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Original Article

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Korea-Registries to Overcome Dementia and Accelerate Dementia Research (K-ROAD): A Cohort for Dementia Research and Ethnic-Specific Insights

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ABSTRACT

Background and Purpose: Dementia, particularly Alzheimer's disease, is a significant global health concern, with early diagnosis and treatment development being critical goals. While numerous cohorts have advanced dementia research, there is a lack of comprehensive data on ethnic differences, particularly for the Korean population. The Korea-Registries to Overcome Dementia and Accelerate Dementia Research (K-ROAD) aims to establish a large-scale, hospital-based dementia cohort to address this gap, with a focus on understanding disease progression, developing early diagnostics, and supporting treatment advancements specific to the Korean population.
Methods: K-ROAD comprises multiple prospective cohorts. Participants underwent clinical evaluations, neuroimaging, and biomarker analysis, with data collected on a range of clinical and genomic markers.
Results: As of December 2023, K-ROAD has recruited over 5,800 participants, including individuals across the Alzheimer's clinical syndrome, subcortical vascular cognitive impairment, and frontotemporal dementia spectra. Preliminary findings highlight significant ethnic differences in amyloid positivity, cognitive decline, and biomarker profiles, compared to Western cohorts.
Conclusions: The K-ROAD cohort offers a unique and critical resource for dementia research, providing insights into ethnic-specific disease characteristics and biomarker profiles. These findings will contribute to the development of personalized diagnostic and therapeutic approaches to dementia, enhancing global understanding of the disease.

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Conflict of Interest
The authors have no financial conflicts of interest.

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INTRODUCTION

Dementia is a growing threat to the public health of the aging world population. There are diverse diseases that can cause dementia, where Alzheimer's disease (AD), vascular dementia, dementia of Lewy body, and frontotemporal dementia (FTD) are major kinds. In the elderly, AD is the most common type of dementia, and has become the focus of dementia research. It is perceived that the initiation of AD processes leading to neurodegeneration and cognitive decline precedes the onset of dementia by 15–20 years, thus early identification of the disease processes and early interventions could produce clinically meaningful benefits. Notably, the rapid progress in biomarker research and the recent approval of disease-modifying treatments for AD offer promising hope for overcoming the disease. For the goal of early diagnosis and treatment development for dementia, many cohorts have been established worldwide; these include the Alzheimer's Disease Neuroimaging Initiative (ADNI) in the U.S., and the Dementia Platform U.K. (DPUK) in the U.K. These efforts have led to significant advancements in the understanding of AD biology. However, these cohorts must address the issue of including diverse ethnic groups to ensure comprehensive insights and the applicability of findings.

Here, we describe the Korean dementia hospital-based cohort named Korea-Registries to Overcome Dementia and Accelerate Dementia Research (K-ROAD) with respective purposes in Korea. As an open cohort with ongoing data accumulation, the K-ROAD recruits participants encompassing Alzheimer's clinical syndrome (ACS) and other dementias with major goals that are 1) to understand disease characteristics, including the clinical progression of different dementia subtypes (largely AD) in Korea, 2) to develop early diagnostics for dementia, and 3) to support advances in dementia treatment. As a potential counterpart for ADNI or DPUK, K–ROAD would be a representative Korean dementia cohort for research, which could also provide additional insight into the ethnic difference of disease characteristics in terms of many clinical and biomarker perspectives.

METHODS

Data sources of the K-ROAD

The K-ROAD cohort aims to develop a genotype–phenotype cohort to accelerate the development of novel diagnostic and therapeutic techniques for AD and other related dementias. It consists of three prospective cohorts supported by the Korea Disease Control and Prevention Agency, the Ministry of Health and Welfare, and the Samsung medical center intramural fund, respectively. These cohorts collect clinical data, imaging data, and/or biospecimens from participants who have been diagnosed with, or are at risk of, dementia. The three cohorts include the precision medicine platform for mild cognitive impairment based on multi-omics, imaging, evidence-based R&BD (PREMIER) consortium, the longitudinal/cohort study of patients with late onset dementia (LLOD) cohort, and the Samsung Medical Center (SMC) amyloid PET cohort. A total of 28 centers have participated in these cohorts. The PREMIER consortium (May 2019 and December 2022) recruited a research cohort to establish an R&BD platform for the development of early diagnosis and

precision medicine-based treatment of mild cognitive impairment (MCI) and dementia. The LLOD cohort (since May 2021) has the purposes of recruiting and following up late-onset dementia/at-risk groups, collecting advanced resources, and encouraging research on early diagnosis, differential diagnosis, and prognosis in late-onset dementia. The SMC amyloid PET cohort is the largest memory clinic-based cohort. Participants who undergo biomarker testing (particularly amyloid PET) for clinical or research purposes are enrolled with their consent, providing clinical data to researchers.

