Chronic subsyndromal depression and risk of dementia in older adults

Dae Jong Oh[1,2], Ji Won Han[3], Jong Bin Bae[3],
Tae Hui Kim[4], Kyung Phil Kwak[5], Bong Jo Kim[6],
Shin Gyeom Kim[7], Jeong Lan Kim[8], Seok Woo Moon[9],
Joon Hyuk Park[10], Seung-Ho Ryu[11], Jong Chul Youn[12],
Dong Young Lee[1,13], Dong Woo Lee[14], Seok Bum Lee[15],
Jung Jae Lee[15], Jin Hyeong Jhoo[16] and Ki Woong Kim[1,3,17] iD

Abstract

Objectives: Subsyndromal depression is prevalent and associated with poor outcomes in late life, but its effect on the risk of dementia has barely been investigated. This study is aimed to investigate the effect of subsyndromal depression on dementia risk in cognitively normal older adults and patients with mild cognitive impairment.

Methods: Data were collected from a nationwide, population-based, prospective cohort study on a randomly sampled Korean elderly population aged 60 years or older, which has been followed every 2 years. Using 6-year follow-up data of 4456 non-demented elderly, the authors examined the risk of dementia associated with late-onset subsyndromal depression using multivariate Cox proportional hazard models. After standardized diagnostic interviews, subsyndromal depression and dementia were diagnosed by the operational diagnostic criteria and *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria, respectively.

Results: Subsyndromal depression tripled the risk of dementia in non-demented elderly individuals (hazard ratio = 3.02, 95% confidence interval = [1.56, 5.85], $p < 0.001$). In subgroup analyses, subsyndromal depression was associated with the risk of dementia in cognitively normal participants only (hazard ratio = 4.59, 95% confidence interval = [1.20, 17.54], $p = 0.026$); chronic/recurrent subsyndromal depression with increasing severity during the follow-up period was associated with the risk of dementia (hazard ratio = 15.34, 95% confidence interval = [4.19, 56.18], $p < 0.001$).

[1]Department of Psychiatry, College of Medicine, Seoul National University, Seoul, South Korea
[2]Department of Psychiatry, SMG-SNU Boramae Medical Center, Seoul, South Korea
[3]Department of Neuropsychiatry, Seoul National University Bundang Hospital, Gyeonggido, South Korea
[4]Department of Psychiatry, Yonsei University Wonju Severance Christian Hospital, Wonju, South Korea
[5]Department of Psychiatry, Dongguk University Gyeongju Hospital, Gyeongju, South Korea
[6]Department of Psychiatry, School of Medicine, Gyeongsang National University, Jinju, South Korea
[7]Department of Neuropsychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea
[8]Department of Psychiatry, School of Medicine, Chungnam National University, Daejeon, South Korea
[9]Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Chungju Hospital, Chungju, South Korea
[10]Department of Neuropsychiatry, Jeju National University Hospital, Jeju, South Korea
[11]Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Medical Center, Seoul, South Korea
[12]Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin, South Korea
[13]Department of Neuropsychiatry, Seoul National University Hospital, Seoul, South Korea
[14]Department of Neuropsychiatry, Inje University Sanggye Paik Hospital, Seoul, South Korea
[15]Department of Psychiatry, Dankook University Hospital, Cheonan, South Korea
[16]Department of Psychiatry, School of Medicine, Kangwon National University, Chuncheon, South Korea
[17]Department of Brain and Cognitive Science, College of Natural Sciences, Seoul National University, Seoul, South Korea

Corresponding author:
Ki Woong Kim, Department of Neuropsychiatry, Seoul National University Bundang Hospital, 82 Gumiro 173 Beongil, Bundanggu, Seongnamsi, Gyeonggido 463-707, Korea.
Email: kwkimmd@snu.ac.kr

Conclusion: Late-onset subsyndromal depression is a potential predictor of incident dementia when it is chronic or recurrent with increasing severity in cognitively normal older adults.

Introduction

Depression in late life has received growing attention due to its close relationship with dementia. Robust longitudinal studies have consistently reported that clinically significant depression increases the risk of dementia in late life (Byers and Yaffe, 2011; Diniz et al., 2013; Kaup et al., 2016; Liew, 2019a, 2019b; Liew et al., 2018; Singh-Manoux et al., 2017). Specifically, clinically significant depression increases the risk of dementia only when it is chronic without remission (Kaup et al., 2016; Mirza et al., 2016).

