Assessing Modifiable Risk Factors for Cognitive Decline: Widowhood and Subtypes of Affective Symptoms

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Thesis Declaration Form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

This doctoral thesis assesses the role of widowhood and subtypes of affective symptoms as possible risk factors for cognitive decline.

Part 1 is a systematic review and meta-analysis on the effect of widowhood on cognition. The review explores the effect of widowhood (vs. being married) on cognition, not only cross-sectionally but also longitudinally, assessing whether widowhood is associated with steeper declines in cognition over time. Furthermore, the review tentatively explores whether length since spousal loss moderates the relationship between widowhood and cognition. Findings from this review may inform bereavement support programmes. Further clinical implications and suggestions for future research are also discussed.

Part 2 is an empirical study that utilises data from the PROTECT study. A Latent Class Analysis (LCA) was conducted to identify subtypes of co-occurring affective symptoms on the PHQ-9 and GAD-7. Multiple linear regressions were conducted to assess for associations between class membership and cognitive decline over a 2-year period, while adjusting for known risk factors for cognitive decline. Findings from this review help to clarify the nature of the relationship between affective symptoms of depression and anxiety, and cognitive decline, and may help to identify specific subgroups of adults over the age of 50 who may be at particular risk of cognitive decline, based on their patterns of co-occurring affective symptoms.

Part 3 is a critical appraisal of the process that was undertaken for the literature review and the empirical paper. Reflections include the impact of the COVID-19 pandemic, and the challenges associated with conducting a secondary data analysis.

Impact Statement

There are currently an estimated 50 million people living with dementia, with this number projected to triple by 2050. Given that there are no effective disease-modifying treatments as of yet, identifying potential modifiable risk factors that may prevent or delay the onset of dementia is paramount. This thesis aimed to assess the relationship between widowhood and cognitive decline (literature review), and affective symptoms and cognitive decline (empirical paper).

The aim of the systematic literature review and meta-analysis was to provide a synthesis on studies examining associations between widowhood and cognitive decline in people aged 50 and above. As far as we are aware, this is the first review that has explored the link between widowhood and cognition (as a continuous measure). This enabled the detection of subtler changes in cognition, which are sometimes not possible if binary categories are used, and non-dementia specific changes in cognition. The meta-analysis found that widowhood was not only associated with poorer cognitive function, but also with steeper declines in cognition over time, compared to those who were married. There was also some evidence that a longer time period since spousal loss was associated with increased cognitive decline. Clinical implications include paying closer attention to the recently bereaved as they may be a particular at-risk group for cognitive impairment. Spousal bereavement intervention programmes may also consider including a module on maintaining cognitive health. Further research however is required to ascertain the precise mechanisms by which widowhood affects cognition so that these can inform interventions. This paper has already been submitted to the Journal - Ageing Research Reviews, and is currently under review.

The aim of the empirical paper was to assess whether co-occurring subtypes of affective symptoms (across anxiety and depression) were differentially associated with cognitive decline over a 2-year follow-up period. As far as we are aware, this is the first study that has examined heterogeneity of affective symptoms using the PHQ-9 and the GAD-7 in a sample of adults over the age of 50. The Latent Class Analysis found five distinct subtypes of affective symptoms, suggesting that there is substantial heterogeneity in co-occurring affective symptoms. Furthermore, all four symptomatic classes were associated with significantly smaller increases in cognition compared to the asymptomatic class, and these differed across different cognitive domains. The aim is to disseminate these findings to the research community by publishing in peer-reviewed journals. The hope is that researchers and clinicians would pay more attention to patterns of anxiety and/or depression symptoms rather than relying solely on total symptom scores when assessing potential risk of cognitive impairment. A particular advantage of this study is that the PHQ-9 and GAD-7 are part of routine outcome measures used in IAPT services in the UK, and therefore the current findings could be easily translated to the IAPT context if necessary in the future.

This thesis adds to the existing literature concerning psychosocial risk factors for cognitive decline, and further highlights the importance of continuing this body of research so that clinicians, researchers and policy-makers can identify particular at-risk populations and implement effective public health strategies to reduce dementia risk in the population.

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To God be the Glory! The Best is Yet to Be!

Part 1: Literature Review

Widowhood and Cognitive Decline in Adults Aged 50 and Over: A Systematic Review & Meta-Analysis

Abstract

***Background*:** Widowhood is considered one of the most stressful events in life. While widowhood has been consistently found to be associated with poorer physical health and mental health outcomes, studies examining the effect of widowhood on cognition have so far yielded mixed results.

Aim: This review aimed to pool together a growing number of studies that have examined associations between widowhood and cognitive decline.

Method: A systematic search of Medline, Embase, PsycInfo, CINAHL and Scopus from inception to December 2020 was conducted to identify studies that reported on the association between widowhood (vs. being married) and cognition in cognitively healthy adults over the age of 50.

Results: In total, 10 studies were included in the meta-analyses (*n* = 24,668). The cross-sectional meta-analysis, which included all 10 studies, found a significant effect of widowhood (vs. married) on cognition (*g* = -0.36, 95% CI [-0.47, -0.25], *p* = <.001). Meta-regressions found that study design, cognitive domain measured, age, and continent of study did not account for the observed heterogeneity. There was also tentative evidence for a potential moderating effect of length since spousal loss, although this did not reach statistical significance. The longitudinal meta-analysis included data from three studies (*n* = 10,378), and found that those who were "continually widowed" from baseline to follow-up showed significantly steeper declines in cognition compared to those who were "continually married" during the same time period (*g* = -0.15, 95% CI [-0.19, -0.10], *p* = <.001).

Conclusion: The findings from this review indicate that widowhood may be a risk factor for cognitive decline, extending the findings of a previous meta-analysis that found widowhood to be associated with increased risk of dementia. Given that there is as yet no effective treatments for cognitive impairment, studying the precise mechanisms by which widowhood might be associated with poorer cognition can inform prevention programs that could be designed for those who have experienced recent spousal bereavement.

Introduction

Spousal loss or widowhood is known to be one of the most stressful experiences in life (Holmes & Rahe, 1967). In 2017, 1 in 4 above the age of 65 were widowed in the UK, and among those above the age of 85, 35% of men and 76% of women were widowed (ONS, 2018). In the US, more than 900,000 older adults are widowed each year (Elliot & Simmons, 2011).

Widowhood is known to be associated with poorer physical health – such as increased risk of illness, disability and mortality (Rendall et al., 2011), weaker immune response (Phillips et al., 2006), weight loss (Stahl & Schulz, 2014) and sleep difficulties (van de Straat & Bracke, 2015), as well as increased rates of mental health difficulties such as depression (Kristiansen et al., 2019a) and substance abuse (O'Farrell et al., 1998). Several studies have directly examined the relationship between widowhood and cognitive decline, and have yielded mixed results. While some studies have found significant associations between widowhood and cognitive decline (e.g., (Aartsen et al., 2005; Karlamangla et al., 2009), other studies have not found such associations (e.g., Vidarsdottir et al., 2014). Other indirect evidence comes from several studies that have found that numerous health – such as hypertension, alcohol intake and obesity (Livingston et al., 2020) and social factors – such as loneliness (Boss et al., 2015) and social isolation (Evans et al., 2019) that are known to be associated with cognitive decline, have also been found to be associated with widowhood (Buckley et al., 2012; Pilling et al., 2012; Shahar et al., 2001). Indeed, a very recent meta-analysis found not only that living alone was associated with a significantly elevated risk of incident dementia, but also that living alone was associated with greater population risk of dementia than relatively more well-known risk factors such as hypertension and obesity (Desai et al., 2020). Given the lack of efficacious treatments to treat cognitive decline, identifying at-risk subgroups within the

population becomes paramount, so that targeted prevention programs can be implemented to delay or slow down the rate of cognitive decline.

Several plausible mechanisms for the link between widowhood and cognitive decline have been suggested. One such mechanism is the marital resources theory (Waite & Gallagher, 2000), which proposes that marriage affords the couple greater social, psychological and economic resources that have long-term positive consequences for health and well-being. For instance, married couples might benefit from economies of scale, and tend to be more actively engaged with social groups (e.g., in-laws or friends of one's spouse), which in line with the cognitive reserve hypothesis (Stern, 2002) might be protective against brain degeneration (Evans et al., 2018). Another plausible mechanism is the stress model, which posits that the stress experienced as a result of such a significant loss leads to negative cognitive outcomes. For example, Geoffroy et al. (2012) found that the experience of widowhood was associated with higher cortisol, which in turn led to declines in memory. Other studies have found that stress causes a dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which in turn impacts cognitive functioning (McEwen & Sapolsky, 1995).

To the best of our knowledge, no meta-analysis has examined the link between widowhood and cognitive functioning. The most closely related meta-analysis (Sommerlad et al., 2018), which examined the relative risk of being widowed on dementia, found that widowed people have a 20% higher risk of developing dementia compared to those who were married. Due to a lack of available data, however, they were unable to address the effect of widowhood duration on cognition. While some studies have pointed to a linear relationship

between time since spousal loss and cognitive decline (Shin et al., 2018), other studies have found no such associations (Lyu et al., 2019).

The present meta-analysis therefore aimed to extend the findings of Sommerlad et al. (2018) meta-analysis in four ways. First, the present meta-analysis will focus on cognition as a continuous outcome rather than a binary outcome (e.g., dementia vs. no dementia), which might enable the detection of subtler differences or changes in cognition, as well as non-dementia related cognitive decline. Second, this study aimed to assess whether widowhood is associated with cognitive function in both cross-sectional and longitudinal studies, in order to explore *changes* in cognition over time. Third, this study will attempt to synthesise the available data to examine whether length since spousal loss moderates the relationship between widowhood and cognitive decline. Fourth, this study aimed to explore whether the data is consistent with a 'reverse causality' hypothesis (i.e. cognitive decline precedes widowhood).

Method

This review was registered on PROSPERO prospectively https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020191976 and is reported according to PRISMA guidelines (Page et al., 2021).

Search Strategy and Selection Criteria

A comprehensive search strategy was implemented across the following databases: MEDLINE, Embase, PsycInfo, CINAHL and Scopus from inception until December 2020. The search strategy consisted of a combination of keyword search and MESH subject heading

search, with terms adapted from two recently published meta-analyses that explored (separately) widowhood (Kristiansen et al., 2019b) and cognitive decline (John et al., 2019). The search terms consisted of two blocks. The first block contained keywords related to widowhood and the second block contained keywords related to cognition. The precise search terms used can be found under Appendix A. The inclusion criteria, which was in line with the registered protocol, was as follows:

- Peer-reviewed journal articles published in English
- Cross-sectional or longitudinal study
- Cognitive function was assessed as a continuous variable
- The study stratified participants by marital status, and must have had a "widowed" group (comparison group) and "married" group (reference group) respectively
- Mean and standard deviation of cognitive function, as well as the sample size for both the "widowed" group and the "married" group, were available (either from the paper or from contacting authors) so that a measure of effect size (hedges' g) could be calculated
- Participants included in the study sample were all over the age of 50, or a separate analysis was run only for participants above the age of 50
- Participants did not have a diagnosis of any form of cognitive impairment or dementia

Screening Procedure

A three-step approach was used to screen: First, articles were reviewed by title. Second, potentially relevant articles were screened by abstract. Finally, the full-text of identified articles were read and the decision on whether to finally include these articles were made based on the abovementioned inclusion criteria. All articles were reviewed for inclusion

by the primary reviewer. At the title and abstract screening stages, 10% of all articles were randomly selected and screened by another independent rater. At the full-text screening stage, 25% of the articles were randomly selected and screened by the independent rater. Disagreements were discussed and resolved during consensus meetings. References lists of all included articles were manually searched to identify any other potentially relevant papers.

Data Extraction

Data extracted for evidence synthesis included the name of the authors, publication year, DOI, country, age of sample (and for "widowed" and "married" respectively), length of follow-up (if any), sample size, cognitive domains assessed, cognitive measure used, cognition score (mean and standard deviation) at each reported wave (for "widowed" and "married" respectively), length of time since spousal loss (if available), and methodological quality rating information (see below). If there was insufficient information to calculate an effect size (e.g., raw mean cognition scores were not reported), authors were contacted for the required additional information. If there were multiple cognitive domains reported, a measure of global cognition (e.g., MMSE) was preferred. If this was not available, then a measure of memory was extracted. If studies reported stratified data (e.g., by gender), data were appropriately combined and pooled together.

Quality Rating

The methodological quality of included studies was assessed using the Newcastle-Ottowa Criteria (Wells et al., 2000) for studies with a longitudinal design, and the Joanna Briggs Institute checklist for studies with cross-sectional design. All cross-sectional studies were rated out of a maximum score of 7 (1 item was not applicable for this review – see

Appendix B). The longitudinal studies were rated out of a maximum score of 8 (1 item was not applicable for this review – see Appendix C). In the present study, for cross-sectional studies, scores of 6-7 were considered 'low risk' of bias, 3-5 were considered 'medium risk' of bias, and scores less than 3 were considered 'high risk' of bias. For longitudinal studies, scores of 7-8 were considered 'low risk' of bias, 4-6 were considered 'medium risk' of bias, and scores less than 4 were considered 'high risk' of bias.

Data Analysis

Cross-Sectional Analysis

Both cross-sectional and longitudinal studies were included in this analysis. For longitudinal studies that reported cognition scores at baseline and also at subsequent waves, only information at the final wave was used for the cross-sectional meta-analysis, as this allows for a longer time for declines in cognition to occur (John et al., 2019). For each study, a measure of effect size (hedges g) was calculated as the standardised mean difference (SMD) between the "widowed" group and the "married" group, using the R package – Metafor (Viechtbauer, 2010). The random-effects model (95% CIs) was used, which is able to account for the presence of heterogeneity and facilitates generalisability of findings (Borenstein et al., 2011). Heterogeneity was assessed using I^2, whereby a value of 0% represents no observed heterogeneity, 25%, 50%, and >75% represent low, moderate and high levels of heterogeneity respectively (Higgins et al., 2003). If substantial heterogeneity was found (pre-determined as $I^2 > 50\%$), meta-regressions would be performed to assess whether study design (cross-sectional vs. longitudinal), cognitive domain measured (global vs. memory-only), age of sample, difference in age (widowed vs. married) or continent (Europe/North America vs. Asia), might account for the observed heterogeneity. If there were sufficient data,

a further meta-regression was planned a priori to assess for the potential moderating effect of length since spousal loss. Publication bias was assessed by inspecting funnel plots and Egger's test.

Longitudinal Analysis

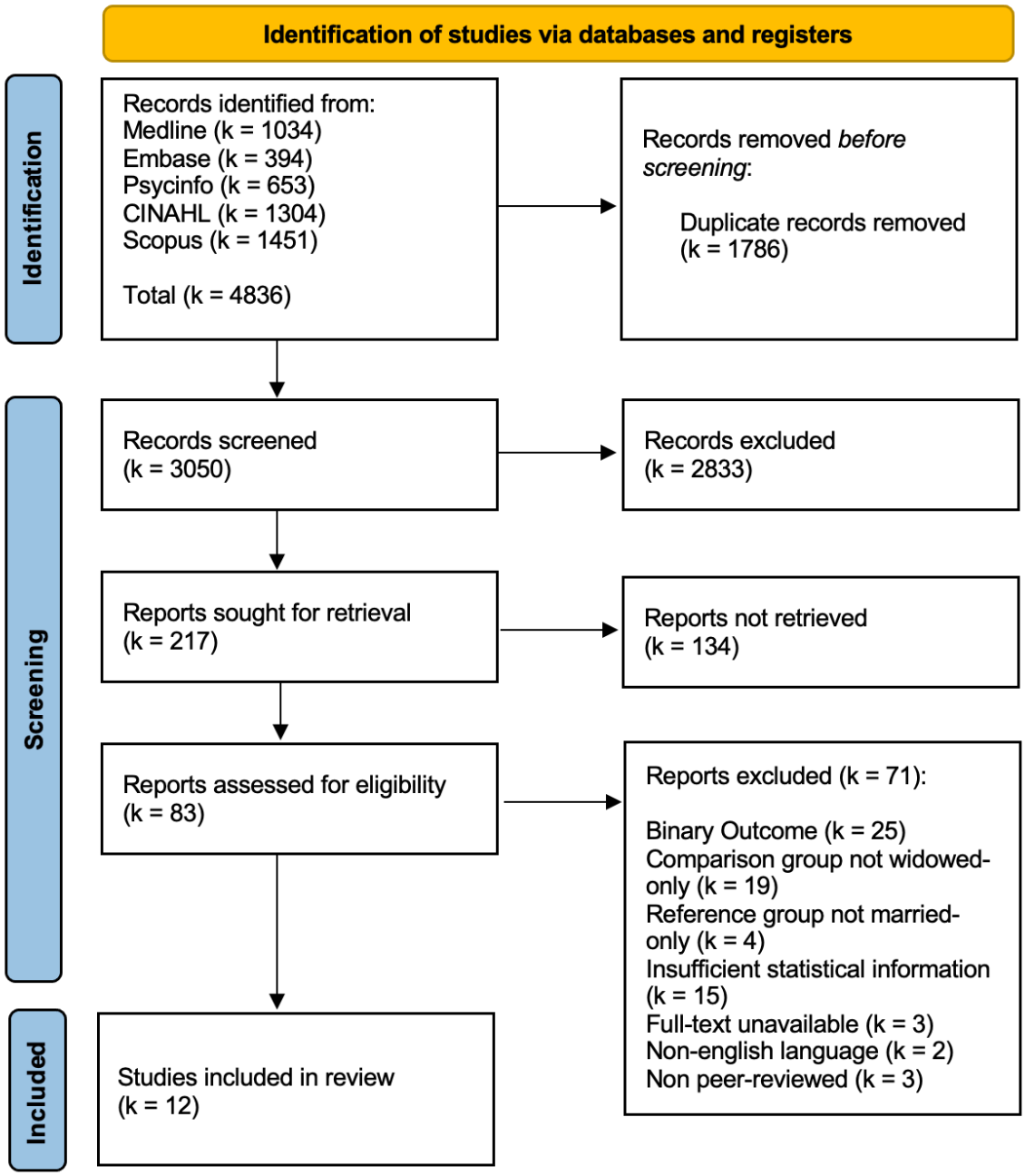
Longitudinal studies that were included in this analysis needed to have a widowed group that were already widowed at T1 and continued to be widowed until T2 – commonly referred to in the literature as "continually widowed". If studies only included a widowed group that was married at T1 and subsequently widowed at T2 (commonly referred to in the literature as "newly widowed"), they were excluded from this analysis. Furthermore, studies must have reported cognition data at T1 and subsequently at T2 for the same group of participants, so that pre-post change could be calculated. The mean and standard deviation of the pre-post change were calculated if this was not reported. Calculating the standard deviation of this pre-post change requires the correlation between the pre-post measures. Where this was not reported, an imputed value of r = 0.6 was used, as has been used in other studies (Hallam et al., 2021) based on the median within-group correlation extracted from 811 measures of pre–post clinical trial arms (Balk et al., 2012). Since it has been found that in cases where this imputed value is considerably different from the true pre-post correlation, the effect sizes tend to be inflated (Cuijpers et al., 2017), additional sensitivity analyses were conducted to evaluate the effect of different imputed r values.