Participants

All participants enrolled in the K-ROAD cohort had to consent to undergo all test procedures, including neuroimaging and blood sampling. Briefly, all participants demonstrated adequate visual and auditory acuity for neuropsychological testing, maintained good general health without unstable medical conditions, and were fluent in Korean. Participants' ages varied, based on the specific objectives of the study.

Eligible participants were either of ACS - cognitively unimpaired (CU), MCI, and dementia of Alzheimer's type (DAT), subcortical vascular cognitive impairment (SVCI), or FTD syndrome. CU was defined to have 1) no major medical/psychiatric history that was likely to affect cognitive function, 2) no objective cognitive impairment observed after a comprehensive neuropsychological test on any cognitive domain (above the −1.0 standard deviation [SD] of age- and education-matched norms in memory, and below −1.5 SD in other cognitive domains).[1] MCI[2] was diagnosed as having: 1) subjective cognitive complaints by the participants or caregiver; 2) objective cognitive impairment in any cognitive domain (below the −1.0 SD of age- and education-matched norms in memory, or below −1.5 SD in other cognitive domains); and 3) no significant impairment in the activities of daily living. The participants with DAT met the NIA–AA diagnostic criteria for AD dementia.[3] SVCI was defined as having 1) subjective cognitive complaints by the patient or caregiver; 2) objective cognitive impairment below −1.0 SD from the age-, sex-, and education-adjusted norms in any cognitive domain, including language, visuospatial, memory, or frontal function on neuropsychological tests[4,5]; and 3) severe ischemia on brain magnetic resonance imaging (MRI), defined as the width of periventricular white matter hyperintensities (WMHs) from the lateral ventricular wall ≥10 mm and the longest diameter of deep WMH ≥25 mm, as modified from the Fazekas ischemia criteria.[6] FTD syndrome encompassed various types: behavioral variant FTD, semantic variant primary progressive aphasia, nonfluent/agrammatic variant primary progressive aphasia, FTD associated with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome, and corticobasal syndrome. Specific diagnoses were established based on the applicable clinical criteria.[741]

Assessment & measurement

Participants underwent clinical evaluation including neuropsychological testing and various questionnaires, neuroimaging, and blood sampling for plasma biomarkers and genomic data analyses (**Table 1**).

Cognitive assessment

All participants underwent neuropsychological tests, with the majority undergoing the Seoul Neuropsychological Screening Battery second edition (SNSB-II).[12,13] All tests included in SNSB-II have been internationally used in clinical practice for several decades.[12,14-25] The items used in the tests were altered due to the linguistic and cultural differences between Korean and English speakers.[12,14,15,26] We used tests that provided numerical scores, such as the

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Table 1. Assessment protocol for the K-ROAD cohort

Assessment	PREMIER consortium: Hospital-based cohort	LLOD	SMC amyloid PET registry
Neuropsychological test			
Baseline	SNSB MMSE CDR	SNSB MMSE CDR	SNSB MMSE CDR
Follow-up	N/A	SNSB MMSE CDR	SNSB or MMSE or CDR
Questionnaires	K-PSQI, MNA, BAI, K-AD9, STR short version, K-ECog, K-NMSS, EQ-5D, IPAQ, CGA-NPI		N/A
Brain MRI protocol	3D T1 (required), FLAIR (optional)		3D T1, FLAIR, DTI, resting fMRI (optional)
Amyloid PET	Florbetaben and flutemetamol		PiB, florbetaben and flutemetamol
Tau PET	N/A	N/A	THK or AV1451 PET
Blood tests	WBC, RBC, Hb, Hct, PLT, ALT, AST, BUN, Cr, Glucose, HbA1C, HDL cholesterol, total cholesterol, LDL cholesterol, TG, TSH, FT4, Folate, Vitamin B12		N/A
Blood collection protocol	DNA, plasma, serum	DNA, plasma, serum, PBMC	DNA, plasma, serum

