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A bi-factor model of the Montgomery Åsberg depression rating scale and future cognitive impairments in older adults: A 6-year follow-up study

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ABSTRACT

Depression has been found to be associated with cognitive decline. This study evaluated the association of general depressive symptoms and motivational-related symptoms with cognitive impairment 6 years later and to explore the role of potential underlying mechanisms. In 2690 cognitively healthy persons aged ≥60 from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) depressive symptoms were derived from the Montgomery Åsberg Depression Rating Scale (MADRS). Cognitive performance was assessed at baseline and 6 years later in 1810 persons with the Mini Mental State Examination (global cognition), Digit Span Forward (short-term memory), Digit Span Backward (working memory), Clock-test (visuospatial construction), and the 5-item test (immediate and delayed recall). Bi-factor analysis on the MADRS yielded a General Depression factor and an unrelated Motivational factor. After adjusting for demographics, the General Depression factor was only associated with 6-year impairment in delayed recall (OR (95% CI): 1.18 (1.04–1.34)). This association was no longer significant after adjusting for demographics, cardiovascular risk, lifestyle factors and medication use. The Motivational factor was not significantly associated with future cognitive impairments after adjusting for demographics. Concluding, almost all associations of general depressive symptoms and motivational-related symptoms with future cognitive impairments appeared to be confounded by demographics. Only the association of general depressive symptoms with future memory impairments appeared to be explained by a combination of demographics, cardiovascular risk, lifestyle and medication use.

1. Introduction

Depression is associated with cognitive decline (Van den Kommer et al., 2013; Gallagher et al., 2016). However, this association may be stronger for some depressive symptom profiles than for others. Furthermore, underlying mechanisms may differ for different depressive symptom profiles, which might be associated with decline in different cognitive domains.

While some studies found motivational-related symptoms (i.e. loss of interest, psychomotor slowing, and concentration problems) to be associated with increased risk of dementia (Berger et al., 1999; Bartolini et al., 2005; Mossaheb et al., 2012), other studies have reported that particularly symptoms of low mood were associated with cognitive outcomes (Devanand et al., 1996; Caracciolo et al., 2011; Richard et al., 2013). It has been proposed that motivational symptoms (i.e. loss of interest, psychomotor retardation) more likely underlie impairments in executive functioning through cerebrovascular damage (Alexopoulos et al., 2002), whereas core mood symptoms (i.e. sadness) might more likely underlie impairments in memory functioning through hippocampal volume loss due to prolonged stress (Steffens et al., 2011; Sawyer et al., 2012; O'Brien et al., 2004).

Previous studies evaluating the association of depressive symptom profiles with cognitive decline have not taken into account the potential overlap between symptoms of depression and symptoms of cognitive disorders. Some of the symptoms included in the clinical diagnosis of depression (i.e. psychomotor change, apathy, lack of interest, sleep difficulties, concentration problems) also frequently occur in patients with cognitive deficits (Janzing et al., 2002; da Silva, 2015; Lanctot

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et al., 2017). Therefore, it may well be that some depressive symptoms are more indicative of cognitive impairments than of depression. Separating symptoms that more often occur in the presence of a depressive disorder from symptoms that more often occur in the absence of a depressive disorder is an important approach to address this knowledge gap. Previous studies often used normal factor analysis or latent class analysis to create symptom profiles or subgroups with specific symptom profiles. These analyses have the assumption that depression is heterogeneous. However, they might be less suitable to separate symptoms into those that often occur in the presence of a depressive disorder from symptom that are unrelated to depressive disorder (and may therefore indicate cognitive disorders). Bi-factor analysis is a specific kind of factor analysis that may be particularly suitable for this purpose as it assumes that all items of a depression instrument capture one general dimension of depression, but that a subset of the items also capture symptoms that are unrelated to this General Depression factor. Instead of assuming depression as a heterogeneous construct, bi-factor analysis assumes a unidimensional construct. Instead of creating different depressive subtypes or symptom profiles, it separates symptoms occurring in the presence of depression from those occurring in the absence of depression. Bi-factor analysis therefore seems particularly suitable to take into account potential overlap between symptoms of depression and symptoms which represent other conditions, such as cognitive disorders.

By using bi-factor analysis the present study aimed to evaluate 1) the association of a General Depression Factor and the other emerging factor(s) with cognitive impairment over 6 years follow-up, and 2) whether different mechanisms explained the associations of the different factors with cognitive impairments at follow-up.

2. Method

2.1. Study population

The Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; Lagergren et al., 2004), is a population-based study including a random sample of persons aged ≥60 years registered as residents in the Kungsholmen municipality in Stockholm, Sweden. Between March 2001 and August 2004 eleven age groups were selected with follow-up intervals 6 years for the younger cohort (60–78 years) and 3 years in the older cohort (78 + years). After complete description of the study, written informed consent was obtained from all participants, or from a proxy (e.g., a family member) in case of cognitive impairment. The SNAC-K study has been approved by the regional ethical review board in Stockholm.

