Title: Temporal relationship between depressive symptoms and cognition in mid and late life: A longitudinal cohort study

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Brief summary: Depressive symptoms may be either a risk factor or prodrome for cognitive decline. Decline in attention predicts depressive symptoms. Future studies should consider dynamic relationships between affective symptoms and cognition.

Acknowledgements:

Abstract

Objectives: To examine the bi-directional temporal relationship between depressive symptoms and cognitive in relation to risk, reaction and prodrome.

Design: Cross-lag analysis of longitudinal data collected on-line at baseline and 12-months follow up.

Setting and Participants: A UK population cohort of 11855 participants aged 50 and over.

Measures: PHQ-9 (depressive symptoms), cognitive measures: Paired Associate Learning, Verbal Reasoning, Spatial Working Memory and Digit Span.

Results: Depressive symptoms predicted a decline in paired associates learning (β = -.020, p = .013, [95% CI: -.036, -.004]) and verbal reasoning (β = -.014, p = .016, [95% CI: -.025, -.003]) but not vice versa. Depressive symptoms predicted (β = -.043, p < .001, [95% CI: -.060, -.026]; β = -.029, p < .001, [95% CI: -.043, -.015]) and were predicted by (β = -.030, p = < .001, [95%CI: -.047, -.014]; β = -.025, p = .003, [95% CI: -.041, -.009]) a decline in spatial working memory and verbal digit span respectively.

Conclusions and implications: Depressive symptoms may be either a risk factor or prodrome for cognitive decline. In addition, a decline in attention predicts depressive symptoms. Clinical implications and implications for further research are discussed.

Introduction

With life expectancy rising across the world, dementia is becoming an increasing global health problem.[1] Currently there are no effective pharmacological interventions to treat dementia,[2] and attention has turned to prevention.[3] Nine potentially modifiable lifestyle factors have been identified, of which depression is one.[3] Despite this assertion there continues to be debate in the research literature over the exact nature of the

relationship between depression and cognitive impairment. Specifically, a question remains as to whether depression occurs before or after the onset of cognitive decline. Jorm[4] has proposed several hypotheses including: (1) depression is a causal risk factor (risk factor hypothesis); (2) depression is a psychological reaction to the subjective experience of cognitive decline (reaction hypothesis); and (3) depression is a prodromal sign of cognitive decline (prodrome hypothesis).

Evidence in support of the 'risk factor' hypothesis comes from longitudinal studies investigating chronicity of depression throughout the life course, severity of depression or the interval between depressive episode and time to onset of dementia. One study found over a period of 24 years each episode of depression increased the risk of all-cause dementia by 14%[5]. A Danish nationwide case register study examined the most severe forms of affective disorders compared to physical health conditions and their relative risks of incident dementia. Patients hospitalised with major affective disorders had an increased risk of being diagnosed with dementia compared to patients hospitalised with physical health conditions[6]. Providing further support for the 'risk factor' hypothesis, a systematic review and meta-analysis of 20 studies found increased risk of dementia was associated with life course history of depression rather than with late onset depression,[7] thereby suggesting depression is more likely to be a risk factor rather than a prodrome for dementia.

An alternative explanation for the association between depression and cognitive decline is that psychological distress is a reaction to the subjective experience of declining cognition. Studies have found that depression occurs either after[8] or at the same time[9] as decline in cognition suggesting the depressive symptoms are a psychological reaction to declining cognition. For example, one study found that

cognitive decline preceded depressive symptoms[8] and another found that depression and cognitive decline were cross-sectionally but not longitudinally associated[9].