K-ROAD: the Korea-Registries to Overcome Dementia and Accelerate Dementia Research, PREMIER: precision medicine platform for mild cognitive impairment based on multi-omics, imaging, evidence-based R&BD, LLOD: longitudinal/cohort study of patients with late onset dementia cohort, SMC: Samsung Medical Center, SNSB: Seoul Neuropsychological Screening Battery, MMSE: Mini-Mental State Examination, CDR: clinical dementia rating, K-PSQI: Korean version of the Pittsburgh Sleep Quality Index, MNA: Mini Nutritional Assessment, BAI: Beck Anxiety Inventory, K-AD9: Korean version of the Alzheimer's Disease 9 scale, STR: stress short version questionnaire, K-ECog: Korean version of the Everyday Cognition scale, K-NMSS: Korean version of the Non-Motor Symptoms Scale, EQ-5D: EuroQol 5-dimension, IPAQ: International Physical Activity Questionnaire, CGA-NPI: Comprehensive Geriatric Assessment-Neuropsychiatric Inventory, MRI: magnetic resonance imaging, 3D T1: three-dimensional T1-weighted imaging, FLAIR: fluid-attenuated inversion recovery, DTI: diffusion tensor imaging, fMRI: functional magnetic resonance imaging, PET: positron emission tomography, PiB: Pittsburgh compound B, THK: [Tau-specific tracer] THK series, AV1451: Tau tracer AV1451 (also known as Flortaucipir), WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, Hct: hematocrit, PLT: platelet count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, TSH: thyroid-stimulating hormone, FT4: free thyroxine (T4), PBMC: peripheral blood mononuclear cell.

Digit Span Forward (DSF), the Korean version of the Boston Naming (K-BNT), Rey complex figure test (RCFT) (copying and delayed recall), Seoul verbal learning test (SVLT) (delayed recall), semantic controlled oral word association test (COWAT), Stroop Test (color reading), Korean-Mini Mental State Examination (K-MMSE), and Clinical Dementia Rating-Sum of Boxes (CDR-SB). The attention and working memory of the participants were assessed using the DSF, and naming ability was evaluated using the K-BNT score. Verbal memory and visual memory were measured using the SVLT (delayed recall) and RCFT (delayed recall) scores, respectively. The visuospatial function was assessed using the RCFT copying test, while the frontal executive function was measured using the semantic COWAT and Stroop test. Global cognition was evaluated using K-MMSE and CDR-SB. If participants scored below 10 on the K-MMSE, the SNSB-II could not be administered.

Questionnaires and laboratory examinations

For a subset of the cohort (PREMIER and LLOD), data on sex, date of birth, age, address, living arrangement, cohabitation, and the primary caregiver (type, age, frequency of meetings (per month or year), time spent (hours and minutes), frequency of phone calls (per month), years of education, literacy, current employment status, current occupation, longest occupation, marital status, hand laterality, and average monthly income were collected. Smoking status, alcohol consumption, physical activity, and quality of life were assessed. Sleep quality was measured, and smartphone use, nutritional and dietary data, and activities of daily living were collected as variables.

Blood tests were performed for complete blood count, liver function tests, renal function tests, APOE genotype, and endocrine metabolism.

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Aβ PET imaging acquisition and analysis

All K-ROAD participants underwent one of the following Aβ PET scans: ^{11}C-Pittsburgh compound B (PiB), ^{18}F-florbetaben (FBB), or ^{18}F-flutemetamol (FMM). Imaging was performed according to the manufacturer's guidelines. To quantify Aβ uptakes on PiB, FBB, and FMM PET, we replicated the image-processing steps described in the previously published Klunk Centiloid (Klunk CL) Project.[27] Furthermore, for the study that utilizes only the FBB and FMM PET dataset, we used an MRI- or CT-based regional direct comparison centiloid (rdcCL) method that harmonizes FBB and FMM PET ligands without ^{11}C-PiB images, which we developed in the previous study.[28]

Tau PET imaging acquisition and analysis

A subset of participants underwent ^{18}F-flortaucipir (FTP) PET using either a Discovery STE PET/CT scanner (GE Healthcare, Chicago, IL, USA) at the SMC, or a Biograph mCT PET/CT scanner (Siemens Medical Solutions) at Gangnam Severance Hospital. The FTP PET images were co-registered onto individual MR images using SPM12. For the regional standardized uptake value ratio (SUVR) analysis, we used FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) to delineate the region of interest (ROI) masks in the native space. The cerebellar gray matter was used as the reference region. The detailed protocols and methods are described in the previous study.[29]