Results

The initial search yielded a total of 4,836 references. After duplicates were removed, 3,050 references remained. After the 1st step whereby all 3050 titles were screened, 217 references were considered to have potential relevance (percentage agreement on a random 10% sample was 93%). In the 2nd step, the 217 retained references were screened at the abstract level, of which 83 were assessed to be eligible (percentage agreement was 92.5%). The final step involved reading the full-text of the remaining 83 articles, after which 71 articles were excluded. Reasons for exclusion are reported in Figure 1. A total of 12 studies met the final inclusion criteria and were thus included in the meta-analysis. More details can be found in Figure 1 below, which is reported according to PRISMA (The Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (Page et al., 2021).

Figure 1

PRISMA flow diagram



There were a total of 25,531 participants across 12 studies, of which *n* = 6,867 were "widowed" (comparison group) and *n* = 18,664 were "married" (reference group). The studies came from a variety of countries including India (k = 1), Singapore (k = 1), China (k = 2), Brazil (k = 1), Australia (k = 1), Netherlands (k = 1), Sweden (k = 1) and the US (k = 4). Amongst these 12 studies, five studies measured cognition as a function of recall and/or recognition memory, and the other seven studies included a global measure of cognition (i.e. based on the MMSE). All studies included participants who were over the age of 50. A total of six studies were designed as cross-sectional studies (i.e. cognition and marital status were measured at the same single time-point), and the other six studies were designed as longitudinal studies. The assessed methodological quality of studies ranged from 'low' to 'medium' risk of bias. Detailed study characteristics of all 12 included studies are reported in Table 1 below.

Table 1

Characteristics of all included studies

Sn	Author	Country	Cognitive Domain Assessed	Cognitive Measure	Study Design	Study Population Age Group	Age[a] ("Widowed" age/"Married" age)	Length since spousal loss (range) at latest time point	N Widowed (% female)	N Married (% female)	Risk of methodological bias ratings
1	Perkins 2016	India	Memory (immediate recall)	Recall of 10 commonly used words	cross-sectional	60+	Median range = 65-69 (Not reported)	0-4years (*n*=879) 5-9years(*n* =793) 10+years (*n* =1,913)	3585 (82.5)	5586 (33.8)	'low risk' of bias (cross)
2	O' Connor 2014	US	Global	MMSE	cross-sectional	62+	72.06 (72.0/72.1)	Not reported	45 (73.4)	32 (69.0)	'low risk' of bias (cross)
3	Feng 2014	Singapore	Global	MMSE	cross-sectional	55+	66.08 (71.5/64.9)	Not reported	414 (90.8)	1857 (56.6)	'low risk' of bias (cross)
4	Shahar 2001	US	Global	3MSE	cross-sectional	65+	77.60 (77.6/77.6)	6+ months (mean = 2.9 years)	58 (82.8)	58 (82.8)	'low risk' of bias (cross)
5	Rosset 2011	Brazil	Global	MMSE	cross-sectional	80+	84.60 (Not reported)	Not reported	163 (Not Reported)	92 (Not Reported)	'medium risk' of bias (cross)
6	Xu 2020	China	Global	MMSE	cross-sectional	60+	71.00 (Not reported)	Not reported	285 (70.5)	1018 (50.2)	'low risk' of bias (cross)
7	Byrne 1997	Australia	Global	MMSE	longitudinal	65+	74.93 (74.5/75.4)	Exactly 6 weeks	57 (0.0)	57 (0.0)	'low risk' of bias (cross)
8	[b]Biddle 2020	US	Global	MMSE	longitudinal	60+	74.00 (73.3/74.6)	5+ years (mean = 12.9, median = 17.4)	31 (45.0)	136 (88.0)	'low risk' of bias (cross) 'low risk' of bias (long)

9	Aartsen 2005	Netherlands	Memory (immediate and delayed recall)	15 words test	longitudinal	60+	75.30 (78.2/74.6)	0-6 years (mean = 37 months)	178 (70.0)	729 (38.0)	'low risk' of bias (cross)
10	Mousavi 2012	Sweden	Memory (recall and recognition)	Recall (Action/Noun) Recognition (Face/Name/Noun)	longitudinal	60+	76.00 (79.6/75.2)	5+ years	30 (87.7)	396 (41.2)	'low risk' of bias (cross)
11	[b]Zhang 2019	China	Memory (immediate and delayed recall)	10 Chinese nouns	longitudinal	55+	Median range = 62-66 (Not reported)	0-2years (N=209) 2+years(N=1084)	1293 (72.2)	6631 (46.5)	'low risk' of bias (cross) 'low risk' of bias (long)
12	[b]Lee 2019	US	Memory (immediate and delayed recall)	10 English nouns	longitudinal	50+	66.14 (72.9/64.6)	0-4 years (N=122) 4+years (N=424)	546 (85.5)	2072 (51.45)	'low risk' of bias (cross) 'medium risk' of bias (long)

Note.

[a] This refers to mean age for Married & Widowed sample only (where possible). If this was not possible, then the mean age of the entire sample was reported (this might include other marital status subgroups e.g., "divorced" and "single"). Age at final wave (where cognitive data was available) was reported as it was at this age that cognitive data was used for the cross-sectional meta-analysis.

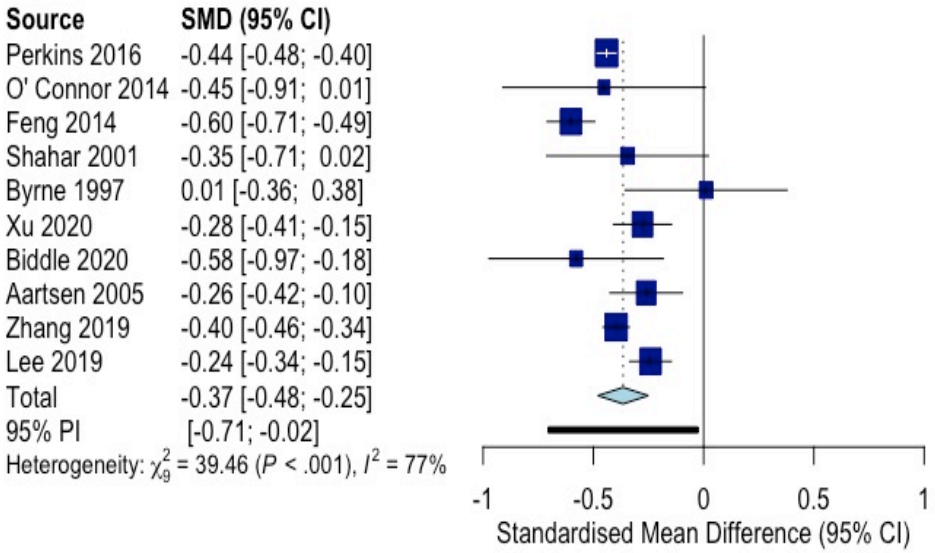
[b] All studies were rated as cross-sectional studies since all studies were included in the cross-sectional meta-analysis. In addition, for studies that were included in the longitudinal meta-analysis, they were additionally rated as longitudinal studies. For such studies, two ratings were given – "(cross)" denoting it's rating as a cross-sectional study, and "(long)" denoting it's rating as a longitudinal study. It is important to note that not all longitudinal studies were included in the longitudinal meta-analysis because they did not measure "continually widowed" status.

Cross-Sectional Meta-Analysis

A meta-analysis of all 12 studies comparing widowed vs. married groups on a continuous measure of cognition found that being widowed was significantly associated with poorer cognitive functioning, as compared to being married (g = -0.80, 95% CI [-1.47, -0.13], p = .02, I^2 = 98%). Based on a visual inspection of the forest plot (see Appendix D), it was evident that two studies (Rosset et al., 2011; Mousavi-Nasab et al., 2012) had effect sizes that were considerably larger than the others. This was also confirmed via diagnostic plots (Viechtbauer & Cheung, 2010) using the 'dmetar' package in R (see Appendix E). Upon further examination of each of their study designs, it was observed that the Rosset et al. (2011) study had a significantly older population (80+ study population, mean age = 85) compared to the other studies, and the Mousavi-Nasab et al. (2012) study measured cognition in terms of z-scores which were calculated based on relative performance compared to a younger, all-male reference group. These may have contributed to them being outliers compared to the other studies. As such, this and henceforth all other meta-analyses were re-run (k = 10; n = 24,668) excluding these two studies.

Figure 2

Forest plot for cross-sectional meta-analysis (k = 10)



As seen in Figure 2 above, there was still a significant effect of widowhood (vs. married) on cognition, although the pooled effect sizes were much reduced, (*g* = -0.37, 95% CI [-0.48, -0.25], *p* = <.001). Although these outliers (k = 2) accounted for some of the heterogeneity, there was still significant heterogeneity in the full model (Q = 39.46, df = 9, *p* < .001, I^2 = 77%). To account for this heterogeneity, we conducted a series of planned meta-regressions to assess if study design (cross-sectional vs. longitudinal), cognitive domain measured (global cognition vs. memory-only), age (as a continuous variable), or continent (Asia vs. Europe/North America) accounted for the observed heterogeneity. Results revealed that study design (*p* = .64), cognitive domain measured (*p* = .64), age of sample (*p* = .35), difference in age between "widowed" and "married" groups (*p = .73)* and continent (*p* = .19) did not significantly explain the observed heterogeneity (see Appendix F for detailed results of subgroup analyses).

Secondary Analysis by Length Since Spousal Loss

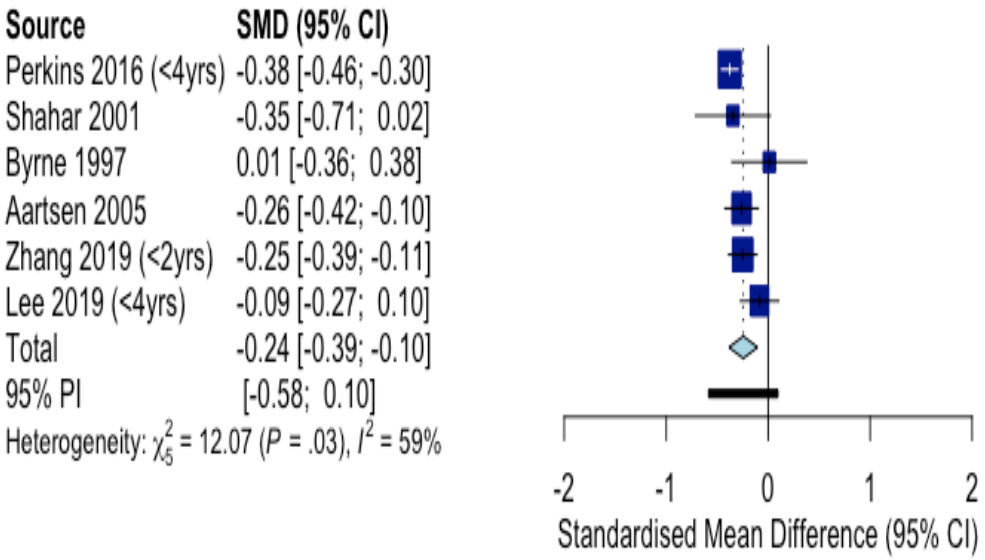
A further factor that could explain the observed heterogeneity might be length since spousal loss. This analysis however involved several complexities that are detailed here. Firstly, not every study reported data on length since spousal loss, but for some it could be inferred. For example, for those who were widowed between T1 and T2 ("newly widowed"), we could safely infer that they were widowed sometime *within* T1-T2. Similarly, for those who were widowed at T1, and continued to be widowed until T2 ("continually widowed"), we could safely infer that they were widowed for *at least* the length of the follow-up period. If the length since spousal loss was not reported or could not be reasonably inferred, the studies were excluded from this analysis. In total, three studies (O'Connor & Arizmendi, 2014; Feng et al., 2014; Xu et al., 2020) were excluded due to a lack of available information. A further complexity was in deciding how best to categorise the studies. Based on available data, it was decided that the studies would be split into two subgroups (less than 4 years since widowhood vs. more than 4 years since widowhood). If a study (e.g., Aartsen et al., 2005) reported a range that overlapped both these periods (i.e. 0-6 years since widowhood), and if the mean length (i.e. 37 months) since widowhood was also reported, the mean was used to finally decide which subgroup the study fell into. In this example (i.e. Aartsen et al., 2005), this study was therefore included in the "less than 4 years since widowhood" subgroup. A final complication was the fact that some studies could be represented in both subgroups. This was because some studies presented results that were stratified by length since spousal loss. For example, in the Perkins et al. (2016) study, they presented results separately for '0-4' years, '5-9' years and '10+' years (as seen above in Table 1). Therefore, the data reported for the '0-4' years was included in the "less than 4 years since widowhood" subgroup, while the data reported for the '5-9' years and the '10+' years were pooled together, and included

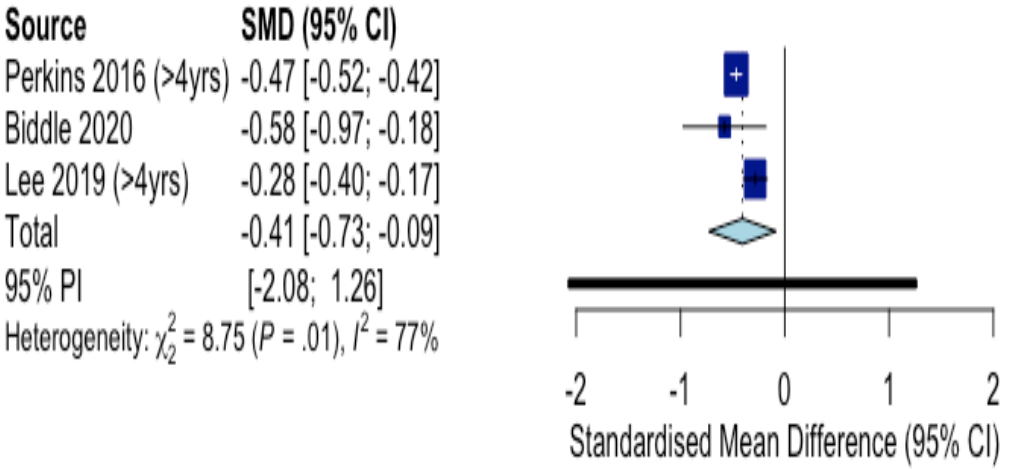
in the “more than 4 years since widowhood” subgroup. A further issue arises however due to the fact that in both cases, the same “married” group was used as the reference group which creates a “unit-of-analysis” error (Higgins & Green, 2020) since there is a ‘double-counting’ of “married” participants. In order to partially overcome this error, the sample size for the “married” reference group was split equally across the different comparisons. This does not however fully account for this error because the resulting comparisons would still remain correlated. Nonetheless, one advantage of this approach is that it tentatively allows for comparisons between “less than 4 years since widowhood” and “more than 4 years since widowhood” (Higgins & Green, 2020).

In total, data from six studies was included in the “less than 4 years since widowhood” subgroup (Perkins et al., 2016; Shahar et al., 2001; Byrne & Raphael, 1997; Aartsen et al., 2005; Zhang et al., 2019; Lee et al., 2019), and data from three studies was included in the “more than 4 years since widowhood” subgroup (Perkins et al., 2016; Biddle et al., 2020; Lee et al., 2019). As shown in Figure 3 below, the pooled effect size for the “less than 4 years since widowhood” subgroup was smaller than the pooled effect size for the “more than 4 years since widowhood” (g = -0.24 vs. g = -0.41) subgroup, although this difference was not statistically significant ($B = 0.16$, p = .11, R^2 = 23.75%). However, as mentioned, direct comparisons should only be made tentatively. Substantial heterogeneity was also present within both subgroups.