However, very few studies have investigated whether subsyndromal depression (SSD) increases the risk of dementia. SSD is more prevalent than clinically significant depression, such as major or minor depressive disorders in late life (Meeks et al., 2011; Oh et al., 2019), and is associated with as many adverse outcomes (e.g. poor physical health, disability, health care utilization and mortality) as clinically significant depression (Beekman et al., 1997; Hybels et al., 2009; Meeks et al., 2011; Penninx et al., 1999). Although there are a number of prospective community-based cohort studies on the effect of SSD on the risk of dementia, participants with prior history of syndromal depression were included in these studies; hence, this effect could be confounded by the residual syndromal depression. Furthermore, their results were inconsistent (Almeida et al., 2017; Chen et al., 2008). Although one study from an Australian cohort reported that depression increases the risk of dementia, regardless of its severity (Almeida et al., 2017), another study involving Chinese and British cohorts found that SSD did not increase the risk of dementia (Chen et al., 2008).

In the patients with mild cognitive impairment (MCI) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI), chronic SSD was associated with low amyloid beta levels in the cerebrospinal fluid, rapid cortical atrophy and cognitive decline, and high risk of dementia due to Alzheimer's disease (AD) (Gonzales et al., 2017, 2018; Lee et al., 2012; Sacuiu et al., 2016). However, the association between chronic SSD and incident AD was independent of cortical atrophy rates in the temporal regions. This suggests that chronic SSD may represent an additional risk factor for dementia rather than the stage of the AD (Sacuiu et al., 2016). The association between SSD and dementia was found only in older adults with MCI, while there is no literature comparing this association between older adults with normal cognition and MCI.

To investigate whether chronic SSD is an additional risk factor for dementia, this population-based prospective cohort study examined (a) the association between baseline SSD and the risk of dementia in older adults with normal cognition and those with MCI and (b) the risk of dementia by the trajectories of SSD.

Methods

Study design, setting and participants

This study was part of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), a nationwide prospective cohort study (Han et al., 2018). We randomly sampled community-dwelling older adults aged 60 years or older by using the 2010 residential rosters for South Korea (response rate = 53.7%). The 6818 participants who underwent the baseline assessment (October 2010–November 2012) were followed-up every 2 years. We used all the available data from the three follow-up assessments which spanned 6 years (first follow-up: from November 2012 to October 2014; second follow-up: from November 2014 to October 2016; and third follow-up: from November 2016 to October 2018). Altogether, 5309 participants underwent the baseline assessment and at least one follow-up assessment. Among these participants, we included 4456 participants in the primary analysis to evaluate the association of baseline SSD with the risk of dementia after excluding participants with dementia (*N* = 166), other neurological or major psychiatric disorders including major and minor depressive disorders (*N* = 251), or previous history of depression (*N* = 436) during the baseline assessment. Among these 4456 participants, we included 3302 participants who underwent two or three follow-up assessments in the secondary analysis to evaluate the association between trajectories of SSD and the risk of dementia. The comparison of baseline characteristics between participants who were included in the secondary analysis (*N* = 3302) and those who were not included (*N* = 1154) is shown in Supplementary Table 1.

The protocol for this study was explained to all participants, and each participant provided a written informed consent. This study was approved by the Institutional

Review Board of the Seoul National University Bundang Hospital.

Assessment of depression

At the baseline and each follow-up evaluation, geriatric psychiatrists administered face-to-face standardized diagnostic interviews for the diagnosis of depressive disorders using the Korean version of the Mini International Neuropsychiatric Interview (MINI-K) (Sheehan et al., 1998; Yoo et al., 2006). They diagnosed syndromal depression such as major and minor depressive disorders using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria and SSD using the operational criteria (Oh et al., 2019). The operational diagnostic criteria for SSD were as follows: (a) the occurrence of two or more symptoms of depression listed in criterion A for major depressive episode in the DSM-IV within the same 2-week period; (b) the presence of at least a depressed mood or anhedonia; (c) each depressive symptom should be present for more than half a day or more than 7 days during the 2-week period; (d) participants must not fulfill the criteria for the diagnosis of major depressive disorder (MDD) or minor depressive disorder (mDD); (e) the symptoms must not be due to the direct physiological effects of a substance or a general medical condition; (f) the symptoms must not be attributable to bereavement, dementia or schizophrenia and other psychotic disorders; and (g) there should not be a history of the occurrence of a manic or hypomanic episode.