Brain MRI acquisition and measurement of hippocampal volume (HV)

A subset of participants (PREMIER consortium, LLOD cohort – required; SMC cohort – optional) underwent brain MRI at each center with a standardized common imaging protocol for 3-dimensional (3D) T1 turbo field echo images and fluid attenuated inversion recovery using a 3.0T MRI scanner. In particular, T1-weighted images were acquired on all MRI scanners using a standard isotropic voxel size of 1 mm^3. All images were centralized at the SMC. The images were processed using the CIVET anatomical pipeline (version 2.1.0).[30] Native MRI images were registered to the MNI–152 template by linear transformation,[31] and corrected for intensity nonuniformity using the N3 algorithm.[32] To measure HV, we used an automated hippocampus segmentation method using a graph cut algorithm combined with an atlas-based segmentation and morphological opening, as described in an earlier study.[33]

Definition of adjusted HV (HVa) and assessment of cerebral small vessel disease (CSVD) on MRI

We averaged right and left HV and adjusted them for intracranial volume (ICV) by calculating the residual from a linear regression of HV vs. ICV among cognitively unimpaired participants. Thus, the HVa can be interpreted as the deviation in cubic millimeters of a participant's HV from what is expected, given their ICV.[34,35]

We also assessed CSVD markers, including WMH, lacunes, and microbleeds. The WMH in the deep subcortical and periventricular regions on FLAIR images was visually assessed using a modified Fazekas scale proposed by the Clinical Research Center for Dementia of South Korea.[6,36] Lacunes were defined as small lesions ($3 \le d \le 15$) mm in diameter, d) with low signal on T1-weighted images, high signal on T2-weighted images, and a perilesional halo on 80 axial slices of FLAIR images.[37] Cerebral microbleeds were defined as lesions ≤10 mm in diameter on 20 T2* GRE-MRI axial slides using criteria.[37]

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ATNV classification

For the study utilizing PiB, FBB, and FMM PET images, we defined Aβ PET positivity (A+) using a Klunk CL cutoff value of 20.0.[38] For the study utilizing only FBB and FMM PET images, Aβ+ was defined using a global MRI-based rdcCL threshold of 25.5, which was obtained using the Gaussian mixture model (GMM). For the GMM clustering, we utilized rdcCL data obtained from 3,753 participants aged 55 or above who underwent FBB or FMM PET. For the cases in which 3D T1 MR images were lacking, the CT-based rdcCL threshold of 25.1 was applied, given the excellent correlation between MRI- and CT-based global rdcCL values in our previous study (R^2=0.99 for FMM, and R^2=0.98 for FBB).[28,39]

To define tau positivity (T+), several cutoffs were used for different studies. FTP SUVR using Braak III/IV ROI (Braak III: parahippocampal, fusiform, lingual gyrus, amygdala; Braak IV: inferior temporal cortex, middle temporal cortex, temporal pole, thalamus, caudal, rostral, isthmus, posterior cingulate, insula) was used to predict the classification of Aβ− CU (n=14) and Aβ+ AD dementia (n=55), and tau positivity can be defined when the FTP SUVR at Braak III/IV ROI was higher than the cut-off of 1.406. Alternatively, temporal meta-ROI were defined, encompassing the entorhinal cortex, amygdala, fusiform gyrus, parahippocampal gyrus, and the inferior and middle temporal gyrus. A tau PET positivity threshold was set at an SUVR of 1.38 in these ROIs, which is two standard deviations above the mean SUVR of the same regions in Aβ PET− CU participants.

We determined neurodegeneration positivity using a HVa cutoff value of −0.478 cm^3,[29] or −0.363 cm^3, respectively, with neurodegeneration classified as positive (N+) if the HVa was lower than the corresponding cutoff. These values were derived through machine learning K–means clustering methods[40,41] applied to independent datasets comprising 1,123 and 1,453 participants across CU, MCI, and DAT. The development of these cutoff values was performed using independent datasets, separate from the main datasets where the cutoffs were applied in accordance with the study objectives. Detailed methods can be found in our previous study.[29]

We lastly defined V+ as severe levels of WMH (deep WMH >10 mm and periventricular WMH >25 mm), based on our visual rating scale for WMH.[36]