Of the 4590 eligible participants, 3363 (73.3%) underwent a comprehensive geriatric assessment, including demographics, medical history, cognitive and psychological testing, physical examination, evaluation of disability, cardiovascular health, and lifestyle, as well as laboratory tests at baseline and at 6 year follow-up (the protocol is available at http://www.snac.org/). There were no significant sex differences between participants and non-participants; however, non-participants were significantly older and more likely to live at home (Santoni et al., 2015). There were 2703 participants after exclusion participants with: 1) severe psychiatric disorder, including schizophrenia or use of antipsychotics, bipolar disorder, or use of lithium, and/or substance use disorder, 2) multiple sclerosis, epilepsy, brain tumor, or head injury, 3) Parkinson's disease or dementia, 4) Mini Mental State Examination (MMSE) score < 24 (Fig. 1).

2.2. Cognitive performance

The physician administering the cognitive tests and the outcome assessors were blind for depression status. Global cognition was measured with the MMSE (Folstein et al., 1975), with a score ranging from 0 to 30.

2.2.1. Executive function

Attention, working memory and visuospatial construction (planning) were assessed as basic processes of executive function. Attention was measured with the subtest digit span from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958). The digit span forward score comprised the longest series of digits a participant could repeat (short-term memory). The digit span backward comprised the longest series of digits a participant could repeat in the reverse order (working memory). Visuospatial construction was measured with the 10-point clock drawing test, which has been shown to be sensitive for AD, even in those with MMSE scores > 23 (Manos, 1999). Potential scores of the clock drawing test range between 0 and 10.

2.2.2. Memory

Immediate recall and delayed recall were assessed as basic processes of memory. Episodic memory was measured with the 5-item test., which had to be recalled after they were hidden (immediate recall). The number of correctly remembered items comprised the immediate recall score ranging between 0 and 5. After a delay of 10–15 min, participants had to report the 5 items again (delayed recall).

2.3. Factor scores

At baseline, experienced physicians carried out the MADRS (Montgomery and Asberg, 1979) comprising a subset of 10 items from the Comprehensive Psychopathological Rating Scale (CPRS; Asberg et al., 1978), which is a semi-structured psychiatric examination for the rating of current psychiatric symptoms with high sensitivity and interrater reliability (Montgomery and Asberg, 1979). Each symptom was rated based on its intensity, frequency and duration, resulting in a rating between 0 and 6. The scoring of the items was mainly based on self-reported information, but also included clinical observation and interpretation of the rater. To our knowledge, previous studies have explored the factor structure of the MADRS in clinically settings, but not in population-based samples with bi-factor analysis. Therefore, we had no a priori knowledge about the possible bi-factor structure of the MADRS.

To obtain the factor scores, bi-factor analysis was performed. It consists two phases: 1) the model building phase, and 2) the model validation phase. The sample was split into two random halves: an exploratory set and a validation set. First, we first explored the factor structure of the 10 ordinal MADRS items with exploratory bi-factor analysis (Jennrich and Bentler, 2011) in the exploratory set by using a bi-factor orthogonal rotation criterion, which yielded uncorrelated factors. This results in clusters of symptoms in all factors except the first factor. As a result, each item can load on one general factor and minimally one other factor. To determine the number of factors, model fit parameters (Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample size adjusted BIC) were compared between models with 1, 2, 3 and 4 factors.

Next, the best fitting model resulting from the exploratory bi-factor analysis was tested using a confirmatory bi-factor analysis in the exploratory set, the validation set, and the whole sample. All indicators were forced to load on the first (general) factor, and indicators loading significantly on the other factor(s) were forced to load on that/those factor(s). Overall model fit parameters were evaluated, including the Chi-Square goodness-of-fit-statistic, root mean squared error of approximation (RMSEA), Tucker Lewis Index (TLI), and Comparative Fit Index (CFI). (Hu and Bentler, 1999).

For the factor analysis Mplus version 7 was used (Muthén and Muthén, 2012).