To investigate whether longitudinal courses of SSD are associated with the risk of developing dementia, participants who underwent at least two depression assessments before their last dementia assessment were divided into three groups: (a) the euthymic group, who were euthymic during baseline and follow-up assessments; (b) the remitted SSD group, who were diagnosed with SSD only once at the baseline, first or second follow-up assessment; and (c) the chronic/recurrent SSD group, who were diagnosed with SSD for the first time at the baseline, first or second follow-up assessment and diagnosed with SSD, mDD or MDD at one or more subsequent follow-up assessments. The chronic/recurrent SSD group was further classified into the following two types: (a) stable severity type, when SSD never progressed to mDD or MDD at subsequent follow-up assessments, and (b) increasing severity type, when mDD or MDD was diagnosed at least once after the initial diagnosis of SSD.

Assessment of dementia

At the baseline and each follow-up evaluation, geriatric psychiatrists conducted face-to-face standardized diagnostic interviews and performed physical and neurological examinations of every participant using the Korean version

of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery (CERAD-K-C) (Lee et al., 2002). Trained research neuropsychologists administered neuropsychological tests which consisted of the CERAD-K Neuropsychological Assessment Battery (Lee et al., 2004; Seo et al., 2010), Digit Span test (Wechsler, 1987) and Frontal Assessment Battery (Kim et al., 2010). Research nurses evaluated demographic characteristics (age, sex and educational level), physical comorbidities (diabetes, hypertension and stroke), alcohol drinking, smoking and antidepressant use. Laboratory tests including complete blood cell counts, chemistry panels, thyroid function test, serologic test for screening syphilis, serum levels of vitamin B_{12} and folate, and apolipoprotein E genotyping were also administered. A panel of geriatric psychiatrists confirmed the final diagnosis of dementia, according to the DSM-IV criteria, and MCI, according to the consensus criteria proposed by the International Working Group (Winblad et al., 2004) through diagnostic consensus conferences.

Statistical analysis

We compared the baseline characteristics between groups using Pearson's chi-square tests for categorical variables and Student's *t*-tests for continuous variables. To analyze the association between baseline SSD diagnosis and the incidence of dementia, Cox proportional hazard models were used for the estimation of hazard ratios (HRs) and 95% confidence intervals (95% CIs). We also used Cox proportional hazard models to estimate risk of dementia according to the course of the SSD among the participants who underwent at least two depression assessments before their last dementia assessment. We reported the HRs after adjusting for age, sex, education level, diabetes, hypertension, stroke, alcohol drinking, smoking, antidepressant use and apolipoprotein E genotype. The proportional hazard assumption was tested using log-minus-log survival plot for each variable (Katz, 2011). There were constant vertical differences in all the survival plots, which meant that all the covariates of our Cox proportional hazard models met the proportional hazard assumption. As the sensitivity analyses, linear regression analyses were performed to examine the association of baseline diagnosis and trajectories of SSD with the *Z*-score of neuropsychological test at the last assessment.

We performed statistical analyses using the IBM SPSS Statistics, version 19.0 (IBM Corporation).

Results

Table 1 shows the baseline characteristics of 4456 participants (mean age, 69.9 years; mean follow-up duration, 4.7 years). Among these participants, 330 (7.4%) had SSD at the baseline assessment. These participants with SSD at

Table 1. Baseline characteristics of the participants.

	Euthymic (N = 4126)	SSD (N = 330)	p[a]
Age, years, mean (SD)	69.8 (6.4)	71.4 (6.8)	<0.001
Women, number (%)	2249 (54.5)	213 (64.5)	<0.001
Educated ≤ 6 years, number (%)	1917 (46.5)	183 (55.5)	0.002
Diabetes, number (%)	766 (18.8)	65 (20.0)	0.593
Hypertension, number (%)	2110 (51.8)	180 (55.4)	0.207
Stroke, number (%)	271 (6.6)	30 (9.2)	0.076
Current drinking, number (%)[b]	569 (13.9)	39 (11.9)	0.307
Current smoking, number (%)	495 (12.0)	37 (11.2)	0.671
Antidepressant use, number (%)	134 (4.4)	18 (7.7)	0.020
APOE ε4 allele, number (%)[c]	511 (23.7)	56 (32.9)	0.007
MCI, number (%)	899 (21.8)	130 (39.4)	<0.001

SSD: subsyndromal depression; APOE: apolipoprotein E; MCI: mild cognitive impairment.
[a]Pearson's chi-square test for categorical variables and analysis of variance for continuous variables.
[b]Above 7 standard units per week within the past year.
[c]Presence of at least one copy of APOE ε4 allele.