Plasma biomarkers

A subset of participants underwent plasma biomarker testing. Blood samples were centrifuged at 1,300 g for 10 minutes, after which the plasma was separated, and aliquoted into 5 or 10 vials, each containing 0.3 mL. The plasma samples were stored at −75°C until analysis, following the guidelines established by the National Biobank of the Republic of Korea for human resource collection and registration. The frozen plasma was then shipped at −70°C to the Department of Psychiatry and Neurochemistry at the University of Gothenburg for analysis. Upon thawing, plasma concentrations of Aβ40, Aβ42, GFAP, and NfL were assessed using the Neurology 4-Plex E kit from Quanterix. Plasma p-tau181 and p-tau231 were quantified through in-house Simoa assays developed at the University of Gothenburg, while p-tau217 was measured using the commercial ALZpath p-tau217 assay.

Genomics and epigenomics data

K-ROAD has acquired genomics and epigenomics data through microarray chip, whole-genome sequencing, as well as DNA methylation assay. These data were primarily generated to identify significant genes by analyzing their association with clinical, imaging, and blood

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biomarkers. The DNA used for genotyping K-ROAD participants was collected from whole blood. In terms of microarray chip data, the majority of samples were genotyped using the Illumina Asian Screening Array BeadChip (Illumina, San Diego, CA, USA) (n=4,787). Additionally, 364 participants were genotyped on the customized Korea Biobank array chip (Affymetrix, CA, USA). Whole genome sequencing data were generated from genomic DNA extracted from blood samples using a QIAmp DNA Mini Kit (QIAGEN, Valencia, CA, USA). For sequencing, library preparation was performed with a TruSeq® DNA PCR–Free Library Prep Kit (Illumina). Sequencing was performed at an average depth of 30× with paired-end sequencing using a NovaSeq™ 6000 instrument with an S4 flow cell. DNA methylation analysis was performed according to the manufacturer's instructions using Infinium MethylationEPIC BeadChip (Illumina). The MethylationEPIC BeadChip contained over 850,000 methylation sites in enhancer regions, gene bodies, promoters, and CpG islands.

RESULTS

Study participants

As of December 2023, the K-ROAD cohort registered a total of 5,856 participants who underwent amyloid PET. A total of 5,121 ACS (1,249 CU, 2,595 MCI, and 1,277 DAT), 583 SVCI, and 152 FTD participants were recruited. **Table 2** demonstrates the baseline characteristics of all the K-ROAD participants.

Frequencies of ATN positivity

The Aβ+ prevalence in the CU, MCI, and DAT stage was 20.8, 48.6, and 79.6%, respectively, while in SVCI, it was 35.2%, and in FTD, 13.8%.

Table 2. Baseline characteristics of participants in the K-ROAD cohort

Variables	Alzheimer's clinical syndrome			SVCI	FTD
	CU	MCI	DAT		
Aβ PET cohort	n=1,249	n=2,595	n=1,277	n=583	n=152
Age (yr)	71.0 (66.0; 76.0)	73.0 (67.0; 78.0)	74.0 (65.0; 79.0)	77.0 (72.0; 80.0)	68.0 (63.5; 74.5)
Sex (female)	928 (65.4)	1,720 (58.9)	910 (61.3)	377 (64.7)	66 (43.4)
Education (yr)	12.0 (6.0; 16.0)	12.0 (6.0; 16.0)	12.0 (6.0; 16.0)	9.0 (6.0; 12.0)	12.0 (6.5; 14.0)
APOE genotype*					
ε2 carrier	142 (10.5)	200 (7.1)	79 (5.6)	58 (9.9)	19 (12.5)
ε3/ε3	890 (65.6)	1,496 (53.4)	645 (45.6)	383 (65.7)	109 (71.7)
ε4 carrier	324 (23.9)	1,108 (39.5)	690 (48.8)	142 (24.4)	24 (15.8)
MMSE	28.0 (2.0; 29.0)	26.0 (23.0; 28.0)	20.0 (16.0; 23.0)	23.0 (19.5; 27.0)	22.0 (16.0; 26.0)
Aβ PET positivity	260 (20.8)	1,261 (48.6)	1,016 (79.6)	205 (35.2)	21 (13.8)
Tau PET subset	n=37	n=51	n=81	n=78	n=28
Aβ PET positivity	20 (54.1)	43 (84.3)	81 (100)	37 (47.4)	3 (10.7)
Tau PET positivity (temporal meta-ROI cutoff)	4 (10.8)	23 (45.1)	68 (84.0)	15 (19.2)	2 (7.1)
Neurodegeneration subset	n=575	n=576	n=437	n=398	
A–N–	413 (71.8%)	160 (27.8%)	17 (3.9%)	101 (25.4%)	
A+N–	62 (10.8%)	107 (18.6%)	57 (13%)	45 (11.3%)	
A–N+	70 (12.2%)	93 (16.1%)	42 (9.6%)	142 (35.7%)	
A+N+	30 (5.2%)	216 (37.5%)	321 (73.5%)	110 (27.6%)	

