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The relationship between late-life depression and cognitive decline and the impact of lifestyle factors

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Abstract

Late-life depression has previously been associated with cognitive decline, and this association may be moderated by severity of depression as well as lifestyle factors. We used a longitudinal dataset of 378 older adults with depression and 132 controls, with six years of follow-up, across six measures of cognitive function (verbal processing speed, interference control, verbal memory imprinting and delayed recall, working memory and memory span). Using linear mixed models, we compared trajectories of cognitive decline between the depressed and control groups, and whether these trajectories were influenced by depression severity and lifestyle factors. We found that depressed older adults experienced more cognitive decline compared to controls, but only on the measure of memory span ($p < .001$). Depression severity did not influence trajectories of cognitive decline. Smoking and physical activity were associated with greater cognitive decline, but only in the control group. Further research into the underlying mechanisms of these associations is warranted to inform targeted interventions.

Introduction

Cognitive decline represents a pressing concern within the elderly population, given its far-reaching implications for overall well-being (Wilson et al., 2013). With advancing age, individuals commonly encounter progressive difficulties associated with memory and executive function (Murman, 2015; Thomas & O'Brien, 2008). This deterioration in cognitive abilities has profound consequences on daily functioning and quality of life (Gurland, 1992; Sivertsen et al., (2015). Cognitive decline has been found to start in adulthood, with variable trajectories in different cognitive abilities, with linear declines in speed, accelerating negative changes in memory and reasoning, while vocabulary increases for most of adult life (Salthouse, 2019).

While virtually all older adults experience some degree of cognitive decline, up to 7% of adults over 60 years of age experience this to such a degree that it interferes with daily activities (Prince et al, 2013). The impact of cognitive decline extends beyond mere cognitive tasks and reaches into various aspects of daily life. For instance, memory impairments may affect an individual's ability to recall important information, such as appointments and names. Difficulties with attention and concentration can interfere with multitasking, following conversations, or staying focused on tasks. Executive function deficits, involving higher-level cognitive processes like planning, decision-making, and problem-solving, may hinder independent living skills, such as managing finances, organizing daily routines, or handling complex responsibilities (Grigsby, Kaye & Robbins1995). Moreover, cognitive decline can have psychological and emotional repercussions. Frustration, anxiety, and a sense of loss may arise as individuals become aware of their declining cognitive abilities and struggle to adapt to these changes (Hugo & Ganguli, 2014). The need for increased reliance on others for assistance may evoke feelings of dependency, loss of control, or a diminished sense of self-worth (Overholser, 1992; Fassino et al., 2002).

Therefore, it is crucial to investigate the factors that contribute to cognitive decline in late life. By understanding these factors, we can develop interventions and strategies to mitigate cognitive decline and improve the overall well-being of older adults.

There are a wide variety of factors known to affect cognitive function in ageing, ranging from physical risk factors such as a lack of physical activity and smoking to psychological risk factors, most importantly depression (Zaninotto et al., 2018). Depression has been linked to cognitive decline in previous research, with many researchers suggesting that depression may be an early marker for cognitive decline, as well as dementia (Paterniti, et al., 2002, John, et al., 2019, Ganguli, et al., 2006). This association may be bidirectional, meaning that depression may contribute to cognitive decline and cognitive decline may contribute to depression (Alexopoulos, 2019). This association has been a subject of considerable interest among researchers because findings from various studies have yielded conflicting results. While some studies have identified depression as a risk factor for cognitive decline (Vinkers et al., 2004) others have failed to find a significant association (Ganguli et al., 2006) These inconsistencies may arise due to several factors, including differences in study design, measurement tools, and participant characteristics.

There are various factors that could explain the observed link between depression and cognitive decline. For instance, lifestyle factors may explain this link, as depressed individuals often consume more alcohol (Rudenstine, Espinosa, & Kumar, 2020), smoke more (Mangialasche, et al., 2012), are more often overweight and exercise less (Xu et al., 2023), all of which are also associated with cognitive decline (Solfrizzi et al., 2008). Some factors may contribute to both depression and cognitive decline, therefore acting as a confounder. One example of this is low educational attainment, as education is known to be a protective factor for

cognitive decline as well as depression (Cohen, et al., 2020, Mondini, et al. 2022). Individuals with lower socioeconomic status are more likely to experience depression and cognitive decline, which could also confound the relationship between the two (Freeman, et al., 2016, Wang, et al. 2023). Previous research in this area has primarily focused on examining the link between depressive symptoms and cognitive decline in the general population. Many of these studies have relied on self-report measures**,** such as the Center for Epidemiologic Studies Depression Scale (CES-D), to assess depressive symptoms (Mirza et al., 2016, John et al., 2019). However, self-report measures may not fully capture the complexity and range of depressive experiences, potentially leading to variability in results (Uher et al., 2012). Furthermore, these surveys can pick up things that are not really depression. For example, physical symptoms from medical issues might be perceived as signs of depression. Similarly, problems with concentration and slowness could be mistakenly labelled as depression when they might actually point to an underlying neurodegenerative condition.

While a substantial body of literature exists on the relationship between depressive symptoms and cognitive decline in the general population, less is known about the course of cognition in patients diagnosed with depression. Understanding whether older adults with depression have an increased risk of cognitive decline and identifying the factors that contribute to this risk is essential for informing clinical practice and improving patient outcomes. The aim of this study is to determine whether late-life depression predicts a decline in cognitive function across time. Furthermore, we aim to determine if depression severity as well as lifestyle factors such as smoking, alcohol use and physical activity influence the trajectory of cognitive decline. We make use of the longitudinal Netherlands Study of Depression in Older Persons (NESDO) database, which includes accurately diagnosed depressed older adults (Comijs, et al. 2011).

Methods

Design and setting

The present study used baseline and two-year and six-year follow-up data from the NESDO study (Comijs, et al. 2011). NESDO is a longitudinal cohort study that aims to investigate the development and consequences of depressive disorders in older individuals.

The study included 510 participants (64,9% female): 378 individuals with depression and 132 individuals without depression serving as controls, aged 60 years through 93 years old at baseline. In the depressed group, participants had to meet the criteria for a diagnosis of depressive disorder according to the DSM-IV, assessed using the Composite International Diagnostic Interview (CIDI)-version 2.1 (Wittchen et al.,1991). Individuals who were diagnosed with dementia, suspected of having dementia by a clinician, or scored below 18 (out of 30 points) on the Mini-Mental State Examination (MMSE) were not included in the study. Additionally, individuals who had a limited proficiency in the Dutch language were also excluded. At the beginning of the study, participants underwent a baseline examination, which included the CIDI, physical examination, cognitive testing, and completion of observer and self-report questionnaires. Baseline characteristics that could change over time were also reassessed during the 2-year and 6-year follow-up. Additionally, postal questionnaires were sent every 6 months to monitor various measures, including the severity of depressive symptoms. The study protocol of NESDO was approved and complied with ethical guidelines and regulations by the ethical review boards of all participating study centres (VU University Medical Center, the Leiden University Medical Center, University Medical Center Groningen and the Radboud

University Medical Center in Nijmegen), and written informed consent was obtained from all participants.

Measures

At baseline, two-year and six-year follow-up, trained research assistants collected data on demographic, psychosocial, biological, cognitive and mental health parameters. Interviews, questionnaires, and physiological examinations were used, and participants who were not able to attend on-site were visited in their homes. If necessary, the assessment was spread over two days. Details on the measures included in the analyses are provided below.