The final hypothesis explaining the association between depression and cognitive decline/dementia is that depression is an early, prodromal sign of cognitive decline. The theory that depression and dementia share the same underlying neuropathology suggests that depression is a result of, and an early sign, of the dementing process.[10] Support for this theory comes from studies that investigate cognitive profiles of patients with depressive symptoms and cognitive decline and studies investigating the temporal relationship between the two. Chronic depression over a three-year period was found more likely to predict cognitive profiles in keeping with sub-cortical impairment as opposed to global cognitive decline or isolated memory impairments. This pattern of impairment is indicative of white matter lesions that are also found in some dementias suggesting that chronic depression in late life and dementia share a similar neuropathology.[11] Further support for the 'prodrome' hypothesis comes from investigations into the temporal relationship and trajectory of depressive symptoms. A peak in incidence of depression, either side or very close to a diagnosis of dementia supports the 'prodrome' hypothesis.[12, 13] In contrast to Ownby's[7] meta-analysis results, several studies have found that late onset depression rather than chronic or depression earlier in the life course is associated with incident dementia.[14] This is the case even when trajectories of depressive symptoms are followed over periods of up to 28 years.[15]

Support for each of the three hypotheses has come in part from the use of longitudinal studies to investigate the temporal nature of the relationship between cognitive decline and depression. There are a number of limitations with some of these studies. One potential problem is the use of screening tools or brief inventories of global cognition. Tools such as the mini mental state examination (MMSE) are widely used in studies[13] to assess cognitive decline and dementia. However, the sensitivity of the MMSE has been called into question particularly when used to detect cognitive decline pre-dementia due to its ceiling effect.[16] Another problem with the use of global measures of cognition is that decline is not necessarily uniform across the different cognitive domains. To get a more comprehensive understanding of how depressive symptoms may interact with different domains of cognition, the current study aimed to use four measures of cognition tapping into the domains of; memory, general intelligence, executive function and attention. Another methodological limitation is the use of correlational regression analyses to test a prior unidirectional hypotheses. In other words, studies tend to either ask: do depressive symptoms predict cognitive decline, or does cognitive decline predict depressive symptoms. However, if there were a dynamic bi-directional relationship between the two, one-directional regression models would always find support for a uni-directional relationship. Cross-lagged analysis is a way of both accounting for cognition and simultaneously examining the bi-directional nature of a relationship between two variables.

The aim of the current study was to examine the temporal relationship between depressive symptoms and cognitive in relation to the three hypotheses using a cross-lagged design. This design was used to investigate the reciprocal nature of the relationship between cognitive and depressive symptoms. If cognitive decline precedes depressive symptoms then this would provide support for the 'psychological reaction'

hypothesis. If, on the other hand, depressive symptoms precede cognitive decline then the results would provide support for either the 'risk factor' or 'prodrome' hypotheses. If there is a dynamic bidirectional relationship between the two this might indicate several mechanisms at play.

Methods

Study design and participants: Longitudinal data was analysed from the ongoing PROTECT Study (www.protect.org.uk) for which a large population cohort of participants was recruited.

Data collection: Baseline data collection commenced in 2015 with 12 months follow-up starting in 2016 and completing in 2017. Participants were recruited via a media campaign and through leaflets advertising the study at GP practices and memory clinics located in South London, UK. Full details of recruitment, eligibility criteria and data collection have been previously reported.[17] However, key eligibility criteria were that participants were aged 50 and over, lived in the UK and had access to the Internet via a computer. A pre-existing self-reported diagnosis of dementia was an exclusion criterion. The PROTECT study received ethical approval from the London Bridge NHS Research Committee (Ref: 13/LO/1578).

Measures

Demographic information (sex, age, marital-status, ethnicity, employment and education) was collected at baseline only. Measures of depressive symptoms and cognition were collected at baseline (T1) and 12-month follow-up (T2).

Depressive symptoms were assessed with the PHQ-9 depression inventory.[18] This 9-item questionnaire has been found to be valid and reliable with a Cronbach's alpha of 0.89.[18] Depressive symptoms are captured on a range of 0-27. Higher scores indicate greater depressive symptomology.

Cognitive measures: Participants completed an on-line battery of four cognitive measures namely Paired Associate Learning, Verbal Reasoning, Spatial Working Memory and Digit Span. At each testing period the participants had the opportunity to attempt the same test battery up to three times across seven days (ensuring a break of 24 hours between each testing session). A summary score for each test was calculated based on the mean of the attempts. The four cognitive measures used in the battery were based on validated 'pen and paper' cognitive tests and adapted for on-line use by Owen et al.[19] The online versions of the tests have been found to be valid (see cambridgebrainsciences.com) and reliable.[20]

The Paired Associate Learning (PAL) test assesses episodic memory and new learning and has been found to be particularly sensitive to deficits seen in memory and learning.[21] The Verbal Reasoning (VR) test was based on Baddeley's Grammatical Reasoning test[22] and is found to correlate well to general intelligence. The Spatial Working Memory (SWM) test used a self-ordered search task that is found to be sensitive to deficits in executive function.[23] The Digit Span (DS) test measures attention.[24] Higher scores indicated greater digit span. Please see[17] for full details of the cognitive measures.