Table 2. Effect of subsyndromal depression at the baseline assessment on the risk of incident dementia.

	Incident cases/total	HR [95% CI][a]	p
All (N = 4456)			
Euthymia	156/4126	Reference	
SSD	32/330	3.02 [1.56, 5.85]	0.001
NC (N = 3427)			
Euthymia	50/3227	Reference	
SSD	7/200	4.59 [1.20, 17.54]	0.026
MCI (N = 1029)			
Euthymia	106/899	Reference	
SSD	25/130	1.99 [0.90, 4.44]	0.091

HR: hazard ratio; CI: confidence interval; NC: normal cognition; MCI: mild cognitive impairment.
[a]Adjusted for age, sex, education level, diabetes, hypertension, stroke, alcohol drinking, smoking, antidepressant use and apolipoprotein E genotype.

the baseline assessment were older, less educated, more likely to be women, more likely to have an apolipoprotein E ε4 allele and MCI, and more likely to use an antidepressant compared to the euthymic participants (Table 1).

As summarized in Table 2, 4.2% (N = 188) of the participants developed dementia during the follow-up period. SSD tripled the risk of dementia during the follow-up period (Table 2). The HR for SSD decreased but remained significant (HR = 2.08, 95% CI = [1.06, 4.10], p = 0.034) after additional adjustment of MCI as a covariate. After evaluating the participants with normal cognition and those with MCI separately, we observed that SSD increased the risk of dementia approximately five times in the participants with normal cognition. However, in those with MCI, the effect of SSD on the risk of dementia was not statistically significant.

Among the 3302 participants who underwent one or more follow-up assessments (mean age, 69.3 years; mean follow-up duration, 5.4 years), 440 (13.4%) exhibited SSD at least once during the baseline, 2-year follow-up or 4-year follow-up assessment. Among these 440 participants, 134 (30.5%) had chronic/recurrent SSD and exhibited SSD twice or more during the baseline, 2-year follow-up or 4-year follow-up assessment; 102 had SSD while 32 progressed to MDD or mDD during the subsequent follow-up assessments. The participants with chronic/recurrent SSD were less educated and more likely to have an apolipoprotein E ε4 allele compared to those with remitted SSD (Table 3).

During the follow-up period, 3.1% (N = 104) of the participants developed dementia. SSD increased the risk of dementia by more than three times when it was chronic/recurrent. However, this increase in risk of dementia was not observed when the SSD was remitted. Among the participants with normal cognition, SSD increased the risk of dementia by more than 12 times when it was chronic/recurrent but did not when the SSD was remitted. However, in those with MCI, SSD did not significantly

Table 3. Baseline characteristics of the participants with non-remitted and remitted subsyndromal depression.

	Euthymic[a]	R-SSD[b]	CR-SSD[c]	Statistics*	
	(N = 2862)	(N = 306)	(N = 134)	p	Post hoc
Age, years, mean (SD)	69.1 (6.1)	70.0 (6.3)	70.8 (6.7)	0.001	a < c
Women, number (%)	1522 (53.2)	203 (66.3)	99 (73.9)	<0.001	a < b, c
Educated ⩽ 6 years, number (%)	1242 (43.4)	160 (52.3)	84 (62.7)	<0.001	a < b < c
Diabetes, number (%)	516 (18.2)	55 (18.2)	23 (17.7)	0.989	
Hypertension, number (%)	1426 (50.3)	151 (50.0)	74 (56.9)	0.333	
Stroke, number (%)	175 (6.2)	18 (6.0)	13 (10.0)	0.208	
Current drinking, number (%)†	404 (14.2)	26 (8.5)	13 (9.8)	0.010	a > b
Current smoking, number (%)	318 (11.1)	36 (11.8)	12 (9.0)	0.683	
Antidepressant use, number (%)	103 (3.7)	22 (7.3)	13 (10.7)	<0.001	a < b, c
APOE ε4 allele, number (%)‡	351 (23.8)	42 (25.9)	25 (36.8)	0.047	a, b < c
MCI, number (%)	553 (19.3)	111 (36.3)	58 (43.3)	<0.001	a < b, c