Inventory of Depressive Symptoms (IDS). The severity of depression was measured using the Inventory of Depressive Symptoms (IDS) self-report questionnaire, which is a previously validated measure of depression severity (Trivedi et al., 2004). Participants had to fill in a comprehensive questionnaire covering various aspects of depression, such as mood, sleep, energy, appetite, and concentration. Respondents rate the severity of each symptom based on their experiences over the last seven days. The scores range between 0 and 84, with higher scores indicating more severe depression.

Cognitive functioning was assessed using the following measures administered at baseline, 2-year and 6-year follow-up:

Global cognitive function. The Mini-Mental State Examination (MMSE) was employed as a cognitive assessment tool to evaluate global cognitive functioning (Folstein et al.,1975). Participants were asked to perform tasks such as recalling a list of words, performing simple calculations, naming common objects, and following verbal instructions. We used the raw total

score on the MMSE, which provides an indication of overall cognitive function, with higher scores suggesting better cognitive abilities.

Primary outcome: cognitive functioning

Verbal memory: imprinting and delayed recall. We used the 10-Word Test, which is a modified version of the auditory verbal learning to assess verbal memory imprinting and delayed recall (Rey, 1964; van der Elst et al. 2005). Participants were presented with a list of ten words and given a specific amount of time to study and memorize them. Immediately after studying the words, and after 20 minutes, participants were then asked to recall as many words as possible from the original list. We used the number of correctly recalled words before (imprinting) and after 20 minutes (delayed recall) predictors in the analyses.

Memory span and working memory. We used the digit span subtest of the Wechsler Adult Intelligence Scale (WAIS) to assess participants' working memory capacity as well as their memory span (Wechsler, 1958). During the test, participants were required to repeat a series of digits recited by the research assistant. With every correct series of digits, the number of digits was increased. We used the raw score (range 0-12) of the forward recitation as an indication of memory span. The tasks also included recalling a sequence of numbers in reverse order. We used the backward recruitment (score range 0-10) as an indication for working memory with a higher score on this test suggesting a greater capacity for memory.

Verbal processing speed and interference control. The Stroop Colour-Word Test was used to assess verbal processing speed and interference control and consists of three parts (Stroop, 1992). First, participants read words printed in black (card I), which include the words "red, blue, green, or yellow." Second, participants are required to verbally name the colours of

patches on a card (card II), which are presented in red, blue, green, or yellow. The goal is to complete this task as quickly and accurately as possible. Verbal processing speed comprised the total number of seconds to complete Stroop I and II. This variable was transformed by taking the multiplicative inverse (i.e. 1/x) to make it normally distributed. Higher scores indicate better cognitive functioning. Stroop III test we used to determine the interference control, which is a component of executive function. Participants are asked to read the words on the card (red, blue, green, or yellow) but this time the words are printed in colours that are incongruent with the word itself, they had to name the colour as fast as possible. Interference control was computed with the formula: (tIII - .5 * (tI + tII)) / (.5 * (tI + tII)) * 100% (t denoting the time needed for the completion of either subtest) (Klein et al., 1997). This variable was transformed by taking the natural logarithm (after adding a constant (50)) to make it normally distributed and multiplied by -1, so higher scores represent better scores. (Zuidersma, M. et al. 2016)

Main determinants: Lifestyle factors and sleep difficulties

Lifestyle factors and sleep difficulties were assessed at baseline using the following measures administered at baseline.

Alcohol use. The Alcohol Use Disorders Identification Test (AUDIT) was used to assess individuals' alcohol consumption patterns and identify potential alcohol use disorders (Babor, 1989). It consists of a series of questions designed to measure alcohol intake, alcohol-related behaviours, and alcohol-related problems.

Smoking. Smoking behaviour was assessed with the questions ‘Do you smoke cigarettes, cigars, pipes, or other tobacco products?’, At what age did you start smoking?’ and ‘Have you smoked cigarettes/tobacco in the past?’.

Sleep difficulties. With the Insomnia Rating Scale participants were asked to rate the frequency and intensity of their sleep difficulty symptoms, as well as the resulting distress and impairment in their daily life (Levine et a., 2003). The scale also assesses factors such as the duration of sleep difficulties, sleep quality, and the participant's overall satisfaction with their sleep.

Physical Activity. We used the ´International Physical Activity Questionnaire to assess physical activity. Participants were asked to remember and report their engagement in various types of physical activities, such as walking, moderate-intensity activities, and vigorous-intensity activities (Craig et al., 2003). From this questionnaire, the number of MET-minutes was derived, which is defined as the ratio of energy expenditure during activity compared to rest, multiplied by the number of minutes performing the activity per week in metabolic equivalent minutes. (Henstra et al., 2022).

Anthropometry. Body composition was measured as body mass index (BMI) and waist-to-hip ratio (WHR).

Covariates

Several covariates were considered in the analysis, including demographic factors such as age, sex, education level, and income which were determined at baseline. Income was self-reported in the categories “usually, enough money left”, “just enough money to make ends meet”, and “not enough money to make ends meet”. These covariates were included to control for their potential influence on the relationship between cognitive functioning and the variables of interest.

Statistics and research questions

We aim to answer three research questions and three corresponding hypotheses: 1) does late-life depression predict cognitive decline across time? with the hypothesis that depressed older adults have a stronger decline in cognitive function over time; 2) does depression severity predict cognitive decline within older adults with depression? hypothesizing that individuals with higher depression severity display more cognitive decline over time; 3) do lifestyle factors moderate the relationship between late-life depression and the decline of cognitive function? With the hypothesis that lifestyle factors moderate the relationship between late-life depression and the decline of cognitive function, meaning that depression has a different magnitude of effect across the presence or absence of lifestyle factors. Across all these questions, cognitive function was operationalized as the scores on different cognitive measures mentioned above.

First, we calculated descriptive statistics across the depressed and control group, as well as the participants that were available for follow-up at 2 and 6 years. We reported demographic variables, as well as the cognitive and lifestyle measures mentioned above.

We used linear mixed models with the cognitive test results at baseline, two years, and six years as dependent variables. Mixed models account for repeated measures data and can handle unbalanced and missing data (Bryk & Raudenbush, 1987). We estimated models of increasing complexity, first a generalized least squares model with a symmetric correlation structure, without any random effects. Next, we estimated linear mixed models with a random intercept for each participant. Next, we added a random slope for time. We assessed model fit using the Bayesian information criterion (BIC) and selected models with the lowest BIC. As we are primarily interested in interaction terms (time x depression, and three-way interactions with lifestyle factors), we did not stepwise estimate more complex models in terms of model terms.

For most research questions and cognitive outcomes, the models with the lowest BIC included only a random intercept. Details on model selection are provided in Appendix A.

All models were adjusted for the covariates age, sex, educational level, and income. For research question 1, we added the terms time, group (depressed vs controls) and an interaction term between time and group. For research question 2 we estimated models in the depressed group. We added time, depression severity and an interaction term between time and depression severity as fixed effects. For research question 3, we added time, group (cases vs. control), lifestyle, and two- and three-way interactions between these variables as fixed effects. We estimated multiple models for the different lifestyle factors.

Descriptive statistics were calculated using SPSS version 27.0 (IBM Corp, 2020). Further statistical analyses were performed in R (version 4.3.1), using the lme4 package (R Core Team, 2023; Bates et al., 2014).

Results

Inclusion procedure and study population.

In Figure 1 the flow of NESDO participants throughout the three assessments is shown. We observed an overall dropout rate of 41.4%. The depressed group experienced a higher dropout percentage (46.8%) compared to the control group (25.8%). On further examination, the leading dropout cause within the depressed group was participant death which accounted for 16.4% of dropouts, with mental health reasons closely following at 15.1%. In contrast, the control group predominantly exhibited refusals as the leading cause of dropout (9.1%).