Data Analyses

Missing data were addressed using full information maximum likelihood (FIML). Assumptions of linear modelling were violated for one variable, namely depression at follow-up. This variable was too skewed for a transformation so the analysis was bootstrapped using 10000 bootstrap draws. Cross-lagged panel analysis was carried out using R programming language and the statistical programming environment provided by RStudio (2016) software version 1.1.419 and the lavaan package for structural equation modelling.[25]

Results

Participant flow: At baseline 24024 participants registered and completed the cognitive assessment battery. Of these, 11855 (49%) completed the cognitive assessment battery at follow-up and were included in the current study.

Participant characteristics: Table 1 shows the demographic characteristics of the participants.

Table 1 Baseline characteristics of participants who completed the study at both time points and those who only participated at T1

	Participants with data at T1 and T2 (N=11855)		Participants with data at T1 only (N=12169)				
	n	(%)	n	(%)	Range	χ^2 (df)/t	p
Sex						13.2 (1)	<.001
Male	3120	(26.3)	3457	(28.4)*			
Female	8735	(73.7)	8712	(71.6)			
Age						28.9 (3)	<.001
50-59	4699	(39.6)	4111	(42.8)*			
60-69	5418	(45.7)	4113	(42.8)*			
70-79	1567	(13.2)	1238	(12.9)			
≥80	171	(1.4)	151	(1.6)			
Marital Status						14.0(6)	.030
Married	8070	(68.1)	6209	(66.1)*			
Civil partner	65	(0.5)	55	(0.6)			
Co-habiting	737	(6.2)	620	(6.6)			
Widowed	754	(6.4)	602	(6.4)			
Separated	192	(1.6)	181	(1.9)			
Divorced	1301	(11.0)	1145	(12.2)*			
Single	723	(6.1)	577	(6.1)			
Ethnicity						19.2(4)	.001
White	11658	(98.4)	9171	(97.7)*			
Mixed	64	(0.5)	67	(0.7)			
Asian	62	(0.5)	87	(0.9)*			
Black	26	(0.2)	34	(0.4)			
Other	32	(0.3)	30	(0.3)			
Employment						95.4(4)	<.001
Employed full-time	2264	(23.9)	2324	(19.1)*			
Employed part-time	1981	(15.9)	1547	(16.7)			
Self-employed	1226	(10.4)	1047	(10.8)			
Retired	6034	(51.0)	4466	(45.9)*			
Unemployed	337	(2.8)	340	(3.5)*			
Education						56.8 (1)	<.001
GCSE/A-Levels/Diploma	5497	(46.4)	5029	(51.6)			
Degree	6374	(53.5)	4724	(48.4)*			
Depressive symptoms							
PHQ-9/Mean (SD)	2.5	(3.0)	2.9	(3.5)	0.0-26.0	-8.5	<.001
Cognition							
PAL/Mean (SD)	4.5	(.8)	4.4	(.9)	0.0-13.3	8.6	<.001
VR/ Mean (SD)	32.3	(9.1)	30.4	(9.6)	-6.0-82.0	14.1	<.001
SWM/Mean (SD)	7.6	(2.2)	7.1	(2.7)	0.0-20.0	12.7	<.001
DS/Mean (SD)	7.4	(1.5)	7.1	(1.2)	0.0-20.0	11.5	<.001

n=number of participants; X^2 Chi-square statistic; df =degrees of freedom; t = t statistic, p =probability, *adjusted standardised residual significant at $p < .05$, T1 =time point 1, T2 =time point 2, PAL =Paired Associates Learning, VR=Verbal Reasoning, SWM=Spatial Working Memory, DS=Digit Span