Figure 3

Forest plots for length since spousal loss subgroups: less than 4 years (above) vs. more than 4 years (below)

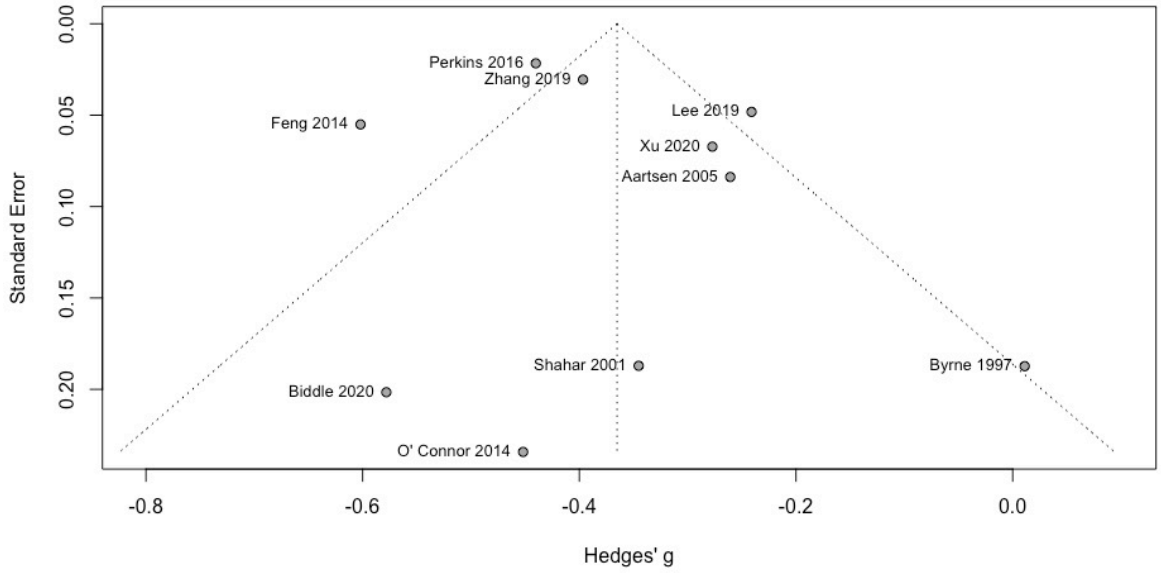




Risk of Publication Bias

Figure 4

Funnel plot for cross-sectional analysis (k = 10)



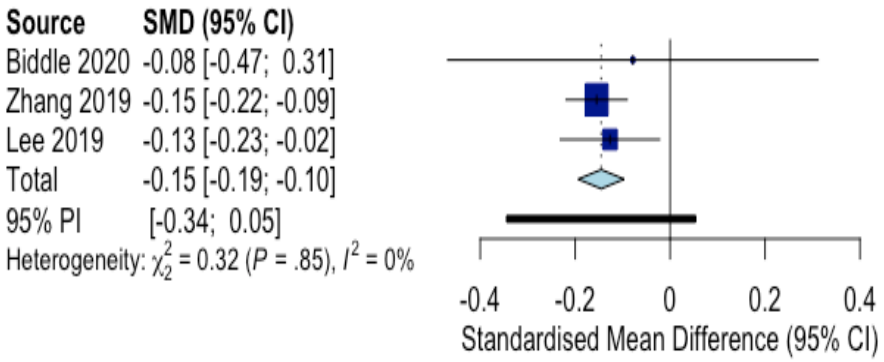
A visual inspection of the funnel plot in Figure 4 was used to assess publication bias. Furthermore, egger's test was used to assess for funnel plot asymmetry. Egger's test was found to be non-significant (t = 0.855, p = .40), which indicated that there was a low likelihood of publication bias.

Longitudinal Meta-Analysis

The aim of the longitudinal meta-analysis was to assess whether those who were "continually widowed" from T1 to T2 experienced a greater decline in cognition, compared to those who were "continually married" over the same time period. Out of the six longitudinal studies, three studies (*n = 10,378)* used such a design and were included in this analysis (Biddle et al., 2020; Zhang et al., 2019; Lee et al., 2019).

Figure 5

Forest plot for longitudinal meta-analysis (k = 3)



With reference to Figure 5 above, the pooled effect size indicated a small and statistically significant effect (*g* = -0.15, 95% CI [-0.19, -0.10], *p* = <.001), suggesting that those who were continually "widowed" showed a steeper decline in cognition over time as compared to those who were continually "married". This effect remained significant even for differing imputed r-values (ranging from r = .20 to .80; see Appendix G). There was no observed heterogeneity in this model.

Exploratory Analysis

To test whether the data was consistent with a reverse causality hypothesis – i.e. that cognitive decline occurs prior to being widowed (pre-widowhood), akin to the effect that has been termed 'anticipatory grief' (Vable et al., 2015) – we performed an exploratory analysis using studies that employed the "newly widowed" longitudinal design, whereby the "newly widowed" were married at T1, and then subsequently widowed by T2. The pre-post *change* in this case represented change that occurred for a period of time *prior* to widowhood, in addition to a period of time *post*-widowhood. This differs from the studies used in the primary

longitudinal meta-analysis, which only included studies that employed the "continually widowed" design, whereby participants were *already* widowed at T1, and continue to be widowed at T2. It was hypothesised that if cognitive decline begins *prior* to widowhood and not just post-widowhood, "newly widowed" participants might already show declines in cognition compared to their "married" counterparts, since a portion of the *change* in cognition would already have happened prior to widowhood. This analysis included data from two studies (Zhang et al., 2019; Lee et al., 2019). Results found no significant differences between those who were "newly widowed" as compared to those who were continually married in terms of declines in cognition over the same time period, (g = 0.04, 95%CI [-0.43, 0.52], p = .46). Similar results were found when differing imputed r-values (ranging from r = .20 to .80) were used. No heterogeneity was observed in this model.

Discussion

This meta-analysis aimed to assess whether widowhood is a potential risk factor for cognitive decline. Overall, there was consistent evidence to suggest that being widowed, compared to being married, was associated with poorer cognition and steeper declines in cognition over time.

The cross-sectional meta-analysis found that those who were widowed had poorer cognition functioning as compared to those who were married. This was irrespective of study design, cognitive domain measured, age, and continent of study. These findings must however be interpreted with caution due to the presence of substantial heterogeneity in all the models. Study design, cognitive domain measured, age, and continent of study all did not account for much of the heterogeneity. This study also extended the findings of a previous

related meta-analysis (Sommerlad et al., 2018) by assessing whether length since widowhood moderated the relationship between widowhood and cognition (less than 4 years vs. more than 4 years since spousal loss). To do so, two subgroups were formed – one for data that corresponded to length since spousal loss being less than 4 years, and the other for data that corresponded to length since spousal loss being more than 4 years. Although comparisons between these two subgroups should be made tentatively, there was some evidence that when compared to those who were married, the effect size for those who were widowed for less than 4 years was smaller than those who were widowed for greater than 4 years, although this difference did not reach statistical significance. These findings trend in the direction of providing evidence for a 'dose-response' effect of widowhood on cognition, which is consistent with previous findings (e.g., Shin et al., 2018), and providing additional evidence in support of widowhood being a risk factor for cognitive decline.

Cross-sectional analyses however have limitations. For example, such analyses cannot assess for whether those who are "widowed" experience steeper *declines* in cognition as compared to those who are "married" over the same period of time. As such, the present study conducted a meta-analysis of longitudinal studies that measured pre-post *change* in cognition. Results found that those who were "continually widowed" had significantly steeper declines in cognition as compared to those who were "continually married" over the same time period. Similar results were found even after sensitivity analyses were conducted for different imputed values of standard deviation of pre-post change. These results provide further evidence for widowhood being a risk factor for declines in cognition over time.

One further issue pertains to reverse causality (i.e. whether declines in cognition precede spousal loss). It was found that those who were "newly widowed" did not have significantly greater declines in cognition as compared to those who were continually married over the same period of time. This tentatively suggests that cognitive decline did not already begin to occur prior to widowhood (i.e. evidence against reverse causality). Combined with the findings from the primary longitudinal meta-analysis, these results lend tentative support to the suggestion that cognitive decline occurs post-widowhood rather than pre-widowhood, and provides further support for widowhood being a potential risk factor for cognitive decline. However, this finding should be interpreted with extreme caution because it assumes that the trajectory of cognition change is unidirectional and does not improve post-widowhood – in line with the theory of cognitive plasticity (Lövdén et al., 2010), which suggests that a mismatch between environmental demands and cognitive supply might lead to a re-adaptation of cognitive functioning to meet the required demands.

Overall, these results are consistent with the theories that have been proposed in the literature such as the marital resources theory (Waite & Gallagher, 2000) and the stress model, which suggests that the stress experienced as a result of such a significant loss leads to negative cognitive outcomes. These results are also consistent with previous related meta-analyses that have found loneliness, living alone, and social isolation to be associated with poorer cognitive outcomes (Boss et al., 2015; Evans et al., 2019; Desai et al., 2020), and complements (Sommerlad et al., 2018) meta-analysis findings that widowhood increases one's risk of dementia.

Strengths and Limitations

To the best of our knowledge, this is the first review that has provided a synthesis on studies examining the link between widowhood and cognition, as measured as a continuous measure. Examining cognition as a continuous measure rather than a binary outcome (e.g., dementia) enabled the detection of subtler changes in cognition, and might have been able to pick up on non-dementia specific cognitive changes that are worth further exploration. Furthermore, this review was able to go a step further in tentatively exploring the moderating role of length since spousal loss. However, the present review has several limitations. First, most of the models presented in this analysis contained at least moderate levels of heterogeneity. Though we tried to account for this heterogeneity, none of the factors that were explored accounted for a significant amount of the heterogeneity, which suggests that there may be further differences between samples on unobserved factors. Second, the lack of sufficient studies, especially for the longitudinal analyses, meant that our analyses might have lacked sufficient power, and also limited the extent to which potential moderators – such as length since spousal loss – could have been further explored. Third, residual confounding (for example by age), rather than widowhood itself, may have underpinned the general trend found in this study that those who were "widowed" (and for a longer period of time) had poorer cognition compared to those who were "married". Finally, selective attrition could underestimate the association between being widowed and cognitive decline on the assumption that those who experience greater declines in cognition as a result of widowhood might be more likely to drop-out.

Future Directions and Clinical Implications

Future research could explore whether widowhood differentially affects different cognitive domains (e.g., semantic memory, executive functioning). Second, more studies with longer follow-ups are required to examine if declines in cognition are sustained linearly over time, or whether there may be a curvilinear relationship, whereby the effects of widowhood on cognition are attenuated over time (e.g., Vidarsdottir et al., 2014), as is consistent with the theory of cognitive plasticity (Lövdén et al., 2010). Third, future meta-analyses could explore whether the effect of widowhood on cognition is moderated by gender as has been suggested in previous studies (Leopold & Skopek, 2016; Worn J. et al., 2020). This could not be explored in the present study due to a lack of available data. Fourth, in order to ascertain whether marital selection theory accounts for part of the association between widowhood and cognitive decline, more studies with longer follow-ups are needed to test whether those who are cognitively 'healthier' are more likely to get married and stay married for longer, as compared to those who experience widowhood earlier in life, as this could partially account for the association between widowhood and poorer cognition. Finally, more research is needed to ascertain the precise mechanisms by which widowhood is associated with cognitive decline. If, for example a key mechanism is found to be via a lack of social or cognitive engagement, bereavement programmes could consider including such components in their intervention. Alternatively, if the key mechanism is found to be via stress and anxiety as a result of spousal loss, then dementia prevention programmes for at-risk groups, such as those who have been recently spousally bereaved, should consider including a component on stress and anxiety management techniques. In the absence of any effective treatments for cognitive impairment, identifying at-risk groups and providing targeted interventions based

on precise mechanisms is paramount in order to delay or prevent older adults from experiencing the most debilitating effects of cognitive ageing.

Conclusion

The present study adds to the current literature by demonstrating that widowhood is associated with poorer cognition in cognitively healthy adults over the age of 50, irrespective of study design, age, cognitive domain measured, and continent of study. This study further demonstrated that widowhood is associated, not just cross-sectionally but also longitudinally, with steeper declines in cognition over time, as compared to those who were married. In addition, the present study found tentative evidence for a dose-response effect of widowhood on cognition whereby the longer the exposure to widowhood, the poorer one's cognitive functioning. Put together, these findings provide good evidence in support of widowhood being a risk factor for cognitive decline.

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Part 2: Empirical Paper

Are Subtypes of Affective Symptoms Differentially Associated with Change in Cognition over time: A Latent Class Analysis

Abstract

***Background*:** In the absence of any known disease-modifying treatments, identifying potential psychosocial risk factors for dementia is paramount. Two previously identified risk factors are depression and anxiety. Studies however have yielded mixed findings, lending possibility to the fact that potential constellations of co-occurring depression and anxiety symptoms may better explain the link between affective symptoms and cognitive decline.

***Aim*:** The study aimed to identify whether subtypes of co-occurring affective symptoms were differentially associated with cognitive decline over 2 years.

***Method*:** The study used data from participants (aged 50 and above) from the PROTECT study over a 2-year follow-up period. In total, 21,684 participants who had complete information on all items of the PHQ-9 and GAD-7 at baseline were included in the Latent Class Analysis (LCA). A series of multiple linear regressions, using a subset of these participants (*N* = 6,812) who had complete cognition data at baseline and at follow-up, were employed to test whether class membership was associated with changes in cognition from baseline to follow-up.

***Results*:** The LCA found a 5-class solution with classes labelled as: "No Symptoms", "Sleep", "Sleep and Worry", "Sleep and Anhedonia", and "Co-morbid Depression and Anxiety". Class membership was significantly associated with change in cognition over the 2-year follow-up period. Compared to the "No symptoms" (reference) group, the "Sleep and Worry" group was associated with significantly smaller increases in the cognitive domains of episodic memory and spatial working memory, the "Sleep" group was associated with significantly smaller

increases in the domain of spatial working memory, the “Sleep and Anhedonia” group was associated with significantly smaller increases in the domain of episodic memory, and the “Co-morbid Depression and Anxiety” group was consistently associated with significantly smaller increases on all four measured cognitive domains.

Conclusion**:** There exists substantial heterogeneity within co-occurring depression and anxiety symptoms in a sample of adults, aged 50 and above. Different subtypes were associated with cognitive changes in different cognitive domains. Identifying particular at-risk subgroups that are at greater risk of cognitive decline may support targeted prevention work.

Introduction

There are currently close to 50 million people who live with dementia worldwide, and this number is projected to triple by the year 2050 (Prince et al., 2016). In the UK, dementia is currently the most common cause of mortality (ONS, 2018). By 2040, it is estimated that more than 1 million people in the UK will be diagnosed with dementia (Ahmadi-Abhari et al., 2017). In the absence of any known disease-modifying treatments, attention has turned towards identifying modifiable risk factors that could potentially prevent or slow the progress of dementia. Depression and anxiety are two such possible risk factors that have been proposed (Gulpers et al., 2016). Several plausible mechanisms have been proposed for the link between affective symptoms – such as depression and anxiety, and cognitive decline. These include the hyper-activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Rodrigues et al., 2014), disruptions in the GABAergic system (Wu et al., 2014), Sapolsky's glucocorticoid cascade hypothesis (Sapolsky et al., 1986), and via cardiometabolic risk (John et al., 2021). It is also possible that a complex interaction of multiple mechanisms and pathways may explain the connection between affective symptoms and cognitive decline, rather than any single factor (Silva et al., 2013).

There are, however, still significant gaps in our understanding of this link between depression and anxiety, and cognitive decline. For instance, while some studies have found significant associations between depression and cognitive decline (e.g., Rajan et al., 2014; (Chang & Tsai, 2015), and anxiety and cognitive decline (e.g., Sinoff & Werner, 2003; Gulpers et al., 2019), some studies have not found such associations (e.g., Bunce et al., 2012; Neubauer et al., 2013; Brailean et al., 2017). Why exactly this is the case, still

remains unclear. Some proposed reasons include inconsistencies in study methodology, design, length of follow-up, and differences in assessment tools (John et al., 2019).

One further possible reason for mixed findings could be due to the heterogeneity of mood and anxiety disorders. For example, a recent study conducted by Marchant et al. (2020) found that Repetitive Negative Thinking (RNT), but not anxiety and depression, was associated with Tau and Amyloid – two biomarkers of Alzheimer's Disease. RNT is part of a recently proposed theory of cognitive debt (Marchant & Howard, 2015), which posits that certain cognitive processes such as RNT, which operates across both anxiety and depression, actively deplete cognitive reserve. RNT, which consists of both rumination (negative thoughts about the past) and worry (negative thoughts about the future), diverts cognitive resources and narrows the attentional scope toward negative thought. This thereby is thought to increase physiological and psychological distress, which in turn might lead to cognitive decline. Marchant et al. (2020) posited that it remains a possibility that general anxiety and depression symptoms may be more indicative of age-related or non-dementia specific cognitive decline, whereas RNT may be a more precise marker of neurodegenerative disease. This hints at the possibility that a subgroup of affective symptoms may be differentially associated with cognitive decline.

If one were to examine depression and anxiety individually, there is also some suggestion of heterogeneity. In the case of depression, there still exists a debate on its latent structure (Wright et al., 2013). While some studies have found a uni-dimensional factor structure of depression (Prisciandaro & Roberts, 2005), others have found a bi-dimensional factor structure (Sunderland et al., 2013) consisting of 'psychological symptoms' and 'somatic

symptoms'. Furthermore, a systematic review that examined the factor structure of depression (van Loo et al., 2012) found that large heterogeneity exists, both in terms of the number of underlying factors, and the content of each factor. Similarly, the factor structure of generalised anxiety has also been debated, with some studies indicating a uni-dimensional factor structure (Rutter & Brown, 2017), and others (Beard & Björgvinsson, 2014) finding a bi-dimensional factor structure consisting of 'cognitive/emotional symptoms' and 'somatic symptoms'. Heterogeneity is a particular issue especially when studying the older adult population, owing to the specificity of the measures used to assess affective symptoms (Pietrzak et al., 2012). In a review conducted by Therrien & Hunsley (2012), it was suggested that several commonly used anxiety measures were weighted heavily with somatic symptoms. This is seen as problematic given that somatic symptoms, which are often measured as part of anxiety (e.g., Bártolo, 2017) or depression (Therrien & Hunsley, 2012), may be a function of normal ageing – owing either to physical health conditions or to the side effects of certain medications, rather than a function of anxiety or depression themselves (Therrien & Hunsley, 2012). These findings once again hint at the possibility that certain aspects of anxiety and/or depression might be associated with cognitive decline, while other aspects are not. If this is the case, this might account for why studies examining the link between anxiety and depression, and cognition have yielded inconsistent findings.