R-SSD: remitted subsyndromal depression; CR-SSD: chronic or recurrent subsyndromal depression; APOE: apolipoprotein E; MCI: mild cognitive impairment.
*Chi-square test for categorical variables and analysis of variance for continuous variables with Bonferroni post hoc comparisons.
†Above 7 standard units per week within the past year.
‡Presence of at least one copy of APOE ε4 allele.

increase the risk of dementia whether it was chronic/recurrent or not (Table 4).

When we further classified chronic/recurrent SSD into stable severity type and increasing severity type, only the increasing severity type was associated with the risk of dementia in the participants with normal cognition (Table 5). In the total non-demented older adults, the HR for chronic/recurrent SSD with increasing severity decreased but remained significant (HR = 9.47, 95% CI = [2.55, 35.11], $p = 0.001$) after additional adjustment of MCI as a covariate.

In the sensitivity analyses, the impacts of baseline SSD and chronic/recurrent SSD on the Z-scores of neuropsychological tests at the last follow-up assessment were analyzed (Supplementary Table 2). The baseline diagnosis of SSD was associated with declines in the global cognition (Mini Mental State Examination), memory (Word List Memory/Recall/Recognition Test) and frontal lobe function (Frontal Assessment Battery). The chronic/recurrent SSD also affected the global cognition, memory and frontal lobe function.

Discussion

No previous population-based cohort study has investigated the effect of SSD on the risk of dementia in cognitively normal older adults and in MCI patients. This prospective cohort study clearly demonstrated that SSD could increase the risk of dementia by approximately 12

Table 4. Comparison of the risks of dementia between remitted subsyndromal depression and non-remitted or recurrent subsyndromal depression.

	Incident cases/total	HR [95% CI][a]	p
All (N = 3302)			
Euthymia	78/2862	Reference	
R-SSD	16/306	1.35 [0.57, 3.19]	0.491
CR-SSD	10/134	3.41 [1.14, 10.18]	0.028
NC (N = 2,580)			
Euthymia	22/2309	Reference	
R-SSD	2/195	0.86 [0.10, 7.18]	0.889
CR-SSD	5/76	12.14 [2.04, 72.35]	0.006
MCI (N = 722)			
Euthymia	56/553	Reference	
R-SSD	14/111	1.13 [0.41, 3.10]	0.817
CR-SSD	5/58	1.11 [0.24, 5.10]	0.896

HR: hazard ratio; CI: confidence interval; R-SSD: remitted subsyndromal depression; CR-SSD: chronic or recurrent subsyndromal depression; NC: normal cognition; MCI: mild cognitive impairment.
*Adjusted for age, sex, education level, diabetes, hypertension, stroke, alcohol drinking, smoking, antidepressant use and apolipoprotein E genotype.

times in cognitively normal older adults when it was chronic/recurrent with increasing severity. However, SSD

Table 5. Comparison of the risks of dementia between remitted subsyndromal depression, non-remitted or recurrent subsyndromal depression with stable severity, and non-remitted or recurrent subsyndromal depression with increasing severity.

	Incident cases/total	HR [95% CI][a]	p
All (N = 3302)			
Euthymia	78/2862	Reference	
R-SSD	16/306	1.37 [0.58, 3.24]	0.469
CR-SSD with stable severity	6/102	1.01 [0.13, 7.64]	0.992
CR-SSD with increasing severity	4/32	15.34 [4.19, 56.18]	<0.001
NC (N = 2580)			
Euthymia	22/2309	Reference	
R-SSD	2/195	0.79 [0.10, 6.59]	0.828
CR-SSD with stable severity	3/61	6.17 [0.59, 64.65]	0.129
CR-SSD with increasing severity	2/15	45.86 [2.65, 792.40]	0.009

HR: hazard ratio; CI: confidence interval; R-SSD: remitted subsyndromal depression; CR-SSD: chronic or recurrent subsyndromal depression; NC: normal cognition.
[a]Adjusted for age, sex, education level, diabetes, hypertension, stroke, alcohol drinking, smoking, antidepressant use and apolipoprotein E genotype.