Characteristics of the study population are displayed in Table 1. The mean age at baseline was 70.5 (SD = 7.33, range 60-90), this was similar across both the depression group and control

group. Of the overall study population, 64.9% of participants were women, this was similar across the control as well as the depression group. The control group reported a mean of 12.45 (SD = 3.49) years of education in comparison to a mean of 10.42 (SD = 3.45) years of education in the depression group, which was significantly different (t (524.4) = 5.76, p =.001). We furthermore observed differences in lifestyle factors between the two groups, with the depressed group scoring on average higher on sleep difficulties (t(487.6) = -8.99, p < .001), alcohol use ($\chi 2$ (2) = 31.7, p < .001), and smoking ($\chi 2$ (1) = 18.1, p < .001) On average the depressed group scored lower on physical activity ($\chi 2$ (2) = 9.31, p =.009) as well as Met-Minutes a week (W= 29300.0, p < .001) compared to the control group. Lastly, we observed significant differences across all cognitive functions between the two groups. On average the depression group performed significantly worse on these cognitive tasks compared to the control group. Processing speed (W = 17200.0, p < .001) , Interference control (W = 16200.0, p < .001), Memory span (t(557.13) =2 .22, p = .003), Working memory (t(548.89) =3.13, p = .001), Verbal memory- imprinting,(t(508.83) = 4.37p <.001) Verbal memory- delayed recall (t(543.49) = 3.27, p = .001), global cognitive functioning(W = 29500.0, p =.001).

Research question 1: Does late-life depression predict cognitive decline?

We observed a significant effect of time on verbal processing speed (t(641) = -6.73, p = < .001, see Table 2), delayed recall (t(667) = -2.34, p = .019), indicating a decline over time in these cognitive outcomes. Furthermore, we found a significant effect of depression on verbal processing speed (t(546) = -3.05, p = .0024), verbal memory - imprinting (t(641) = -3.36, p < .001), Interference control (t(696) = -3.8, (p < .001) and Verbal memory- delayed recall (t(605) = -2.92, p = .0036), indicating that depressed patients scored worse on these cognitive domains

across all timepoints. Only for memory span ($t(719) = -3.88$, $p < .001$), we found a significant interaction of time*depression, indicating that depressed patient deteriorated had a larger decline than non-depressed controls. Model-predicted values of depressed and control individuals are displayed in Figure 2. We repeated the model estimation for memory span in a stratified analysis, for depressed and control individuals separately (table 3). Among controls, the time variable was not significant, indicating that memory span did not change significantly over time ($t(213) = 1.466$, $p = .14$). However, in the depressed subsample, the time variable was significant, indicating a decline in memory span over time in the depressed individuals ($t(524) = -4.607$, $p <.001$), with each additional year being associated with 0.1 fewer words remembered.

Research question 2: Does depression severity predict cognitive decline?

We observed a significant effect of time on verbal processing speed ($t(453)= -4.35$, $p <.001$, see Table 4), Verbal memory-delayed recall ($t(485)= -2.48$, $p = .013$), and memory span ($t(525)= -2.78$, $p = .0056$), indicating a decline in these cognitive domains over time. Furthermore, we found a significant effect of depression severity on verbal processing speed ($t(407)= -2.96$,$p = .0033$), verbal memory - imprinting ($t(361)= -2.57$, $p = .01$), memory span ($t(532)= -2.89$, $p = .004$). with more severe depressed patients scoring worse on these cognitive domains. We did not find a significant interaction effect of depression severity on the effect of time across cognitive outcomes, suggesting that the course over time of cognitive performance is similar across different levels of depression severity.

Research question 3: Do lifestyle factors moderate the relationship between late-life depression and cognitive function?

We observed a significant three-way-interaction on verbal processing speed of time x depression x smoking ($t(273)= 2.88$, $p = .0043$, see table 5), in the direction of smoking being associated with a stronger decline in verbal processing speed among controls. In the stratified analysis, the result was similar, with the interaction between time and smoking only being significant in the control group, with the same direction of effect (table 6). Among controls, the interaction term time x smoking was significant ($t(196) = -2.86$, $p = .005$), indicating that among smoking controls there was a larger decrease in verbal processing speed across time than in non-smoking controls. In the depressed group, trajectories of verbal processing speed were similar irrespective of smoking status ($t(455 = 1.29$, $p = 0.2$). Secondly, we observed a significant effect of time x depression x physical activity ($t(630)= 2.29$, $p = .022$) in the direction of high physical activity being associated with a stronger decline in verbal processing speed among controls. However, in the stratified analysis, the interaction term time x physical activity was not significant in our for depressed ($t(448) = 1.69$, $p = .092$) and control individuals ($t(194) = -1.82$, $p = 0.07$) separately.

Lastly, we observed a significant three-way-interaction on time x depression x total met-minutes a week ($t(627)= 2.44$, $p = .015$) in the direction of a higher number of total met-minutes (>5000) a week being associated with a stronger decline in verbal processing speed among controls. The stratified analysis of the interaction term time x total met-minutes a week was significant for the control group ($t(190) = -2.46$, $p = .015$), indicating that there was a larger decrease in verbal processing speed across time for individuals of the control group which were more active at baseline. In the depressed group, trajectories of verbal processing speed were similar irrespective of total met-minutes a week ($t(448) = 1.20$, $p = 0.23$). We did not find other significant effects of depression x time x lifestyle factor across the other outcomes.

Discussion

Summary of main findings

The aim of this study was to investigate the impact of depression on the trajectory of cognitive decline in older adults (hypothesis one), the influence of depression severity on this trajectory (hypothesis two), and the potential moderation of this association by lifestyle factors (hypothesis three).

Hypothesis one received partial support, indicating a significant effect of depression on cognitive function trajectories, however, this was limited to one cognitive measure: memory span. Depressed individuals exhibited a more pronounced decline in memory span over time compared to controls. None of the other trajectories of cognitive function were influenced by depression status. Furthermore, our study did not find a robust moderation effect for hypothesis two; there was not a greater decline in cognitive function in depressed individuals experiencing more depressive symptoms compared to depressed individuals experiencing fewer symptoms. Regarding hypothesis three, the lifestyle factors smoking, total met-minutes per week, and physical activity were linked to worse cognitive decline in the control group, specifically in verbal processing speed, but not in the depressed group. None of the other lifestyle factors or sleep difficulties were associated with greater decline in either depressed or control individuals.

Interpretation of findings and comparison to previous research

We found stronger decline in memory span over time in depressed participants as compared to controls. This aligns with the work of Nebes et al. (2000), which reports that depression in older adults is associated with stronger cognitive decline. Other studies that report

similar associations between depression and cognitive decline include Wiels, Baeken & Engelborghs (2020) and Vinkers et al. (2004). As our findings are in line with much of the prior literature, we conclude this represents a true effect, in which depressed individuals experience more decline in memory span over time.

We also expected to find stronger cognitive decline across other cognitive measures, which we did not find. An explanation for this could be that the effect is not captured within our sample. At baseline, there were already differences in cognitive function between the control and depressed groups across multiple domains. Possibly, depression exerts an effect on trajectories of cognitive function already at an earlier age than at the ages of individuals present within the study. This is also supported by the study of James et al. (2021) which found lower episodic memory in depressed individuals compared to controls, also in cross-sectional studies.