While several studies have investigated the subtypes of depression and anxiety respectively in the general population, as far as we are aware, very few studies have examined the heterogeneity within *both* depression and anxiety symptoms, especially in the older adult population. Most previous studies have tended to examine *either* anxiety *or* depression respectively, and their link with cognition, and not their co-occurrence (John et al., 2019). This

is particularly important given that there is a high rate of co-morbidity between anxiety and depression in the older adult population (Schoevers et al., 2005), and because the concept of RNT spans aspects of both depression and anxiety (Marchant & Howard, 2015). Furthermore, it is also the case that in some studies examining depression and anxiety respectively, as risk factors for cognitive decline/dementia, the presence of the other (e.g. studies examining the link between anxiety and cognition do not control for depression) was often not controlled for (John et al., 2019). Having said that, controlling for the other may lead to over-correction given its high rate of co-occurrence (Gulpers et al., 2019). This could mean, therefore, that what was being detected might have been the effect of co-morbid depression and anxiety on cognition, rather than depression or anxiety itself. Latent Variable Mixture Modelling (LVMM; Berlin et al., 2014), which includes Latent Class Analysis (LCA), is a clustering approach by which participants can be subtyped based on their response patterns across *multiple* outcome measures. This has particular advantages over more traditional variable-centered approaches (e.g., multiple regression), which struggle to model large numbers of potentially interacting independent variables (Saunders et al., 2020; Aiken et al., 1991). This is crucial as it may be that understanding the potential constellations of co-occurring depression and anxiety symptoms may yield more value in understanding the relationship between affective symptoms and cognitive decline.

Previous studies in the general adult population have found distinct subgroups within affective symptoms of both depression and anxiety. One such study, which included 25 mood and anxiety items, found a 7-class solution that consisted of depression and anxiety subgroups of varying severity, a worry subgroup, and co-morbid depression/anxiety subgroups of varying severity (Rudenstine & Espinosa, 2018). Another study (Unick et al.,

2009) found meaningful heterogeneity in the presentation of co-morbid major depressive disorder and generalised anxiety disorder, resulting in a 7-class solution including a 'somatic anxiety' group, a 'somatic depression' group, a 'psychological mixed anxiety/depression' group, and a 'somatic mixed anxiety/depression' group – although this study measured lifetime occurrence of anxiety/depression and not necessarily its simultaneous co-occurrence, which is the focus of the present study. However, as far as we are aware, no studies have examined such subgroups of affective symptoms within a sample that is limited to those aged 50 and above. Furthermore, to the best of our knowledge, no studies have examined the heterogeneity within affective symptoms specifically using items of the PHQ-9 (Patient Health Questionnaire; Kroenke et al., 2001) and GAD-7 (Generalised Anxiety Disorder Scale; Spitzer et al., 2006), which in the context of the UK, has particular advantages given its applicability in the IAPT (Improvement to Access in Psychological Therapies) service.

The present study aimed to address these gaps in the literature. The first aim was to conduct a Latent Class Analysis (LCA) in order to identify distinct subgroups of individuals based on their responses on a measure of depression (PHQ-9) and anxiety (GAD-7). Based on previous studies, it was tentatively hypothesised that we might find distinct subgroups that differ by symptom severity (e.g., mild, moderate, high) and/or symptom type (e.g., somatic-only, anxiety-only, depression-only, co-morbid anxiety and depression). The second aim of this study was to investigate whether identified classes were differentially associated with cognitive decline. The general hypothesis was that the extent of cognitive decline would differ across classes. Identifying subgroups of adults (aged 50 and above) based on their affective symptom profiles, who might be particularly at-risk of subsequent cognitive decline, may

allow for targeted prevention programs further upstream that aim to prevent or delay cognitive decline.

Method

Study Design and Participants

The present study utilised a longitudinal dataset from the ongoing PROTECT study (www.protectstudy.org.uk), which was launched in 2015 (Huntley et al., 2018). The primary aim of the PROTECT study was to examine age-related changes to the brain in the context of aging. Inclusion criteria for the PROTECT study include: adults living in the UK over the age of 50, have a good understanding of the English language, and are able to use a computer with internet access. Participants who had a known diagnosis of dementia were excluded from the study. The present study utilised data (*N* = 24,012) over a 2-year follow-up period, from the 1st wave (baseline; T1) and the 3rd wave (follow-up; T2) of data collection. Ethical approval for this study was granted by the UK London Bridge National Research Ethics Committee (Ref: 13/LO/1578).

Recruitment and Procedure

Participants were recruited via a widely publicised media campaign, and via GP practices and memory clinics. Participants who were interested in taking part in the study were asked to register their interest online, and to download the study information sheet. Consent for the study was then requested through an approved online platform. Participants were asked to complete a series of online self-report questionnaires annually, including sociodemographic information, lifestyle, and mental health measures. In addition, they were

asked to complete a battery of online cognitive assessments. The cognitive tests took approximately half an hour to complete.

Measures

Depression

Depression symptoms were assessed using the PHQ-9 (Kroenke et al., 2001). There were nine items in total, each rated on a scale ranging from 0-3 (“0” = not at all; “1” = several days; “2” = more than half the days; “3” = nearly every day). A higher score indicates more severe depressive symptoms. The PHQ-9 has been found to be a valid and reliable scale measure of depression symptoms in the general population (Kroenke et al., 2001) and in the older adult population (Zhang et al., 2020).

Anxiety

Anxiety symptoms were assessed using the GAD-7 (Spitzer et al., 2006). There were seven items in total, each rated on a scale ranging from 0-3 (“0” = not at all; “1” = several days, “2” = more than half the days, “3” = nearly every day). A higher score indicates more severe anxiety symptoms. The GAD-7 has been found to be a valid and reliable measure of anxiety symptoms in the general population (Löwe et al., 2008) and in the older adult population (Wild et al., 2014).

Cognitive measures

Participants were asked to complete a battery of cognitive measures that included four tasks – Digit Span, Paired Associate Learning, Spatial Working Memory, and Verbal Reasoning. These online cognitive tests used the previously published test paradigms, and is

based on validated 'pen and paper' cognitive tests, adapted for online use (Owen et al., 2010). These online tests have been found to be valid (Corbett et al., 2015) and reliable (Wesnes et al., 2017). Participants were asked to attempt each measure three times over seven days, ensuring there is at least 24 hours before each session. The scores from successfully completed attempts were then averaged to compute a total summary score for each cognitive domain. A complete description of these cognitive tasks has been described elsewhere (Corbett et al., 2015; Huntley et al., 2018; Owen et al., 2010), but a brief description of each task is provided below:

The Digit Span (DS) task was included to measure immediate recall and attention. Participants were asked to remember a sequence of digits that appeared on the screen. If they were able to recall the digits correctly and in the correct sequence, the next trial was one digit longer in length. If they were incorrect, the next trial was one digit shorter in length. The final score was calculated as the mean number of digits in successfully completed trials. Higher scores indicated better performance.

The Paired Associate Learning (PAL) task was included to measure episodic memory and new learning. In this task, participants were presented with a series of objects in their respective "window locations". They were then asked to remember the "window location" where they had seen each object appear. If they chose the correct "window location", they would move to the next level, where the number of objects would increase by one. Participants were allowed three attempts at each level. The final score was calculated by the average number of correct object-place associations in successfully completed trials. The PAL test has been found to be particularly sensitive to learning and memory deficits in Mild

Cognitive Impairment (Fowler et al., 1995) and the early stages of Alzheimer's disease (Bondi et al., 2009). Higher scores indicated better performance.

The Spatial Working Memory (SWM) task was included to measure aspects of executive function (working memory) using a self-ordered search task (Owen et al., 1990). Participants were asked to 'search' through a series of boxes presented on the screen until they found an object (e.g., diamond). For the next series, participants were asked again to find the hidden object, but crucially were told to remember that the hidden object would not be in the same location. The test was terminated after three errors were made. The final score was calculated from the mean number of boxes in successfully completed trials. Higher scores indicated better performance.

The Verbal Reasoning (VR) task was based on Baddeley's Grammatical Reasoning task, and has been found to be strongly correlated with measures of general intelligence (Baddeley, 1968). In this task, a sentence is shown at the bottom of the screen, and a square and a circle appears above this sentence. Participants are then asked to choose whether they think the sentence accurately describes the configuration of the circle and the square (e.g., "the square is bigger than the circle"). The total score was calculated from the number of correct answers provided in 180 seconds, whilst subtracting the number of errors that were made. The final score was calculated as the mean score across successfully completed trials. Higher scores indicated better performance.

Sociodemographic and Lifestyle measures

The following socio-demographic information were collected at each wave, and were categorised as follows in the analysis: gender (male vs. female), age, marital status (married/cohabiting/civil partnership vs. divorced/widowed/single), ethnicity (white vs. non-white), education (highest educational qualification: GCSE/A-levels/Diploma holders vs. degree holders), current employment status (employed vs. unemployed), lifestyle factors such as history of smoking (yes vs. no), frequency of alcohol consumption (less than once per week vs. more than once per week), physical activity ("participated in physical activity lasting at least 20 minutes that has left you out of breath in the last month": yes vs. no), and history of diagnosis of depression/anxiety (yes vs. no).

Statistical Analysis

Latent Class Analysis (LCA)

The analysis was conducted in two steps: First, a Latent Class Analysis (LCA) was performed. Unlike "variable-centered" approaches such as factor analysis, where the goal is to identify associations between variables that are seen to be common across individuals, LCA is considered a more "person-centered" approach, whereby the goal is to identify sub-groups within a particular population, based on individuals' pattern of responses on a series of multivariate categorical data (Saunders et al., 2020). The aim of LCA is to identify mutually exclusive classes of participants, each with its own set of response patterns, whereby classes are as homogeneous as possible, whilst trying to ensure that differences between classes are as large as possible. In this study, the LCA was conducted using data from participants who had complete data on the PHQ-9 and GAD-7 items at T1. The LCA therefore was performed on 16 items in total, which were all converted into binary indicators to reflect either the

presence or absence of each symptom. This was seen as preferential over severity of symptoms for two reasons: First, in order to identify possible subsyndromal symptoms that have been found to be missed in the older adult population, and yet have been associated with poorer health outcomes (Yuan et al., 2020). Second, due to the positively skewed distribution on the PHQ-9 and GAD-7 in this dataset, whereby a vast majority of participants scored "0" on most of the items. Fifty random sets of starting values were used. To identify the model of best fit, the Vuong-Lo-Mendell-Rubin Likelihood Ratio test (VLMR-LRT; Lo et al., 2001) and the Bootstrap Likelihood Ratio Difference test (B-LRT; Geiser, 2013) were performed. Both the B-LRT and the VLMR-LRT compare the current model (K) with the model with one less class (K-1). If this difference is statistically significant ($p < .05$), this indicates that the K model is a better fit than the K-1 model. If it is found to be non-significant, this indicates that the K-1 model is a better fit than the K model. Since there was no hypothesis on the precise number of classes, the analysis was conducted starting with a 2-class model, and increasing the number of classes by one until the VLMR-LRT became non-significant. The B-LRT was then used to confirm the K-1 model using a parametric bootstrap procedure (Geiser, 2013). This was complemented by evaluating model fit based on the following commonly-used fit indices: Akaike information criterion (AIC), the Bayesian Information Criterion (BIC), sample size adjusted BIC (Vrieze, 2012), and Entropy values. Smaller values of AIC and BIC, and larger values of Entropy, which reflects better separation between latent classes, indicate better model fit (Nylund et al., 2007). In the case of multiple possible class solutions, model interpretability and clinical relevance would be taken into consideration, as recommended in the literature (Nylund et al., 2007). Furthermore, classes with a prevalence of less than 5% were not considered as it has been argued that they may be of limited clinical relevance (Yuan et al., 2020).

Associations between Class Membership and Cognitive Outcomes

The second step, and main aim of this study, was to test whether identified class membership was associated with changes in cognition over time. Prior to this, associations between identified classes and various socio-demographic and lifestyle risk factors were examined using chi-square tests of independence for categorical variables, to identify potential covariates. These included gender, ethnicity, marital status, education level, employment status, alcohol consumption, smoking history, and physical activity. If any of these were found to be statistically significant, they were included as covariates in the regression model of the main analysis.

The main analysis involved performing a series of linear regressions to examine whether the affective symptom classes were associated with changes in cognition (measured by subtracting cognition scores at T1 from cognition scores at T2). This analysis therefore only included participants who had complete cognition data both at T1 and T2. Change in cognition score was used as the outcome because prior research has found cognitive *change* to improve the prediction of subsequent cognitive impairment over and above baseline cognition scores (Nation et al., 2019). The biggest class (which was hypothesised to be the group with the least symptoms given the sample under investigation) was used as the reference class in the analysis, and mean change in cognition for all other classes was compared to mean change in this reference class. In model 1, baseline cognition at T1 was included as a covariate to control for potential regression to the mean effects (Barnett et al., 2005). In model 2, the socio-demographic and lifestyle factors that were found to be significant from the chi-square tests (above) were additionally included in the model as covariates. The analysis was conducted

separately for each of the four cognitive domains. Prior to this analysis, the raw data and residuals were checked for normality by a visual inspection of the respective histograms and Q-Q plots. In addition, multicollinearity was assessed by inspecting Tolerance/VIF values.

All analyses were performed using MPLUS version 8.2 (Muthén & Muthén, 2017) and Rstudio 1.4.

Results

LCA of Affective Symptoms

The LCA analysed data from 21,684 participants who had complete data on the PHQ-9 and the GAD-7 at T1. Based on the fit indices (see Table 1 below), a number of potential solutions could be adopted. The VLMR-LRT and B-LRT became non-significant after running the 10-class model, which using this metric would mean that the 9-class model would be the most parsimonious model. However, as can be observed, from the 6-class solution onwards, the smallest class size was less than 5% of the total sample, and therefore the 5-class solution was preferred. This was complemented by a visual inspection of the scree-plot of the BIC and AIC values, both of which confirm that the 5-class solution could be considered a good fit (see Appendix H). The 5-class solution was also found to be clinically interpretable (see below).

Table 1

Fit criteria for latent class analysis (N = 21,684)

Classes	AIC	BIC	Adjusted BIC	Entropy	Log Likelihood	VLMR-LRT	B-LRT	% in each class
2	256958	257221	257117	0.904	-128446	<.001	<.001	69/31
3	248247	248647	248488	0.841	-124074	<.001	<.001	57/31/12
4	243704	244238	244026	0.822	-121785	<.001	<.001	54/22/13/11
5	**241349**	**242019**	**241752**	**0.774**	**-120590**	**<.001**	**<.001**	**41/27/13/9/10**
6	240413	241219	240898	0.771	-120105	<.001	<.001	35/30/12/10/9/4
7	239749	240691	240316	0.773	-119757	<.001	<.001	41/24/11/9/7/4/4
8	239222	240300	239871	0.775	-119476	<.001	<.001	36/25/9/6/7/6/4/4/4
9	238816	240030	239547	0.76	-119256	0.0021	0.0022	36/25/9/6/7/6/4/4/4
10	238566	239915	239378	0.755	-119114	0.061	0.063	36/23/9/7/6/4/4/4/4/3

The item response probabilities, which is the probability of the presence of any of the symptoms conditional on latent class membership, for the 5-class model are shown below in Table 2 and graphically illustrated in Figure 1. Based on these probabilities, the following labels were assigned to each class: Class 1 (*N* = 8,790; 40.5%) was labelled as “No symptoms”,

because it showed an absence of symptoms on almost all 16 items (Mean number of symptoms = 0.38). Class 2 (*N* = 5,845; 27.0%) was labelled as "Sleep", because it showed high response probabilities on items related to sleep and tiredness. Class 3 (*N* = 2,904; 13.4%) was labelled as "Sleep and Worry", because while it showed a similar response pattern to Class 2 on items related to sleep and tiredness, it also showed elevated probabilities on items related to worry such as feeling nervous, difficulties stopping worrying, worrying about different things, and having trouble relaxing. Class 4 (*N* = 2,031; 9.3%) was labelled as "Sleep and Anhedonia", because it also showed elevated probabilities on items related to sleep (as in Class 2) as well as on items related to anhedonia on the PHQ-9 such as loss of pleasure, feeling hopeless, and feeling like a failure. Class 5 (*N* = 2,114; 9.7%) was labelled as "Co-morbid Depression and Anxiety" because it showed elevated probabilities on a majority of the 16 items (Mean number of symptoms = 11.24), related to both depression and anxiety. The characteristics of each class, and whether each of these characteristics was significantly associated with class membership, are shown below in Table 3.