There was a high level of attrition between time points one and two, with 12169 (51%) participants withdrawing from the study after baseline data collection. The majority of the remaining participants were female (73.7%), with a mean age of 62.0 years (*SD*=7.2), married (68.1%), white (98.4%), retired (51.0%) and educated to degree level (53.1%). They were significantly more likely to be female [χ^2 (1) = 13.2, p < .001], fall within the age group of 50 to 69 years [χ^2 (3) = 28.9, p <.001], either married or divorced [χ^2 (6) = 14.0, p =.030], either white or Asian [χ^2 (4) = 19.2, p =.001], in full time employment, unemployed or retired [χ^2 (4) = 95.4, p < .001], and educated to degree level [χ^2 (1) = 56.8, p < .001] than their counterparts who withdrew before T2. Those who remained in the study reported significantly lower levels of depressive symptoms [t (1)=-8.5, p <.001] at baseline than participants who withdrew from the study. In addition, those who remained in the study performed significantly better in all measures of cognition than those who withdrew.

Missing data ranged from 0% for the cognitive variables to 2.7% for total PHQ-9 depression score at T1 and 8.4% for PHQ-9 depression score at T2. Little's (1988) MCAR test indicated that the data were not missing completely at random [χ^2 (26) = 255.9, p < .001].

Temporal relationship between depressive symptoms and cognition

The cross-lagged path analysis was run in one model that included depression at both time points and all four cognitive variables. For ease of presentation, results are illustrated in four separate diagrams. Figure 1 shows the cross-lagged relationship between depressive symptoms and PAL. There was a significant negative relationship between depressive symptoms and PAL (β = -.020, p = .013, [95% CI: -.036, -.004]) at T2

with no significant association for the reciprocal relationship (β = .001, p = .872, [95% CI: -.018, .016]).

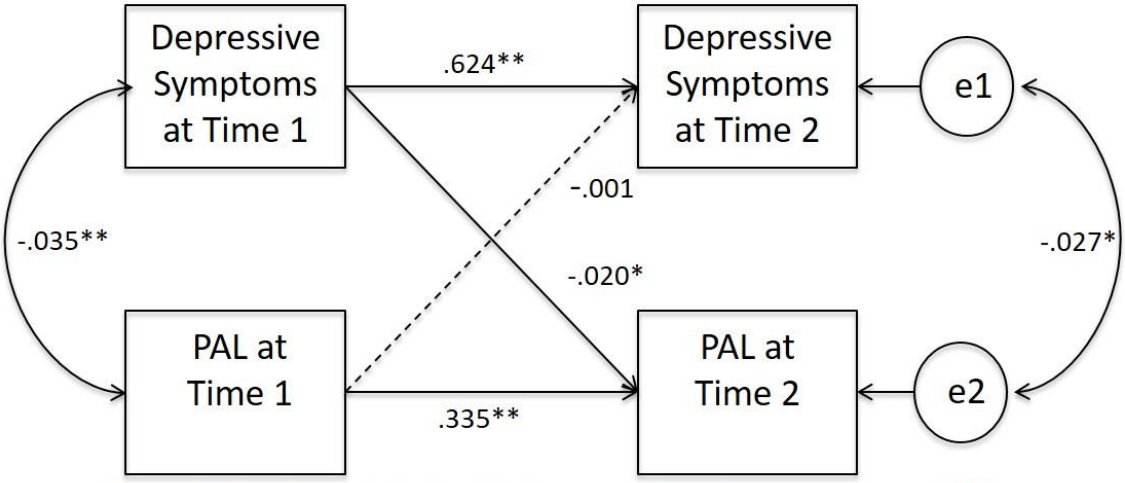

Figure 1 *Cross-lagged relationship between depressive symptoms and PAL shown with standardised regression coefficients, numbers in brackets are 95% confidence intervals. Solid lines indicate significant positive paths ,and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001.*

Figure 2 shows the cross-lagged relationship between depressive symptoms and VR. There was a significant negative relationship between depressive symptoms and VR (β = -.014, p = .016, [95% CI: -.025, -.003]) at T2 but no significant association for the reciprocal relationship (β = .001, p = .869, [95% CI: -.015, .018]).