Our study did not find an association between depression severity and greater decline in cognitive functioning, with more depressive symptoms not being associated with stronger cognitive decline. This is in line with research by Ganguli et al. (2006) which report that depression severity in their study of 1094 participants was not associated with the rate of cognitive decline over time. However, this finding deviates from most of the comparable prior studies. In research by Butters (2004) as well as Sheline et al. (2006) depression severity was significantly associated with overall cognitive impairments, even after adjusting for other factors influencing cognitive functioning in late-life depression. Dotson et al. (2020) conducted a systematic review and meta-analysis across 76 studies involving 16,806 participants which concluded that more severe depression was associated with more cognitive decline, and furthermore observed a stronger relationship between depression and cognitive decline in studies including older participants.

For hypothesis three, we found that smoking was associated with more decline in verbal processing speed in controls, but not in depressed participants. This is contrary to our expectation, as we expected that smoking would be a moderator of cognitive decline especially in depressed participants. This finding is however in line with much literature that associates smoking with cognitive decline. For instance, Zhong et al. (2015) reported in their meta-analysis of 37 cohort studies that smoking was associated with an increased risk of dementia.

We furthermore found physical activity to be associated with a stronger decline in processing speed, again only in controls and not in depressed participants. This is also contrary to our expectation, as we expected more active older adults to be less likely to experience cognitive decline, both for depressed and control participants. We do not think this represents a true effect, as a substantial body of literature has found physical activity to contribute to the prevention of cognitive decline (Carvalho et al.,2014). Likely, this finding rather represents regression to the mean, as older adults who were very active and with high verbal processing speed, likely represent extreme cases. Which, on follow-up will have a decline in verbal processing speed. Likely, physical activity is protective against cognitive decline in both depressed and control adults; however, we did not find this in our study.

Implications

Our study shows that depression is associated with decline in memory span, suggesting increased memory deficits in depressed older adults, the magnitude of which increases over time. This has implications for clinicians. For psychologists, memory deficits in depressed older adults can be targets for interventions, for instance using training methods (Dziemian, 2021). Older adults already in psychiatric care will likely already be screened for cognitive deficits, therefore

our findings have fewer implications for clinicians in this field. However, as we found that depression severity was not associated with cognitive decline, we emphasize that clinicians should also be aware of cognitive problems in older adults irrespective of depression severity. Other clinicians, such as those in primary care, should be aware of the relationship between depression and decline in memory, as depression is common in older adults, while memory deficits have far-reaching consequences.

Future studies should include participants already at a younger age, as our study found little change across time, but substantial baseline differences in cognitive function. Furthermore, future studies should address attrition, and develop strategies to counteract this, such as visiting the patients at home instead of having them come to a hospital to take measures, more frequent contact moments to establish rapport in place of infrequent visits but frequent postal questionnaires (Gardette et al., 2007). Another possibility to address this would be oversampling of these groups at baseline to ensure a sufficient number of participants in both groups at follow-up (Chatfield, Brayne, & Matthews, 2005). Investigations into the mechanisms underlying the observed associations between depression, lifestyle factors, and cognitive decline could provide deeper insights and inform targeted interventions.

Strengths and limitations

Strengths of our study include the use of a large sample of clinically diagnosed depressed elderly, a longitudinal design, and the use of validated instruments. We identify three limitations concerning the results of this study.

A first limitation is that our results likely suffer from attrition bias. Our study had a substantial dropout rate over time, especially within the depressed group. This dropout was often

due to mental health reasons. Participants who dropped out may have experienced more severe depressive symptoms, stronger cognitive decline, or both. This is also supported by the fact that across most cognitive measures, we did not find a decline over time in the first place (as the time variable was only significant for the outcomes of verbal processing speed and delayed recall). This may have biased the results, as participants that dropped out due to cognitive decline, may have also been depressed. This pattern is consistent with previous research in longitudinal studies in older adults, where they reported that attrition is associated with among others cognitive decline (Godin & Theou, 2021).

A second potential limitation is a lack of power, especially for detecting effects of three-way interactions. Such interactions require much larger sample sizes to reach sufficient power (Heo & Leon, 2010). Furthermore, given that we did not detect a robust effect of the two-way interaction between time and depression, this makes it more unlikely that the observed three-way interactions represent a real effect.

Another limitation is that our study did not correct for multiple comparisons, for instance using the Bonferonni correction. Due to this, the significant results we report may be due to type I error, especially in the context of lower power for the three-way interactions.

Conclusion

The present study found that depression in older adults is associated with a stronger decline in memory span across time. Furthermore, we found that cognitive decline in depressed older adults was similar across levels of depression severity. Also, we found an association between smoking and cognitive decline, but only in controls and not in depressed older adults. Clinicians should be

aware of memory span deficits in late-life depression. Furthermore, more research is needed to understand this relationship and its moderators.

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Table 1

Total sample at Baseline

	Overall Group at Baseline	Control Group at Baseline	Depression Group at Baseline	df	Statistic	p
Demographics:						
n	510	132	378			
Age, mean (SD)	70.56 (7.33)	70.07 (7.16)	70.73 (7.39)	512.64	-0.911	.363
Sex, n (%) female	331 (64.9)	81 (61.4)	250 (66.1)	1	0.78*	.377
Education in years, mean (SD)	10.95 (3.56)	12.45 (3.49)	10.42 (3.45)	524.4	5.76	<.001
Income, n (%)				2	14.4*	<.001
usually, enough money left	359 (70.9)	107 (82.9)	252 (66.8)			
just enough money to make ends meet	130 (25.7)	22 (17.1)	108 (28.6)			
not enough money to make ends meet	17 (3.4)	0 (0.0)	17 (4.5)			
Depression characteristics:						
IDS score, mean (SD)	24.40 (15.22)	7.81 (6.40)	30.14 (13.02)	501.82	-25.4	<.001
Lifestyle characteristics:						
Smoking						
Smoking n (%) currently	111 (21.9)	11 (8.3)	100 (26.7)	1	18.1*	<.001
Cigarette years, average number of cigarettes smoked per day times numbers of years smoking, median (IQR)	110.00 [0.00, 450.00]	48.00 [0.00, 340.00]	138.00 [0.00, 484.00]	-	22000.0**	.0663
Anthropometry						
Body Mass Index (BMI), mean (SD)	26.50 (4.34)	26.98 (4.06)	26.33 (4.42)	518.36	1.55	.123
Waist to Hip ratio, mean (SD)	0.91 (0.09)	0.91 (0.09)	0.91 (0.09)	553.56	0.495	.621
Insomnia Rating Scale: Total scale score, mean (SD)	9.46 (5.60)	6.20 (4.31)	10.58 (5.56)	487.6	-8.99	<.001

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Statistics are t-statistics, expect for * = Chi Square, ** =W- statistic of Wilcoxon test