2.4. Diagnosis of depression

Major depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria (American

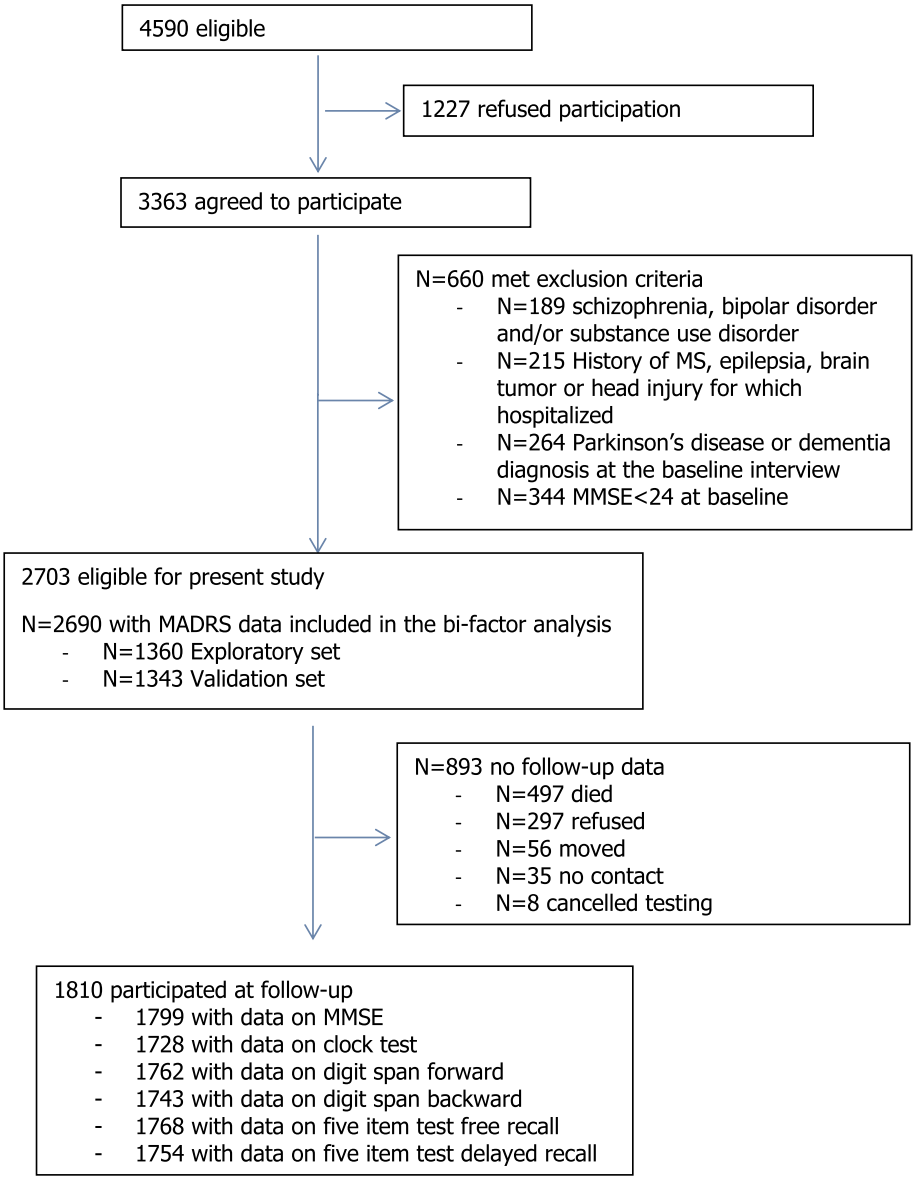

Fig. 1. Flow-chart of the sample.

Psychiatric Association, 2013) and minor depression according to DSM-IV-TR criteria (American Psychiatric Association, 2000) based on items from the CPRS (Sjoberg et al., 2017). For a diagnosis of major depression a minimum of five symptoms had to be present, including at least one of the two core symptoms (depressed mood or loss of interest/pleasure). For a diagnosis of minor depression a minimum of two and no more than four symptoms had to be present, including at least one of the two core symptoms.

2.5. Covariates

According to the second aim of the present study, we investigated whether different covariates explain the association of the different factors with cognitive outcomes. Cardiovascular risk factors/diseases/medication and lifestyle factors, including engagement in cognitive, social and physical activities, were included as covariates because of their association with both the risk of depression (Mast et al., 2008; Boden and Fergusson, 2011; Michèle et al., 2017) and cognitive impairments (Fillit et al., 2008; Abete et al., 2014; Di Marco et al., 2014; Sachdeva et al., 2016). Finally, we included use of medications that was previously found to increase the risk of cognitive impairments or dementia (Gray et al., 2015; Wang et al., 2018)

2.5.1. Cardiovascular risk factors and diseases

Total cholesterol levels were first evaluated in non-fasting blood samples. If total cholesterol levels exceeded 6.5 mmol/l, a fasting blood sample was drawn. High cholesterol levels were defined as a fasting total cholesterol level of ≥6.5 mmol/l. Blood pressure was measured twice in the left arm with a 5 min interval in sitting position after > 5 min rest. The average of the two readings was taken to define systolic and diastolic blood pressure. Hypertension was defined as a systolic blood pressure ≥140 mmhg and/or diastolic blood pressure ≥90 mmhg (Perk et al., 2012) or use of antihypertensive drugs. Diabetes mellitus was defined as self-reported history of diabetes mellitus type I or II, current use of glucose-lowering agents/insulin injection, or having hemoglobin A1c level ≥6.5% (The International Expert Committee, 2009). Smoking status was defined as current smoker or non-smoker. The number of cardiovascular risk factors (high cholesterol, hypertension, diabetes mellitus, and smoking) ranged between 0 (none present) and 4 (all present).

Information on history of cardiac disease (ICD-10 codes: I20-I25 for ischemic heart disease, I48 for atrial fibrillation, and I50 for heart failure) and cerebrovascular disease (ICD-10 codes I60-I69 for stroke) was obtained by medical history and the computerized inpatient register system from all hospitals in Stockholm since 1969 (Ludvigsson et al., 2011).