Table 2

Item response probabilities for 5-class model (N = 21,684)

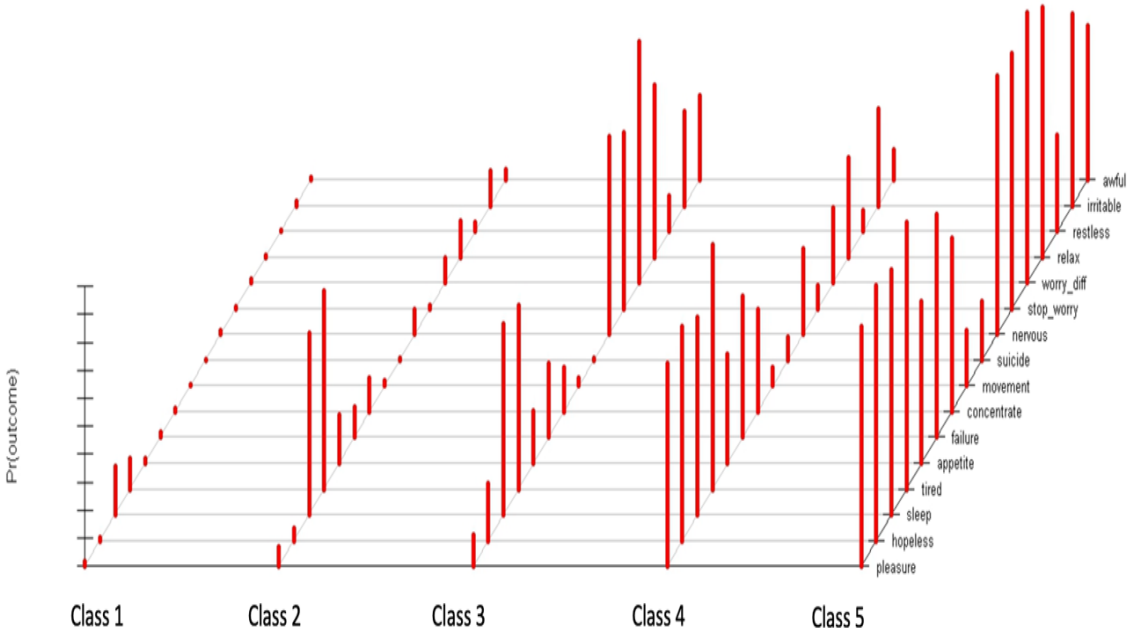
Items	Class 1	Class 2	Class 3	Class 4	Class 5
PHQ-9 items					
Pleasure	0.0133	0.0655	0.1075	**0.7237**	**0.8544**
Hopeless	0.0077	0.0416	0.2005	**0.7637**	**0.9108**
Sleep	0.1695	**0.6491**	**0.6787**	**0.7037**	**0.8716**
Tired	0.1067	**0.7069**	**0.6562**	**0.8691**	**0.9496**
Appetite	0.0154	0.1716	0.1842	0.3869	**0.5736**
Failure	0.0146	0.1073	0.2618	**0.5028**	**0.7941**
Concentration	0.0093	0.1185	0.1570	0.3616	**0.6201**
Movement	0.0011	0.0177	0.0251	0.0625	0.1968
Suicide	0.0008	0.0024	0.0052	0.0814	0.2047

GAD-7 items					
Nervous	0.0120	0.0848	**0.7061**	0.3052	**0.9205**
Stop_worry	0.0014	0.0082	**0.6270**	0.0773	**0.9118**
Worry_diff	0.0099	0.0871	**0.8589**	0.2651	**0.9619**
Relax	0.0038	0.1256	**0.6139**	0.3520	**0.8900**
Restless	0.0010	0.0292	0.1225	0.0730	0.3396
Irritable	0.0131	0.1213	0.3343	0.3428	**0.6811**
Awful	0.0048	0.0352	0.2994	0.1043	**0.5464**

Note. Item response probabilities > .50 are in **bold.** Items are presented here in the same order as in the original questionnaires (e.g., 'Pleasure' = PHQ-9 item 1 of 9, 'Awful' = GAD-7 item 7 of 7).

Figure 1

LCA plot showing item response probabilities for 5-class solution (N = 21,684)



Note. Items are arranged in the same order as in Table 2; from PHQ-9 item 1 (near) to GAD-7 item 7 (far).

As can be seen in Table 3 below, the classes differed by cognition at baseline, age, gender, marital status, education level, employment status, and alcohol consumption. As was expected, the classes also differed in terms of number of PHQ-9 and GAD-7 symptoms, total scores on the PHQ-9 and GAD-7, and history of depression/anxiety diagnosis. Class 1 ("No Symptoms") had the highest average age, highest proportion of participants who were married/cohabiting/in a civil partnership, highest proportion currently unemployed, highest proportion who drink alcohol more than once per week, lowest scores on the PHQ-9 and GAD-7, and lowest proportion of diagnosed depression/anxiety. Class 5 ("Co-morbid Depression & Anxiety"), on the other hand, had the lowest average age, the highest proportion of participants who were widowed/divorced/single, highest proportion of GCSE/A-levels/Diploma holders, highest proportion who drink alcohol less than once per week, highest proportion of those with smoking history, highest proportion of non-regular physical activity, highest scores on the PHQ-9 and GAD-7, and highest rates of history of depression/anxiety diagnosis. In addition, Class 5 generally had the lowest baseline cognition scores on all domains, except VR, and the highest rate of attrition (as defined as those who had cognition data at T1, but not at T2). Class 3 ("Sleep & Worry") had the highest proportion of female participants, highest proportion in current employment, highest proportion who participated in regular physical activity, and the lowest rate of attrition.

Table 3

Socio-demographic, lifestyle and clinical characteristics of the five classes

	Total ***N = 21684*** **(%)**	**Class 1** ***N* = 8790** **(40.5%)**	**Class 2** ***N* = 5845** **(27.0%)**	**Class 3** ***N* = 2904** **(13.4%)**	**Class 4** ***N* = 2031** **(9.3%)**	**Class 5** ***N* = 2114** **(9.7%)**	**X^2 / *F* & *p-value***
Socio-demographic characteristics							
Gender							
Female	15773 (73.7)	6034 (69.6)	4348 (75.4)	2376 (82.8)	1386 (69.4)	1629 (78.1)	X^2 (4) = 248.58, p <.001*
Male	5619 (26.3)	2639 (30.4)	1421 (24.6)	492 (17.2)	611 (30.6)	456 (21.9)	
Ethnicity							
White	21004 (98.2)	8527 (98.3)	5665 (98.2)	2812 (98.0)	1964 (98.3)	2036 (97.6)	X^2 (4) = 4.80, p =.31
Non-White	388 (1.8)	146 (1.7)	104 (1.8)	56 (2.0)	33 (1.7)	49 (2.4)	
Marital Status							
Married/Civil Partnership/ Cohabiting	15951 (74.6)	6670 (76.9)	4290 (74.4)	2169 (75.6)	1394 (69.8)	1428 (68.5)	X^2 (4) = 91.32, p <.001*
Widowed/Divorced/ Single	5441 (25.4)	2003 (23.1)	1479 (25.6)	699 (24.4)	603 (30.2)	657 (31.5)	
Education							
GCSE/A-levels/Diploma	10205 (47.7)	4110 (47.4)	2715 (47.1)	1329 (46.3)	959 (48.0)	1092 (52.4)	X^2 (4) = 21.75, p <.001*
Graduate	11187 (52.3)	4563 (52.6)	3054 (52.9)	1539 (53.7)	1038 (52.0)	993 (47.6)	
Employment							
Employed	9891 (46.2)	3551 (40.9)	2691 (46.6)	1484 (51.7)	1029 (51.5)	1136 (54.5)	X^2 (4) = 212.68, p <.001*
Unemployed	11501 (53.8)	5122 (59.1)	3078 (53.4)	1383 (48.3)	968 (48.5)	949 (45.5)	
Age at baseline Mean (SD)	61.30 (7.21)	62.22 (7.13)	61.33 (7.34)	60.51 (6.96)	60.41 (7.27)	59.32 (6.85)	F (4,21387) = 92.47, p <.001*
Lifestyle Characteristics							
Alcohol Consumption							
<once/week	8565 (39.5)	3222 (36.7)	2362 (40.4)	1114 (38.4)	858 (42.3)	1009 (47.8)	X^2 (4) = 99.91, p <.001*
>once/week	13101 (60.5)	5559 (63.3)	3481 (59.6)	1788 (61.6)	1171 (57.7)	1102 (52.2)	
Smoking History							
No	8838 (55.0)	3687 (55.6)	2374 (55.1)	1227 (55.5)	771 (53.5)	779 (52.4)	X^2 (4) = 6.65, p =.155
Yes	7235 (45.0)	2940 (44.4)	1934 (44.9)	984 (44.5)	669 (46.5)	708 (47.6)	
Physical Activity							
No	5323 (32.0)	2163 (31.8)	1423 (32.0)	691 (30.3)	502 (33.0)	544 (34.6)	X^2 (4) = 8.48, p =.075
Yes	11297 (68.0)	4632 (68.2)	3028 (68.0)	1588 (69.7)	1019 (67.0)	1030 (65.4)	
Baseline Clinical Characteristics							
DS Mean (SD)	7.40 (1.53)	7.46 (1.59)	7.41 (1.51)	7.36 (1.46)	7.35 (1.52)	7.21 (1.42)	F (4,19365) = 11.20, p <.001*
PAL Mean (SD)	4.51 (0.79)	4.52 (0.80)	4.51 (0.78)	4.48 (0.80)	4.51 (0.80)	4.44 (0.79)	F (4,19365) = 4.865, p <.001*
SWM Mean (SD)	7.46 (2.33)	7.52 (2.35)	7.53 (2.25)	7.38 (2.25)	7.49 (2.26)	7.10 (2.59)	F (4,19365) = 14.48, p < .001*
VR Mean (SD)	32.20 (9.32)	31.83 (9.29)	32.61 (9.24)	32.17 (9.23)	32.69 (9.35)	32.19 (9.72)	F (4,19365) = 6.86, p < .001*
PHQ-9 no. of symptoms Mean (SD)	2.03 (2.02)	0.35 (0.48)	2.13 (0.85)	2.23 (1.19)	4.60 (1.27)	6.01 (1.41)	F (4,6807) = 4.67 p < .001*

GAD-7 no. of symptoms Mean (SD)	1.31 (1.91)	0.03 (0.18)	0.59 (0.73)	3.67 (1.20)	1.50 (1.12)	5.26 (1.12)	*F* (4,6807) = 6.68, *p* < .001*
PHQ-9 total score Mean (SD)	2.67 (3.23)	0.42 (0.67)	2.64 (1.49)	2.79 (1.86)	5.87 (2.75)	8.83 (4.26)	*F* (4,6807) = 9.53, *p* < .001*
GAD-7 total score Mean (SD)	1.56 (2.64)	0.03 (0.19)	0.61 (0.80)	4.00 (1.83)	1.61 (1.31)	7.07 (3.54)	*F* (4,6807) = 2.47, *p* = .04*
History of depression/ anxiety diagnosis							
No	13608 (71.6)	6604 (79.9)	3761 (71.6)	1546 (64.2)	1067 (61.9)	630 (46.9)	X^2 (4) = 19.98, *p* <.001*
Yes	5386 (28.4)	1664 (20.1)	1491 (28.4)	861 (35.8)	656 (38.1)	714 (53.1)	
Attrition							
Cognition only available at T1	12558 (64.8)	4995 (63.7)	3454 (65.5)	1645 (63.3)	1196 (66.4)	1268 (68.1)	X^2 (4) = 19.01, *p* <.001*
Cognition available at T1 and T2	6812 (35.2)	2845 (36.3)	1817 (34.5)	953 (36.7)	604 (33.6)	593 (31.9)	

Note. Absolute number of participants down the column do not always add up to column total because of missing values. X^2 test statistics are presented for categorical variables, *F*- test statistics for continuous variables. Significant between-class differences denoted as *p <.05.

Is Class Membership Associated with Cognitive Decline?

In order to test whether the LCA classes were differentially associated with changes in cognition from T1 to T2, a series of multiple linear regressions were conducted with class membership as the main predictor (reference class: "No symptoms"), and change in cognition (all four cognitive domains) between T1 and T2 as the outcome. Cognition at T1 and socio-demographic and lifestyle factors that were found to be significantly associated with class membership (see Table 3) were additionally controlled for. Only participants who had cognition data both at T1 and T2 were included in this analysis. Out of the 21,684 participants that were included in the LCA, 19,370 participants had complete cognition data at T1, of which 6,812 participants had complete cognition data both at T1 and T2. With reference to Table 4 below, those who did not have cognition data available at T2 were more likely to be younger, non-white, GCSE/A-levels/Diploma holders, employed, and have lower alcohol consumption, lower baseline cognition (SWM and VR), higher average number of PHQ-9 symptoms and GAD-7 symptoms, higher total scores on the PHQ-9 and GAD-7, and higher rates of history of depression/anxiety diagnosis.

Table 4

Socio-demographic, lifestyle, and clinical characteristics of participants who had available cognition data at T1 only compared to those who had available cognition data at T1 and T2

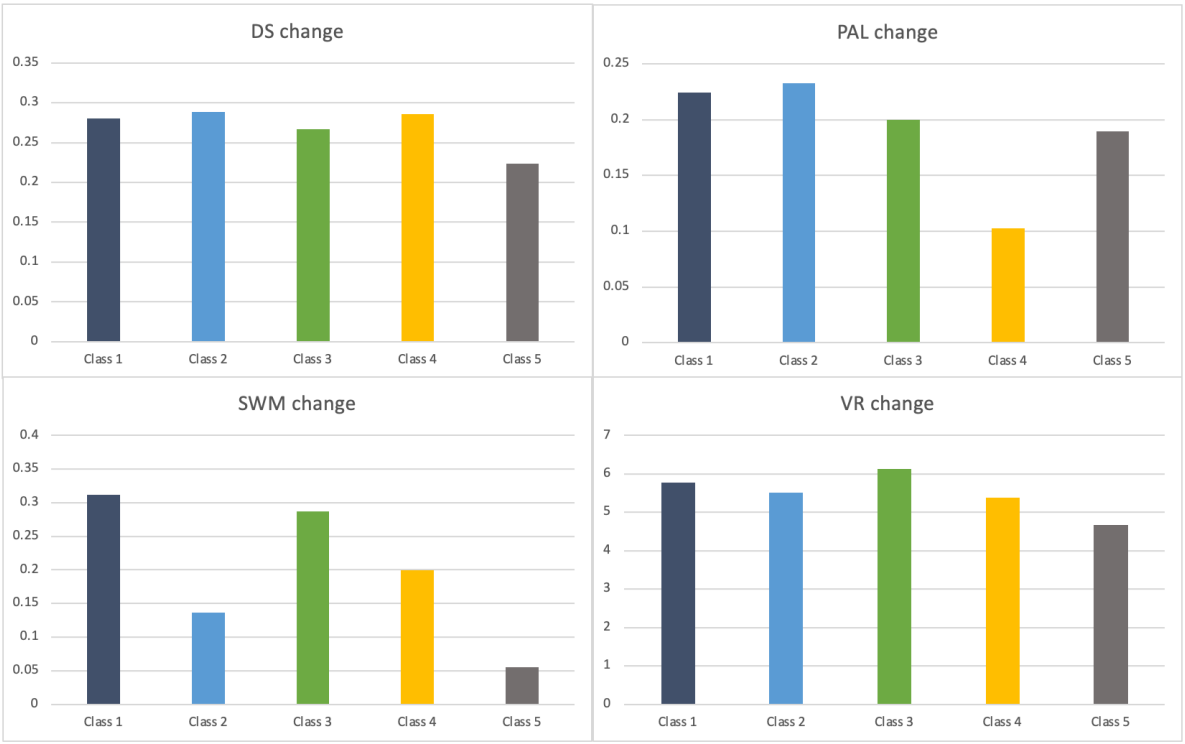
	Cognition data available at T1 only (*N* = 12,558)	**Cognition data available at T1 & T2 (*N* = 6,812)**	***X²* / *t* & *p-value***
	***N* (%)**	***N* (%)**	
Socio-demographic Characteristics			
Gender			
Female	9272 (73.8)	5023 (73.7)	X^2 (1) = 0.02, *p* = .898
Male	3286 (26.2)	1789 (26.3)	
Ethnicity			
White	12311 (98.0)	6714 (98.6)	X^2 (1) = 6.75, *p* = .009*
Non-White	247 (2.0)	98 (1.4)	
Marital Status			
Married/Civil Partnership/Cohabiting	9399 (74.8)	5084 (74.6)	X^2 (1) = 0.09, *p* = .759
Widowed/Divorced/Single	3159 (25.2)	1728 (25.4)	
Education			
GCSE/A-levels/Diploma	6075 (48.4)	3121 (45.8)	X^2 (1) = 11.50, *p* <.001*
Graduate	6483 (51.6)	3691 (54.2)	
Employment			
Employed	5952 (47.4)	2953 (43.3)	X^2 (1) = 28.95, *p* <.001*
Unemployed	6606 (52.6)	3859 (56.7)	
Age at baseline Mean (SD)	61.10 (7.27)	61.79 (7.02)	*t* (14389) = 6.42, *p* <.001*
Lifestyle Characteristics			
Alcohol Consumption			
<once/week	5015 (40.0)	2585 (38.0)	X^2 (1) = 7.29, *p* =.007*
>once/week	7533 (60.0)	4223 (62.0)	
Smoking History			
No	4555 (54.4)	3541 (55.6)	X^2 (1) = 2.11, *p* =.15
Yes	3821 (45.6)	2828 (44.4)	
Physical Activity			
No	2799 (32.2)	2082 (31.8)	X^2 (1) = 0.23, *p* = .62
Yes	5885 (67.8)	4456 (68.2)	
Baseline Clinical Characteristics			
DS Mean (SD)	7.39 (1.55)	7.41 (1.49)	*t* (14509) = 0.97, *p* = .332
PAL Mean (SD)	4.50 (0.82)	4.52 (0.75)	*t* (14960) = 1.69, *p* = .090
SWM Mean (SD)	7.39 (2.44)	7.59 (2.11)	*t* (15787) = 6.02, *p* <.001*
VR Mean (SD)	32.09 (9.54)	32.41 (8.91)	*t* (14812) = 2.30, *p* = .021*
PHQ no. of symptoms Mean (SD)	2.07 (2.05)	1.94 (1.96)	*t* (14505) = 4.56, *p* <.001*
GAD no. of symptoms Mean (SD)	1.33 (1.93)	1.28 (1.87)	*t* (14370) = 1.80, *p* = .071
PHQ-9 total score Mean (SD)	2.74 (3.27)	2.49 (2.98)	*t* (15142) = 5.48, *p* <.001*
GAD-7 total score Mean (SD)	1.57 (2.64)	1.49 (2.53)	*t* (14499) = 2.02, *p* = .044*
History of depression/ anxiety diagnosis			
No	7774 (71.1)	4427 (73.0)	X^2 (1) = 6.86, *p* = .008*
Yes	3163 (28.9)	1639 (27.0)	

Note. Absolute number of participants down the column do not always add up to column total because of missing values. X^2 test statistics are presented for categorical variables, *t*-test statistics for continuous variables. Significant between-group differences denoted as *p <.05.