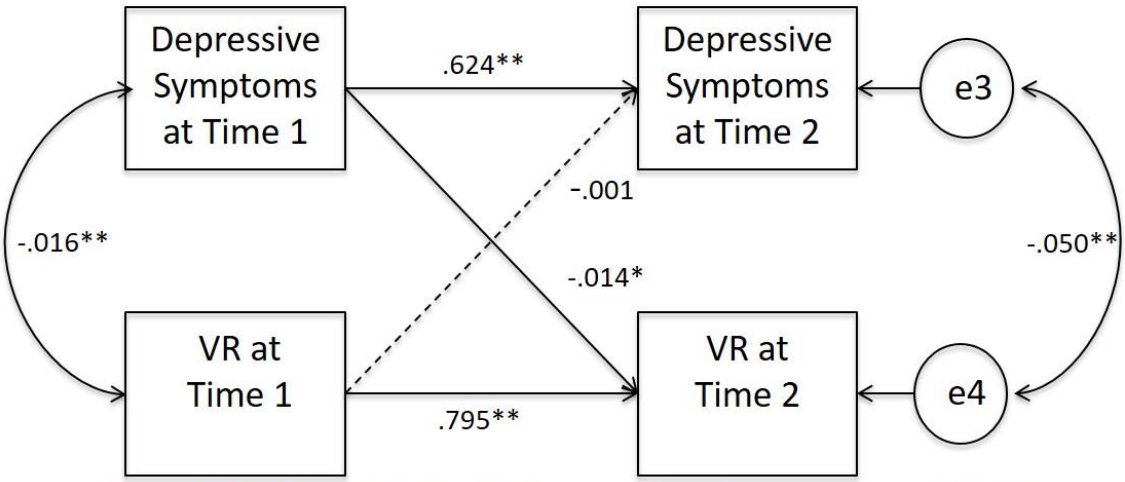

Figure 2 *Cross-lagged relationship between depressive symptoms and VR shown with standardised regression coefficients, numbers in brackets are 95% confidence intervals. Solid lines indicate significant positive paths ,and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001.*

Figure 3 shows the cross-lagged relationship between depressive symptoms and SWM. There was a significant negative relationship between depressive symptoms and SWM (β = -.043, p < .001, [95% CI: -.060, -.026]) at T2 as well as a significant negative relationship between SWM at T1 and depressive symptoms at T2 (β = -.030, p < .001, [95% CI: -.047, -.014]). In other words, the relationship between depressive symptoms and SWM was reciprocal.

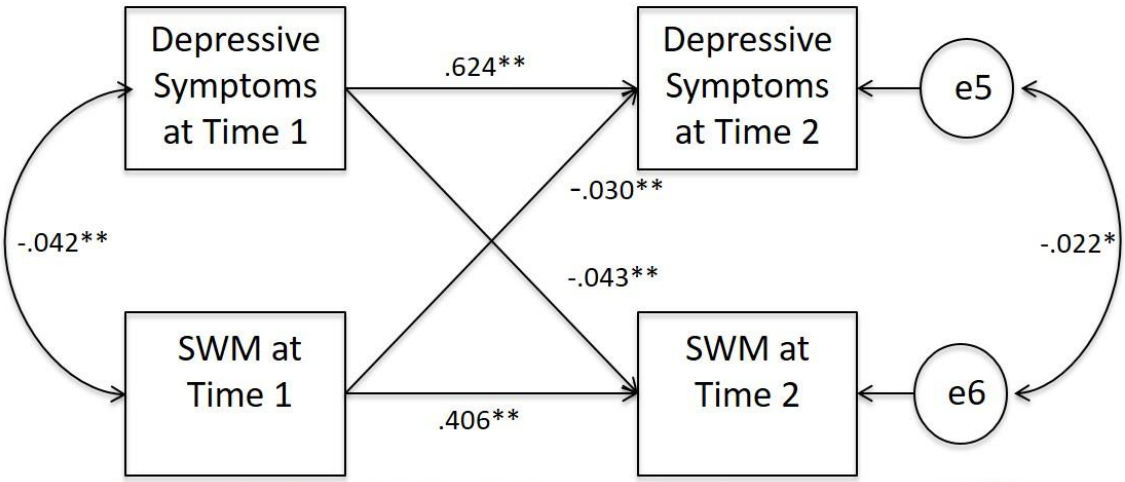

Figure 3 *Cross-lagged relationship between depressive symptoms and SWM shown with standardised regression coefficients, numbers in brackets are 95% confidence intervals. Solid lines indicate significant positive paths ,and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001.*

