For example, sensory impairment might cause long-term deafferentation, while overloaded brain circuity also might cause poor signal-to-noise ratios.[34-36] As further evidence, accelerated brain volume atrophy was shown in individuals with hearing impairment compared to those with normal hearing.[37] Sensory impairment may lead to depression, social isolation, and physical inactivity, and cognitive impairment.[38,39] The results of this study suggest that an SSI may not exceed the threshold of neurodegeneration, while, in contrast, a DSI may imply significant neurodegeneration and clinical cognitive decline. According to a previous study, the visual sense is particularly important to individuals with hearing impairments because they depend more on visual cues for their activities of daily living. Vision recruits and repurposes auditory brain areas for visual processing in individuals with hearing loss.[40] In other words, in SSI, cognitive function is maintained by compensating with other sensory functions, but because in DSI that compensation is impossible, cognitive function worsens.

In DSI, previous studies have shown its association with increased depression and anxiety, decreased quality of life, reduced social support and network, and increased loneliness.[41-43] In this study, depression and poor social contact (proxies of decreased social support) were more prevalent in the DSI group. Logistic and Cox regression analysis revealed a significant relationship in models 1 and 2, but the relationship was no longer significant in model 3. In the analytic model, depression and low social support were associated with an increase in dementia prevalence (depression: OR 2.98, 95% CI 2.14–4.15; social support: OR 0.99, 95% CI 0.99–1.00). This suggests that depression and poor social contact might mediate the association between sensory impairment and dementia. Furthermore, as inferred from the results of this study, elderly people with only a visual or hearing impairment can maintain social contact and the feeling of depression is relatively mild (see also table 1), but the presence of a DSI increases the risk of both factors, which could affect dementia prevalence and incidence and long-term cognitive decline.

In this study, although we did not determine the interaction between *APOE* genotype and sensory impairment, we found a difference in the effect of sensory impairment on dementia in the *APOE* ε4-positive and -negative group. Sensory impairment,

especially DSI, raised the incidence of dementia and facilitated cognitive decline. A potential explanation for these results is that the increased risk of AD (and probably dementia) due to the presence of the *APOE* ε4 allele renders the risk caused by other factors insubstantial.[44] The exact mechanism is unclear, but the results of this study suggest that in the *APOE* ε4-negative subgroup, that is, in the group with a lower probability of AD development, visual and hearing impairment have a greater impact on dementia progression. The results of this study suggest that preventing visual and hearing impairment in the *APOE* ε4-negative group might have a greater effect in preventing dementia development and progression.

In the survival analysis for AD subgroup, DSI did not significantly increase AD dementia incidence. First, the statistical power of this analysis can be considered weak due to the low number of events (new diagnoses of AD dementia, n = 185). Nevertheless, the value of HR (1.65) was lower than HR (1.9) when overall dementia was inserted as dependent variable (see table 3 and Results). From this it can be inferred that visual and hearing impairment does not specifically increase AD incidence. Linking these results to the results of *APOE* ε4 subgroup analysis, we suggest that cognitive decline due to visual and hearing impairment is more likely to work with non-Alzheimer–related pathologies or with mixed pathologies rather than the typical pathology involved in AD.

The strength of this study is that, by focusing on a large-scale Asian cohort based on a community elderly population, we could analyze various demographic information, clinical evaluations, neuropsychological tests, and *APOE* genotyping test results. Moreover, the study design with retrospective analysis of prospective and longitudinal data, the rigorous classification of dementia and its subtypes based on established criteria, and the use of collected data as covariates are all key points of this study.