As seen in Figure 2 below, the mean change scores between T1 and T2 for all five classes on all four cognitive domains were all in the positive direction (exact means and standard deviations can be found in Appendix I). As shown in Table 5 below, after adjusting for all potential confounders, Class 5 ("Co-morbid Depression and Anxiety") was consistently associated with significantly smaller increases in cognition compared to Class 1 (reference group: "No symptoms") on all four cognitive domains. As compared to Class 1, Class 3 ("Sleep and Worry") was associated with significantly smaller increases on PAL and SWM, but not for DS and VR; Class 2 ("Sleep") was associated with significantly smaller increases on SWM, but not for DS, PAL and VR; Class 4 ("Sleep and Anhedonia") was associated with significantly smaller increases on PAL, but not for DS, SWM and VR.

Figure 2

Mean change in cognition on all cognitive domains between T1-T2 across all classes



Note. Change was calculated by subtracting T1 cognition score from T2 cognition score. Positive (+ve) change indicates improvement in cognitive test performance over time. See Appendix I for exact values.

Table 5

Main regression analysis assessing associations between class membership and cognitive change over 2-year follow up by cognitive domain

		Model 1[a]			Model 2[b]		
Domains	**Class Comparisons (ref class: Class 1)**	**Coeff**	**p-value**	**95% CI**	**Coeff**	**p-value**	**95% CI**
Digit Span (DS)	**1v2 ("Sleep")**	-0.027	.431	(-0.094 , 0.040)	-0.031	.369	(-0.098 , 0.036)
	1v3 ("Sleep & Worry")	-0.023	.578	(-0.105 , 0.059)	-0.036	.395	(-0.118 , 0.047)
	1v4 ("Sleep & Anhedonia")	-0.021	.675	(-0.119 , 0.077)	-0.032	.532	(-0.131 , 0.067)
	1v5 ("Depression & Anxiety")	-0.148	.004*	(-0.247 , -0.049)	-0.164	.001*	(-0.265 , -0.064)
Paired Associate Learning (PAL)	**1v2 ("Sleep")**	-0.016	.450	(-0.057 , 0.025)	-0.030	.155	(-0.071 , 0.011)
	1v3 ("Sleep & Worry")	-0.045	.097	(-0.098 , 0.008)	-0.079	.004*	(-0.132 , -0.026)
	1v4 ("Sleep & Anhedonia")	-0.115	<.001*	(-0.178 , -0.052)	-0.139	<.001*	(-0.202 , -0.076)
	1v5 ("Depression & Anxiety")	-0.100	.002*	(-0.163 , -0.037)	-0.138	<.001*	(-0.202 , -0.074)
Spatial Working Memory (SWM)	**1v2 ("Sleep")**	-0.183	.001*	(-0.295 , -0.072)	-0.204	<.001*	(-0.314 , -0.094)
	1v3 ("Sleep & Worry")	-0.085	.232	(-0.225 , 0.054)	-0.145	.042*	(-0.284 , -0.005)
	1v4 ("Sleep & Anhedonia")	-0.062	.471	(-0.231 , 0.107)	-0.141	.101	(-0.310 , 0.028)
	1v5 ("Depression & Anxiety")	-0.424	<.001*	(-0.597 , -0.252)	-0.516	<.001*	(-0.609 , -0.343)
Verbal Reasoning (VR)	**1v2 ("Sleep")**	-0.236	.200	(-0.598 , 0.125)	-0.332	.069	(-0.690 , 0.026)
	1v3 ("Sleep & Worry")	0.397	.090	(-0.062 , 0.856)	0.126	.592	(-0.334 , 0.585)
	1v4 ("Sleep & Anhedonia")	-0.342	.215	(-0.883 , 0.199)	-0.422	.127	(-0.963 , 0.119)
	1v5 ("Depression & Anxiety")	-1.058	<.001*	(-1.609 , -0.507)	-1.194	<.001*	(-1.749 , -0.639)

*Note. * p < .05; Coeff = Unstandardised Beta Coefficients; CI = Confidence Intervals.*

[a] Model 1 compares classes controlling for baseline cognition at T1.

[b] Model 2 additionally controls for gender, marital status, education, employment status, age and alcohol consumption.

Post-hoc analyses were conducted to test if the "Sleep and Worry" group experienced significantly smaller increases in cognition compared to the "Sleep" group, so as to test the potential additional effect of worry (over and above sleep difficulties) on cognition. Similar comparisons were also conducted between the "Sleep and Anhedonia" group, and the "Sleep" group. This would test the potential additional effect of anhedonia symptoms (over and above sleep difficulties). Finally, the "Co-morbid Depression and Anxiety" group was compared to both the "Sleep and Anhedonia" group and the "Sleep and Worry" group, in order to assess the additional effect of having co-morbid depression and anxiety symptoms, as compared to just having either one.

Table 6

Post-hoc analyses assessing differences between other specified (see above) comparisons

Comparisons[c]	Domains	Model 1[a]			Model 2[b]		
		Coeff	p-value	95% CI	Coeff	p-value	95% CI
2v3 ("Sleep" vs "Sleep & Worry")	DS	0.003	.954	(-0.085 , 0.090)	-0.010	.832	(-0.098 , 0.079)
	PAL	-0.027	.325	(-0.082 , 0.027)	-0.051	.066	(-0.105 , 0.003)
	SWM	0.099	.198	(-0.052 , 0.250)	0.082	.288	(-0.069 , 0.232)
	VR	0.627	.014*	(0.128 , 1.126)	0.432	.087	(-0.063 , 0.928)
2v4 ("Sleep" vs "Sleep & Anhedonia")	DS	0.006	.915	(-0.098 , 0.109)	-0.004	.942	(-0.108 , 0.100)
	PAL	-0.098	.002*	(-0.161 , -0.035)	-0.112	<.001*	(-0.175 , -0.050)
	SWM	0.120	.195	(-0.061 , 0.300)	0.071	.440	(-0.109 , 0.251)
	VR	-0.109	.709	(-0.684 , 0.465)	-0.150	.605	(-0.720 , 0.420)
3v5 ("Sleep & Worry" vs "Co-morbid Depression & Anxiety")	DS	-0.123	.026*	(-0.231 , -0.015)	-0.138	.013*	(-0.246 , -0.029)
	PAL	-0.066	.079	(-0.140 , 0.008)	-0.068	.070	(-0.142 , 0.006)
	SWM	-0.340	.002*	(-0.552 , -0.128)	-0.365	.001*	(-0.578 , -0.152)
	VR	-1.453	<.001*	(-2.139 , -0.766)	-1.385	<.001*	(-2.075 , -0.695)
4v5 ("Sleep & Anhedonia" vs "Co-morbid Depression & Anxiety")	DS	-0.125	.039*	(-0.243 , -0.006)	-0.121	.045*	(-0.238 , -0.003)
	PAL	0.012	.773	(-0.068 , 0.092)	0.009	.819	(-0.070 , 0.089)
	SWM	-0.362	.004*	(-0.610 , -0.114)	-0.356	.005*	(-0.603 , -0.109)
	VR	-0.725	.056	(-1.468 , 0.018)	-0.762	.044*	(-1.504 , -0.019)

*Note. * p < .05; Coeff = Unstandardised Beta Coefficients; CI = Confidence Intervals.*

[a] Model 1 compares classes while controlling for baseline cognition at T1.

[b] Model 2 additionally controls for gender, marital status, education, employment status, age and alcohol consumption.

[c] Reference class is always the class mentioned first e.g., Class 2 vs. 3 (Class 2 is the ref class).

As seen in Table 6 above, the post-hoc analyses found that there were no significant differences between the "Sleep" group and the "Sleep and Worry group" on all the cognitive domains. The "Sleep and Anhedonia" group experienced significantly smaller increases compared to the "Sleep" group on PAL, but not on the other cognitive domains. The "Co-morbid Depression and Anxiety" group experienced significantly smaller increases compared to the "Sleep and Anhedonia" group and the "Sleep and Worry" group on all cognitive domains except for PAL. Additional class comparisons that are not shown here were also run as exploratory analyses, and can be found in the Appendix J.

Discussion

The aim of the present study was twofold: First, the aim was to investigate whether there were distinct subgroups of participants based on the presence or absence of 16 depression (PHQ-9) and anxiety (GAD-7) symptoms. Results found five classes that differed largely in terms of symptom type: “No symptoms” (Class 1), “Sleep” (Class 2), “Sleep and Worry” (Class 3), “Sleep and Anhedonia” (Class 4), and “Co-morbid Depression and Anxiety” (Class 5). These results reflect both the distinct nature of depression and anxiety symptoms, and at the same time the degree of heterogeneity within, and comorbidity between, depression and anxiety. These subgroups were largely consistent with our hypothesis, which was based on previous studies that have conducted an LCA taking into consideration both depression and anxiety symptoms (e.g., Rudenstine & Espinosa, 2018; Unick et al., 2009), except for the identification of a “Sleep” subgroup in the present study. Previous studies have tended to find a subgroup with sleep difficulties either in the context of other somatic symptoms such as lack of concentration and psychomotor agitation, or sleep difficulties in the context of other affective symptoms such as depression (similar to Class 4 in the current study). One explanation for the “Sleep”-only subgroup could be due to the current sample being limited to adults over the age of 50 (rather than the general adult population). Older adults are known to have an increased prevalence of sleep difficulties (Foley et al., 2004). Indeed, in the present study, it was observed that there was a slight elevation in items pertaining to sleep and tiredness even in the “No symptoms” group.

The second and main aim was to investigate if the classes of affective symptoms were associated with declines in cognition over a 2-year period. As observed in Figure 2, rather than declines in cognition, what was observed instead was general increases in cognition,

although this varied between classes and by cognitive domain. This increase in cognitive scores was likely to be due to practice effects that represent the expected improvement in cognitive test performances as a function of repeated testing in the absence of intervention (Salthouse, 2010), and are common in repeated neuropsychological testing (Goldberg et al., 2015). The attenuation or absence of practice effects have been found to be indicative of future cognitive impairment. In a systematic review conducted by Jutten et al. (2020), they found consistent evidence that less robust practice effects was an indicator of both current cognitive status and future cognitive decline, and that attenuated practice effects were also associated with the presence of biomarkers that were indicative of neurodegeneration. The results of the present study were therefore interpreted in light of this.

In comparison to the reference group ("No symptoms"), all other classes showed significantly smaller increases in at least one cognitive domain; The "Sleep" group showed significantly smaller increases on SWM, the "Sleep and Worry" group showed significantly smaller increases on SWM and PAL, the "Sleep and Anhedonia" group showed significantly smaller increases on PAL, and the "Co-morbid Depression and Anxiety" group showed significant smaller increases on all four cognitive domains. These results remained significant even after adjusting for cognition at T1, age, gender, marital status, education, employment, and alcohol consumption. Overall, this suggests that the presence of affective symptoms (both sleep and cognitive-emotional symptoms) were significantly associated with cognitive changes over a 2-year period. The finding that sleep difficulties were associated with significantly smaller increases in cognition was not specifically hypothesised a priori, because it was not possible to know beforehand the outcome of the LCA. Nevertheless, this finding is consistent with previous studies that have found sleep disturbances to be highly prevalent in

early-stage dementia (Rongve et al., 2010) and associated with subsequent diagnosis of dementia (Sabia et al., 2021), as well as related to specific deficits in the area of working memory in the younger age group (Peng et al., 2020) and among older adults (Okuda et al., 2021).

There was also some evidence that having co-morbid depression and anxiety symptoms was associated with the greatest risk to cognition. Post-hoc analyses found that the "Co-morbid Depression and Anxiety" group experienced significantly smaller increases compared to the "Sleep and Anhedonia" group and the "Sleep and Worry" group on all cognitive domains except for PAL. Given that RNT spans both depression and anxiety, one might expect co-morbid depression and anxiety symptoms to have a greater impact on cognition compared to having *either* one. This therefore provides support for the concept of RNT (Marchant & Howard, 2015), and hints at the potential increased risk associated with having co-morbid anxiety and depression symptoms, over and above depression symptoms alone or anxiety symptoms alone. However, it is unclear whether this is due solely to the presence of co-morbid symptoms or due to the increased severity of symptoms. These tend to be highly correlated and often difficult to tease apart, and therefore warrants further exploration.

The "Sleep and Worry" group did not experience significantly smaller increases in cognition compared to the "Sleep" group on all four cognitive domains, contrary to what one might expect. On the other hand, the "Sleep and Anhedonia" group was found to experience significantly smaller increases compared to the "Sleep" group on PAL. Put together, these findings were largely consistent with the findings of Bierman et al. (2005), who found that

mildly elevated anxiety levels actually had a protective effect on cognition, whereas depression at all levels was consistently associated with cognitive decline. The finding that the "Sleep and Anhedonia" group experienced significantly smaller increases compared to the "Sleep" group on PAL might indicate that the cognitive-emotional symptoms of depression was associated with poorer episodic memory, over and above sleep difficulties, which is consistent with the findings of Korten et al. (2014), who found that the depression dimensions of 'motivation' and 'apathy' were particularly associated with poorer episodic memory. Given that a literature review found anhedonia to be closely associated with RNT (Burrows-Kerr, 2015), this provides tentative support once again for the link between RNT and cognitive decline (Marchant & Howard, 2015).

A notable finding was that the "Sleep and Anhedonia" group experienced significantly smaller increases in cognition even as compared to the "Co-morbid Depression and Anxiety" group on PAL (even though this difference was not statistically significant), contrary to expectations. In all other domains, the "Co-morbid Depression and Anxiety" group showed the least increases in cognition over time. One potential explanation for this could be that depression particularly hinders episodic memory and new learning, which is assessed by the PAL task. This is in line with the findings of Javaherian et al. (2019), which found in a sample of preclinical Alzheimer's disease participants, that depression symptoms were associated with poorer cognition in the domain of episodic memory, but not in the domains of executive function, language or processing speed. However, one could argue that this should similarly apply to the "Co-morbid Depression and Anxiety" group. One potential explanation for why the "Co-morbid Depression and Anxiety" group saw greater improvements relative to the "Sleep and Anhedonia" group on PAL could again be due to the potential protective effect of

mild anxiety, which might have 'counter-balanced' the effects of depression (Bierman et al., 2005), specifically in the domain of episodic memory. An alternative explanation might be that having "Co-morbid Depression and Anxiety" symptoms is not merely a more 'severe' form of having only Depression symptoms, but may represent a completely heterogeneous subtype with its own aetiology, which may not impact episodic memory to the same extent as other domains. Given that episodic memory deficits are most commonly associated with Alzheimer's disease (Vos et al., 2013), this is worth further research.

Overall, this study demonstrates firstly that there is heterogeneity based on affective symptom response patterns in a sample of adults aged 50 and above, and class membership was associated with changes in different cognitive domains. The study found that all four symptomatic classes ("Sleep", "Sleep and Worry", "Sleep and Anhedonia" and "Co-morbid Depression and Anxiety") were associated with smaller increases in cognition on at least one cognitive domain compared to the "No symptoms" class. Furthermore, a fairly consistent finding was that having co-morbid depression and anxiety symptoms was associated with the greatest risk to cognition. Overall, the observed heterogeneity within co-occurring symptoms of depression and anxiety may be one explanation for the mixed findings in the literature concerning the link between anxiety and/or depression, and cognition.

Clinical Implications

First, the present study provides evidence in favour of there being considerable heterogeneity within affective symptoms of depression and anxiety in a sample of adults over the age of 50, and that even sub-clinical symptoms may have a longitudinal impact on cognition. This is particularly useful for clinicians, given that sub-clinical levels of affective

symptoms are often overlooked, but are extremely common in the older adult population (Laborde-Lahoz et al., 2015). The present study suggests therefore that clinicians should be encouraged not just to look out for total symptom scores on a *single* affective domain (ie. depression *or* anxiety) that meet clinical cut-offs, but to look for the presence of *patterns* of symptoms (even if sub-clinical) on measures across *multiple* affective symptoms (ie. depression *and* anxiety). Second, the finding that different patterns of affective symptoms were related to different cognitive domains also has clinical implications. For example, there is considerable evidence that episodic memory (measured by the PAL task) is commonly impacted in Alzheimer's disease (Tromp et al., 2015). Therefore, for example, it could be suggested that the "Sleep" group may be at less risk of Alzheimer's disease compared to when sleep difficulties occur in the context of anhedonia ("Sleep and Anhedonia" group). This is especially useful when trying to identify particular at-risk groups for the purposes of early cognitive intervention. Furthermore, if deficits in certain cognitive domains are found to be more predictive of certain types of neurodegenerative disease (e.g., Lewy body, frontotemporal dementia), then affective profiles more highly associated with those cognitive domains could be targeted for early intervention or diagnosis. It should be noted however that because cognition was used as an outcome, rather than dementia diagnosis, any conclusions in relation to neurodegenerative disease is made tentatively. An incidental, but perhaps useful finding, was that class membership was associated with drop-out rate. Knowing which subgroups were more or less likely to drop-out may provide an indication as to the likelihood of them engaging with online interventions and platforms, which are becoming increasingly popular (Huntley et al., 2018).

