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Research paper

Depressive subfactors and cognitive function in midlife

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ABSTRACT

Background: This study aimed to evaluate the heterogeneous association of depressive subtypes with cognitive function, according to age and sex.
Methods: This cross-sectional study utilized the baseline data from the Cardiovascular and Metabolic Disease Etiology Research Center cohort and included 5271 midlife participants. For identifying depressive subtypes of the Beck Depression Inventory II items, factor analyses were utilized and yielded two factors —melancholic- and somatic-depressive subtypes. The information of Mini-Mental State Examination was used for screening cognitive function. The association between depressive subtypes and cognitive function was analysed using multiple regression after adjusting for all covariates.
Results: We observed heterogeneous association between depressive subtypes and cognitive dysfunction in midlife participants. The results of sex- and age- stratified analyses indicated that the somatic subtype was associated with dysfunction in cognitive ability. Among women, especially those aged over 60 years, MMSE scores decreased as the somatic depression scores increased. These results might suggest that the somatic subtype, rather than the melancholic subtype, has a greater association with cognitive assessment in a general midlife population, particularly older women.
Limitations: Although a confirmatory factor analysis was performed, depressive subtypes need validation and reliability tests.
Conclusions: Given this heterogeneity, characterisation of depressive subtypes according to sex and age may improve our understanding of how each depressive symptom is associated differently with cognitive dysfunction in midlife.

1. Introduction

Leading to poor quality of life and even mortality, dementia among older adults poses a considerable burden on public health. Worldwide, approximately 50 million people are diagnosed with dementia (Livingston et al., 2020; Ponjoan et al., 2019), and research suggests that by 2050, this number will grow to about 152 million people (Livingston et al., 2020). Overall, a growing body of studies suggest that potentially modifiable risk factors for dementia (e.g., depression) might be associated with cognitive deficits (Livingston et al., 2020). Thus, addressing risk factors for depression might be positively modifiable for cognitive function among older adults.

A number of previous studies have indicated that depression is not a homogeneous entity and requires personalized characterisation of symptom profiles (Maj, 2018; Maj et al., 2020). According to the Diagnostic and Statistical Manual of Mental Disorders-5, depression diagnosis relies on the identification of a number of key symptoms, the primary being emotional symptoms, then neurovegetative symptoms, and finally, neurocognitive symptoms (APA 2013). However, symptoms can span several domains, and which symptoms warrant priority remains unclear (Malhi and Mann, 2018). Clinically, melancholic and non-melancholic/atypical subtypes are classified as the core subtypes of depressive symptoms, and are considered as diagnostic specifier of depression (Maj et al., 2020; Uher et al., 2011). Notwithstanding, some depression screening assessments, such as the Beck Depression Inventory-II (BDI-II), account for varying symptoms that can be divided into two or more subtypes: among them, the most frequently noted subtypes of depressive symptoms are categorized as ‘cognitive’, ‘affective’, and ‘somatic’ (Jeon et al., 2020; Manian et al., 2013; Arnau et al., 2001; Steer and Clark, 1997; Huang and Chen, 2015; Gary et al., 2018).

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Cognitive deficit is considered a core dimension of depressive symptoms (McIntyre et al., 2013), and research has shown a link between depression severity, depressive subtype, and cognitive performance (Austin et al., 2001). Among neuropathological deficits of cognitive function, verbal and visual memory domains, in particular, are associated with depressive subtypes (Austin et al., 2001). These findings have been reported in all age groups, although more frequently in older participants (McDermott and Ebmeier, 2009; Shimada et al., 2014). Furthermore, depressive symptoms contributed significantly to the explained variance by sex and age interactions, and which may have additional impact on the lifestyle factors (McDermott and Ebmeier, 2009; Daig et al., 2009). However, available results are conflicting (McDermott and Ebmeier, 2009). Therefore, our study was designed to investigate associations among depressive subtypes and cognitive function according to age and sex.

2. Methods

2.1. Data collection and participants

This cross-sectional study utilized baseline data from the Cardiovascular and Metabolic Disease Etiology Research Center (CMERC) cohort and initially included 8097 participants. We excluded individuals who did not respond to the BDI-II questionnaires, were under 50 years of age, and did not undergo Mini-Mental State Examination (MMSE) screening for dementia. Finally, this study included 5271 individuals for analysis, totalling 1684 men and 3567 women.

2.2. Assessing depressive symptoms and defining depressive subtypes

In the CMERC cohort, BDI-II was administered to measure the severity of depression over the previous 2 weeks. This questionnaire was conducted as a self-assessment measure. It was not designed to generate a diagnosis of major depressive disorders, but to screen for depressive symptoms in non-diagnosed populations or to identify the intensity of diagnosed depressive episodes (Lim et al., 2011). BDI-II, which has been validated in the Korean population (Lim et al., 2011), consisted of 21 self-rated items about depressive symptoms. Each item is rated on a 4-point scale from 0 to 3, and the total sum of the questionnaires ranges from 0 to 63, with total scores indicating depression levels as follows: 0–13 = ‘minimal’, 14–19 = ‘mild’, 20–28 = ‘moderate’, and 29–63 = ‘severe’.

To investigate depressive subtypes with BDI-II items, we performed exploratory factor analysis on the basis of previous studies (Jeon et al., 2020; Manian et al., 2013; Gary et al., 2018). Among them, one study utilizing the same data source as our study (i.e., the data from the CMERC cohort) suggested two latent factors from the BDI-II items and categorized them as ‘cognitive’ (items 1 to 3 and 5 to 11) and ‘somatic-affective’ (items 4, 12, 13, and 15 to 21) factors (Jeon et al., 2020). Similarly, in our study, we defined two subtypes: ‘melancholic’ depressive factors (factor 1) and ‘somatic’ depressive factors (factor 2). Melancholic depressive factors included 12 items (BDI-II items 1 to 11 and 14), while somatic included nine items (BDI-II items 12, 13, and 15 to 21). In addition, depressive subtype scores were subdivided into quartiles. By considering the quartiles, our study reported differences between the lowest verses each of the three higher quartiles of depressive subtype scores in order to aid in the interpretation of our findings and examined whether cognitive function decreased as depressive subtype scores increased.

2.3. Cognitive function assessed by the MMSE

In our study, participants aged over 50 years responded to MMSE questionnaires for cognitive assessment. In community and primary care, screening tools, such as the MMSE and Montreal Cognitive Assessment, is utilized for the purpose of mapping out levels of cognitive function (Ismail et al., 2010). However, these are sometimes under-diagnosed in older adults (Ismail et al., 2010). Despite significant limitations, MMSE remains the most frequently used cognitive screening instrument in community populations (Ismail et al., 2010). The MMSE has been verified in the Korean population, with inter-rater reliability and test and retest reliability values of 0.999 ($p < 0.001$) and 0.935 ($p < 0.001$), respectively (Kim et al., 2010; Han et al., 2010). The MMSE contained 19 items and evaluated state of cognitive function in orientation, verbal memory, concentration and calculation, language, praxis, and visuospatial construction domains. The total sum of the examination ranges from 0 to 30, with lower total scores indicating cognitive deficit. The cut-off score of the MMSE for screening for cognitive deficit is traditionally 24 points; however, we calculated total scores as continuous variables in our study (Folstein et al., 1983; Kukull et al., 1994).

2.4. Covariates

Covariates included age, sex, socio-economic status, lifestyle factor, disease history, and current medication intake. Socio-economic status reflected marital status, educational year, and household income level. Marital status was classified as never married, living together with a partner, living alone, and separation due to death of a partner. Information on educational years was categorized as 6 years or less (under elementary school), 9 years or less (under middle school), 12 years or less (under high school), and over 12 years (more than college). Household income was measured as quartiles on a cumulative distribution (i.e., the lowest was the first quartile and the highest was the fourth quartile). Lifestyle factors included smoking, alcohol consumption, and physical activity. Smoking and alcohol consumption was categorized as never, past, and currently smoking or drinking. Physical activity was measured by self-responses and categorized into three groups based on both amount and intensity of regular exercise per week: ‘low’, if people never exercised; ‘middle’, if people exercised less than 150 min, and ‘high’, if people exercised more than 150 min at moderate to vigorous activity during the week on an average. Disease history was assessed via self-administered questionnaires surveying diagnoses by physicians during each participant’s lifetime. The list of diseases was as follows: hypertension, any kind of cancer, diabetes, stroke, myocardial infarction, angina, heart failure, chronic renal failure, dyslipidaemia, liver disease, chronic hepatitis, liver cirrhosis, thyroid disorders, asthma, chronic obstructive pulmonary disease, osteoporosis, arthritis, and autoimmune disease. A comorbid condition was categorized as ‘yes’ if the participants responded that they had been diagnosed with any of these diseases, otherwise, it was categorized as ‘no’. Current medication intake was indicated as ‘yes’ if the respondents indicated they took a medication prescribed by a physician due to any comorbid condition(s); otherwise, it was recorded as ‘no’.

3. Statistical analysis

Population characteristics according to cognitive deficit were assessed using the chi-square test and *t*-test. The two latent subtypes based on BDI-II were classified utilizing exploratory factor analysis with varimax rotation. Factor loading for exploratory factor analysis to sort the factors was 0.40. Factor 1 included items 1 to 11 and 14 (i.e., ‘melancholic’ factors), and factor 2 consisted of items 12, 13, and 15 to 21 (i.e., ‘somatic’ factors). Following the exploratory factor analysis, factor scores was constructed using weighted sum scores, which could take into consideration the loading values in the factor score creation and recognize the strength for items (DiStefano et al., 2009). Considering the factor loading values of each item, weighted sum scores were assessed by multiplying loading values of each item to the raw data, after standardizing the items to the same mean and standard deviation items (DiStefano et al., 2009). The associations between depressive subtypes and cognitive function were analysed using multiple regression with a generalised linear model to determine coefficients (βs) and standard

errors (SEs). Each model was regressed including a series of independent variables (melancholic and somatic subtypes) and covariates (sex, age, socio-economic status, lifestyle factors, disease history, and medication intake). Stratified analyses were performed by age and sex (see Fig. S1). *P* values < 0.05 were considered statistically significant. Bonferroni correction was additionally applied for multiple comparisons of quartiles of depressive subtype scores (significance *P* values < 0.0125). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Characteristics of the study population according to cognitive function

Table 1 shows the characteristics of the study population according to cognitive function. The total number of participants included in this study was 5271. Of the 787 individuals with cognitive deficit, 577 were women, and 210 were men. For the cognitive deficit group, the mean age was approximately 57.4 years, which was relatively higher than that of the normal group (56.8 years), and most had less than 12 years of education. Additionally, in the cognitive deficit group, total BDI-II scores (mean score of 12.6) and subtotal scores for both melancholic (mean score of 5.3) and somatic (mean score of 7.3) factors tended to show higher mean scores and significant differences, compared to the normal group (*p*-for difference <0.01).

Table 1
Characteristics of study population by cognitive function assessed by the MMSE.

	Normal[a] (*N* = 4484)		Cognitive deficit[b] (*N* = 787)		*p*-value
BDI-II score, Mean(SD)	10.4	(7.4)	12.6	(8.5)	<0.01
Sex, *N* (%)					<0.01
Men	1494	(33.3)	210	(26.7)	
Women	2990	(66.7)	577	(73.3)	
Age, Mean (SD)	56.8	(3.9)	57.4	(3.9)	<0.01
Marital status, *N* (%)					0.06
Never married	46	(1.0)	3	(0.4)	
Living together	3945	(88.0)	680	(86.4)	
Living alone	56	(1.3)	8	(1.0)	
Divorced or widowed	437	(9.8)	96	(12.2)	
Education, *N* (%)					<0.01
≤ 6 years	286	(6.4)	117	(14.9)	
≤ 9 years	518	(11.6)	210	(26.7)	
≤ 12 years	2103	(46.9)	346	(44.0)	
> 12 years	1577	(35.2)	114	(14.5)	
Household Income, *N* (%)					<0.01
Q1 (Low 25th percentile)	1142	(25.5)	303	(38.5)	
Q2	140	(31.2)	239	(30.4)	
Q3	750	(16.7)	113	(14.4)	
Q4 (High 25th percentile)	1191	(26.6)	132	(16.8)	
Smoking, *N* (%)					
Never	3212	(71.6)	606	(77.0)	<0.01
Past	879	(19.6)	115	(14.6)	
Current	393	(8.8)	66	(8.4)	
Drinking, *N* (%)					<0.01
Never	1299	(29.0)	252	(32.0)	
Past	189	(4.2)	17	(2.2)	
Current	2996	(66.8)	518	(65.8)	
Regular exercise, *N* (%)					<0.01
Low (0 min/per week)	2219	(49.5)	468	(59.5)	
Middle (less 150 min/per week)	541	(12.1)	94	(11.9)	
High (over 150 min/per week)	1724	(38.5)	225	(28.6)	
Disease history[c], *N* (%)					0.61
No	1996	(44.5)	358	(45.5)	
Yes	2488	(55.5)	429	(54.5)	
Current medication intake, *N* (%)					0.37
No	2380	(53.1)	404	(51.3)	
Yes	2104	(46.9)	383	(48.7)	

Notes. Sum of numbers may not reflect the total number in group due to missing values.

[a] Normal reflect the participants with a score of 24 or more in the Mini-Mental State Examination.

[b] Cognitive deficit reflect the participants with a score of less than 24 in the Mini-Mental State Examination.

[c] Disease history include the diagnosed experiences of hypertension, any kinds of cancer, diabetes, stroke, myocardial infarction, angina, heart failure, chronic renal failure, dyslipidemia, liver diseases, chronic hepatitis, and liver cirrhosis, thyroid disorders, asthma, and chronic obstructive pulmonary disease, osteoporosis, arthritis, and autoimmune disease.

4.2. Associations between depressive subtypes and cognitive assessment according to sex

The sex-specific associations between depressive subtypes and cognitive assessment according to quartiles of depressive symptoms are listed in Table 2. Among depressive subtypes, somatic scores were associated with decreased cognitive assessment than melancholic scores in both sexes: for a 1-unit increase in the score of somatic subtypes, the coefficient of the MMSE scores were likely to decrease. In addition, both sexes reported a significant tendency for lower MMSE scores when somatic scores increased (somatic score; in men, *p* for trend=0.04; in women, *p* for trend=<0.01), whereas the same trend in BDI-II scores was observed only in women (see Table S1 and Fig. S2). Considering quartiles of the somatic subtypes, in women, higher quartiles of somatic subtotal scores were more strongly associated with lower MMSE scores in succession, with significance mainly in the somatic quartile. Compared to the lowest 25% (Q1) of somatic subtotal scores, the highest 25% (Q4) tended to lower the coefficient of MMSE scores by 0.50 per unit increase in somatic subtotal scores; the third quartile (Q3) lowered it by 0.39; and the second quartile (Q2) lowered it by 0.37 (Q2: β=-0.37, $p < 0.01$; Q3: β=-0.39, $p < 0.01$; Q4: β=-0.50, $p < 0.001$). However, in men, there were no significant results for MMSE results according to quartiles of somatic subtype scores.

4.3. Associations between depressive subtypes and cognitive assessment according to age

The age-stratified associations between depressive subtypes and cognitive assessment according to quartiles of depressive symptoms are provided in Table 3. In midlife participants older than 50 years, higher BDI-II scores were associated with a dysfunction in cognitive assessment (see Table S2 and Fig. S3). Only the somatic subtype tends to show an association with lower cognitive assessment (age >50 years, *p* for trend<0.01; age >60 years, *p* for trend<0.01). In the somatic subtype, dysfunction seemed to be greater in individuals older than 60 years than in those in their 50s (age >50 years, β=-0.17, $p < .01$; age >60 years, β=-0.21, $p = 0.01$). However, in comparison with the lowest quartile of somatic scores (the least depressed), those in the highest quartile showed a greater dysfunction in MMSE scores, although most of the estimates were not significant in all age groups.

4.4. Associations between depressive subtypes and cognitive assessment according to sex and age

Table 4 shows the results of stratified analyses according to sex and age for the associations between depressive subtypes and cognitive assessment in a midlife population. In women older than 50 years, higher scores on BDI-II were associated with a dysfunction in cognitive assessment (see Table S3 and Fig. S4). In women over 50 years, the somatic subtype tends to show an association with dysfunction in MMSE score. Given the quartiles of depressive symptoms, the more depressed participants appeared to have significantly lower MMSE scores, only in women (somatic score; in women of 50 years, *p* for trend<0.01; in women over 60 years, p for trend=0.01). Dysfunction seemed to be more robust in women older than 60 years, compared to those in their 50s (in 50 years, β=-0.18, $p < 0.01$; in over 60 years, β=-0.25, $p = 0.02$).

Table 2
Sex-specific associations between depressive subtypes and MMSE scores according to depressive subtypes quartiles.

	MMSE scores									
	Men ($N = 1704$)					Women ($N = 3567$)				
	N	**β[a]**	**(SE)**	***p*-value**	***p* for trend**	***N***	**β[a]**	**(SE)**	***p*-value**	***p* for trend**
BDI-II scores	1704	-0.02	(0.01)	0.01		3567	-0.03	(0.01)	<0.01	
Melancholic scores		-0.08	(0.08)	0.32			-0.14	(0.05)	<0.01	
Q1	356	ref			0.79	962	ref			0.02
Q2	485	0.47	(0.17)	0.01*		833	-0.08	(0.12)	0.52	
Q3	444	0.07	(0.17)	0.68		873	-0.09	(0.12)	0.43	
Q4	419	0.15	(0.18)	0.40		899	-0.30	(0.12)	0.01*	
Somatic scores		-0.16	(0.08)	0.04			-0.20	(0.05)	<0.01	
Q1	603	ref			0.04	715	ref			<0.01
Q2	487	0.30	(0.15)	0.04		824	-0.37	(0.13)	<0.01*	
Q3	372	-0.13	(0.16)	0.42		952	-0.39	(0.13)	<0.01*	
Q4	242	-0.19	(0.19)	0.32		1076	-0.50	(0.13)	<0.01*	

Notes. Coefficients were adjusted for age, socio-economic status (marital status, education, household income), life style (smoking, drinking, regular exercise), disease history and medication intake.
"Melancholic" and "somatic" subtypes of BDI-II were derived from factor analysis of study participants.
Q1: first quartile (low 25th percentile); Q2: second quartile; Q3: third quartile; Q4 fourth quartile (high 25th percentile)
[a] β: Coefficients adjusted for all covariates.
* Significant in Bonferroni correction.

Table 3
Age-specific associations between depressive subtypes and MMSE scores according to depressive subtypes quartiles.

	MMSE scores									
	50 years ($N = 3774$)					Over 60 years ($N = 1497$)				
	N	**β[a]**	**(SE)**	***p*-value**	***p* for trend**	***N***	**β[a]**	**(SE)**	***p*-value**	***p* for trend**
BDI-II scores	3774	-0.03	(0.01)	<0.01		1497	-0.03	(0.01)	<0.01	
Melancholic scores		-0.12	(0.05)	0.01			-0.13	(0.08)	0.10	
Q1	962	ref			0.06	356	ref			0.30
Q2	941	0.00	(0.12)	0.99		377	0.27	(0.19)	0.16	
Q3	954	-0.10	(0.11)	0.36		363	0.02	(0.19)	0.90	
Q4	917	-0.20	(0.12)	0.08		401	-0.13	(0.19)	0.51	
Somatic scores		-0.17	(0.05)	<0.01			-0.21	(0.09)	0.01	
Q1	932	ref			<0.01	386	ref			<0.01
Q2	949	-0.11	(0.12)	0.36		362	-0.07	(0.19)	0.71	
Q3	961	-0.24	(0.12)	0.04		363	-0.30	(0.19)	0.13	
Q4	932	-0.31	(0.12)	0.01*		386	-0.47	(0.20)	0.02	

Notes. Coefficients were adjusted for age, socio-economic status (marital status, education, household income), life style (smoking, drinking, regular exercise), disease history and medication intake.
"Melancholic" and "somatic" subtypes of BDI-II were derived from factor analysis of study participants.
Q1: first quartile (low 25th percentile); Q2: second quartile; Q3: third quartile; Q4 fourth quartile (high 25th percentile)
[a] β: Coefficients adjusted for all covariates.
* Significant in Bonferroni correction.

5. Discussion

This study showed varying associations between two depressive subtypes (melancholic versus somatic factors) and cognitive assessment in a general midlife population. The results of sex- and age- stratified analyses indicated that the somatic subtype was associated with cognitive dysfunction. Among women, especially those aged over 60 years, MMSE scores decreased as the somatic depression scores increased. These results might suggest that the somatic subtype, rather than the melancholic subtype, has a greater association on cognitive assessment in a general midlife population, particularly older women.

Research suggests that if depressive symptoms and cognitive deficits occur at the same time, the cognitive dysfunction tends to persist even after the symptoms of depression are relieved (Hasselbalch et al., 2011; Ahern and Semkovska, 2017). Furthermore, some studies have shown that approximately 40% of currently or formerly depressed participants have experienced concurrent cognitive deficits (Gualtieri and Morgan, 2008; LeMoult and Gotlib, 2019). Some preliminary experimental studies have indicated that mood-related cognitive deficits often accompany specific domains of cognitive deficits, such as problems in the memory domains (LeMoult and Gotlib, 2019; Whitmer and Gotlib, 2013). Indeed, depression-related decreases in cognitive function, especially attention and/or interpretation functions, are considered as a part of the depressive symptoms, and the severity of depression is well correlated with greater cognitive impairment (APA 2013; Lezak et al., 2004; Everaert et al., 2017).

It is well-recognized that cognitive function, comprising various domains, is not a unitary construct and that each specific domain is associated differently with risk factors, such as sex, sociodemographic variables, depression, vascular risk, APOE-e4, and others (MacAulay et al., 2020; Singh-Manoux et al., 2010). Moreover, considering the hierarchy among key depressive symptoms, such as emotional, neurovegetative, and neurocognitive symptoms, this depressive hierarchy could diversely interact with each cognitive domain (Malhi and Mann, 2018; Uher et al., 2011). In our study, these depressive symptoms were categorized by using factor analysis as melancholic and somatic factors, and the heterogeneous subtypes interacted differently with cognitive dysfunction. However, it remains unclear which subtype has a greater weighting than the other subtype (Malhi and Mann, 2018; Uher et al., 2011). Therefore, further longitudinal study might be required to

Table 4
Sex- and age-specific associations between depressive subtypes and MMSE scores according to depressive subtypes quartiles.

	MMSE scores									
	Men ($N = 1704$)					Women ($N = 3567$)				
	N	**β**[a]	**(SE)**	***p*-value**	***p* for trend**	***N***	**β**[a]	**(SE)**	***p*-value**	***p* for trend**
50 years ($N = 3774$)										
BDI-II scores	1133	-0.02	(0.01)	0.10		2641	-0.03	(0.01)	<0.01	
Melancholic scores		-0.05	(0.09)	0.58			-0.15	(0.06)	0.01	
Q1	241	ref			0.94	721	ref			0.03
Q2	322	0.44	(0.20)	0.03		619	-0.19	(0.14)	0.19	
Q3	304	0.07	(0.20)	0.72		650	-0.15	(0.14)	0.26	
Q4	266	0.14	(0.21)	0.51		651	-0.33	(0.14)	0.02	
Somatic scores		-0.14	(0.10)	0.14			-0.18	(0.06)	<0.01	
Q1	403	ref			0.22	529	ref			<0.01
Q2	320	0.13	(0.18)	0.48		629	-0.26	(0.15)	0.10	
Q3	260	-0.09	(0.23)	0.65		701	-0.37	(0.15)	0.01*	
Q4	150	-0.12	(0.23)	0.62		782	-0.42	(0.15)	<0.01*	
Over 60 years ($N = 1497$)										
BDI-II scores	571	-0.03	(0.02)	0.03		926	-0.03	(0.01)	0.01	
Melancholic scores		-0.17	(0.14)	0.21			-0.10	(0.10)	0.32	
Q1	115	ref			0.47	241	ref			0.48
Q2	163	0.40	(0.31)	0.21		214	0.23	(0.25)	0.36	
Q3	140	-0.01	(0.32)	0.98		223	0.04	(0.24)	0.88	
Q4	153	-0.01	(0.32)	0.98		248	-0.15	(0.24)	0.55	
Somatic scores		-0.19	(0.15)	0.20			-0.25	(0.11)	0.02	
Q1	200	ref			0.09	186	ref			0.01
Q2	167	0.61	(0.27)	0.03		195	-0.73	(0.27)	0.01*	
Q3	112	-0.27	(0.30)	0.37		251	-0.49	(0.26)	0.05	
Q4	92	-0.28	(0.33)	0.40		294	-0.75	(0.25)	<0.01*	

Notes. Coefficients were adjusted for age, socio-economic status (marital status, education, household income), life style (smoking, drinking, regular exercise), disease history and medication intake.
"Melancholic" and "somatic" subtypes of BDI-II were derived from factor analysis of study participants.
Q1: first quartile (low 25th percentile); Q2: second quartile; Q3: third quartile; Q4 fourth quartile (high 25th percentile)
[a] β: Coefficients adjusted for all covariates
* Significant in Bonferroni correction.

explore if the hierarchy exists even in depressive subtypes and which subtypes would be greater on cognitive function.

Additionally, our study showed that somatic factors elicited a greater likelihood of cognitive deficits in women over the age of 60 years; however, we could not find any significant results for any age range in men. This result highlights the importance of identifying different roles of depressive subtypes in cognitive function according to sex. In fact, there is a well-founded association between sex hormone and cognitive function and depression (Castanho et al., 2014; Wolf and Kirschbaum, 2002). Through aging, changes mediated by declines in sex-related hormones, especially estradiol, have been shown to be associated with lower overall cognition and depression (Castanho et al., 2014; Wolf and Kirschbaum, 2002). A progressive decline in sex hormone with age is more noticeable in women than in men, especially post menopause, and lower concentrations of dehydroepiandrosterone, a precursor of sex hormone, appears to be associated with a more pronounced decrease in cognitive function and an overall depressed mood (Castanho et al., 2014; Wolf and Kirschbaum, 2002; Davis et al., 2011; Harsh et al., 2009). These cited studies may provide some explanation for our results. However, to our knowledge, no study has taken a fine-grained approach to investigate the impact of various depressive subtypes on cognitive function in a midlife adult population based on sex. The mechanisms behind the effects of depressive subtypes on cognitive function according to sex remain to be further explored.

Depression has been shown to be broadly related to poor cognitive function in older adults (Singh-Manoux et al., 2010; Bassuk et al., 1998; Paterniti et al., 2002). Depression in older adults may occur as an extension of their experiences as adolescents. Due to cumulated sex-differenced experiences of stressful life events and other risk factors from adolescence, there may exist a possibility for greater cognitive deficits and higher prevalences of depressive symptoms in older women (Wolf and Kirschbaum, 2002; Hamilton et al., 2015; Abela and Hankin, 2009). In addition, some longitudinal studies have indicated that the emergence of sex differences in depression occurs in early adolescence and continues into adulthood (Hamilton et al., 2015; Hankin et al., 1998). Several longitudinal studies from the UK and France, on late midlife, have examined the association between history and frequency of depressive symptoms using the General Health Questionnaire or Center for Epidemiologic Study Depression scale and cognitive deficits using the MMSE (Singh-Manoux et al., 2010; Paterniti et al., 2002). They suggested that depressive episodes tend to cluster in individuals and that individuals with persistent depressive symptoms face a greater risk of cognitive deficits in late midlife (Singh-Manoux et al., 2010; Paterniti et al., 2002). However, this interpretation does not consider the fact that depressive symptoms tend to have varying characteristics. Thus, more research is needed regarding the extent of depressive subtypes in cognitive deficits in midlife, with consideration of temporal aspects.

5.1. Strengths

This study has several strengths. First, it used information on a sufficient number of midlife participants. Second, it employed sophisticated modeling utilizing a wide range of potential confounders for analysis. Third, by dividing depressive symptoms into two factors using factor analysis, a narrower definition of depressive symptoms was used. Fourth, sufficient MMSE data were collected for a midlife population. Finally, sex- and age-specific analyses elucidated associations for depressive subtypes with cognitive function.

5.2. Limitations

This study has some limitations. First, given that the design of this study was cross-sectional, it was difficult to make causal inferences from regression results. Second, although a factor analysis was utilized, depressive subtypes need further validation from other populations. Third, cognitive function assessed by MMSE reflects only the cognitive

status and does not consider the executive cognitive function and individual cognitive domains. Fourth, BDI-II was based on self-reports, and it was not designed to confirm a diagnosis of major depressive disorders. Fifth, executive cognitive dysfunction was a common symptom of major depressive disorders. Sixth, we only utilized screening tools of major depressive disorders and dementia, not diagnostic information from a physician. Finally, due to the lack of information, we could not consider the history of psychiatric disorders and medication use.

6. Conclusion

This study showed varying associations for depressive subtypes (melancholic and somatic factors) with cognitive function assessed by the MMSE in general midlife participants. Among these depressive subtypes, we observed a trends of an association between the somatic factor and cognitive deficits in older women, but not men, after controlling for covariates. Given this heterogeneity, characterization of the depressive subtypes according to sex and age may improve our understanding of how each depressive symptom is associated differently with cognitive deficits in midlife.

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Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Ethical standards

The study protocol was approved by the institutional review board of the hospital at Yonsei University College of Medicine (4-2013-0661), and written informed consent was obtained from all participants. All procedures in this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and were carried out in accordance with the Ethical Principles for Medical Research from the Helsinki Declaration of 1975 revised in 2008.

CRediT authorship contribution statement

Yu Jin Lee: Funding acquisition, Writing – review & editing, Supervision, Writing – original draft. **Hyeon Chang Kim:** Formal analysis. **Sun Jae Jung:** Data curation, Formal analysis, Conceptualization, Supervision, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.152.

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