Figure 4 shows the cross-lagged relationship between depressive symptoms and DS. There was a significant negative relationship between depressive symptoms and DS (β = -.029, p < .001, [95% CI: -.043, -.015]) at T2 as well as a significant negative relationship between DS at T1 and depressive symptoms at T2 (β = -.025, p = .003, [95% CI: -.041, -.009]). In other words, the relationship between depressive symptoms and DS was reciprocal.

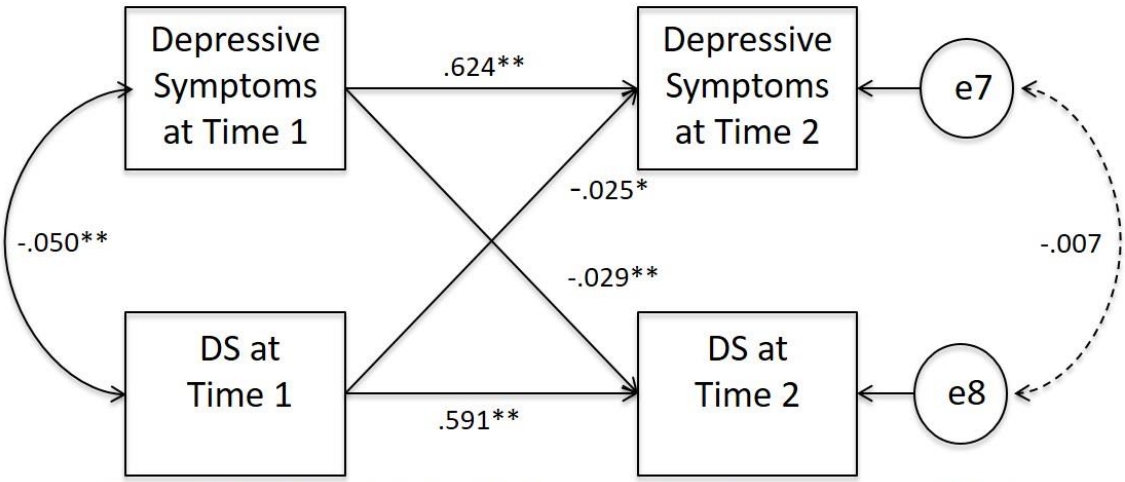

Figure 4 *Cross-lagged relationship between depressive symptoms and DS shown with standardised regression coefficients, numbers in brackets are 95% confidence intervals. Solid lines indicate significant positive paths ,and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001.*

The analysis was repeated using cognitive scores from the first trial only; the pattern of results was unchanged.

Discussion

Cross-lagged analysis found that depressive symptoms predicted a decrease in new learning, verbal reasoning, spatial working memory and digit span with effect sizes ranging from -.02 to -.04 (standardised beta coefficients). In addition, in the case of spatial working memory and digit span the relationship was found to be bi-directional. That is, lower spatial working memory and a shorter digit span also predicted depressive symptoms. To the best of the authors' knowledge, this is the first study to find evidence that the relationship between some aspects of cognitive function and depressive symptoms is dynamic and bi-directional.

The aim of this study was to examine the temporal relationship between depressive symptoms and cognition in relation to three hypotheses currently subject to debate. For all four cognitive measures higher depressive symptomatology predicted poorer cognitive performance indicating that depressive symptoms could either be a risk factor, or prodrome of, cognitive decline.