There are several limitations to this study. First, visual and hearing function were evaluated via self-report. Thus, recall bias could have affected the results of this study. However, by presenting clear criteria, such as hearing aids and glasses, in the questionnaire, the reliability of the questionnaires was maximized to overcome these limitations. Moreover, from the results of supplemental analysis based on diagnosis of disease, considered to be an objective informant, not single but dual disease significantly increased the incidence of dementia. This result could also support the main results of this study. Second, dementia and AD were defined according to clinical diagnostic criteria, and in vivo pathology was unknown because amyloid PET and CSF tests were not performed. However, we expect the correlation between clinical diagnosis and pathologic diagnosis to be relatively high because psychiatry experts have determined dementia and AD through consensus meetings according to recognized diagnosis criteria. Moreover, we also checked whether there was a difference in significance dependent on *APOE* ε4 positivity. In the future, it will be necessary to perform an in vivo pathology study or a postmortem autopsy study to confirm the brain pathology associated with visual and hearing impairments. Lastly, the attrition rate of the overall cohort was 50% by the third follow-up. Attrition may have affected our results. Nevertheless, >3,000 participants completed the final evaluation and we tried to minimize selection bias by correcting various demographic and clinical variables.

This study showed that coexistence of visual and hearing impairments increases dementia prevalence, incidence, and cognitive decline but visual and hearing impairments alone do not.

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Disclosure

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Appendix 1 Authors

Name	Location	Contribution
Gihwan Byeon, MD	Department of Psychiatry, Kangwon National University Hospital, Chuncheon, Korea	Study concept and design, analysis and interpretation of data, drafting and critically revising the manuscript for intellectual content
Gyu Han Oh, MD	Public Health Medical Service, Seoul National University Hospital, Korea	Study concept and design, analysis and interpretation of data, drafting and critically revising the manuscript for intellectual content
Jin Hyeong Jhoo, MD, PhD	Department of Psychiatry, Kangwon National University School of Medicine, Chuncheon, Korea	Study concept and design, acquisition, analysis, and interpretation of data, drafting and critically revising the manuscript for intellectual content

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Jae-Won Jang, MD, PhD	Department of Neurology, Kangwon National University Hospital, Chuncheon, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Jong Bin Bae, MD	Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Ji Won Han, MD, PhD	Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea	Acquisition, analysis, and interpretation of data, data curation, critically revising the manuscript for intellectual content
Tae Hui Kim, MD	Department of Psychiatry, Yonsei University Wonju Severance Christian Hospital, Wonju, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Kyung Phil Kwak, MD, PhD	Department of Psychiatry, Dongguk University Gyeonju Hospital, Gyeongju, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Bong Jo Kim, MD, PhD	Department of Psychiatry, Gyeongsang National University School of Medicine, Jinju, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Shin Gyeom Kim, MD	Department of Neuropsychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Jeong Lan Kim, MD, PhD	Department of Psychiatry, School of Medicine, Chungnam National University, Daejeon, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Seok Woo Moon, MD, PhD	Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Chungju Hospital, Chungju, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Joon Hyuk Park, MD, PhD	Department of Neuropsychiatry, Jeju National University Hospital, Jeju, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Seung-Ho Ryu, MD, PhD	Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Medical Center, Seoul, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Jong Chul Youn, MD, PhD	Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin, Republic of Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Dong Woo Lee, MD, PhD	Department of Neuropsychiatry, Inje University Sanggye Paik Hospital, Seoul, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Seok Bum Lee, MD, PhD	Department of Psychiatry, Dankook University Hospital, Cheonan, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Jung Jae Lee, MD, PhD	Department of Psychiatry, Dankook University Hospital, Cheonan, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Dong Young Lee, MD, PhD	Department of Neuropsychiatry, Seoul National University Hospital; Department of Psychiatry, Seoul National University College of Medicine, Korea	Acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content
Ki Woong Kim, MD, PhD	Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam; Department of Psychiatry, Seoul National University College of Medicine; Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Korea	Study concept and design, acquisition, analysis, and interpretation of data, critically revising the manuscript for intellectual content

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Dual Sensory Impairment and Cognitive Impairment in the Korean Longitudinal Elderly Cohort

Gihwan Byeon, Gyu Han Oh, Jin Hyeong Jhoo, et al.

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