Table 1 continued

Total sample at Baseline

	Overall Group at Baseline	Control Group at Baseline	Depression Group at Baseline	df	Statistic	p
Alcohol Use Disorder Identification Test (AUDIT): Sum Score, median (IQR)	2.00 [0.00, 4.00]	3.00 [2.00, 4.00]	1.00 [0.00, 4.00]	-	31100.0**	<.001
Alcohol use, n (%):				2	31.7*	<.001
Abstainers	167 (33.3)	17 (13.3)	150 (40.2)			
Moderate drinkers	232 (46.3)	80 (62.5)	152 (40.8)			
At-risk drinkers	102 (20.4)	31 (24.2)	71 (19.0)			
Physical activity, n (%)				2	9.31*	.00949
Low physical activity	136 (27.5)	22 (17.2)	114 (31.1)			
Moderate physical activity	195 (39.4)	56 (43.8)	139 (37.9)			
High physical activity	164 (33.1)	50 (39.1)	114 (31.1)			
Total Met-Minutes a week, median (IQR)	1836.00 [693.00, 3865.50]	2560.95 [1458.75, 4441.50]	1546.50 [562.75, 3631.50]	-	29300.0**	<.001
Cognitive performance						
Verbal Processing speed, median (IQR)	44.00 [39.00, 50.00]	42.00 [38.00, 47.00]	45.00 [40.00, 51.00]	-	17200.0**	<.001
Interference control, median (IQR)	1.15 [0.87, 1.49]	0.96 [0.73, 1.29]	1.21 [0.92, 1.61]	-	16200.0**	<.001
Memory span, mean (SD)	8.13 (1.80)	8.44 (1.83)	8.03 (1.77)	557.13	2.22	0.0275
Working memory, mean (SD)	5.31 (1.87)	5.74 (1.77)	5.16 (1.89)	548.89	3.13	.00196
Verbal memory; imprinting, mean (SD)	32.16 (7.09)	34.34 (6.48)	31.39 (7.14)	508.83	4.37	<.001
Verbal memory; delayed recall, mean (SD)	5.97 (2.27)	6.50 (2.09)	5.79 (2.30)	543.49	3.27	.00122
Global cognitive function; median (IQR)	28.00 [27.00, 29.00]	29.00 [27.75, 30.00]	28.00 [27.00, 29.00]	-	29500.0**	.00127

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Statistics are t-statistics, expect for * = Chi Square, ** =W- statistic of Wilcoxon test

Table 2

Regression Results for the Relationship Between Depression and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal processing speed				Stroop interference control				Verbal memory imprinting			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Constant	0.0347 ($2.06x10^{-3}$)	486	16,8	<.001	-3.9 ($6.55x10^{-3}$)	489	-596	<.001	44.9 (3.26)	509	13,8	<.001
Time	$-3.21x10^{-4}$ ($4.77x10^{-5}$)	641	-6,73	<.001	$-1.47x10^{-4}$ ($2.57x10^{-4}$)	672	-0,57	.57	-0.195 (0.108)	677	-1,8	.072
Depression	$-1.26x10^{-3}$ ($4.14x10^{-4}$)	546	-3,05	.0024	$-5.27x10^{-3}$ ($1.39x10^{-3}$)	696	-3,8	<.001	-2.25 (0.671)	641	-3,36	<.001
Sex	$-9.61x10^{-6}$ ($3.59x10^{-4}$)	471	-0,03	.98	$1.77x10^{-4}$ ($1.12x10^{-3}$)	442	0,16	.87	2.67 (0.557)	476	4,8	<.001
Age	$-1.69x10^{-4}$ ($2.39x10^{-5}$)	484	-7,08	<.001	$-5.31x10^{-4}$ ($7.56x10^{-5}$)	485	-7,03	<.001	-0.302 (0.0373)	511	-8,1	<.001
Years of education	$1.84x10^{-4}$ ($5.04x10^{-5}$)	476	3,65	<.001	$6.10x10^{-4}$ ($1.57x10^{-4}$)	457	3,87	<.001	0.51 (0.0785)	481	6,49	<.001
Income	$-9.44x10^{-4}$ ($3.26x10^{-4}$)	476	-2,9	.0039	$3.83x10^{-5}$ ($1.02x10^{-3}$)	456	0,04	.97	0.108 (0.51)	481	0,21	.83
Time x Depression	$8.44x10^{-5}$ ($5.83x10^{-5}$)	649	1,45	.15	$6.74x10^{-6}$ ($3.13x10^{-4}$)	697	0,02	.98	-0.114 (0.132)	695	-0,86	.39

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 2 continued

Regression Results for the Relationship Between Depression and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal memory delayed recall				Working memory				Memory span			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Constant	10.3 (1.09)	505	9,41	<.001	4.7 (0.873)	520	5,38	<.001	7.98 (0.833)	537	9,58	<.001
Time	-0.0763 (0.0326)	667	-2,34	.019	0.00279 (0.029)	673	0,1	.92	0.0396 (0.0292)	698	1,36	.17
Depression	-0.652 (0.223)	605	-2,92	.0036	-0.217 (0.18)	651	-1,2	.23	0.0134 (0.173)	688	0,08	.94
Sex	0.89 (0.188)	480	4,74	<.001	0.0701 (0.149)	483	0,47	.64	0.106 (0.142)	498	0,75	.46
Age	-0.0956 (0.0125)	508	-7,63	<.001	-0.0117 (0.01)	522	-1,17	.24	-0.014 (9.55x10-3)	540	-1,46	.14
Years of education	0.0979 (0.0265)	484	3,7	<.001	0.156 (0.021)	490	7,42	<.001	0.119 (0.02)	505	5,92	<.001
Income	0.278 (0.172)	485	1,62	.11	-0.145 (0.137)	491	-1,06	.29	-0.282 (0.13)	506	-2,16	.031
Time x Depression	-0.035 (0.0397)	682	-0,88	.38	-0.029 (0.0354)	693	-0,82	.41	-0.138 (0.0355)	719	-3,88	<.001

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 3

Regression results for the outcome memory span across depression cases and controls.

	Controls				Depressed			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Constant	8.09 (1.56)	127	5,17	<0.001	8.27 (0.928)	409	8,92	<0.001
Time	0.0389 (0.0265)	213	1,47	0.14	-0.097 (0.0211)	524	-4,61	<0.001
Sex	-0.0817 (0.267)	121	-0,3	0.76	-0.143 (0.168)	374	-0,85	0.4
Age	-0.0104 (0.0186)	132	-0,56	0.58	-0.0138 (0.0112)	405	-1,24	0.22
Years of education	0.156 (0.0396)	123	3,93	<0.001	0.101 (0.0234)	379	4,33	<0.001
Income	-0.812 (0.354)	123	-2,29	0.024	-0.196 (0.142)	375	-1,39	0.17

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 4

Regression Results for the Relationship Between Depression Severity and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal processing speed				Stroop interference control				Verbal memory imprinting			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Constant	0.0366 ($2.50x10^{-3}$)	360	14,7	<.001	-3.9 ($8.53x10^{-3}$)	375	-458	<.001	46.7 (3.95)	367	11,8	<.001
Time	$-3.95x10^{-4}$ ($9.07x10^{-5}$)	453	-4,35	<.001	$-7.33x10^{-4}$ ($5.27x10^{-4}$)	523	-1,39	.17	-0.702 (0.24)	208	-2,92	.0038
IDS sum score	$-4.84x10^{-5}$ ($1.64x10^{-5}$)	407	-2,96	.0033	$-6.93x10^{-5}$ ($6.01x10^{-5}$)	549	-1,15	.25	-0.0663 (0.0258)	361	-2,57	.01
Sex	$-1.66x10^{-4}$ ($4.30x10^{-4}$)	345	-0,39	.7	$-1.25x10^{-4}$ ($1.43x10^{-3}$)	329	-0,09	.93	2.19 (0.675)	351	3,25	.0013
Age	$-1.96x10^{-4}$ ($2.86x10^{-5}$)	355	-6,87	<.001	$-5.82x10^{-4}$ ($9.70x10^{-5}$)	363	-6	<.001	-0.316 (0.045)	365	-7,01	<.001
Years of education	$2.14x10^{-4}$ ($5.96x10^{-5}$)	347	3,59	<.001	$6.36x10^{-4}$ ($1.99x10^{-4}$)	335	3,21	.0015	0.477 (0.0938)	350	5,09	<.001
Income	$-8.10x10^{-4}$ ($3.59x10^{-4}$)	349	-2,25	.025	$-1.56x10^{-4}$ ($1.20x10^{-3}$)	337	-0,13	.9	0.123 (0.569)	353	0,22	.83
Time x IDS sum score	$5.27x10^{-6}$ ($2.85x10^{-6}$)	457	1,84	.066	$2.04x10^{-5}$ ($1.65x10^{-5}$)	531	1,23	.22	0.0116 ($7.53x10^{-3}$)	208	1,54	.12