2.5.2. Lifestyle factors

Alcohol consumption was categorized into no alcohol consumption, social drinking (below the level of heavy drinking), and heavy drinking (≥4 times a week ≥5 units/day or > 21 units/week for men and ≥4 times a week ≥3 units/day or > 14 units/week for women) (Royal College of Physicians, 1987; Department of Health, 1995).

Information on leisure activities and social network were derived from baseline questionnaires. Cognitive activities included reading newspapers/magazines or books, play chess, playing an instrument, and using a computer/internet, etc. Social activities included attending movies, concerts, sport events, travelling, and doing voluntary work. Physical activities included moderate (e.g. walking, short bike rides, light gym), intense (e.g. brisk walking, jogging, intense gym, etc), and other physical activities (gardening, picking mushrooms/berries, car mechanics). Each activity dimension was classified as "0 = low", "1 = moderate" and "2 = high" according to the number of activities performed at least weekly. Leisure activity level was calculated as the sum score of these three activity dimensions, which could therefore range between 0 and 6.

Items describing social network included marital status; living alone; number of living children; frequency of contact with relatives, neighbors, and friends; the number of individuals the participant feels that he/she knows well and can talk with; satisfaction with the aforementioned contacts; perceived material and psychological support; sense of belonging with association members, relatives, and residence area; and being part of a group of friends with common activities. From these items a social network variable was derived, with scores "0 = limited", "1 = moderate", or "2 = rich".

2.5.3. Medication use

Medication use that might affect cognitive performance included the current use of drugs with anticholinergic properties, glucocorticoids, opioids, antiepileptics, dopaminergic agents, and psychotropics.

2.6. Statistical analysis

Descriptive statistics were used to evaluate whether baseline characteristics differed between those who participated, those who dropped out, and those who died before 6 years follow-up. To examine the association between the factor scores and covariates, non-parametric tests (Spearman correlation, Mann-Whitney U, Kruskal-Wallis test) were used for the General Depression factor (abnormally distributed), and one-way ANOVA was used for the Motivational factor (normally distributed). To verify to what extent the symptoms in the factor scores occurred in the presence of a depressive disorder, the associations between both factor scores and depression were examined.

After this, the missing values of the factor scores and the covariates were imputed using multiple imputation (Supplementary material). There were 375 (20.7%) participants who had missing values in cardiovascular factors, Supplemental Table 1). Of all values 4.2% was missing.

Because three of the five cognitive outcomes were skewly distributed and the aim was to identify persons with cognitive impairments at 6 years follow-up, cognitive outcomes were dichotomized at pre-established cut-off scores (MMSE: ≥24 vs < 24 (Tombaugh and McIntyre, 1992), 10-points clock test: ≥8 vs < 8 (Manos and Wu, 1994), digit span forward: ≥5 or < 5, digit span backward: ≥4 or < 4, five item test: 5 or < 5). Logistic regression was performed to examine the association of both factors with the dichotomized cognitive measures at 6 years follow-up. Model 1 included the two factor scores, which were standardized for interpretation purposes and the baseline score of the cognitive test. Model 2 included the variables in model 1 and demographics (age, sex, and education level), model 3 included the variables in model 2 and cardiovascular health, model 4 included the variables in model 2 and lifestyle variables, and model 5 included the variables in model 2 and the use of medication known to affect cognitive performance. Finally, the association of depression diagnosis with cognitive outcomes was examined, adjusting for baseline cognitive performance.

3. Results

3.1. Study population

Of the 2703 eligible participants, 2690 had complete data on the MADRS, and were therefore included in the bi-factor analysis. Of these, 1810 participants participated at 6 years follow-up (Fig. 1). Compared to participants, those who dropped out (n = 396) and deceased (n = 497) at follow-up were older, less well educated, more likely not to consume alcohol, had lower activity levels and a smaller social network size, more often had cardiovascular disease, or used medications likely to affect cognition, and had worse baseline cognitive performance. In addition, those who were deceased at follow-up also had more cardiovascular risk factors/diseases, and had higher scores on both of the two factors at baseline than those who participated at follow-up (Table S1).

3.2. Factor scores

3.2.1. The model building phase

Although the BIC and sample size adjusted BIC were lowest for 1 factor, the AIC was substantially higher for a model with 1 factor compared to a model with 2 factors (Table S2). Based on the 3 model fit parameters combined, a model with 2 factors was chosen to proceed to the model validation phase.

3.2.2. The model validation phase

In the exploratory bi-factor analysis, all MADRS items loaded significantly on the general factor (F1), which was defined as the General Depression factor, and six items loaded significantly on the second factor (F2). When entering these items in a bi-factor CFA, there was a negative residual (for the item "loss of initiative" on F2), which disappeared after deleting the item with the lowest factor loading (0.074) on F2 ('sleep disturbance', p = 0.304). Therefore, F2 in the final CFA-model included the items 'sadness', 'reduced appetite', 'loss of initiative', 'pessimistic thoughts', and 'observed sadness'. The Eigenvalues of F1 and F2 were 4.798 and 0.979 respectively. To evaluate the robustness of this CFA-model, it was also run in the validation set and in the whole sample. The overall model fit was very good in both subsamples as well as in the whole sample, suggesting robustness of the model (CFI > 0.97; TLI > 0.96; RMSEA < 0.05, Table S3).