did not increase the risk of dementia in the participants with MCI regardless of whether it was chronic/recurrent. These results suggest that chronic/recurrent SSD with increasing severity may be a high-risk condition for dementia distinct from MCI, and our results are consistent with those of previous studies that reported that mild behavioral impairment, especially affective dysregulation, increases the risk of dementia in the psychiatric outpatient population (Ismail et al., 2016; Liew, 2020). Late in life, SSD is about 2.5 times more prevalent and has about five times greater incidence compared with clinically significant syndromal depression, such as MDD and mDD (Oh et al., 2019). More than half of the cases of SSD are chronic in both community (59–74%) (Beekman et al., 2002; Cohen et al., 2009) and primary care (51–70%) (Cui et al., 2008; Lyness et al., 2002, 2009) settings. Annually, about 10% of cases involving SSD progress to syndromal depression, which also increases the risk of dementia (Schoevers et al., 2006). Therefore, clinicians need to pay more attention to the risk of dementia in older adults with chronic/recurrent SSD.

In this study, chronic/recurrent SSD increased the risk of dementia only when its severity increased to the syndromal level during the follow-up assessments. This was the case in the Rotterdam study (Mirza et al., 2016). In that study, the authors identified five 10-year trajectories of depressive symptoms in 3325 participants using their Center for Epidemiology Depression Scale (CES-D) scores: low trajectory (73% of participants maintained low CES-D scores); decreasing trajectory (11% of participants had moderately high starting CES-D scores, which subsequently decreased); remitting trajectory (5% of the participants had low starting CES-D scores, which then increased, and subsequently decreased); increasing trajectory (8% of participants had low starting CES-D scores that steadily increased); and high

trajectory (3% of participants maintained high CES-D scores). Among these trajectories, only the increasing trajectory was associated with a higher risk of dementia compared to the low trajectory. The high risk of dementia observed only during the increasing trajectory of depression in our study and in the Rotterdam study further supports the prodromal hypothesis, which suggests that depressive symptoms during old age possibly represent a prodrome or an early stage of dementia (Mirza et al., 2016; Ng et al., 2019). However, previous studies showed that chronic SSD is associated with the atrophy rates in the frontal and anterior cingulate cortices but not with the atrophy rates in typical AD-related regions such as the hippocampus and entorhinal cortex. This suggests that SSD may increase the risk of dementia using another process in addition to the typical neurodegeneration associated with AD (Sacuiu et al., 2016). Moreover, chronic/recurrent SSD may also increase the risk of dementia via long-term processes involving subclinical cerebrovascular changes and/or glucocorticoid cascades (Barnes et al., 2012; Dotson et al., 2010).

All previous studies that investigated the effect of mild depression on the risk of dementia evaluated depression using self-rating scales such as the CES-D instead of structured clinical interviews according to the diagnostic criteria (Almeida et al., 2017; Byers and Yaffe, 2011; Chen et al., 2008; Diniz et al., 2013; Kaup et al., 2016; Singh-Manoux et al., 2017). Compared to the diagnostic criteria evaluated using structured clinical interviews, cutoff scores of the self-rating scales are overinclusive and susceptible to bias due to cultural background (Lee et al., 2011; Meeks et al., 2011). Since the operational diagnostic criteria for SSD in this study were based on the DSM-IV diagnostic criteria for depressive disorders, we minimized the overinclusive misclassification of SSD. In addition, our observations are

unlikely to have been confounded by residual syndromal depression or early-onset chronic symptomatic depression since we excluded participants with prior history of depressive disorders. Furthermore, we demonstrated that the risk of dementia associated with chronic SSD was not confounded by the coexistence of MCI by evaluating the participants with normal cognition and MCI separately.

However, this study has several limitations. First, the number of incident dementia cases was small, which clearly decreased the statistical power of our analyses after adjustment of various covariates. In particular, the association between the trajectories of SSD and incident dementia should be cautiously interpreted due to the small number of cases. Second, a relatively small sample size of participants with MCI might reduce the statistical power to verify the association between SSD and dementia in MCI. Third, the information about the degree of antidepressant exposure was limited, although several studies have identified the association between anticholinergic antidepressants and dementia risk (Coupland et al., 2019; Richardson et al., 2018). Finally, although the epidemiological and biological characteristics of SSD defined by our operational diagnostic criteria were well documented (Jeong et al., 2012; Oh et al., 2019; Park et al., 2015), the criteria need consensus from experts.