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 4 continued

Regression Results for the Relationship Between Depression Severity and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal memory delayed recall				Working memory				Memory span			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Constant	10.8 (1.32)	372	8,19	<.001	4.7 (1.05)	383	4,46	<.001	8.9 (1)	407	8,9	<.001
Time	-0.159 (0.064)	485	-2,48	.013	-0.0161 (0.0525)	486	-0,31	.76	-0.153 (0.055)	525	-2,78	.0056
IDS sum score	-0.017 ($8.79x10^{-3}$)	467	-1,93	.054	-0.012 ($7.10x10^{-3}$)	482	-1,69	.092	-0.0197 ($6.82x10^{-3}$)	532	-2,89	.004
Sex	0.648 (0.223)	347	2,9	.0039	0.139 (0.178)	353	0,78	.43	0.187 (0.168)	370	1,12	.27
Age	-0.0989 (0.015)	369	-6,59	<.001	-0.0134 (0.012)	379	-1,12	.27	-0.0188 (0.0114)	400	-1,65	.099
Years of education	0.0903 (0.0311)	346	2,91	.0039	0.159 (0.0248)	354	6,42	<.001	0.0927 (0.0234)	372	3,97	<.001
Income	0.33 (0.188)	347	1,75	.081	-0.0582 (0.15)	355	-0,39	.7	-0.162 (0.142)	372	-1,14	.25
Time x IDS sum score	0.0016 ($2.00x10^{-3}$)	491	0,8	.42	-0.000438 ($1.65x10^{-3}$)	493	-0,27	.79	0.00183 ($1.72x10^{-3}$)	533	1,06	.29

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 5

Regression Results for the Relationship Between Depression, Time, Lifestyle factor and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal processing speed				Stroop interference control				Verbal memory imprinting			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Times x Depression x Alcohol use	$9.36x10^{-5}$ ($9.33x10^{-5}$)	636	1	.32	-3.00×10^{-4} (5.03×10^{-4})	683	-0,597	.55	0.0796 (0.211)	678	0,377	.71
Times x Depression x Alcohol Use Disorder Test	$1.34x10^{-5}$ ($1.99x10^{-5}$)	641	0,676	.5	-6.93×10^{-5} (1.06×10^{-4})	697	-0,652	.51	0.0288 (0.0433)	668	0,665	.51
Times x Depression x Body Mass Index	$1.72x10^{-5}$ ($1.51x10^{-5}$)	646	1,14	.25	-1.16×10^{-5} (8.12×10^{-5})	704	-0,142	.89	-0.0196 (0.0341)	700	-0,576	.56
Times x Depression x Waist to Hip ratio	$-3.50x10^{-4}$ ($6.75x10^{-4}$)	633	-0,519	.6	-2.42×10^{-3} (3.70×10^{-3})	696	-0,654	.51	-0.3 (1.55)	692	-0,194	.85
Times x Depression x Cigarette years	$8.25x10^{-8}$ ($1.75x10^{-7}$)	273	2,88	.0043	2.56×10^{-7} (9.33×10^{-7})	685	0,275	.78	1.20×10^{-4} (3.92×10^{-4})	680	0,306	.76
Times x Depression x Smoking	$5.49x10^{-4}$ ($1.91x10^{-4}$)	639	0,472	.64	3.51×10^{-4} (9.97×10^{-4})	665	0,352	.72	0.563 (0.453)	695	1,24	.21
Times x Depression x Physical activity	$1.90x10^{-4}$ ($8.27x10^{-5}$)	630	2,29	.022	-2.42×10^{-4} (4.33×10^{-4})	677	-0,56	.58	-0.0424 (0.189)	680	-0,224	.82
Times x Depression x Total Met-Minutes a week	$5.31x10^{-8}$ ($2.18x10^{-8}$)	627	2,44	.015	-5.07×10^{-8} (1.14×10^{-7})	673	-0,445	.66	2.09×10^{-5} (5.16×10^{-5})	677	0,404	.69
Times x Depression x Insomnia Rating Scale	$-8.63x10^{-6}$ ($1.39x10^{-5}$)	622	-0,621	.54	8.44×10^{-5} (7.46×10^{-5})	682	1,13	.26	-0.0266 (0.0312)	665	-0,851	.4

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Table 5 continued

Regression Results for the Relationship Between Depression, Time, Lifestyle factor and Verbal Processing speed, Verbal memory – imprinting, Interference control, Verbal memory – delayed recall, Memory span, Working memory.

	Verbal memory delayed recall				Working memory				Memory span			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Times x Depression x Alcohol use	-0.0478 (0.0634)	666	-0,754	.45	0.0311 (0.0561)	678	0,555	.58	-0.0848 (0.0568)	703	-1,49	.14
Times x Depression x Alcohol Use Disorder Test	-0.0154 (0.013)	658	-1,18	.24	-6.97×10^{-3} (0.0114)	665	-0,609	.54	-0.0168 (0.0116)	689	-1,45	.15
Times x Depression x Body Mass Index	-0.0151 (0.0103)	685	-1,46	.14	-0.0108 (9.20×10^{-3})	702	-1,17	.24	-1.41×10^{-3} (9.20×10^{-3})	730	-0,153	.88
Times x Depression x Waist to Hip ratio	-0.209 (0.465)	674	-0,45	.65	-0.204 (0.421)	689	-0,485	.63	0.343 (0.416)	716	0,824	.41
Times x Depression x Cigarette years	-5.25×10^{-5} (1.18×10^{-4})	669	-0,444	.66	-5.99×10^{-5} (1.06×10^{-4})	688	-0,567	.57	-1.03×10^{-4} (1.06×10^{-4})	712	-0,969	.33
Times x Depression x Smoking	-8.28×10-3 (0.134)	667	-0,0619	.95	-0.0469 (0.114)	669	-0,411	.68	-0.147 (0.114)	691	-1,29	.2
Times x Depression x Physical activity	0.0475 (0.0564)	664	0,842	.4	0.0803 (0.0509)	684	1,58	.12	-0.0722 (0.0506)	710	-1,43	.15
Times x Depression x Total Met-Minutes a week	1.21×10^{-5} (1.54×10^{-5})	661	0,786	.43	2.12×10^{-5} (1.35×10^{-5})	679	1,58	.12	-1.56×10^{-5} (1.34×10^{-5})	704	-1,16	.24
Times x Depression x Insomnia Rating Scale	-6.93×10^{-3} (9.45×10^{-3})	654	-0,734	0.46	-3.21×10^{-3} (8.25×10^{-3})	663	-0,389	0.7	2.66×10^{-3} (8.35×10^{-3})	689	0,318	.75

Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

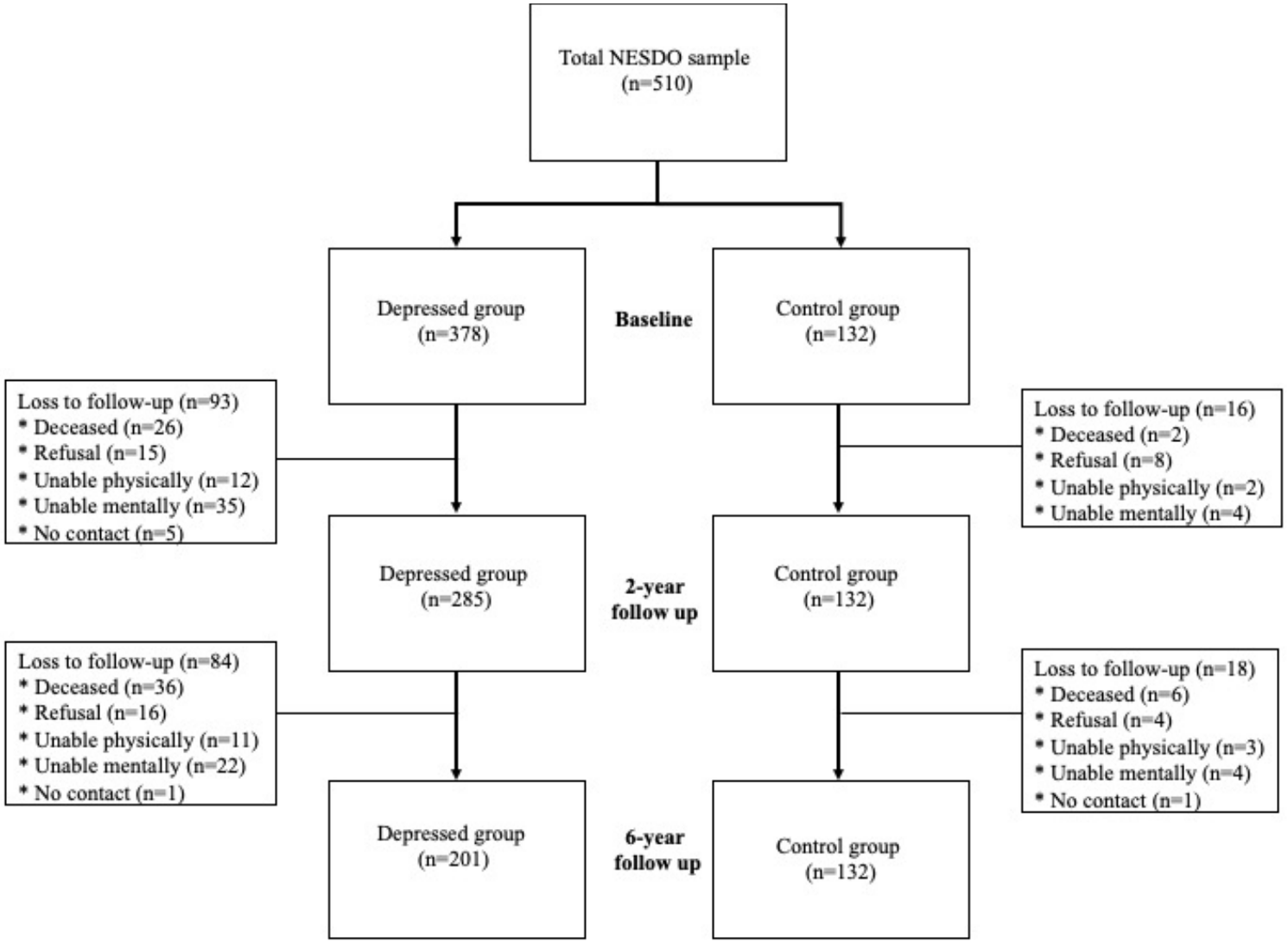
Table 6

Regression results for the outcome verbal processing speed across depression cases and controls. Displayed are only the two-way interactions, which were tested in separate models.

	Controls				Depressed			
	Estimate (SE)	df	t	p	Estimate (SE)	df	t	p
Time × Smoking	-4.33×10^-4 (1.51×10^-4)	196	-2,86	0.0047	0.000104 (8.07×10^-5)	455	1,29	0.2
Time × Physical activity	-1.15×10^-4 (6.33×10^-5)	194	-1,82	0.07	7.96×10^-5 (4.71×10^-5)	448	1,69	0.092
Time × Physical activity in MET-minutes/week	-3.55×10^-8 (1.45×10^-8)	190	-2,46	0.015	1.85×10^-8 (1.54×10^-8)	448	1,2	0.23

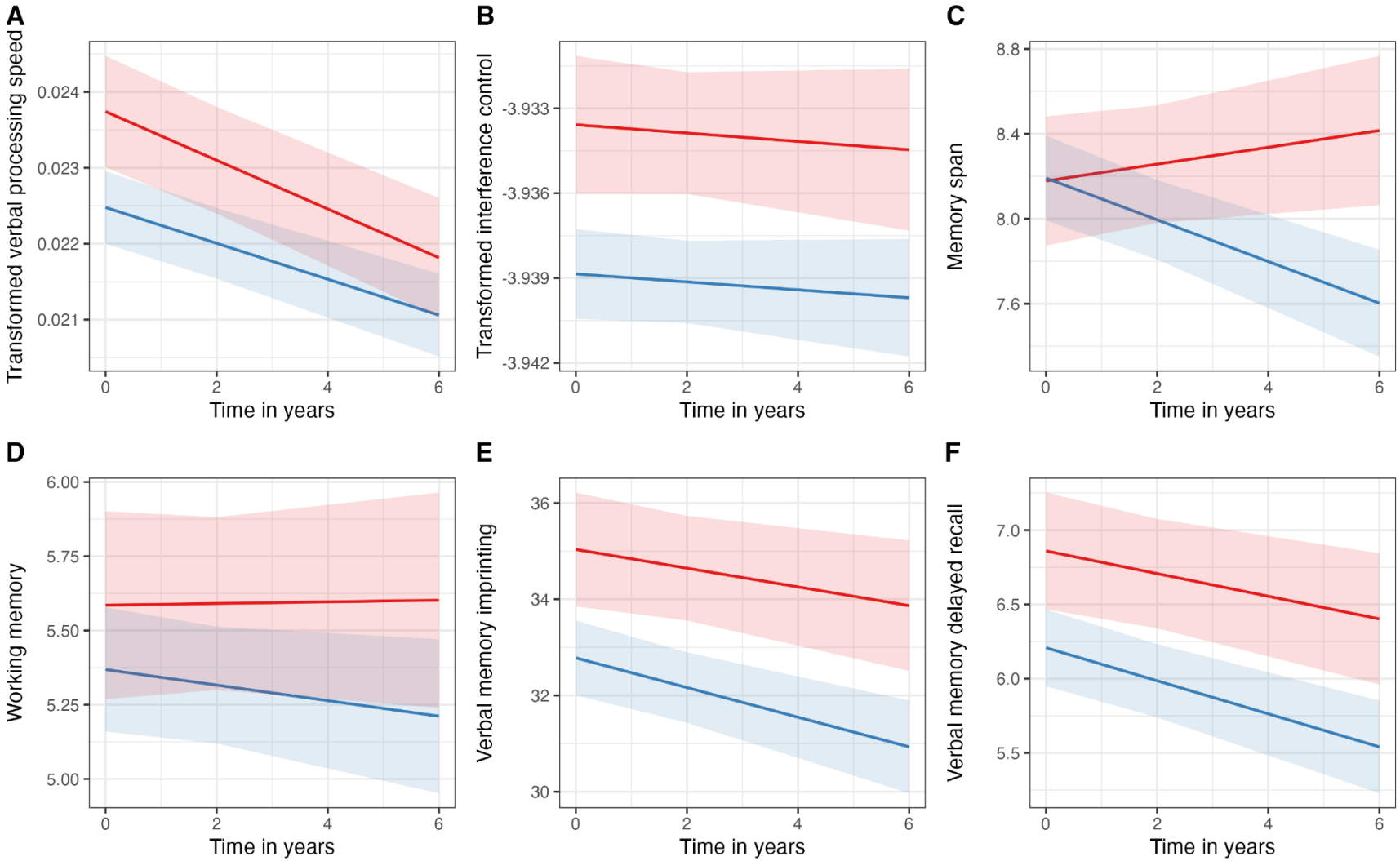
Note. SE = Standard Error. p-values less than 0.001 are denoted as <0.001.