Table 1 shows the standardized factor loadings on the two factors in the exploratory set, the validation set, and the whole sample. The second factor was dominated by loss of initiative and, to a lesser extent, reduced appetite. It was also characterized by the absence of sadness and pessimistic thoughts (reflected in negative factor loadings). As a result, participants scoring high on loss of initiative and decreased appetite, but low on pessimistic thoughts and sadness would get the highest score on this second factor, which was therefore defined as the Motivational factor. The Pearson's correlation coefficient between the two factors was −0.053. The General Depression factor explained 83%

Table 1
Standardized factor loadings of the MADRS items.

	Bi-factor EFA in exploratory set (n = 1354)		CFA in exploratory set (n = 1354)		CFA in validation set (n = 1336)		CFA in whole sample (n = 2690)	
	F1: general depression	F2: motivation	F1: general depression	F2: motivation	F1: general depression	F2: motivation	F1: general depression	F2: motivation
MADRS Sadness	0.844*	−0.137*	0.820*	−0.107	0.851*	−0.270*	0.838*	−0.197*
MADRS Anxiety thoughts	0.648*	−0.100	0.630*		0.592*		0.608*	
MADRS Sleep disturbance	0.354*	−0.138*	0.349*		0.331*		0.339*	
MADRS Reduced appetite	0.543*	0.146*	0.503*	0.262	0.584*	0.240*	0.546*	0.235*
MADRS Concentration	0.566*	0.047	0.557*		0.608*		0.584*	
MADRS Loss of initiative/lack of initiative	0.682*	0.712*	0.570*	0.531*	0.629*	0.422*	0.603*	0.481*
MADRS Inability to feel	0.714*	−0.037	0.704*		0.734*		0.717*	
MADRS Pessimistic thoughts	0.774*	−0.148*	0.770*	−0.132	0.729*	−0.197	0.749*	−0.173*
MADRS Suicidal thought	0.816*	0.071	0.808*		0.814*		0.808*	
MADRS Sadness observed	0.739*	−0.222*	0.734*	−0.196*	0.786*	−0.263*	0.765*	−0.230*
Eigenvalue	4.798	0.979	NA	NA	NA	NA	NA	NA

CFA: confirmatory factor analysis; EFA: exploratory factor analysis; MADRS: Montgomery Åsberg Depression Rating Scale, NA: not applicable.

of the common variance, and the motivational factor 17% (Eigenvalue F1/(Eigenvalues F1 + F2) = 4.798/5.777 = 0.83).

3.3. Association of the participants' characteristics and factor scores at baseline

Those with higher scores on both factors were more often women, less well educated, less active, had poorer social network, more cardiovascular risk factors and cardiovascular and cerebrovascular diseases, and performed worse on the clock test and delayed recall test at baseline (Table 2). Higher scores on the General Depression factor (but not the Motivational factor) were also associated with no drinking and heavy drinking, more use of, worse scores on the baseline MMSE, digit span forward and backward, and the immediate recall of the five-item test (Table 2 and Supplemental Table S5).

3.3.1. Association of factor scores with depression diagnosis

Persons with major depression and those with any (major or minor) depression had significantly higher scores on the General Depression factor. The Motivational factor did not differ between persons with and without major depression. Persons with any depression had lower scores on the Motivational factor than those without (Table 2).

3.4. Factor scores at baseline in relation to cognitive outcomes after 6 years

After adjustment for baseline cognitive performance and the Motivational factor, the General Depression factor was significantly associated with worse scores on the MMSE, digit span backward, and delayed recall at follow-up (Table 3). After additional adjusting for demographics, all associations disappeared, except the association between the General Depression factor and delayed recall (OR 1.18; 95% CI: 1.04–1.34; p = 0.011). This association was no longer significant (OR 1.10; 95% CI: 0.96–1.26; p = 0.173) when all covariates were entered in the model.

After adjustment for baseline cognitive performance and the General Depression factor, the Motivational factor was significantly associated with worse follow-up scores on the MMSE, the clock test, and the immediate recall. After additional adjusting for demographics the Motivational factor was not significantly associated with any of the cognitive outcomes.

3.5. Depression diagnosis at baseline in relation to cognitive outcomes after 6 years

Depression diagnosis was not significantly associated with cognitive performance at 6 years follow-up after adjustment of the baseline cognitive performance (Table 4).

4. Discussion

In a population sample of cognitively healthy older adults, we separated MADRS-symptoms into a General Depression factor and a Motivational factor (which was unrelated to the General Depression factor) using bi-factor analysis. The association between the General Depression factor and future delayed recall impairments appeared to be explained by a combination of demographic variables, cardio- and cerebrovascular disease and lifestyle variables. All other associations of both factors with future cognitive impairments were explained by demographics. We found no evidence for different mechanisms underlying the associations of the two factors with cognitive outcomes. Both factors were not differentially associated with demographics, cardiovascular risk, and lifestyle factors.