Conclusion

In conclusion, late-onset SSD is a robust predictor of incident dementia when it is chronic or recurrent with increasing severity in community-dwelling older adults with normal cognition and is worth noting as a high-risk condition for dementia distinct from MCI in older adults.

Declaration of Conflicting Interests

The authors(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

ORCID iD

Ki Woong Kim https://orcid.org/0000-0002-1103-3858

Supplemental Material

Supplemental material for this article is available online.

References

Almeida OP, Hankey GJ, Yeap BB, et al. (2017) Depression as a modifiable factor to decrease the risk of dementia. *Translational Psychiatry* 7: e1117.

Barnes DE, Yaffe K, Byers AL, et al. (2012) Midlife vs late-life depressive symptoms and risk of dementia: Differential effects for Alzheimer disease and vascular dementia. *Archives of General Psychiatry* 69: 493–498.

Beekman AT, Deeg DJ, Braam AW, et al. (1997) Consequences of major and minor depression in later life: A study of disability, well-being and service utilization. *Psychological Medicine* 27: 1397–1409.

Beekman AT, Geerlings SW, Deeg DJ, et al. (2002) The natural history of late-life depression: A 6-year prospective study in the community. *Archives of General Psychiatry* 59: 605–611.

Byers AL and Yaffe K (2011) Depression and risk of developing dementia. *Nature Reviews Neurology* 7: 323–331.

Chen R, Hu Z, Wei L, et al. (2008) Severity of depression and risk for subsequent dementia: Cohort studies in China and the UK. *The British Journal of Psychiatry* 193: 373–377.

Cohen CI, Goh KH and Yaffee RA (2009) Depression outcome among a biracial sample of depressed urban elders. *The American Journal of Geriatric Psychiatry* 17: 943–952.

Coupland CAC, Hill T, Dening T, et al. (2019) Anticholinergic drug exposure and the risk of dementia: A nested case-control study. *JAMA Internal Medicine* 179: 1084–1093.

Cui X, Lyness JM, Tang W, et al. (2008) Outcomes and predictors of late-life depression trajectories in older primary care patients. *The American Journal of Geriatric Psychiatry* 16: 406–415.

Diniz BS, Butters MA, Albert SM, et al. (2013) Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry* 202: 329–335.

Dotson VM, Beydoun MA and Zonderman AB (2010) Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* 75: 27–34.

Gonzales MM, Insel PS, Nelson C, et al. (2017) Cortical atrophy is associated with accelerated cognitive decline in mild cognitive impairment with subsyndromal depression. *The American Journal of Geriatric Psychiatry* 25: 980–991.

Gonzales MM, Insel PS, Nelson C, et al. (2018) Chronic depressive symptomatology and CSF amyloid beta and tau levels in mild cognitive impairment. *International Journal of Geriatric Psychiatry* 33: 1305–1311.

Han JW, Kim TH, Kwak KP, et al. (2018) Overview of the Korean longitudinal study on cognitive aging and dementia. *Psychiatry Investigation* 15: 767–774.

Hybels CF, Pieper CF and Blazer DG (2009) The complex relationship between depressive symptoms and functional limitations in community-dwelling older adults: The impact of subthreshold depression. *Psychological Medicine* 39: 1677–1688.

Ismail Z, Smith EE, Geda Y, et al. (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia* 12: 195–202.

Jeong HG, Min BJ, Lim S, et al. (2012) Plasma adiponectin elevation in elderly individuals with subsyndromal depression. *Psychoneuroendocrinology* 37: 948–955.

Katz MH (2011) *Multivariable Analysis: A Practical Guide for Clinicians and Public Health Researchers*, 3rd Edition. Cambridge: Cambridge University Press.

Kaup AR, Byers AL, Falvey C, et al. (2016) Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry* 73: 525–531.

Kim TH, Huh Y, Choe JY, et al. (2010) Korean version of frontal assessment battery: Psychometric properties and normative data. *Dementia and Geriatric Cognitive Disorders* 29: 363–370.

Lee DY, Lee KU, Lee JH, et al. (2004) A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. *Journal of the International Neuropsychological Society* 10: 72–81.

Lee GJ, Lu PH, Hua X, et al. (2012) Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biological Psychiatry* 71: 814–821.

Lee JH, Lee KU, Lee DY, et al. (2002) Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): Clinical and neuropsychological assessment batteries. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences* 57: 47–53.

Lee JJ, Kim KW, Kim TH, et al. (2011) Cross-cultural considerations in administering the center for epidemiologic studies depression scale. *Gerontology* 57: 455–461.

Liew TM (2019a) Depression, subjective cognitive decline, and the risk of neurocognitive disorders. *Alzheimer's Research & Therapy* 11: 70.

Liew TM (2019b) Symptom clusters of neuropsychiatric symptoms in mild cognitive impairment and their comparative risks of dementia: A cohort study of 8530 older persons. *Journal of the American Medical Directors Association* 20: 1054.e1–1054.e9.

Liew TM (2020) Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. *Alzheimer's Research & Therapy* 12: 35.

Liew TM, Yu J, Mahendran R, et al. (2018) Neuropsychiatric and cognitive subtypes among community-dwelling older persons and the association with DSM-5 mild neurocognitive disorder: Latent class analysis. *Journal of Alzheimer's Disease* 62: 675–686.

Lyness JM, Caine ED, King DA, et al. (2002) Depressive disorders and symptoms in older primary care patients: One-year outcomes. *The American Journal of Geriatric Psychiatry* 10: 275–282.

Lyness JM, Chapman BP, McGriff J, et al. (2009) One-year outcomes of minor and subsyndromal depression in older primary care patients. *International Psychogeriatrics* 21: 60–68.

Meeks TW, Vahia IV, Lavretsky H, et al. (2011) A tune in 'a minor' can 'b major': A review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *Journal of Affective Disorders* 129: 126–142.

Mirza SS, Wolters FJ, Swanson SA, et al. (2016) 10-year trajectories of depressive symptoms and risk of dementia: A population-based study. *The Lancet Psychiatry* 3: 628–635.

Ng KP, Chiew HJ, Rosa-Neto P, et al. (2019) Brain metabolic dysfunction in early neuropsychiatric symptoms of dementia. *Frontiers in Pharmacology* 10: 1398.

Oh DJ, Han JW, Kim TH, et al. (2019) Epidemiological characteristics of subsyndromal depression in late life. *Australian and New Zealand Journal of Psychiatry* 54: 150–158.

Park JH, Lee SB, Lee JJ, et al. (2015) Epidemiology of MRI-defined vascular depression: A longitudinal, community-based study in Korean elders. *Journal of Affective Disorders* 180: 200–206.

Penninx BW, Geerlings SW, Deeg DJ, et al. (1999) Minor and major depression and the risk of death in older persons. *Archives of General Psychiatry* 56: 889–895.

Richardson K, Fox C, Maidment I, et al. (2018) Anticholinergic drugs and risk of dementia: Case-control study. *The British Medical Journal* 361: k1315.

Sacuiu S, Insel PS, Mueller S, et al. (2016) Chronic depressive symptomatology in mild cognitive impairment is associated with frontal atrophy rate which hastens conversion to Alzheimer dementia. *The American Journal of Geriatric Psychiatry* 24: 126–135.

Schoevers RA, Smit F, Deeg DJ, et al. (2006) Prevention of late-life depression in primary care: Do we know where to begin? *American Journal of Psychiatry* 163: 1611–1621.

Seo EH, Lee DY, Lee JH, et al. (2010) Total scores of the CERAD neuropsychological assessment battery: Validation for mild cognitive impairment and dementia patients with diverse etiologies. *The American Journal of Geriatric Psychiatry* 18: 801–809.

Sheehan DV, Lecrubier Y, Sheehan KH, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry* 59: 22–33; quiz 34–57.

Singh-Manoux A, Dugravot A, Fournier A, et al. (2017) Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry* 74: 712–718.

Wechsler D (1987) *Instruction Manual for the Wechsler Memory Scale Revised*. New York: Psychological Corporation.

Winblad B, Palmer K, Kivipelto M, et al. (2004) Mild cognitive impairment—beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine* 256: 240–246.

Yoo SW, Kim YS, Noh JS, et al. (2006) Validity of Korean version of the mini-international neuropsychiatric interview. *Anxiety and Mood* 2: 50–55.