Values are presented as median (interquartile range) or number (percentage), appropriately.
K-ROAD: the Korea-Registries to Overcome Dementia and Accelerate Dementia Research, Aβ: amyloid-beta, PET: positron emission tomography, SVCI: subcortical vascular cognitive impairment, FTD: frontotemporal dementia, CU: cognitively unimpaired, MCI: mild cognitive impairment, DAT: dementia of the Alzheimer type, APOE: apolipoprotein E, MMSE: Mini-Mental State Examination, ROI: region of interest, A–N–: amyloid negative, neurodegeneration negative, A+N–: amyloid positive, neurodegeneration negative, A–N+: amyloid negative, neurodegeneration positive, A+N+: amyloid positive, neurodegeneration positive.
*APOE ε2/ε4 was excluded.

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A subset of participants underwent FTP PET (n=275). In this subset, Aβ+ individuals were more selectively recruited in ACS and SVCI, in CU, MCI, and DAT at 54, 84, and 100%, respectively, and in SVCI, at 47.4%. Using the meta-ROI cutoff for tau positivity, the prevalence of tau positivity in each diagnostic group in the CU, MCI, and DAT stages of ACS was 10.8, 45.1, and 84.0%, respectively. Tau positivity in SVCI was 19.2%. Among FTD participants who underwent both Aβ and tau PET, only 10 and 7% were Aβ and tau positive, respectively.

A subset of participants (CU, n=575; MCI, n=576; DAT, n=437; SVCI, n=398) who underwent both Aβ PET and 3D T1 MRI at SMC were analyzed for HVa cutoff. Among CU, N (+) was found in 17% (A−N+ 12%, A+N+ 5%), 54% of MCI (A−N+ 16%, A+N+ 38%), 83% of DAT (A−N+ 10%, A+N+ 73%), and 63% of SVCI (A−N+36%, A+N+ 27%).

DISCUSSION

The K-ROAD cohort, one of the largest and most comprehensive dementia datasets in Korea, was designed to provide standardized clinical and imaging data from over 20 nationwide memory clinics. This extensive dataset offers unique opportunities to: 1) explore Korean-specific aspects of AD; 2) investigate ethnic differences in dementia prevalence, risk factors, and phenotype/genotype characteristics; 3) develop biomarker-based algorithms for early diagnosis and prognosis prediction; and 4) understand the interaction between AD and CSVD burden.

First, the K-ROAD cohort is a representative Korean dementia cohort that could significantly advance our understanding of dementia characteristics specific to the Korean population. The dominance of research on non-Hispanic white (NHW) populations, largely due to the extensive data from Western cohorts like the ADNI,[42,43] has limited our understanding of AD biomarker traits in other ethnic groups. Koreans, who have been underrepresented in previous studies, need their own evidence base for accurate diagnosis, prognosis prediction, and policy development, particularly as new Aβ-targeting treatments are becoming increasingly available worldwide. In addition to AD-specific Aβ and tau biomarkers, neurodegeneration is a key factor in dementia research, as it directly relates to cognitive impairment, and may reflect co-pathologies. Also, Neurodegeneration could occur without Aβ biomarkers, known as Suspected Non-Alzheimer Pathophysiology (SNAP). Thus, investigating the prevalence of neurodegeneration and related clinical characteristics would be important, as they might represent and provide insights into Korean-specific comorbid diseases and SNAP characteristics.

Second, the K-ROAD cohort dataset offers a valuable resource for studying ethnic differences in dementia prevalence, risk factors, and phenotype/genotype characteristics. In terms of inherited differences, our previous GWAS study using a subset of the K-ROAD cohort identified SNPs associated with Aβ positivity. In this study, ethnic similarity and differences in genetic variants associated with Aβ were noted, particularly a stronger effect of the variant in *APOE* (rs429358) on Aβ positivity in the Korean, than in the European, population.[44] Given that various other AD risk factors may differ across ethnicities, the K-ROAD cohort allows for a detailed exploration of these disparities. For example, Koreans typically have lower education levels, with a median of 12 years, compared to the median of 16 years reported in the ADNI cohort for NHWs. Such differences in education, along with other ethnic and genetic factors, could lead to distinct clinical and biomarker profiles. Our preliminary

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findings indicate significant differences between Koreans and NHWs in terms of Aβ positivity and cognitive decline. For example, in CU individuals, the odds of Aβ positivity were lower in Koreans compared to NHWs, while in the MCI and DAT stages, no significant differences were observed. Additionally, even in the same Aβ+ status, cognitive decline progressed more rapidly in Koreans at the CU and MCI stages, but not at the DAT stage. These insights emphasize the importance of considering ethnic differences in dementia research, particularly in the context of treatment efficacy and participant recruitment for clinical trials, and will contribute to the broader goal of personalized dementia care globally.

Third, the K-ROAD cohort can be used to develop various machine-learning algorithms or modeling for early diagnosis and prognosis prediction, which will be ultimately utilized in clinics and research. The K-ROAD cohort included both clinical data, conventional dementia research imaging including MRI or amyloid PET, and advanced resources, such as plasma biomarkers, tau PET, and genetic data. Thus, wide ranges of research in various fields and the development of algorithms for early diagnosis, differential diagnosis, and prognosis prediction have been possible. For example, various studies can be performed to predict Aβ+ based on cognitive characteristics, APOE genotypes, or MR images,[45-48] while longitudinal follow-up could be used to develop disease progression models, or to explore risk factors predicting outcomes.[49,50] These studies may provide valuable information.

Finally, the interaction between AD pathology and CSVD burden is worth to be investigated. CSVD commonly coexists with AD pathology, and has synergistic effects on cognitive decline in AD. The representative CSVD marker is severe WMH on MRI, which defines SVCI. Using a large cross-sectional AD and SVCI clinical dataset, which formed the basis of the current K-ROAD cohort, we systematically explored the relationship between AD pathology and vascular pathology.[6,51] Specifically, investigating clinical outcomes based on AD biomarkers in SVCI could demonstrate the impact of these biomarkers, and that this AD biomarker-based classification framework can be applied to SVCI. Thus, we found that SVCI with both A/T biomarker abnormalities had the worst neurodegeneration and clinical outcomes, compared to SVCI without A/T biomarker abnormalities.[52] From a different perspective, we also found that the distribution and longitudinal outcomes of AT(N) abnormalities varied according to vascular burden, suggesting that the CSVD burden could be incorporated as a V biomarker into the AT(N) system, to better categorize participants and predict prognosis.[29]

The K-ROAD cohort had some limitations. First, since the study was based on multiple separate cohorts over the long term, different Aβ PET ligands were used across the studies. However, these three ligands are strongly correlated,[53] and we used the CL method for harmonization, ensuring comparability. Second, not all participants in the K-ROAD cohorts (e.g., PREMIER consortium) were followed up longitudinally, due to study design and budget constraints, limiting the feasibility of prognosis studies. Third, although other neurodegenerative dementias, particularly dementia with Lewy bodies, are prevalent, they are not included in the current K-ROAD. However, we are planning to include them into the ongoing future cohort, which will further broaden the scope of our study. Despite these challenges, the K-ROAD cohort is generating comprehensive research on biomarker characteristics in Koreans, encompassing clinical, imaging, plasma biomarkers, and genomic studies. In addition to the investigations mentioned above, enriched genotype-phenotype datasets from the K-ROAD cohort offer valuable opportunities for more advanced analyses, including Mendelian randomization studies. Thus, the K-ROAD cohort is expected to make a significant impact on advancing scientific understanding and policymaking in dementia research in Korea.

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In summary, the K-ROAD cohort provides a valuable and comprehensive resource for understanding dementia in the Korean population, offering unique insights into ethnic differences in disease progression and biomarker characteristics. This large-scale dataset will contribute to the development of more accurate diagnostic and treatment strategies that are tailored to diverse populations. Moving forward, K-ROAD has the potential to significantly advance global dementia research by incorporating findings from underrepresented ethnic groups.

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