Strengths and Limitations

The present study has several strengths. First, as far as we are aware, this is the first study that has conducted an LCA specifically on the PHQ-9 and GAD-7. This is a particular strength given that these two questionnaires are used routinely as outcome measures in primary mental health care services such as Improving Access to Psychological Therapies (IAPT) services in the UK, and therefore these findings can be easily translated into the IAPT context. Second, to the best of our knowledge, this is also the first study that has assessed for subtypes of affective symptoms exclusively amongst adults aged 50 and above. This has particular advantages given that adults in older age groups may experience different types of affective symptoms compared to the general adult population. At the same time, assessing participants from as early as age 50 and above (rather than e.g., age 65 and above) may allow for the detection of very early cognitive changes, which is of clinical importance given that dementia is known to have a long prodromal period (Bilgel et al., 2017). Third, the large sample size ensured that there was sufficient statistical power to detect small effect sizes. Fourth, the longitudinal design allowed us to model cognitive change over time, rather than just at a single time point.

However, the findings of this study should also be interpreted in light of the following limitations. First, given that the PROTECT study used an online platform, all data collected were completely by self-report, with no possibility of objectively verifying participants' responses. Second, the sample included in the PROTECT study may not be entirely representative of the general population. For example, the sample was largely ethnically homogenous, females consisted of more than 70% of the sample, and more than 50% of the sample were graduates. This may limit the generalisability of these findings. Furthermore,

there was large selective attrition between baseline and follow-up in this study, which could further reduce generalisability. Third, the sample could generally be described as a relatively 'healthy' sample. For instance, the overall sample had extremely low levels of depression or anxiety symptoms, and thus there was a heavy positive skew. While it was because of this positive skew on PHQ-9 and GAD-7 symptoms that a decision was taken to dichotomise the variables, this may have resulted in a loss of information. However, given that it was extremely rare for someone to have any severe symptoms in this 'healthy' sample, the benefits of dichotomisation seemed to outweigh the disadvantages. Fourth, while participants with a diagnosis of dementia were excluded from the study, it is well-known that pre-clinical dementia begins up to 15 years before symptoms may be observed (Bilgel et al., 2017). Therefore, it remains a possibility that some of the participants in the study may already present with underlying neuropathology that they were unaware of. Finally, due to the exploratory nature of this study, multiple comparisons were not controlled for, due to the risk of inflating Type II error (Perneger, 1998). However, it should be noted that a majority of the comparisons were significant at the $p < .01$ level, and these exploratory findings should stimulate further research into the role of depression and anxiety in cognitive decline.

Future directions

Future studies could aim to replicate the current analysis in clinical samples, and with longer follow-ups. First, this would allow for assessing whether different affective classes are associated with different trajectories of cognitive decline over a longer time period, and additionally whether they predict conversion to mild cognitive impairment or dementia. Second, longer follow-ups will be able to assess whether latent class membership remains static or is more dynamic, as this may have implications for their associated cognitive

trajectories. Third, longer follow-ups will also be able to test whether the practice effects are sustained over time, as the lack of *sustained* practice effects have been found to be predictive of subsequent cognitive decline (Machulda et al., 2017). Future research should also examine whether different symptom classes may represent different underlying neuropathology, and whether they represent different pathways to cognitive impairment. These may help to ascertain the direction of causality, i.e. whether the affective symptoms are a prodrome or indeed a risk factor for cognitive impairment, and to elucidate potential mechanisms between affective symptoms and cognitive decline.

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Part 3: Critical Appraisal

Introduction

This critical appraisal includes my personal reflections in relation to both the literature review and the empirical study. Given that the COVID-19 pandemic spanned the majority of my thesis journey (and sadly beyond), my reflections have undoubtedly been influenced by my experiences and thoughts during the past year in 'lockdown'. My reflections on the literature review will focus on first, the increased relevance of the topic (Impact of 'Widowhood') during a pandemic, and second, on the challenges related to conducting a systematic review. My reflections on the empirical project will focus on first, the challenges of learning the language of a whole new software (MPLUS), and second, the potential exciting role of computerised cognitive testing in the future.

Reflections on the Literature Review

Increased Relevance of 'Widowhood' During a Pandemic

My literature review was one of those pieces of academic work whereby as I spent hours researching for my literature review, it became apparent to me that this piece of academic work was of immediate relevance in the wider global context I found myself in. With each passing day, I saw the death toll rising exponentially, both globally and in the UK, due to the COVID-19 pandemic. At the time of writing, there have been 3.8 million reported deaths due to COVID-19 globally. The statistics also showed a clear trend: those over 65 were most vulnerable to this virus. Naturally, this also meant that there was likely to be a surge in widows/widowers globally in the coming years owing to the disastrous effects of the pandemic. While I was unable to retrieve the exact number of recently bereaved widows around the world from the pandemic thus far, a study created a 'COVID-19 bereavement multiplier' to assess the downstream impact of COVID-19 mortality (Verdery et al., 2020).

Based on their estimates from the US, they estimated that the bereavement multiplier for spouses was approximately 0.46. This means that for every 100,000 deaths from COVID-19 in the US, 46,000 people would have been widowed. Not only that, but those also recently bereaved would have to live without their spouses for much longer than they might have previously anticipated. It is also of course this age-group that is most susceptible to age-related cognitive decline and neurodegenerative diseases such as dementia. My literature review topic was gaining relevance with each passing day – does being widowed put someone at higher risk of developing dementia? Does being widowed for a longer duration of time increase one's risk of cognitive decline? Already, the papers I was sifting through were constantly reminding me that current projections are that by the year 2040, 1 million people in the UK will be diagnosed with dementia (Ahmadi-Abhari et al., 2017), and that the total cost of dementia care in England is projected to increase from £23.0 billion in 2015 to £80.1 billion in 2040 (Wittenberg et al., 2020). The scale of the problem was already staggering prior to the pandemic, but I was left wondering whether the projections will have to be revised upwards following the pandemic given the rapid increase in the number of widows in the world, not to mention the increasing reports suggesting a link between being infected with COVID-19 and potential neurological symptoms.

On the one hand, thinking about the potential downstream effects of the COVID-19 pandemic only added to my already-high levels of uncertainty and anxiety. However, it did give me an added sense of motivation knowing that my literature review was going to have immediate relevance to the current global situation, and for future policy making. It also reminded me of the applicability of research into the real-world. In the past, I sometimes

viewed research as being purely 'academic', but the relevance of this literature review highlighted to me that research can (and should) have a very translatable real-world impact.

Labour-intensive Process to Conduct a Systematic Review

The literature review process was completely new to me. While my undergraduate thesis provided me with some valuable experience to carry out the empirical paper, I have had no prior experience doing a systematic review, let alone a meta-analysis. I am extremely thankful to my supervisors, my lab team, and to a whole host of online resources including YouTube videos and resources on UCL Moodle, that really helped to guide me through the process. The two parts of the process that I found more difficult were first, conducting the search, and second, the sheer number of papers I needed to sift through. Prior to this, I needed to first identify the search terms. What I found most helpful in narrowing down the search terms was to look at recently published reviews that investigated "cognition" and "widowhood". Once these terms were identified, I needed to acquaint myself with how each database was different, in order to conduct the search. For my review, I had to acquaint myself with three different search platforms - OVID, Scopus, and EBSCO. This required me to first perfect my search on one search platform, before then translating the equivalent search onto other search platforms.

Second, sifting through >3000 papers even after removing duplicates was not only mind-numbing, but also extremely time consuming. It took me the good part of two months to get through just the title-screening stage. While going through this process, I remember two thoughts that came to mind. First, as much as I was finding this a tedious process, I began to wonder how such systematic reviews were conducted in the pre-technology era. After all, all I really needed was a sound internet connection and a computer. I can only imagine how

much more tedious this process must have been back in the day. It probably would have involved spending days in the library, and copying copious amounts of handwritten notes. Second, I realised that even with technology, it was still a very manually labour-intensive process. Borah et al. (2017) found that the average systematic review takes 67 weeks to write and publish. Given that the number of registered studies also increasing at an exponential rate (Schmidt et al., 2020), I began to wonder if in the advent of artificial intelligence, there will be newer technology in the near future that would help to speed up the process. I did a google search for such technologies, and found a paper by Marshall & Wallace (2019) entitled *"Toward systematic review automation: a practical guide to using machine learning tools in research synthesis".* This paper provided a recent review of machine learning approaches that can aid the systematic review process. I was intrigued to learn about tools such as – "RobotSearch" (https://robotsearch.vortext.systems), which helps to identify RCTs vs. non-RCT studies, "SWIFT-Review" (https://www.sciome.com/swift-review) where abstracts relating to similar topics are grouped together during the screening process, and "RobotReviewer" (https://robotreviewer.vortext.systems), which can aid in the extraction of data elements (e.g. sample size) from an article. Although most of these automation tools are more tailored towards RCTs, I am sure we are not far away from more of such tools being made available for other types of study designs. Having said this, I do not foresee the possibility that the entire systematic review process can be fully automated given that there is quite some subjectivity involved in any given research study, which might require human expert judgment. I cannot wait to see what the systematic review process would be like for a doctoral candidate in 5-10 years' time.

Reflections on the Empirical Paper

The Boon and Bane of a Secondary Data Project

It goes without saying that I consider myself extremely fortunate to have been involved in a secondary data project. This is especially so given that I am well aware that many of my course mates have had to make substantial changes to their research projects, some entirely revamped, due to the restrictions caused by the COVID-19 pandemic. When I applied for this project back in mid-2019, it was purely because of my interest in the topic and in analysing large datasets, which I had some prior experience in. I do remember wondering if I might lose out on the experience of collecting face-to-face data from clinical samples. In hindsight, this decision might have saved me much anxiety.

Having said that, a secondary data project also comes with its own challenges. Personally, the main difficulty was getting acquainted with statistical software that I had no experience with, and that was not taught on the course. While I had some prior experience in 'R', MPLUS was a whole new 'language' for me. As such, I had to search for ways in which I could learn this new 'language'. There were a few MPLUS training courses that were recommended to me. However, they were either too expensive (I was unsure if I could get funding for these courses), or they were postponed because of COVID-19. This made me quite uneasy as I was not sure how else I could get acquainted with MPLUS. Fortunately, my supervisor recommended an MPLUS textbook – "*Data Analysis with MPLUS"* by Christian Geiser (Geiser, 2013), which provided a step-by-step guide for the analysis that I needed – from reading in the data file, right up to conducting the actual latent class analysis and producing the necessary output files. This textbook, in conjunction with close supervision

from my supervisor, and some prior experience with different coding 'languages' helped me to overcome my initial anxieties.

After running the latent class analysis in MPLUS, I became curious about whether I could run the same analysis in 'R' – since this was the statistics software I was most familiar with. Furthermore, because MPLUS is not open-source (i.e. free), I wondered how I would be able to run a similar analysis in future (e.g. in the work context) if I did not have access to an MPLUS subscription. Therefore, for the sake of my own professional development, I went in search of an 'R' package that could run a similar Latent Class Analysis. After some searching, I chanced upon an 'R' package called 'PoLCA', which was designed for such an analysis. After learning the appropriate syntax for the Latent Class Analysis using the 'PoLCA' package, I decided to satisfy my curiosity to test whether 'PoLCA' gave me the same results as in MPLUS – and it did! However, as far as I am aware, the 'PoLCA' package was unable to conduct the likelihood ratio tests (VLMR-LRT and B-LRT) that statistically compares the various class-solutions, which helps to decide the model of best fit. This made me reflect on the importance of knowing the 'ins and outs' of each statistical software, and planning exactly what is required from the statistical analysis, before commencing the actual analysis. For example, in this case, had I decided to do away with MPLUS entirely, I would have been stuck at the last stage of the LCA analysis, when needing to conduct the likelihood ratio tests.

Imagining the Future: Online Cognitive Testing

The PROTECT study collected participants' cognitive data through a fully-online platform. This made me reflect on the usefulness of such online platforms in the future detection of neuropsychological disease. It is well-known that there is a long pre-clinical

prodromal period for Alzheimer's disease, with some studies suggesting that this could be up to 15 years before changes in cognitive performance is first observed using neuropsychological tests (Bilgel et al., 2017). We also know that even though there are limited efficacious pharmacological interventions for those with dementia, earlier detection is associated with better prognosis (Galvin, 2018). However, several notable obstacles have been identified in the literature. These include stigma (Herrmann et al., 2018), and lack of system resources to conduct regular dementia screening (Bradford et al., 2009). Computerised neuropsychological tests might therefore have certain advantages over more traditional pen-and-paper tests in this regard. First, computerised neuropsychological tests can be done in the comfort and privacy of one's home, thereby potentially reducing stigma and increasing access. In 2014, it was found that 70% of over 7 billion mobile phone subscriptions globally in 2014, were from low or middle-income developing countries (International Telecommunications Union, 2016). Second, computerised tests do not put a strain on healthcare resources. Furthermore, computerised tests have been found to have greater test sensitivity compared to more traditional tests, test presentation is arguably more consistent, and reaction times can be more accurately measured (Brooker et al., 2020). Put together, computerised cognitive tests could hold the key to the future of dementia detection and dementia care.

This made me curious to find out whether there were already applications (Apps) available that were designed for cognitive screening. I chanced upon a review by (Brooker et al., 2020), which reviewed a number of mobile Apps on the Apple and Google App stores. The review found 20 dementia screening Apps that met their inclusion criteria. These included: 'Braincheck' (Ehrensperger et al., 2014), 'BrainTest' (Thabtah et al., 2020), and 'Cognity'

(https://cognity.app), which uses Artificial Intelligence (AI) tools to compute participants' dementia risk. These screening Apps provide great promise, but challenges still remain – such as making the tests more comprehensive (across multiple cognitive domains), cost (some of them are not free), and making them more time-efficient, while bearing in mind the trade-offs between sensitivity and specificity.

Technology is undoubtedly going to play an ever increasing role in our lives. The COVID-19 pandemic will only further accelerate this. We would never have imagined having to whip out one's phone to 'test and trace' before entering a restaurant or a café, or having to get accustomed to tele-consultation appointments with one's GP over the telephone or via video call. The older age groups all around the globe have adapted exceedingly well to the technological demands of living in a pandemic world. This means that there is a whole generation of older adults who may not have previously been as familiar with using smart phones, using the internet, or downloading Apps from an Apps store prior to the pandemic, but who are now much more familiar with these technologies. This provides a unique opportunity for us to leverage on the power of newer technologies to improve health outcomes, especially for the older generation. Having said that, based on the data from the PROTECT study, there was significant attrition already at the 2-year follow-up. Whether this was specific to the study, or whether this generalises to the real-world setting is something I remain curious about, and policy-makers will have to take this into consideration.

Nevertheless, I imagine a day where computerised neuropsychological testing is part of the annual routine check-up with one's GP, that everyone above the age of 50 will need to attend. Prior to attending this check-up, perhaps they will get a notification via the 'NHS App'

saying that they need to complete a battery of online questionnaires related to their recent physical and mental health, but that also invites them to do a series of computerised tests that measures their performance on various cognitive domains. This information will then be fed into a back-end NHS system that uses an artificial intelligence algorithm to analyse their cognitive test performance in their own individualised context – taking into consideration their age, ethnicity, education background, medical history, and their cognitive performance from previous years. The system will then compute an overall dementia risk score, which will be fed back to them via the 'NHS App', and this can be downloaded as an automated 'personalised cognitive report' that forms the basis of their annual check-up consultation with their GP.

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Appendices

Appendix A

Review *Search Terms*

1. widow*.mp.
2. bereave*.mp.
3. (spous* adj2 death).mp.
4. (spous* adj2 loss).mp.
5. (conjugal adj2 loss).mp.
6. (conjugal adj2 death).mp.
7. (partner adj2 loss).mp.
7. (partner adj2 death).mp.
9. exp *Widowhood/
10. exp *bereavement/
11. conigiti*.mp.
12. memory
13. “reaction time”.mp.
14. (speed adj2 processing).mp.
15. “processing speed”.mp.
16. intelligence.mp.
17. “Mental Ability”.mp.
18. “Executive Function”.mp.
19. “Neuropsychological Testing”.mp.
20. “Mini Mental State”.mp.
21. “Mental Status”.mp.
22. *Cognition/
23. exp *Neuropsychological Tests/
24. exp *Cognitive Dysfunction/
25. exp Executive Function/
26. exp Memory/
27. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
28. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
29. 27 and 28

Appendix B

Complete Methodological Quality Ratings for Each Study (Cross-Sectional) Based on Joanna Briggs Institute Checklist

Studies included in cross-sectional analysis	Perkins 2016	O'Connor 2014	Feng 2014	Shahar 2001	Rosset 2011	Byrne 1997	Xu 2020	Biddle 2020	Aartsen 2005	Mousavi 2012	Zhang 2019	Lee 2019
Were the criteria for inclusion in the sample clearly defined?	1	1	1	1	1	1	1	1	1	1	1	1
Were the study subjects and the setting described in detail?	1	1	1	1	1	1	1	1	1	1	1	1
Was the exposure measured in a valid and reliable way?	0	0	0	0	0	1	0	0	0	0	0	0
[a]Were objective, standard criteria used for measurement of the condition?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were confounding factors identified?	1	1	1	1	0	1	1	1	1	1	1	1
Were strategies to deal with confounding factors stated?	1	1	1	1	0	1	1	1	1	1	1	1
Were the outcomes measured in a valid and reliable way?	1	1	1	1	1	1	1	1	1	1	1	1
Was appropriate statistical analysis used?	1	1	1	1	1	1	1	1	1	1	1	1
Total	6	6	6	6	4	7	6	6	6	6	6	6

Note.