To our knowledge, only one previous study has taken into account the potential overlap of symptoms of depression with symptoms of cognitive disorders by using bi-factor analysis to create depressive symptom profiles based on 25 items of the Geriatric Mental State Schedule in 1911 cognitively healthy older adults from the general population (Lugtenburg et al., 2016). The General Depression factor in that study was significantly associated with incident dementia 3 years later after adjustment for potential covariates, whereas the Cognitive/Motivational factor (dominated by cognitive problems, loss of interest and absence of mood problems) was associated with incident dementia only in non-depressed persons.

It has been suggested that depression may act as a risk factor for future cognitive impairments through hippocampal neurodegeneration as a result of increased lifetime exposure to glucocorticoids due to stress-related alterations in the HPA-axis (O'Brien et al., 2004; Steffens et al., 2011; Sawyer et al., 2012). However, the present study found no evidence for depression as a true risk factor for future cognitive impairments, because the association of the General Depression factor with 6-year memory impairments was explained by a combination of demographic variables, cardio- and cerebrovascular disease and lifestyle variables. Furthermore, the diagnosis of minor or major depressive

Table 2
Association of factor scores with baseline variables in 2690 participants.

	F1 General depression factor (median (IQR))	F2 Motivational factor (mean (SD))
Demographics		
Age, n = 2685	Spearman's rho: 0.195[a] ***	Spearman's rho: 0.138[a] ***
Sex		
- Male, n = 983	−0.23 (−0.49–0.53)	−0.02 (0.41)
- Female, n = 1707	0.04 (−0.49–0.64)[b] ***	0.02 (0.44)[c] *
Education level		
- Elementary school, n = 409	0.17 (−0.49–0.77)	0.05 (0.46)
- High school, n = 1335	−0.02 (−0.49–0.59)	0.01 (0.44)
- University, n = 941	−0.17 (−0.49–0.54)[d] ***	−0.03 (0.40)[c] **
Lifestyle		
Alcohol drinking behaviour		
- No drinking (n = 240)	0.07 (−0.49–0.76)	0.06 (0.45)
- Social drinking (n = 2386)	−0.09 (−0.49–0.57)	0.00 (0.43)
- Heavy drinking (n = 51)	0.18 (−0.49–0.82)[d] **	−0.06 (0.42)[c]
Leisure activity level		
- Level < 4, n = 1775	−0.02 (−0.49–0.57)	0.00 (0.44)
- Level ≥4, n = 550	−0.49 (−0.49–0.35) [b]***	−0.06 (0.33)[c] **
Social network		
- Poor, n = 680	0.16 (−0.49–0.74)	0.02 (0.47)
- Moderate, n = 698	−0.17 (−0.49–0.46)	−0.04 (0.39)
- Rich, n = 703	−0.49 (−0.49–0.23)[d] ***	−0.02 (0.36)[c] *
Cardiovascular risk factors and disease		
Number of cardiovascular factors		
- ≤ 1, n = 1543	−0.17 (−0.49–0.56)	−0.01 (0.42)
- > 1, n = 546	−0.04 (−0.49–0.56) [b]	0.03 (0.46)[c]
Heart disease		
- No, n = 1851	−0.17 (−0.49–0.53)	−0.03 (0.40)
- Yes, n = 839	0.17 (−0.49–0.85)[b] ***	0.08 (0.48)[c] ***
Cerebrovascular disease		
- No, n = 2444	−0.09 (−0.49–0.56)	0.00 (0.42)
- Yes, n = 246	0.23 (−0.49–0.88)[b] ***	0.07 (0.53)[c] *
Medication		
Use of medication that could influence cognition		
- No, n = 1846	−0.49 (−0.49–0.38)	0.00 (0.38)
- Yes, n = 843	0.44 (−0.43–1.03)[b] ***	0.02 (0.53)[c]
Cognition		
MMSE baseline		
- ≥24, n = 2686	−0.02 (−0.49–0.57)	0.01 (0.43)
- < 24, n = 0	NA	NA
10 point clock test		
- ≥8, n = 1892	−0.17 (−0.49–0.48)	−0.02 (0.40)
- < 8, n = 393	0.17 (−0.49–0.90) [b]***	0.06 (0.49)[c] **
Digit span forward		
- ≥5, n = 2139	−0.09 (−0.49–0.55)	0.00 (0.43)
- < 5, n = 230	0.08 (−0.49–0.75) [b]**	0.00 (0.44)[c]
Digit span backward		
- ≥4, n = 1859	−0.17 (−0.49–0.53)	−0.01 (0.42)
- < 4, n = 501	0.17 (−0.49–0.73) [b]***	0.01 (0.47)[c]
5 Item test, immediate recall		
- 5, n = 2331	−0.09 (−0.49–0.55)	0.00 (0.43)
- < 5, n = 43	0.55 (−0.49–1.36) [b]***	0.02 (0.47)[c]
5 Item test, delayed recall,		
- 5, n = 1917	−0.17 (−0.49–0.54)	−0.01 (0.41)
- < 5, n = 449	0.17 (−0.49–0.82) [b]***	0.04 (0.50)[c] *
Formal depression diagnosis according to DSM-IV-TR and DSM-V criteria		
Major depression		
- No major depression (n = 2667)	−0.02 (−0.49–0.57)	0.01 (0.53)
- Major depression (n = 15)	2.52 (2.30–2.75) [b]***	0.09 (0.52)
Any depression (major or minor depression)		
- No depression (n = 2562)	−0.17 (−0.49–0.53)	0.02 (0.42)
- Major or minor depression (n = 120)	1.92 (1.48–2.19) [b]***	−0.22 (0.65) [c] ***