Figure 1. Flowchart



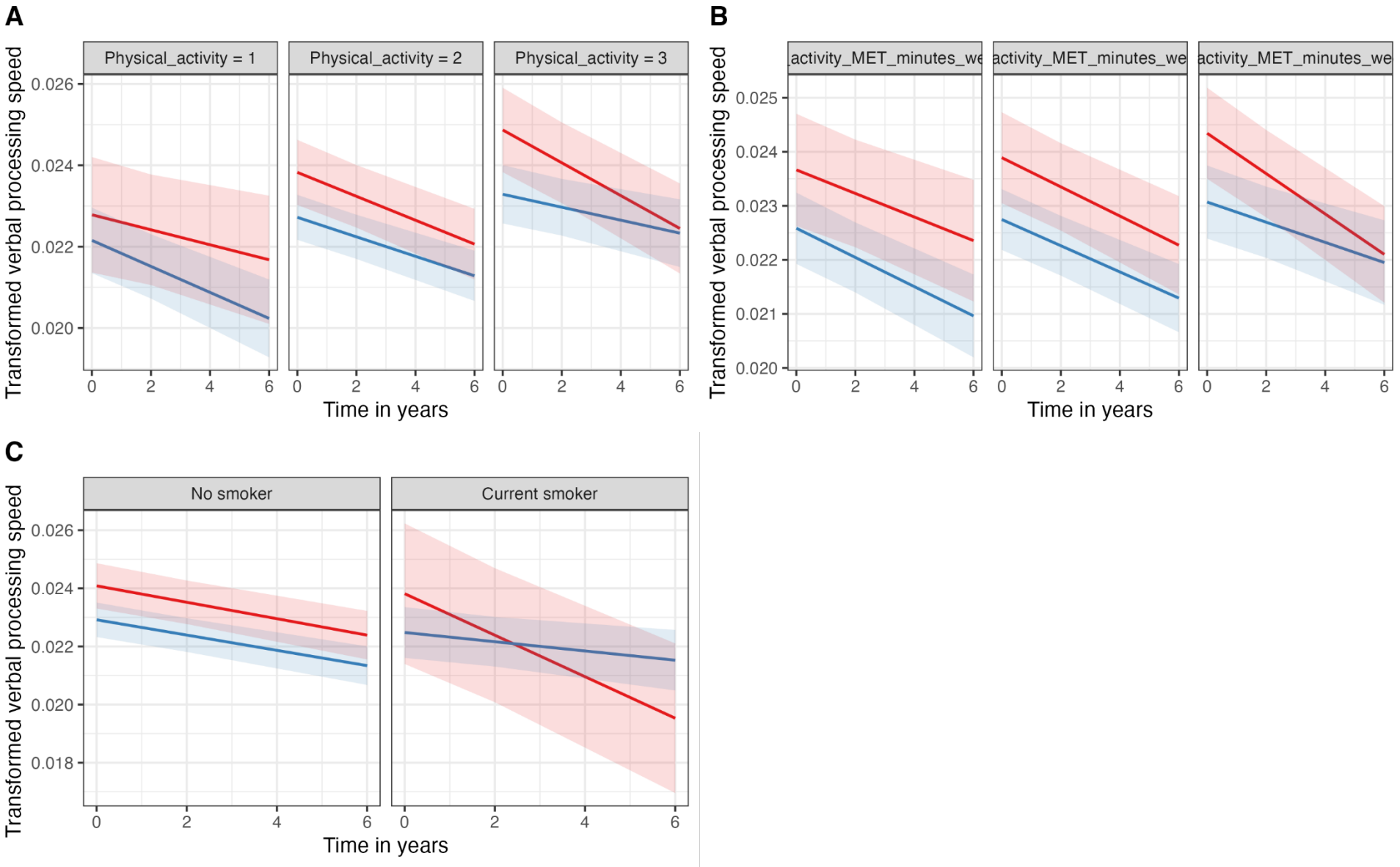
Note. This flowchart represents the NESDO sample split by depressed and control group and is mentioning the respective drop-out reasons. (Jeuring, 2018)

Figure 2. Displayed are model predicted values of cognitive measures across time.



Note**.** The red line depicts model predicted values of controls, while the red line corresponds to the depressed group. A: Predicted values of transformed verbal processing speed. B: Transformed interference control. C: Memory span. D: Working memory. E: Verbal memory imprinting. F: Verbal memory delayed recall.

Figure 3. Displayed are model predicted values of transformed verbal processing speed across time.



Note. The red line depicts model predicted values of controls, while the red line corresponds to the depressed group. A: Predicted values across low (1), moderate (2) and high (3) categories of physical activity. B: Predicted values across three levels (500, 2000, 5000) of physical activity in MET-minutes. C: Predicted values across non-smokers and current smokers.

Appendix A

Comparison of model fits for research question one and three using Bayesian Information Criterion

RQ	Model	Model	RS	RI	I	BIC
1&3	**Verbal Processing speed transformed**					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**-9661,75**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	-9174,15
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	-9647,18
	Verbal memory imprinting					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**7438,443**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	7617,222
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	7468,409
	Interference control transformed					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**-6328,42**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	-6225,63
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	-6319,35
	Verbal memory delayed recall					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**4824,922**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	5095,399
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	4872,466
	Memory span					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**4359,939**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	4533,388
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	4387,107
	Working Memory					
	1	**~ Intercept + Time + Group + Time × Group + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**4381,048**
	2	~ Intercept + Time + Group + Time × Group + Covariates + (Time | 1)	yes	no	yes	4583,592
	3	~ Intercept + Time + Group + Time × Group + Covariate + (1 | 1)	no	no	yes	4393,573

Note. RQ= Research question, RS=Random slope, RI= Random intercept, I= Interaction term

Comparison of model fits for research question two using Bayesian Information Criterion

RQ	Model	Model	RS	RI	I	BIC
2	**Verbal Processing speed transformed**					
	1	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)	yes	yes	yes	-6651,042
	2	**~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**-6661,294**
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	-6332,091
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	-6650,12
	Verbal memory imprinting					
	1	**~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)**	**yes**	**yes**	**yes**	**5319,622**
	2	~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)	no	yes	yes	5327,076
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	5429,222
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	5343,705
	Interference control transformed					
	1	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)	yes	yes	yes	-4202,239
	2	**~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**-4213,935**
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	-4153,497
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	-4209,101
	Verbal memory delayed recall					
	1	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)	yes	yes	yes	3491,729
	2	**~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**3483,176**
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	3635,954
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	3507,151
	Memory span					
	1	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)	yes	yes	yes	3124,184
	2	**~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**3119,381**
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	3215,099
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	3144,542
	Working memory					
	1	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | ID)	yes	yes	yes	3098,297
	2	**~ Intercept + Time + IDS + Time × IDS + Covariates + (1 | ID)**	**no**	**yes**	**yes**	**3097,162**
	3	~ Intercept + Time + IDS + Time × IDS + Covariates + (Time | 1)	yes	no	yes	3241,034
	4	~ Intercept + Time + IDS + Time × IDS + Covariate + (1 | 1)	no	no	yes	3103,549

Note. RQ= Research question, RS=Random slope, RI= Random intercept, I= Interaction term