[a] This item was seen as being not applicable ("NA") because there was no "condition" involved in the study due to the fact that the main outcome was a continuous (not binary) measure of cognition in a cognitively healthy sample.

Appendix C

Complete Methodological Quality Ratings for Each Study (Longitudinal) Based on Newcastle-Ottowa Criteria

Studies included in longitudinal analysis		**Biddle 2020**	**Zhang 2019**	**Lee 2019**
Selection				
Representativeness of the exposed cohort				
Representative of the average in the community	*	1	1	1
Selected group of users e.g., nurses, volunteers etc.				
No description of the derivation of the cohort				
Selection of the non-exposed cohort				
Drawn from the same community as the exposed cohort	*	1	1	1
Drawn from a different source				
No description of the derivation of the non-exposed cohort				
Ascertainment of exposure				
Secure record (e.g., surgical records)	*			
structured interview	*			
written self-report		0	0	0
no description				
[a]*Demonstration that outcome of interest was not present at start*				
yes	*	NA	NA	NA
no				
Comparability				
Comparability of cohorts on the basis of the design or analysis				
study controls for (AGE & GENDER)	*	1	1	1
study controls for any additional factor (EDUCATION or SES)	*	1	1	1
Outcome				
Assessment of outcome				
Independent blind assessment / record linkage	*	1	1	1
self-report				
no description				

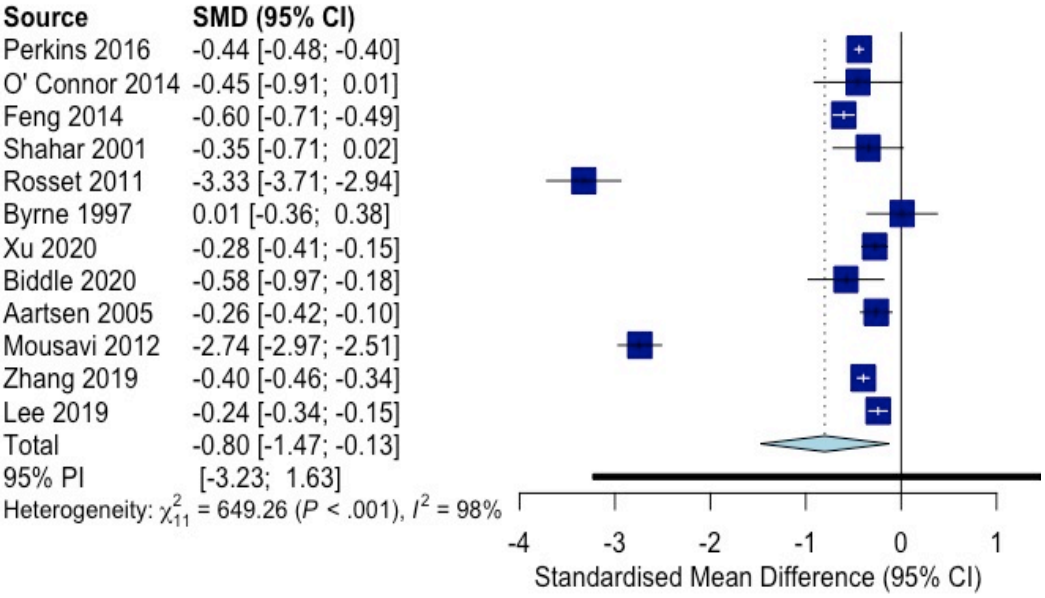
Was follow-up long enough for outcomes to occur?				
yes	*	1	1	1
no				
Adequacy of follow up of cohorts				
Complete follow up or subjects lost to follow up & description provided of those lost	*	1	1	
No description of those lost				0
no statement				
Total		**7**	**7**	**6**

Note.

[a] This item was seen as being not applicable ("NA") because the "outcome of interest" in this study was not binary, but rather a continuous measure of cognition in a cognitively healthy sample.

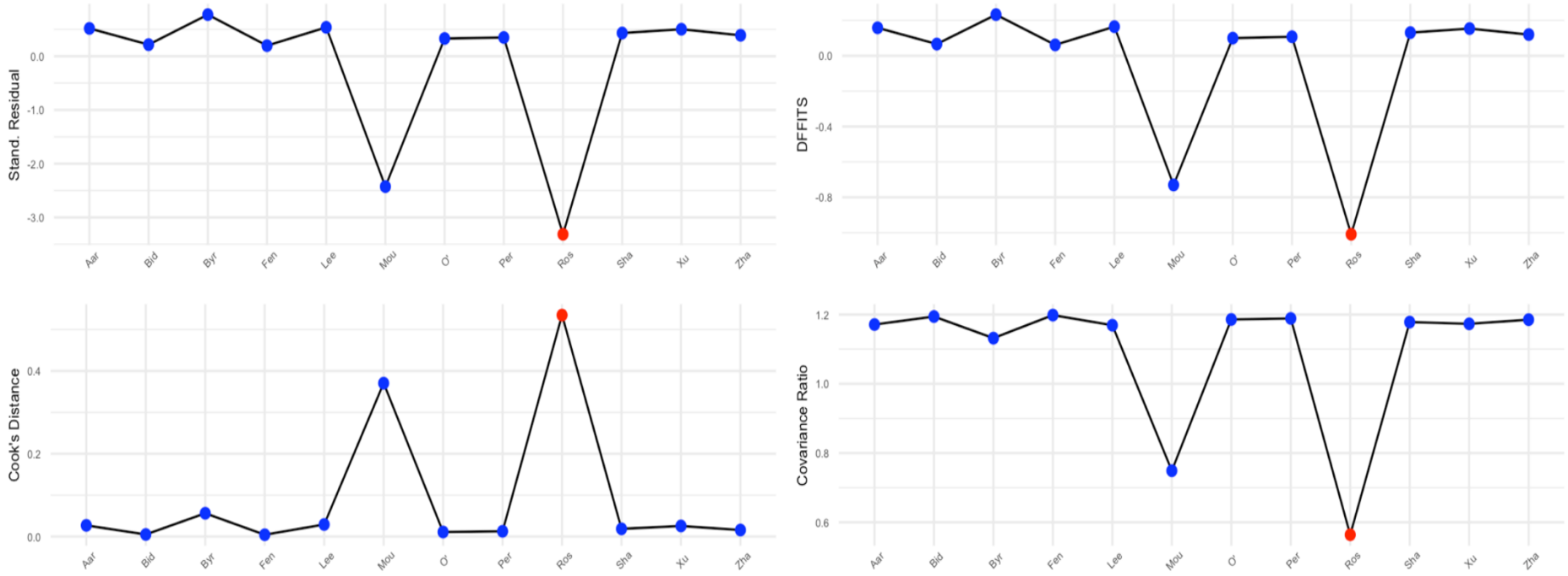
Appendix D

Forest Plot for Cross-Sectional Meta-Analysis Including Outliers (k = 12)



Appendix E

Diagnostic Plots (Viechtbauer & Cheung, 2010) to Detect Potential Outliers using 'Dmetar' package in R



Appendix F

Summary of All Analyses Conducted (Cross-Sectional Meta-Analysis), Including Results Within and Between Subgroups

Variable	Subgroup	k	Hedges' g (95% CI)	p-value	Heterogeneity	Meta-regression	Egger's test
All studies		12	-0.80 (-1.47, -0.13)	.020*	I^2 = 98.0%		*p* = .20
All studies excluding outliers		10	-0.36 (-0.47, -0.25)	<.001*	I^2 = 77.2%		*p* = .40
Study Design							
	Cross-sectional	6	-0.38 (-0.58, -0.17)	.005*	I^2 = 75.7%		*p* = .53
	Longitudinal	4	-0.32 (-0.51, -0.14)	.010*	I^2 = 69.5%	*B* = 0.05, *p* = .64, R^2 = 0%	*p* = .84
Cognitive Domain Measured							
	Memory (e.g., Recall)	4	-0.34 (-0.50, -0.19)	.005*	I^2= 82.4%		*p* = .12
	Global (e.g., MMSE)	6	-0.38 (-0.62, -0.15)	.008*	I^2 = 76.2%	*B* = 0.05, *p* = .64, R^2 = 0%	*p* = .49
Continent							
	Asia	4	-0.43 (-0.63, -0.22)	.006*	I^2 = 81.6%		*p* = .98
	Europe/North America	5	-0.30 (-0.44, -0.15)	.004*	I^2 = 0.00%	*B* = 0.12, *p* = .19, R^2 = 7.66%	*p* = .04*
Length since spousal loss							
	Less than 4 years	6	-0.24 (-0.38, -0.10)	.006*	I^2 = 62.2%		*p* = .09
	More than 4 years	3	-0.41 (-0.73, -0.09)	.030*	I^2 = 79.5%	*B* = 0.16, *p* = .11, R^2 = 23.75%	*p* = .80
[a] Age of sample		9				*B* = 0.01, *p* = .35, R^2 = 0.00%	
[a] Difference in age between "widowed" and "married"		7				*B = -0.01, p = .73, R^2 = 0.00%*	

*Note. *p < .05; CI = Confidence Intervals*

[a] Age was entered as a continuous predictor. Where mean age was not reported, the mean age was estimated to be the middle value of the median age range. For example, if the median age range was reported to be 60-64 years, the mean age was estimated to be 62 years of age

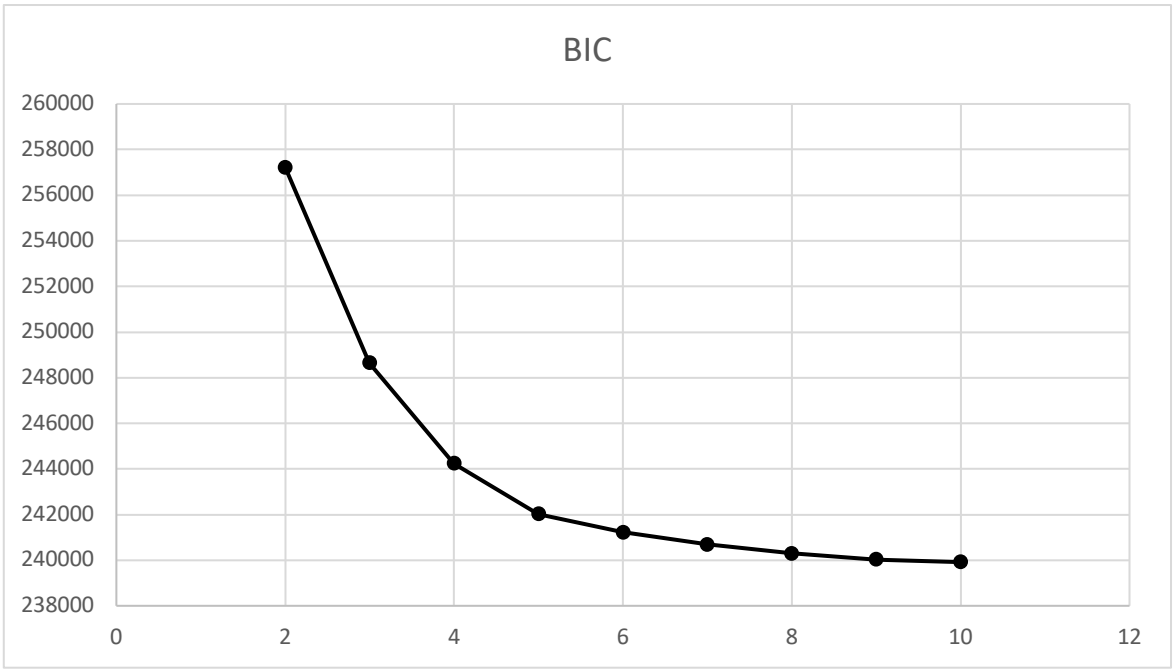
Appendix G

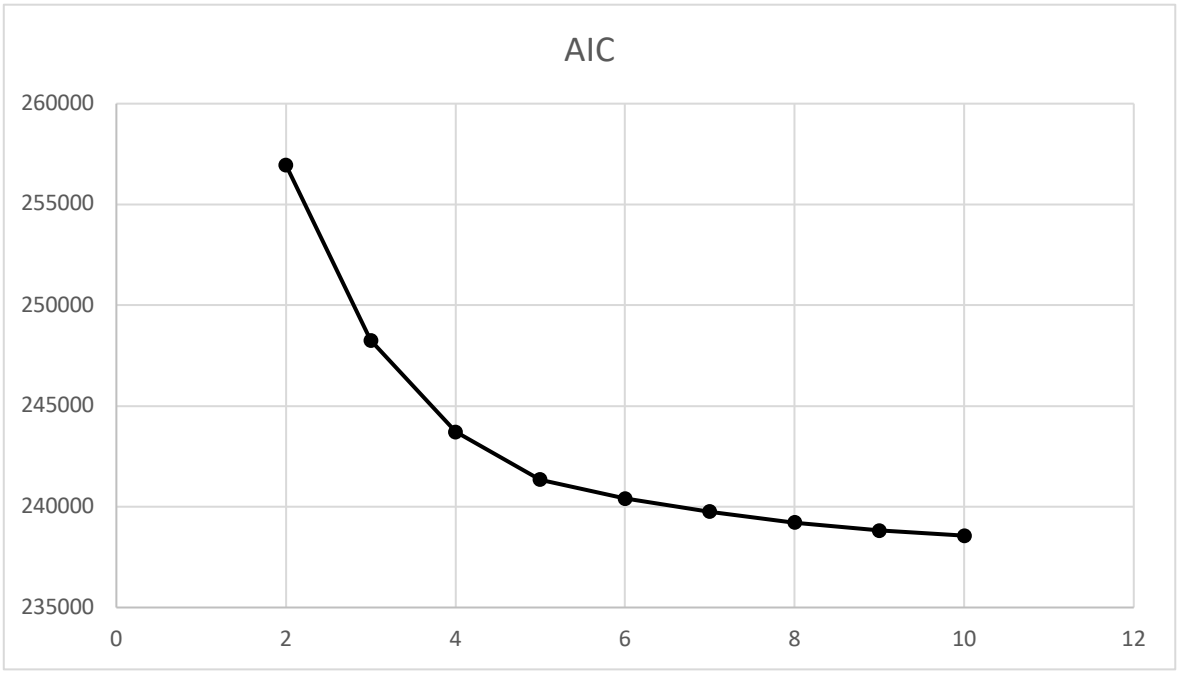
Sensitivity Analysis for Various Imputed r-Values (Longitudinal Meta-Analysis)

	K	Hedges' g (95% CI)			
Imputed r value		**r = .60 (used in analysis)**	r = .20	r = .40	r = .80
Pre-post Change in cognition (ref group: married)	3	-0.15 (-0.19, -0.10)	-0.10 (-0.13, -0.07)	-0.11 (-0.15, -0.08)	-0.19 (-0.28, -0.10)

Appendix H

Scree Plots of BIC (Bayesian Information Criterion; top) and AIC (Akaike Information Criterion; bottom) Versus Number of Latent Classes (from 2 to 10)





Appendix I

Mean and Standard Deviation of Change in Cognition from T1-T2 for Each Class

Class	DS change Mean (SD)	PAL change Mean (SD)	SWM change Mean (SD)	VR change Mean (SD)
Class 1	0.28 (1.29)	0.22 (0.81)	0.31 (2.15)	5.77 (6.13)
Class 2	0.29 (1.27)	0.23 (0.79)	0.14 (2.15)	5.50 (6.22)
Class 3	0.27 (1.21)	0.20 (0.90)	0.29 (2.22)	6.13 (6.70)
Class 4	0.29 (1.18)	0.10 (0.79)	0.20 (2.33)	5.37 (6.34)
Class 5	0.22 (1.25)	0.19 (0.81)	0.06 (2.50)	4.67 (6.79)

Note. Change was calculated by subtracting T1 cognition score from T2 cognition score. Positive (+ve) change indicates improvement in cognitive test performance over time.

Appendix J

All Other Exploratory Class-Comparisons

Comparisons[c]	Domains	Model 1[a]			Model 2[b]		
		Coeff	p-value	95% CI	Coeff	p-value	95% CI
2v5 ("Sleep" vs "Co-morbid Depression & Anxiety")	**DS**	-0.117	.029*	(-0.221 , -0.012)	-0.132	.014*	(-0.237 , -0.026)
	PAL	-0.087	.007*	(-0.150 , -0.024)	-0.113	<.001*	(-0.176 , -0.050)
	SWM	-0.239	.012*	(-0.424 , -0.053)	-0.291	.002*	(-0.476 , -0.105)
	VR	-0.827	.006*	(-1.415 , -0.239)	-0.909	.002*	(-1.496 , -0.322)
3v4 ("Sleep & Worry" vs "Sleep & Anhedonia")	**DS**	0.003	.950	(-0.104 , 0.111)	-0.012	.829	(-0.120 , 0.096)
	PAL	-0.067	.076	(-0.141 , 0.007)	-0.057	.127	(-0.131 , 0.016)
	SWM	0.021	.842	(-0.186 , 0.227)	-0.007	.945	(-0.215 , 0.200)
	VR	-0.727	.033*	(-1.395 , -0.059)	-0.631	.066	(-1.304 , 0.041)

Note.

** p < .05; Coeff = Unstandardised Beta Coefficients; CI = Confidence Intervals.*

[a] Model 1 compares classes while controlling for baseline cognition at T1.

[b] