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Changes in dementia risk along with onset age of depression: a longitudinal cohort study of elderly depressed patients

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Abstract

Background Depression in late-life is linked to an increased risk of Alzheimer's dementia (AD), with the risk potentially varying according to the age at onset of depression. Previous studies have typically dichotomized depression onset ages between 55 and 65 years; however, the specific age at which depression onset increases AD risk in older adults remains unclear. In this study, we aimed to investigate the relationship between the age at onset of depression and AD risk, and compare the characteristics between different age groups.

Methods A longitudinal cohort of 251 older patients diagnosed with major depressive disorder was followed for up to 22 years. Participants were categorized into four groups based on depression onset age: ≤ 54 years, 55–64, 65–74, and ≥ 75 years. Annual cognitive assessments were conducted using the Korean Mini-Mental State Examination, with further neuropsychological testing when cognitive decline was suspected. Cox proportional hazards models were used to assess AD conversion risk across groups, adjusting for covariates.

Results During follow-up ranging from 1.0 to 22.9 years, 75 patients (29.88%) converted to AD. Depression onset after age 75 years was significantly associated with a higher risk of AD conversion (hazard ratio [HR], 8.95; 95% confidence interval [CI], 3.41–23.48; $p < 0.0001$) and a shorter time to conversion compared to onset before age 55 (40.93 vs. 83.40 months). After adjusting for covariates, depression onset after age 75 remained significantly associated with AD conversion (adjusted HR, 5.20; 95% CI, 1.04–25.93; $p = 0.0431$). This group also had milder depressive symptoms and a higher prevalence of hypertension and cerebrovascular disease than those with depression onset before 55 years of age.

Conclusions The onset of depression after the age of 75 years was strongly associated with an increased risk of AD and a shorter time to dementia onset. Individuals with depression onset after age 75 appear more closely linked to vascular comorbidities, while those with depression onset before age 55 are characterized by severe and recurrent

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depressive episodes. The mechanisms underlying AD in individuals with depression may differ from those in individuals without prior depression.

Keywords Depression in late-life, Onset age of depression, Dementia, Alzheimer's disease, Alzheimer's dementia

Background

Many patients with depression develop Alzheimer's dementia (AD) in real-world settings [1]. We previously demonstrated that depression is an independent risk factor for dementia in a nationwide cohort, with an adjusted hazard ratio (HR) of 2.35 (95% confidence interval [CI] 2.21–2.49) [2]. Depressive symptoms frequently precede or co-occur with neurodegenerative conditions in many patients with dementia [3]. Extensive research has explored the link between late-life depression and AD [1, 3–7]; however, the heterogeneity of late-life depression complicates our understanding of the pathways through which depression contributes to dementia risk [8, 9].

One factor that may explain this heterogeneity is age at the onset of depression [10]. Depression that begins early in life is often associated with a familial history and strong genetic predisposition to mood disorders [11]. Early-onset depression is hypothesized to be a risk factor for dementia, contributing to cognitive dysfunction through mechanisms such as chronic stress, dysregulation of the hypothalamic-pituitary-adrenal axis and neuroinflammation [12]. By contrast, depression that occurs later in life is thought to result from brain damage [8], and may be a prodrome of dementia, indicating its impending onset [13]. A notable example is vascular depression [14], a subtype of late-life depression associated with cerebrovascular disease.

If depression onset at different ages reflects distinct characteristics and mechanisms, there may be a specific age interval at which the risk of dementia significantly diverges. In particular, later-onset depression may signal a higher dementia risk and a shorter time to onset. Despite this rationale, previous studies have typically dichotomized depression onset between the ages of 55 and 65 years without establishing a precise age criterion [15]. While prior research has explored the link between late-life depression and dementia, the relationship between depression onset age and dementia risk remains unclear.

To address this, we conducted a longitudinal study of a hospital cohort of patients with depression, with up to 22 years of follow-up to examine the relationship between age at onset of depression and dementia risk. We also compared the characteristics of different onset-age groups to explore variations in dementia risk.

Methods

Study cohort and participant selection

This was an observational post hoc analysis based on a longitudinal cohort originally established for research on antidepressant treatment responses in patients with major depressive disorder (MDD) [16–18]. The original cohort consisted of clinically referred Korean outpatients who visited a geropsychiatry clinic at Samsung Medical Center between June 1995 and January 2012. All participants met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD [19]. Participants were included if they were experiencing a current unipolar major depressive episode (based on DSM-IV criteria) and had a baseline 17-item Hamilton Depression Rating Scale (HAM-D) score of at least 15 [20]. We excluded individuals with psychotic disorders (e.g., schizophrenia, delusional disorder), bipolar disorder, neurological illnesses (e.g., Parkinson's disease, epilepsy), intellectual developmental disability, major medical conditions (e.g., advanced cancer, systemic infections), history of alcohol or drug dependence, personality disorders, head trauma with loss of consciousness, malignancy, abnormal baseline laboratory findings, or unstable psychiatric conditions (e.g., recent suicide attempt during the current episode) to minimize the influence of comorbidities and ensure stable follow-up. This cohort was developed in a naturalistic clinical setting and comprised individuals seeking treatment for depression. Over time, the cohort was expanded and followed longitudinally, allowing the investigation of long-term clinical and biological outcomes beyond the initial scope of antidepressant response studies. This design enabled us to explore clinically relevant questions regarding late-life depression and dementia in a real-world clinical population with consistent and sustained follow-up.

We identified 251 participants aged 55 or older who were cognitively normal (Korean Mini-Mental State Examination [K-MMSE] score ≥ 28/30 [21]) after an initial 6 weeks of antidepressant treatment. This selection provided an opportunity to examine the association between the age at depression onset and dementia risk in cognitively healthy individuals with MDD.

Study protocol

The study was approved by the ethics review board of Samsung Medical Center (IRB No. 1999-10-14), and written informed consent was obtained from all participants. At baseline, all participants underwent a structured research interview using the Samsung Psychiatric

Evaluation Schedule (SPES) [22]. The SPES collected data on psychiatric symptoms, cognitive screening, comorbid physical diagnoses (hypertension, diabetes mellitus, dyslipidemia, cardiac disease, and cerebrovascular disease), and psychosocial factors (age, sex, onset age of depression, duration of the current episode, number of depressive episodes, family history of depression, and initial HAM-D score). Each diagnostic interview involved the patient and at least one family member. A board-certified psychiatrist confirmed all diagnoses using SPES, clinical observations, and medical records. Peripheral blood samples were collected at baseline for apolipoprotein E (ApoE) genotyping and plasma biomarker analyses.

Participants were followed up every 3 months starting from their initial clinic visit, which served as the entry point for this study. The entry point was defined as the date of depression diagnosis at which detailed information on depressive symptoms and medical status was collected. The follow-up continued until December 31, 2023, with dementia onset, patient death, or the end of the follow-up period. The K-MMSE was administered annually, and if cognitive decline was reported by the patient, caregivers, or clinician, further neuropsychological assessments, brain magnetic resonance imaging (MRI), and laboratory tests were performed. Neuropsychological assessments included the K-MMSE, clinical dementia rating (CDR) scale [23], Seoul neuropsychological screening battery-dementia version [24], Seoul-activities of daily living [24], Seoul-instrumental activities of daily living [25], Korean version of the neuropsychiatric inventory [26], and Korean version of the geriatric depression scale [27]. All tests were repeated annually during the follow-up period of up to 22 years. The brain MRI results were interpreted by board-certified neuroradiologists and served as an auxiliary measure to differentiate other diseases that may cause dementia syndromes. To ensure clarity in clinical diagnosis, we excluded patients exhibiting signs of degenerative non-Alzheimer's disease dementia, including Parkinsonian features or behavioral and personality changes. At our geropsychiatry clinic, the interobserver diagnostic reliability for distinguishing AD from non-AD was 91.4% [28].

Onset age of depression

At enrollment, participants reported the age of their first depressive episode, primarily based on patient and caregiver recall, and cross-referenced with medical records when available. We hypothesized that depression onset at different life stages may exhibit distinct characteristics and arise from different mechanisms [29], with a specific age interval at which dementia risk diverges. To identify this potential inflection point, we categorized the onset age of depression into 10-year intervals and calculated AD risks for each group. Participants were categorized into four groups based on the age of their first depressive episode: 54 years or earlier, 55 to 64 years, 65 to 74 years, and 75 years or later.

Characteristics of depression

Baseline clinical data on depression were collected at enrollment through interviews, with additional information gathered during follow-up. This included a family history of depression, multiple tendency, chronicity of depression, and comorbid medical conditions (e.g., hypertension, diabetes, dyslipidemia, cardiac disease, and cerebrovascular disease). Patients with three or more lifetime depressive episodes were classified as having multiple tendencies [30], while chronicity of depression was defined as episodes lasting 24 months or longer at any point in the patient's life [19]. During follow-up, the antidepressant treatment response and remission were assessed using the HAM-D score. The response was defined as a 50% or greater reduction in the HAM-D score at 6 weeks, while remission was defined as a HAM-D score of 7 or lower at 6 weeks of treatment [31].

Conversion to AD

The primary outcome was conversion to AD as defined by the DSM-IV. Participants with a CDR score of > 1 had their diagnoses confirmed by a clinician using the DSM-IV criteria, neuropsychological testing, and impairments in activities of daily living. Probable AD was diagnosed according to the National Institute of Neurological and Communicative Diseases and the Stroke-Alzheimer's Disease and Related Disorders Association criteria [32]. Participants with newly diagnosed dementia underwent annual follow-up examinations to confirm their dementia status and subtype, with the date of dementia onset recorded as the first confirmed diagnosis.

Biomarkers of AD

At baseline, we measured the ApoE4 genotype and plasma levels of amyloid-beta 40 (Aβ40), amyloid-beta 42 (Aβ42), total Tau, and Interleukin-1β (IL-1β) to assess their predictive value for future dementia risk, as these biomarkers are relevant to AD [33]. Notably, IL-1β has been associated with AD development in patients with depression [34]. Owing to the significant time elapsed since cohort recruitment, only 68 usable blood specimens were available and were collected at enrollment rather than at the time of AD diagnosis. Despite this limitation, these biomarkers can provide a predictive value for AD risk, as pathological changes often begin decades before clinical symptoms appear [35, 36]. While this analysis is constrained and exploratory, it serves as a preliminary investigation to inform future studies. Although this analysis is constrained and exploratory, it is a preliminary investigation for future research. The Additional Material

(Additional file 1) further details the biomarker measurement methods.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), with statistical significance set at $p < 0.05$. Clinical and demographic characteristics of participants were presented as categorical variables (frequencies and proportions) or continuous variables (mean ± standard deviation [SD] or median [first quartile, third quartile]). Univariable Cox proportional hazards regression was used to estimate HRs and 95% CIs for depression onset age, and other clinical and demographic characteristics. Multivariable Cox proportional hazards regression was used to assess AD conversion risk based on depression onset age, adjusting for variables with $p < 0.05$ in the univariable analysis. The proportional hazard assumption was verified using Schoenfeld residuals, and collinearity was evaluated using the variance inflation factor to ensure independent contributions of the predictors. Bonferroni's correction was applied to account for multiple comparisons among the four depression-onset-age groups. Cross-sectional comparisons between onset-age groups were conducted using the Wilcoxon rank-sum test for non-normally distributed continuous variables and Fisher's exact test or chi-square test for categorical variables, as appropriate.

In a subset of patients with available plasma biomarker data to evaluate their association with dementia risk, univariable and multivariable Cox proportional hazards regression analyses were performed. To choose the variables in the multivariable model, forward stepwise variable selection with entry and exit criteria of 0.05 was employed and the adequate number of variables was limited to two to minimize overfitting.

Results

Participant characteristics

Table 1 presents the baseline clinical and demographic characteristics of the participants, along with the univariable Cox proportional hazard regression results. Of the 251 participants, 75 (29.88%) converted to AD during the follow-up period ranging from 1.0 to 22.9 (mean = 5.4) years, and median follow-up time (95% CI) was 5.8 (4.3–7.4) years estimated by reverse Kaplan–Meier method. Among the remaining 176 individuals, 73 died, 83 were lost to follow-up, and 20 completed the follow-up as of December 31, 2023. Age was significantly associated with a higher risk of AD conversion, with participants who converted being older (71.47 ± 6.92 years) than those who did not (69.64 ± 6.93 years) (HR, 1.09; 95% CI, 1.05–1.13; $p < 0.0001$). Education was also significantly associated with a lower risk of AD conversion, with participants who converted having fewer years of education (7.52 ± 5.20 years) compared to those who did not (8.90 ± 4.61 years) (HR, 0.94; 95% CI, 0.89–0.99; $p = 0.0113$). Furthermore, participants who responded to antidepressant treatment had an increased risk of AD conversion (HR, 2.40; 95% CI, 1.37–4.18; $p = 0.0021$). A family history of depression was linked to a reduced risk of AD conversion (HR, 0.38; 95% CI, 0.17–0.83; $p = 0.0158$), while those with a multiple tendency (three or more lifetime depressive episodes) had a lower risk of conversion (HR, 0.56; 95% CI, 0.32–0.97; $p = 0.0390$). Chronicity of depression, defined as episodes lasting 24 months or longer, was associated with a higher risk (HR, 1.85; 95% CI, 1.16–2.96; $p = 0.0101$). In addition, participants with cerebrovascular disease exhibited a significantly higher risk of AD conversion (HR, 2.59; 95% CI, 1.52–4.43; $p = 0.0005$). However, the presence of the ApoE4 allele was not significantly linked to AD conversion (HR, 1.27; 95% CI, 0.75–2.12, $p = 0.3713$).

Association between onset age of depression and AD conversion

In the univariable analysis (Table 1; Fig. 1, Additional file 2), participants with depression onset after age 75 years exhibited the highest risk of AD conversion (HR, 8.95; 95% CI, 3.41–23.48; $p < 0.0001$) compared to those with onset before age 55 years (reference group), with a shortest average time to conversion of 40.93 months (SD, 32.15). Participants with onset between ages 65 and 74 years had a significantly elevated risk (HR, 2.67; 95% CI, 1.07–6.66; $p = 0.0310$), with an average time to conversion of 60.07 months (SD, 45.97). The group with onset between ages 55 and 64 years showed no significant increase in AD risk (HR, 2.29; 95% CI, 0.89–5.85; $p = 0.1068$); however, their average time to AD conversion gradually increased to 72.59 months (SD, 54.54), while the reference group had an average of 83.40 months (SD, 57.42).

For the multivariable analysis, covariates were selected based on a p-value < 0.05 from the univariable analysis. Additionally, sex was defined as a covariate because of its clinical significance, regardless of statistical significance. After adjusting for sex, age, education, antidepressant treatment response, family history of depression, multiple tendency, chronicity, and cerebrovascular disease, the age at depression onset remained significantly associated with AD conversion risk ($p = 0.0206$, Table 2, and Fig. 2). Participants with depression onset after age 75 years had a significantly higher adjusted risk of AD conversion (adjusted HR, 5.20; 95% CI, 1.04–25.93; $p = 0.0431$) compared to those with onset before age 55 years. In contrast, onset between ages 65 and 74 years showed a non-significant trend toward increased risk (adjusted HR, 1.66; 95% CI, 0.50–5.52; $p = 0.9357$). Onset between ages 55 and 64 years was not significantly associated with

Table 1 Demographic and clinical characteristics of participants

	Total	Converted to AD		Hazard Ratio	*p*-value
	(*n* = 251)	No (*n* = 176)	Yes (*n* = 75)	(95% CI)	
Baseline Demographics					
Sex (Female)	203 (80.88)	140 (79.55)	63 (84.00)	1.16 (0.62–2.15)	0.6455
Age	70.18 ± 6.96	69.64 ± 6.93	71.47 ± 6.92	1.09 (1.05–1.13)	**< 0.0001**
Education (years)	8.49 ± 4.82	8.90 ± 4.61	7.52 ± 5.20	0.94 (0.89–0.99)	**0.0113**
Onset Age of Depression					**< 0.0001**
54 Years or Earlier	57 (22.71)	47 (26.70)	10 (13.33)	1 (Reference)	
55 to 64 Years	61 (24.30)	42 (23.86)	19 (25.33)	2.29 (0.89–5.85)	0.1068
65 to 74 Years	93 (37.05)	68 (38.64)	25 (33.33)	2.67 (1.07–6.66)	**0.0310**
75 Years or Later	40 (15.94)	19 (10.80)	21 (28.00)	8.95 (3.41–23.48)	**< 0.0001**
Characteristics of Depression					
Initial HAM-D	19.52 ± 4.42	19.58 ± 4.32	19.29 ± 4.79	0.96 (0.90–1.03)	0.2820
Response	162 (64.54)	103 (58.52)	59 (78.67)	2.40 (1.37–4.18)	**0.0021**
Remission	90 (35.86)	60 (34.09)	30 (40.00)	1.27 (0.80–2.01)	0.3170
Family History of Depression	42 (16.73)	35 (19.89)	7 (9.33)	0.38 (0.17–0.83)	**0.0158**
Multiple Tendency*	63 (25.10)	47 (26.70)	16 (21.33)	0.56 (0.32–0.97)	**0.0390**
Chronicity**	62 (24.70)	33 (18.75)	29 (38.67)	1.85 (1.16–2.96)	**0.0101**
Comorbidities					
Hypertension	115 (45.82)	74 (42.05)	41 (54.67)	1.42 (0.90–2.24)	0.1300
Diabetes Mellitus	46 (18.33)	34 (19.32)	12 (16.00)	1.13 (0.61–2.10)	0.6984
Dyslipidemia	26 (10.36)	19 (10.80)	7 (9.33)	0.83 (0.38–1.82)	0.6499
Cardiac Disease	22 (8.76)	14 (7.95)	8 (10.67)	1.30 (0.62–2.73)	0.4870
Cerebrovascular Disease	28 (11.16)	10 (5.68)	18 (24.00)	2.59 (1.52–4.43)	**0.0005**
Biomarker of AD					
ApoE4 allele, 0	199 (79.28)	144 (81.82)	55 (73.33)		
ApoE4 allele, 1 or 2	52 (20.72)	32 (18.18)	20 (26.67)	1.27 (0.75–2.12)	0.3713
Neuropsychological Test on Diagnosis of AD					
MMSE	24.60 ± 5.75	27.53 ± 2.40	18.00 ± 5.64		
CDR	0.48 ± 0.66	0.12 ± 0.22	1.28 ± 0.61		
CDR-SB	2.70 ± 3.56	0.81 ± 0.76	7.06 ± 3.66		
GDS	2.52 ± 1.53	1.64 ± 0.75	4.47 ± 0.86		

HAM-D, 17-item Hamilton Rating Scale for Depression; AD, Alzheimer's dementia; ApoE4, apolipoprotein E4; MMSE, Mini Mental State Examination; CDR, Clinical Dementia Rating; CDR-SB, Sum of Boxes of CDR; GDS, Global Deterioration Scale; CI, confidence interval

* Multiple tendency refers to patients with three or more lifetime depressive episodes

** Chronicity is defined as depressive episodes lasting 24 months or longer at any point in the patient's life

Data are presented as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. Cox proportional hazards regression analysis was performed to determine the association between demographic and clinical factors and conversion to AD

AD conversion (adjusted HR, 1.84; 95% CI, 0.67–5.06; $p = 0.4454$). The estimated survival curves from the multivariable Cox proportional hazards model, adjusted for male gender, age of 70 years, education of 8.5 years, no treatment response, no family history of depression, no cerebrovascular disease, no chronicity of depression, and no multiple tendency, are depicted in Fig. 2. Participants with depression onset at age 75 years or later had the lowest AD-free survival rate, indicating the highest risk of AD conversion and the shortest estimated median survival time. Conversely, participants with depression onset before the age of 55 years exhibited the highest AD-free survival rate and the longest median survival time. Those with depression onset between ages 55 and 74 years exhibited intermediate survival rates, with survival curves for the 55–64 and 65–74 years age groups closely aligned, indicating similar risk profiles.

Comparison of onset age before 55 and after 75 years

We specifically compared patients with depression onset before the age of 55 years and those with depression onset at or after the age of 75 years, as these groups exhibited the most significant differences in dementia risk. Including other onset-age groups that did not show significant differences could dilute the effects of depression onset age on dementia risk. Therefore, we excluded them to ensure clearer distinctions between the groups with the most pronounced risk differences.

Participants with depression onset at or after 75 were significantly older (median age, 79.00 years; interquartile range [IQR], [76.00, 81.00]) than those with onset before

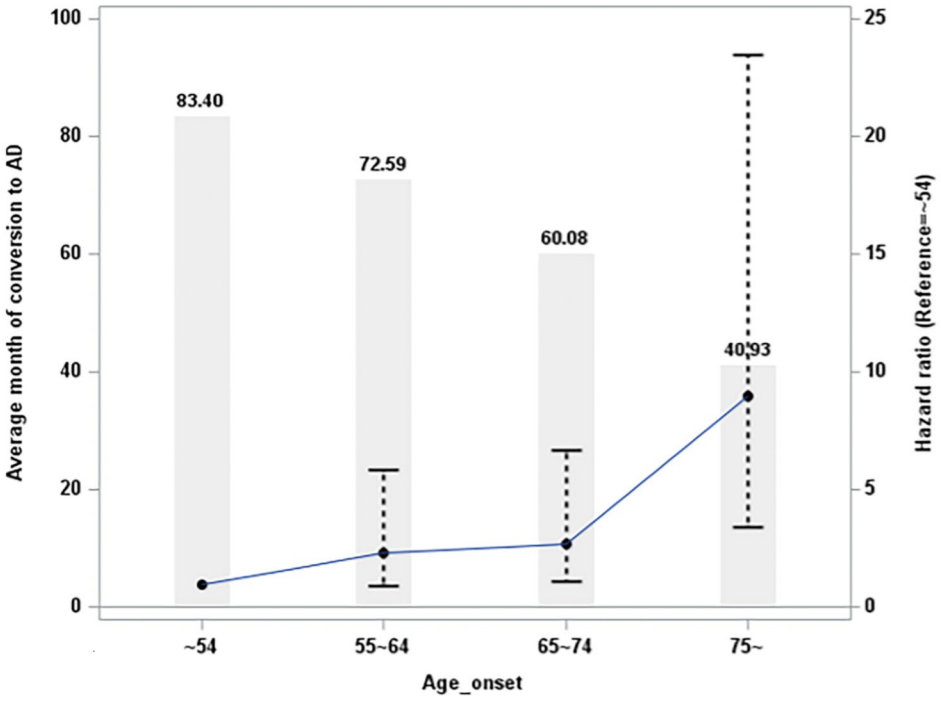

Fig. 1 Hazard Ratio for Alzheimer's Dementia and Average Conversion Time Based on Onset Age of Depression. Hazard ratios (HRs) for Alzheimer's dementia (AD) according to the onset age of depression in the univariable analysis, along with the average months of conversion to AD. The solid line represents the HR for each onset-age group, with the corresponding confidence intervals displayed as dotted error bars. The grey bars indicate the average months of conversion to AD for each onset-age group. Onset-age groups include onset of depression at < 55 years, 55–64 years, 65–74 years, and ≥ 75 years

Table 2 Association between onset age of depression and Alzheimer's dementia risk

	Multivariable Analysis	
	adjusted HR (95% CI)	***p*-value**
Onset Age of Depression		0.0206
54 Years or Earlier	1 (Reference)	
55 to 64 Years	1.84 (0.67–5.06)	0.4454
65 to 74 Years	1.66 (0.50–5.52)	0.9357
75 Years or Later	5.20 (1.04–25.93)	**0.0431**
Sex (Female)	1.09 (0.53–2.26)	0.8145
Age	1.03 (0.97–1.09)	0.3309
Education	0.96 (0.91–1.02)	0.1973
Response	1.92 (1.05–3.50)	**0.0337**
Family History of Depression	0.57 (0.25–1.29)	0.1757
Multiple Tendency*	0.93 (0.47–1.85)	0.8347
Chronicity**	2.34 (1.41–3.89)	**0.0011**
Cerebrovascular Disease	1.32 (0.71–2.45)	0.3794

HR, hazard ratio; CI, confidence interval.

* Multiple tendency refers to patients with three or more lifetime depressive episodes

** Chronicity is defined as depressive episodes lasting 24 months or longer at any point in the patient's life

Cox proportional hazard regression analysis was used to determine the association between the onset age of depression and conversion to AD after adjusting for covariates. Covariates were selected based on a p-value < 0.05 in the univariable analysis

age 55 years (median age, 64.00 years; IQR, [59.00, 71.00]; $p < 0.0001$). Educational attainment was lower in the group with onset at or after age 75 years (median years of education, 6.00; IQR, [0.00, 11.00]) than in the group with onset before age 55 years (median years of education, 9.00; IQR, [6.00, 12.00]; $p = 0.0337$). Initial depression severity was lower in the group with onset at or after age 75 (median HAM-D score, 18.00; IQR, [15.50, 20.00]) compared to the group with onset before age 55 (median HAM-D score, 19.50; IQR, [17.00, 23.00]; $p = 0.0264$). A greater proportion of participants with depression onset at or after age 75 responded to treatment (75.00% vs. 52.63%; $p = 0.0256$). Furthermore, 64.91% of the participants with depression onset before age 55 had a higher prevalence of multiple depressive episodes, experiencing three or more lifetime episodes. In comparison, only 2.50% of those with onset at or after age 75 had this history ($p < 0.0001$). Hypertension (55.00% vs. 29.82%; $p = 0.0128$) and cerebrovascular disease (25.00% vs. 3.51%; $p = 0.0031$) were more common in the group with depression onset at or after 75 years of age.

Association between biomarkers and AD conversion

An Additional table file presents the results of both univariable and multivariable analyses assessing the association between biomarkers and the risk of AD conversion

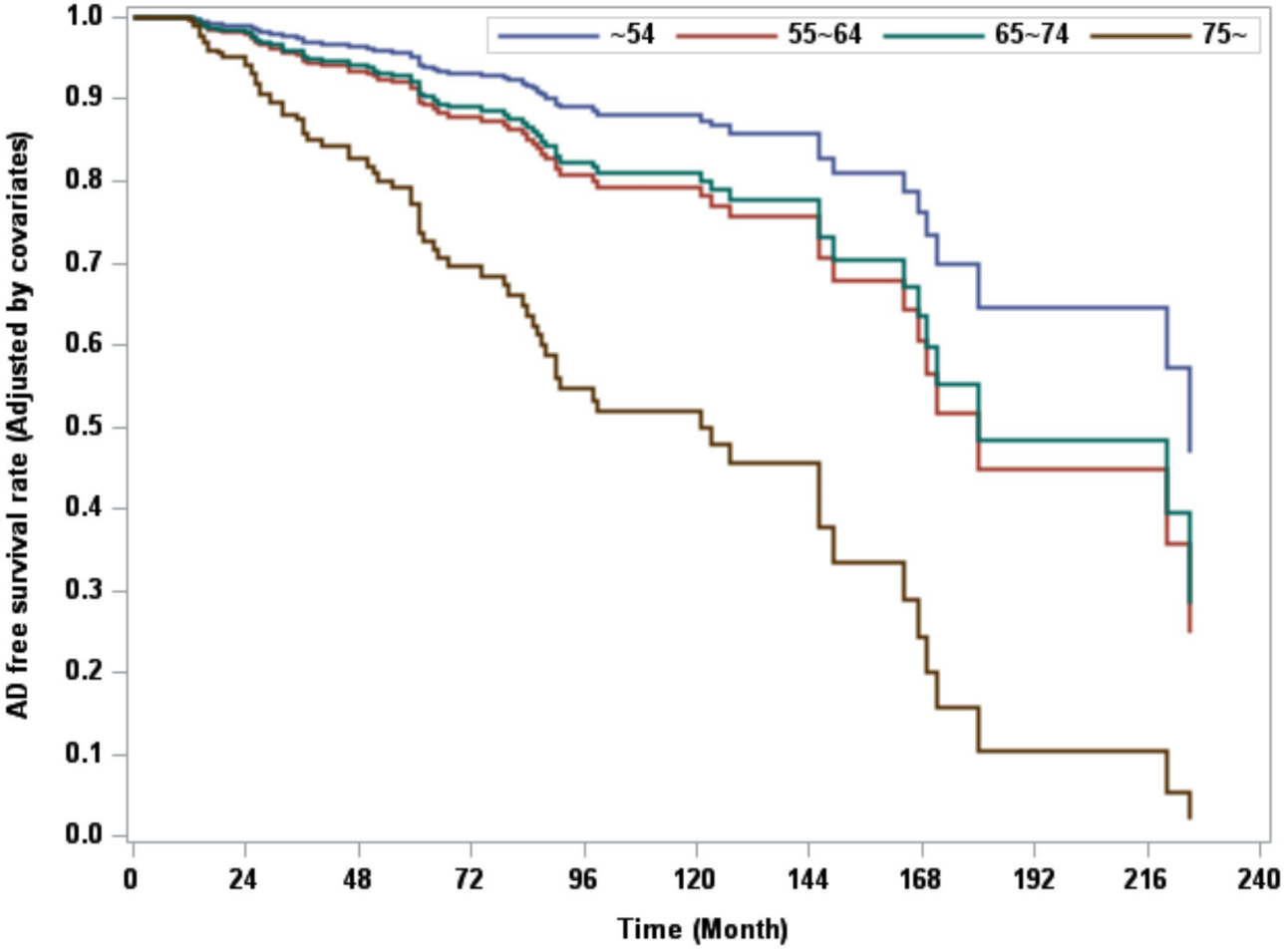

Fig. 2 Estimated Alzheimer's Dementia-Free Survival Curves Based on Onset Age of Depression. Estimated Alzheimer's dementia (AD)-free survival curves based on onset age of depression using Cox proportional hazards regression, adjusted for covariates. The onset age of depression is divided into four categories: <55 years, 55–64 years, 65–74 years, and ≥ 75 years. The x-axis represents time in months, and the y-axis represents the estimated AD-free survival rate after adjustment for covariates. The covariates were set by male gender, age of 70 years, education of 8.5 years, no response, no family history of depression, no cerebrovascular disease, no chronicity of depression and single depressive episodes. The group with depression onset at ≥ 75 years shows a markedly lower AD-free survival rate compared to the groups with earlier onset, indicating a higher risk of AD conversion in this latest onset group

in the 68 participants (see Additional file 3). Owing to the smaller sample size in the subset, we simplified the classification into two groups—depression onset before age 75 and after age 75—aligning with the main analysis findings, instead of using the original four groups. The analysis indicated that participants with depression onset after the age of 75 years had a significantly higher risk of AD conversion than those with depression onset before the age of 75 years, consistent with the main analysis. In the univariable analysis, the HR for the after-75-group was 3.90 (95% CI: 1.16–13.08; $p = 0.0278$), which further increased in the multivariable analysis to an adjusted HR of 7.39 (95% CI: 1.87–29.18; $p = 0.0043$).

In the univariable analysis, Aβ42 levels were lower in those who converted to AD (HR, 0.83; 95% CI, 0.69–0.99; $p = 0.0432$). No significant associations were found for ApoE4 allele status, Aβ40 levels, Aβ42/Aβ40 ratio, or total Tau protein levels. Elevated plasma levels of the inflammatory marker IL-1β were strongly associated with an increased risk of AD conversion (log-transformed; HR, 5.48; 95% CI, 2.06–14.60; $p = 0.0007$). After adjusting for depression onset after age 75, this association strengthened, yielding an adjusted HR of 8.68 (95% CI: 2.83–26.63; $p = 0.0002$).

Discussion

In this longitudinal cohort study, we identified significant changes in dementia hazard ratios based on the age at depression onset. Patients with depression onset at age 75 years or later had a significantly higher risk of developing AD and experienced a faster dementia progression compared to those with onset before the age of 55 years. Even after adjusting for covariates, including chronological age, depression onset after the age of 75 years

Table 3 Comparison of depression onset age before 55 and after 75

	Onset Age of Depression		*p*-value
	< 55 Years (*n* = 57)	≥ 75 Years (*n* = 40)	
Baseline Demographics			
Sex (Female)	48 (84.21)	29 (72.50)	0.1605
Age	64.00 [59.00, 71.00]	79.00 [76.00, 81.00]	**< 0.0001**
Education	9.00 [6.00, 12.00]	6.00 [0.00, 11.00]	**0.0337**
Characteristics of Depression			
Initial HAM-D	19.50 [17.00, 23.00]	18.00 [15.50, 20.00]	**0.0264**
Response	30 (52.63)	30 (75.00)	**0.0256**
Remission	20 (35.09)	14 (35.00)	0.9929
Family History of Depression	14 (24.56)	5 (12.50)	0.1406
Multiple Tendency*	37 (64.91)	1 (2.50)	**< 0.0001**
Chronicity**	15 (26.32)	5 (12.50)	0.0978
Comorbidities			
Hypertension	17 (29.82)	22 (55.00)	**0.0128**
Diabetes Mellitus	7 (12.28)	5 (12.50)	1.0000†
Dyslipidemia	4 (7.02)	5 (12.50)	0.4814†
Cardiac Disease	2 (3.51)	4 (10.00)	0.2262†
Cerebrovascular Disease	2 (3.51)	10 (25.00)	**0.0031†**
Biomarkers of AD			
ApoE4 allele, 0	46 (80.70)	33 (82.50)	
ApoE4 allele, 1 or 2	11 (19.30)	7 (17.50)	0.8226

HAM-D, 17-item Hamilton Rating Scale for Depression; AD, Alzheimer's dementia; ApoE4, apolipoprotein E4

* Multiple tendency refers to patients with three or more lifetime depressive episodes

** Chronicity is defined as depressive episodes lasting 24 months or longer at any point in the patient's life

Data are presented as median [first quartile, third quartile] for continuous variables, and as frequency (percentage) for categorical variables. Wilcoxon rank sum test was used to compare continuous variables. Fisher's exact test(†) or chi-square test was used for comparisons of categorical variables, depending on expected frequency distributions

was significantly associated with a higher risk of AD and a shorter time to dementia onset. Individuals with depression onset after age 75 had less severe depressive symptoms and a higher prevalence of hypertension and cerebrovascular disease than those with depression onset before age 55.

Our results align with the findings of previous studies reporting an increased likelihood of dementia in patients with late-life depression [6, 7, 37, 38]. Age at onset of depression significantly influences dementia risk. Depression occurring later in life appeared to signal impending dementia, with a higher risk and shorter time to AD conversion (Table 2, Fig. 1). This increased risk may be due to an "age-by-disease interaction effect," where the impact of depression on dementia varies by age [10]. Thus, depression later in life may have a more detrimental impact on cognitive decline. However, our cohort was limited to patients aged 55 and older, meaning most of our comparison group (onset before age 55) consisted of individuals with early-onset 'recurrent' depression, some of whom may have had recurrent episodes after the age of 75. If depression in older adults had a greater impact on cognitive function regardless of initial onset, we would expect recurrent depression later in life to be a significant dementia risk factor. However, our multivariable analysis did not support this, as late-life recurrent depression (indicated by "multiple tendency") did not independently increase dementia risk beyond the age of depression onset (Table 2). Furthermore, we conducted age-stratified and age-matched analyses, and confirmed that the association between depression onset age and dementia risk remained consistent beyond the effects of chronological age (data not shown). This suggests that the age-by-disease interaction alone does not fully account for our findings.

A plausible explanation is that depression onset after age 75 may result from pre-existing brain damage or neurodegeneration. The higher prevalence of vascular-related comorbidities, such as hypertension and cerebrovascular disease, supports this hypothesis (Table 3). In our previous nationwide cohort study, we observed an additive interaction between depression and cerebrovascular disease with respect to AD risk [2]. Furthermore, mounting biological evidence suggests that cerebrovascular disease [39, 40] and hypertension [41] contribute to an increased amyloid burden in the brain, potentially linking late-life depression to Alzheimer-related pathology. Future research should examine how vascular damage accelerates neurodegeneration and triggers depressive

symptoms, by focusing on the interplay between vascular comorbidities and Alzheimer's disease-related pathology.

Our study suggests that the age of 75 years may serve as an important indicator for distinguishing between early- and late-onset depression, as dementia risk increases significantly beyond this age (Table 2). As the global population ages, researchers have increasingly subdivided older populations into specific age groups. Individuals aged 75 years and older are often referred to as the "old-old," while those aged 65 to 74 years are considered the "young-old" [42, 43]. The old-old group experiences more chronic health conditions, functional impairments, and cognitive decline compared to the young-old [42]. Although 65 years of age is typically used to define older adulthood, our study supports the evidence that significant neuropsychiatric changes, including increased AD risk, may occur around the age of 75 years.

In our cohort, depression onset after age 75 was characterized by older age, low education, milder depressive symptoms, fewer recurrent episodes, and a higher prevalence of hypertension and cerebrovascular disease than onset before age 55 (Table 3). These vascular-related comorbidities may partly reflect the older baseline age in this group. However, we emphasized the characteristics of late-onset depression itself, rather than representing specific markers of dementia risk. The key finding of our study was that depression onset age remained an independent risk factor for dementia even after adjusting for covariates (Table 2). This indicates that differences in baseline characteristics such as age, education, and vascular comorbidities do not fully explain the higher dementia risk observed in the late-onset depression group. Instead, these results suggest that late-onset depression may originate from neurodegeneration and vascular damage, with an observed clinical profile that includes milder depressive symptoms and a higher prevalence of vascular-related comorbidities, reflecting the consequences of these underlying pathological processes. Our findings are consistent with those of previous studies using a lower threshold of 60 years, which also linked later-onset depression to older age, less severe depression, and poorer cognitive functioning [29]. Although we used a higher threshold of 75 years, the findings were comparable. However, our results diverge from those of previous reports, suggesting that severe, recurrent depression is a significant contributor to dementia risk [44, 45]. This discrepancy may arise from not accounting for the onset age of depression. For instance, Dotson et al. [44]. reported a mean depression onset in the mid-to-late 50s, with few patients whose depression began after the age of 75 years. Since depression onset after age 75 constitutes a very small subset of the overall depression population, its unique characteristics may not have been fully captured in studies focusing on earlier-onset cases. This could help explain why depressive symptoms in later life might have a different association with dementia risk than earlier-onset depression, further emphasizing the need for onset-age-specific analysis to understand the link between depression and dementia.

Given the distinct characteristics and minority status of depression onset after the age of 75 years, our findings suggest that the factors influencing dementia risk may differ between those with depression before and after this age. Although analyzing the longitudinal association with dementia risk in both groups was not within the scope of our study, exploring these differences could offer valuable insights into group-specific dementia risk factors. In our cohort, chronic depression—defined as depressive episodes lasting 2 years or more—was linked to an increased risk of AD, even after adjusting for covariates including age of depression onset (Table 2). While depressive symptoms were less severe in the high-risk group with depression onset after the age of 75 years, chronic depressive episodes may still contribute to dementia risk in the earlier-onset group, which comprised 84% of the cohort. Future research should focus on identifying distinct risk factors through longitudinal studies that examine the pathways linking depression and dementia in individuals with depression onset before or after 75 years of age.

Contrary to our initial prediction, established AD biomarkers such as the Aβ42/Aβ40 ratio, total Tau, and ApoE status were not significantly associated with AD risk. One explanation is the small sample size, which limited the statistical power. Additionally, the characteristics of the late-life depression cohort may have influenced our findings. For example, ApoE4 has been linked to an earlier onset of depression [46] and its recurrent episodes [47]. Both were associated with a lower risk of dementia in our study, which may explain the reduced role of ApoE4 in AD risk. However, the inflammatory marker IL-1β was a significant factor promoting AD conversion, regardless of depression onset age (see Additional file 3). These results suggest that dementia following depression may develop through mechanisms distinct from those seen in non-depressed populations [38, 48–50]. Our findings indicate that the inflammatory process, marked by elevated IL-1β, may drive dementia pathogenesis across the broader depression cohort. However, given the limitation of sample size and the timing of biomarker collection, these findings should be interpreted cautiously and considered as preliminary groundwork for future research.

Limitations

This study has certain limitations that should be acknowledged. First, the naturalistic setting lacked a healthy control group, which limited our ability to confirm the

specific association between depression and dementia. Without a non-depressed comparison group, it would have been difficult to isolate the direct effect of depression on AD risk. However, rather than using healthy controls, we compared depression onset at age 75 or later with depression onset before age 55 to explore whether later-onset depression was more closely linked to AD conversion. This approach highlighted depression onset after age 75 as a potential dementia indicator, supporting the hypothesis that specific phenotypes of late-life depression are more strongly associated with AD progression. Furthermore, the naturalistic setting allowed for the observation of real-world clinical outcomes, enhancing external validity by providing valuable insights into how depression and AD interact in typical clinical practice.

Second, our small sample size, particularly in the group with depression onset after the age of 75 years, limited our ability to perform longitudinal comparisons between early- and late-onset depression. Our initial objective was to investigate whether depression serves as a prodrome or risk factor for dementia through cross-sectional comparisons and biomarker-based longitudinal analyses. However, the small number of participants in the late-onset group and insufficient biological samples constrained our exploration of the mechanisms that distinguish early- and late-onset depression. Further research with larger sample sizes and comprehensive biomarker information is needed to confirm these findings and better delineate the relationship between depression onset age and dementia risk.

Third, the cohort was drawn from a single geropsychiatric clinic consisting of clinically referred patients, which may have introduced a selection bias, limiting the generalizability of the findings to community-dwelling older individuals with depression. Furthermore, all participants were of Korean descent, and unique genetic, cultural, or environmental factors may have influenced the relationship between depression and dementia. Therefore, caution should be exercised when applying these findings to other ethnic groups or settings.

Fourth, our use of stringent baseline cognitive criteria (K-MMSE ≥ 28) may have selectively included individuals with higher cognitive reserve. This could introduce bias especially in older participants, as cognitive decline is more common with aging. Consequently, we may have overrepresented individuals with exceptionally preserved cognition for their age. However, we acknowledge that dementia often starts more than a decade before diagnosis, making it challenging to determine whether depression precedes or indicates early progression, particularly in older participants. Although these stringent criteria may have limited the generalizability of our findings, establishing a clear temporal relationship between depression and cognitive decline is necessary.

Fifth, recall bias may have affected the accuracy of the reported age of depression onset, potentially leading to misclassification within the onset age categories. This could have influenced the observed relationship between depression onset and dementia risk. To mitigate this issue, we cross-referenced patient and caregiver reports with available medical records to enhance data accuracy. Moreover, we grouped the age of onset into broad 10-year categories (≤ 54 years, 55–64, 65–74, and ≥ 75 years), which likely reduced recall bias, as individuals tend to more reliably recall the approximate decade of depression onset [51].

Sixth, an extended follow-up period of more than 20 years resulted in a notable attrition rate. Although the naturalistic clinical setting allowed for consistent tracking of many participants, this attrition may have introduced bias and limited the generalizability of our findings.

Lastly, while plasma biomarkers are less invasive and more affordable than cerebrospinal fluid biomarkers or positron emission tomography imaging, they may be less precise in detecting Alzheimer's pathology. Plasma biomarkers can be influenced by peripheral factors, potentially reducing their sensitivity and specificity compared with cerebrospinal fluid measuresments [33]. This limitation may have affected the accuracy of our findings regarding biological markers associated with AD risk.

Conclusions

Our study demonstrates that among individuals with MDD, depression occurring after the age of 75 years is associated with the highest risk of AD conversion and the shortest time to dementia onset. Depression that begins after 75 years of age is more closely linked to vascular comorbidities, whereas depression with an onset before 55 years of age is associated with severe, recurrent depression. The physiological pathways leading to AD in depressed individuals may differ from those in individuals without prior depression. Further research is needed to clarify these mechanisms and explore targeted interventions to mitigate dementia risk in these populations.

Abbreviations

AD	Alzheimer's dementia
MDD	Major depressive disorder
HR	Hazard ratio
CI	Confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
SPES	Samsung Psychiatric Evaluation Schedule
HAM-D	Hamilton Depression Rating Scale
K-MMSE	Korean Mini-Mental State Examination
ApoE	Apolipoprotein E
MRI	Magnetic resonance imaging
CDR	Clinical dementia rating
Aβ	Amyloid-beta
IL	Interleukin

SD Standard deviation

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions
YJJ, MJK, YKM, SWL, and DKK have full access to all data of this study and take responsibility for the integrity of the data and accuracy of the data analysis. YJJ, MJK, YKM, SWL, and DKK conceived and designed the study. MJK performed statistical analyses. YJJ drafted the manuscript. SWL and DKK supervised the entire study. All authors contributed to the interpretation of the data and have read and approved the final draft for submission.

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Data availability
The dataset supporting the conclusions of this article is included within the article and its additional files.

Declarations

Ethics approval and consent to participate
The protocol was approved by the ethics review board of the Samsung Medical Center (IRB No. 1999-10-14) and conducted in accordance with the Declaration of Helsinki. All research procedures were performed in accordance with relevant guidelines. Signed informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit this paper for publication.

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