OR (95% CI)'s for impaired cognitive functions on the cognitive tests for both factors are reported in Supplemental Table S5.
* = p < .05; ** = p < .01; *** = p < .001.
[a] Spearman correlation.
[b] Man Whitney U.
[c] One way ANOVA.
[d] Kruskal Wallis test.

Table 3
Factor scores in relation to cognitive outcomes at 6 year follow-up.

	F1: General depression factor (per SD increase)		F2: Motivational factor (per SD increase)	
	Odds ratio (95% CI)[1]	p-value	Odds ratio (95% CI)[1]	p-value
MMSE < 24, n = 133/1799				
- Model 1: basic model	1.22 (1.00–1.50)	0.047	1.31 (1.09–1.57)	0.004
- Model 2: model 1 + demographic	1.17 (0.95–1.45)	0.143	1.12 (0.93–1.35)	0.226
- Model 3: model 2 + cardiovascular	1.11 (0.89–1.38)	0.359	1.11 (0.92–1.34)	0.267
- Model 4: model 2 + lifestyle variables	1.09 (0.87–1.35)	0.456	1.10 (0.91–1.32)	0.337
- Model 5: model 2 + medication	1.13 (0.91–1.40)	0.279	1.13 (0.94–1.36)	0.195
10 point clock test score < 8, n = 228/1728				
- Model 1: basic model	1.17 (1.00–1.36)	0.054	1.16 (1.01–1.34)	0.042
- Model 2: model 1 + demographic	1.09 (0.93–1.28)	0.311	1.05 (0.91–1.22)	0.492
- Model 3: model 2 + cardiovascular	1.06 (0.90–1.25)	0.492	1.04 (0.90–1.21)	0.591
- Model 4: model 2 + lifestyle variables	1.07 (0.91–1.27)	0.403	1.04 (0.90–1.21)	0.572
- Model 5: model 2 + medication	1.05 (0.88–1.24)	0.602	1.06 (0.92–1.23)	0.428
Digit span forward score < 5, n = 172/1762				
- Model 1: basic model	1.07 (0.90–1.27)	0.460	1.13 (0.96–1.32)	0.148
- Model 2: model 1 + demographic	1.02 (0.86–1.22)	0.789	1.07 (0.91–1.26)	0.414
- Model 3: model 2 + cardiovascular	1.00 (0.84–1.20)	0.971	1.07 (0.91–1.26)	0.431
- Model 4: model 2 + lifestyle variables	1.02 (0.85–1.21)	0.871	1.06 (0.90–1.25)	0.465
- Model 5: model 2 + medication	1.04 (0.87–1.24)	0.698	1.07 (0.91–1.26)	0.437
Digit span backward score < 4, n = 395/1743				
- Model 1: basic model	1.16 (1.02–1.31)	0.025	1.00 (0.88–1.13)	0.998
- Model 2: model 1 + demographic	1.12 (0.99–1.28)	0.076	0.95 (0.84–1.08)	0.422
- Model 3: model 2 + cardiovascular	1.11 (0.98–1.21)	0.116	0.94 (0.83–1.07)	0.375
- Model 4: model 2 + lifestyle variables	1.12 (0.98–1.28)	0.087	0.95 (0.84–1.08)	0.415
- Model 5: model 2 + medication	1.14 (1.00–1.31)	0.052	0.95 (0.83–1.07)	0.385
5 items test immediate recall < 5, n = 51/1768				
- Model 1: basic model	1.24 (0.92–1.65)	0.153	1.29 (1.00–1.67)	0.049
- Model 2: model 1 + demographic	1.08 (0.79–1.47)	0.648	1.07 (0.82–1.39)	0.626
- Model 3: model 2 + cardiovascular	1.00 (0.73–1.38)	1.000	1.06 (0.81–1.38)	0.667
- Model 4: model 2 + lifestyle variables	0.96 (0.70–1.32)	0.795	1.06 (0.81–1.39)	0.663
- Model 5: model 2 + medication	1.05 (0.76–1.45)	0.772	1.08 (0.83–1.40)	0.590
5 items test delayed recall < 5, n = 394/1754				
- Model 1: basic model	1.25 (1.10–1.41)	< 0.001	1.11 (0.98–1.24)	0.090
- Model 2: model 1 + demographic	1.18 (1.04–1.34)	0.011	1.02 (0.91–1.15)	0.744
- Model 3: model 2 + cardiovascular	1.17 (1.03–1.32)	0.018	1.02 (0.90–1.15)	0.798
- Model 4: model 2 + lifestyle variables	1.15 (1.01–1.30)	0.040	1.02 (0.90–1.15)	0.771
- Model 5: model 2 + medication	1.14 (1.00–1.29)	0.056	1.03 (0.91–1.16)	0.640