Depressive symptoms at follow up were predicted by lower levels of spatial working memory and shorter digit span at baseline but not new learning or verbal reasoning. This gives partial support for the 'psychological reaction' hypothesis. The different findings for the spatial working memory and digit span tests compared to new learning and verbal reasoning, may be explained by the two former domains being aspects of executive functioning. This is in keeping with the results reported by Vinkers and colleagues[8] who, as well as using a global screening tool, also used a validated measure of executive function as one of their measures of cognitive function. The study found that depressive symptoms increased with impaired performance on tests of executive function. Executive function is the aspect of cognition that allows for individuals to attend to, plan, organise and carry out tasks.[24] Deficits in this domain, even if only minimal, can potentially have consequences for an individual's capacity to care for themselves and engage in autonomous, meaningful behaviours.[24] Unlike other domains of cognitive function, impairments of executive function are difficult for an individual to independently circumnavigate. For example, an individual could employ executive functioning skills to plan and work around a decline in memory. If on the other hand, there were deficits in executive function no other aspect of cognition would be able to help with organising a compensatory strategy. Thus, it may be that even a minimal decline in executive function is the most evident in an individual's experience

of daily life, impacts the most on their sense of independence and therefore is associated most with depressive symptoms.

One novel finding of the current study was the reciprocal nature of the relationship between depressive symptoms and spatial working memory and digit span. Two previous studies[26, 27] assessed the temporal relationship between depressive symptoms and cognitive decline for the possibility of bi-directional relationships. Contrary to the present findings, neither of the previous studies found evidence in support of a bi-directional relationship between depressive symptoms and cognition. However, this may be explained by study design. The Cui et al.[26] study did not find evidence of a bi-directional relationship between executive function and depressive symptoms over a two-year follow-up period in a geriatric sample of 709 participants. However, the sample size used by Cui et al.[26] was much smaller that that used in the current study and therefore may have been underpowered to detect an effect. Panza and colleagues[27] assessed the bi-directional temporal relationship between depressive symptoms using a measure of global cognitive function and episodic memory. This study found a uni-directional relationship between depressive symptoms and cognitive decline after a three and half year follow-up period. However, Panza et al.[27] may not have found evidence of a bi-directional relationship because measures of executive function were not included in their study.

Strengths and limitations

Strength of the current study was in its use of a very large population cohort sample allowing the detection of small effects and the use of cross-lag analysis to simultaneously examine bi-directional relationships between depressive symptoms and cognition. There are a number of limitations imposed by the nature of conducting large

on-line studies. Participants were eligible for inclusion if they had access to the Internet via a computer. These requirements may have created bias in the sample due to inaccessibility for those potential participants from lower socio-economic backgrounds, those with lower levels of literacy as well as those with visual impairments. An exclusion criterion of the study was diagnosis of dementia. However, as there was no objective screen for this and relied on participants to self-report dementia diagnosis this may not have effectively controlled for dementia at baseline. Participants could attempt the cognitive tests once, twice or on three occasions, which may have created a practice effect bias in the scores. Additionally, attrition between baseline and one-year follow-up was slightly over 50% with significant differences between those who did not continue in terms of age, marital status, educational attainment, mood state and cognitive performance. Sample bias must therefore be considered. Age, marital status and educational attainment are, in themselves, independent predictors of better cognitive function.[28, 29, 30] Those who remained in the study had less depressive symptomatology and performed better in all tests of cognitive function than those who did not continue with the study. This suggests that the sample analysed here might be biased towards representing a younger population that has better mood and higher overall cognitive function. In addition, it should be noted that due to the level of attrition and the very small effect sizes of the relationships reported here the generalisability and clinical relevance are yet to be determined.

Conclusions and implications

Depressive symptoms predicted decreases in all four measures of cognitive function providing support for the 'risk factor' or 'prodrome' hypotheses. The temporal relationship between depressive symptoms and spatial working memory and digit span

was bi-directional. Study designs that account for the possibility of a bi-directional relationship between depressive symptoms and cognitive decline should at least be considered in future studies of depressive symptoms and cognitive decline.

Future research may focus on investigating the dynamic bi-directional relationship between depressive symptoms and executive function and attention as this finding raises several questions. Is this pattern of relationship between depressive symptoms and cognitive function the same in clinical populations? Does the dynamic nature of the relationship between executive function and attention accelerate decline in these domains of cognitive function?

Conflict of Interests

No conflicts of interest.

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