[1] Logistic regression based on imputed data, results represent odds ratio (95% CI). Rubin's rules were used to pool the data.
Model 1: basic model adjusted for the baseline score on the cognitive test and both factors.
Model 2: includes those in model 1 + age, sex, and education level.
Model 3: includes those in model 2 + number of cardiovascular factors, cardiac- and cerebrovascular diseases.
Model 4: includes those in model 2 + lifestyle variables (alcohol drinking behavior, leisure activity score, and social network size).
Model 5: includes those in model 2 + medication use that might affect cognitive performance.

Table 4
Depression diagnosis in relation to cognitive outcomes at 6 years follow-up.

	Any depression (n = 52/1810)[a]	
	OR (95% CI)[b]	p-value
MMSE < 24, n = 133/1799	1.86 (0.72–4.81)	.202
10 point clock test score < 8, n = 228/1728	1.80 (0.83–3.90)	.139
Digit span forward score < 5, n = 172/1762	0.45 (0.13–1.53)	.201
Digit span backward score < 4, n = 395/1743	1.67 (0.87–3.22)	.126
5 items test immediate recall < 5, n = 51/1768	0.76 (0.10–5.60)	.789
5 items test delayed recall < 5, n = 394/1754	1.63 (0.87–3.04)	.129

Model included the baseline score on the cognitive test and dummy variable for any depression yes (n = 52) or no (n = 1750).
[a] n = 3 with major depression + n = 49 with minor depression.
[b] Logistic regression based on imputed data, results represent odds ratio (95% CI). Rubin's rules were used to pool the data.

disorder was not associated with 6-year cognitive impairments, not even in unadjusted models. However, the absence of this relationship might be explained by lack of power, as reflected in the wide confidence intervals.

The depression-executive dysfunction hypothesis (Alexopoulos et al., 1997, 2002) states that vascular disease and a disruption of frontal-subcortical pathways underlie both motivational-related symptoms of depression and executive deficits. However, the results from the present study could not support this hypothesis because the association of the Motivational factor with 6-year cognitive impairments was completely explained by demographics. Perhaps motivational-related symptoms that occur in the absence of a depression may rather reflect a general process of ageing.

4.1. Methodological considerations

In contrast to some previous studies evaluating motivational symptoms of depression, the Motivational factor in the present study did not include 'inability to feel' and 'concentration problems'. The discrepancy with previous studies might be because they did not use bi-factor analysis to create motivational symptoms and thus have not defined motivational symptoms as symptoms occurring in the absence of a depression. Instead, the motivational symptoms in these studies might have occurred in the presence as well as the absence of a depression. Perhaps this discrepancy also explains why our findings do not support the depression-executive dysfunction hypothesis (Alexopoulos et al., 1997, 2002), which may apply only to symptoms

occurring in the presence of a depression. An alternative approach would be to create latent variables for symptom profiles in relation to cognitive abilities (for instance using a multiple-indicators-multiple-causes model (MIMIC)) in order to evaluate the role of specific depressive symptom profiles dominated by cognitive impairments on cognitive outcomes.

One might suggest that the Motivational factor is not clinically meaningful, because the additional variance explained by the Motivational factor is relatively low. However, this is an intrinsic characteristic of bi-factor analysis, and the Motivational factor in the present study was associated with several patient characteristics and cognitive outcomes, suggesting that the variance it represents is clinically meaningful.

The study has a number of limitations. Because of selective loss to follow-up, dropouts may have developed more cognitive impairments than the included sample, which may have biased the results. Next, we excluded persons with MMSE-scores < 24 at baseline, which might have led to the exclusion of more severely depressed persons who tend to score lower on cognitive screening instruments. We also excluded persons on antipsychotics (n = 33) at baseline which are sometimes also prescribed in patients with affective disorders. As people with more severe depression may be at higher risk of cognitive decline, we might have underestimated the risk of cognitive impairments for the General Depression factor.

Strengths of this study are the large sample of older adults, including the oldest-old. In addition, the follow-up period of 6 years made it possible to detect the development of cognitive impairments at follow-up.

5. Conclusion

With bi-factor analysis we separated MADRS-symptoms into a General Depression factor and a Motivational factor. The association of general depressive symptoms with future memory impairments was explained by a combination of demographic variables, cardiovascular and lifestyle variables. The association of motivational-related symptoms with future cognitive impairments in the executive domain appeared to be confounded by older age, female sex and lower education level.

Declaration of interest

None.

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Appendix A. Supplementary data

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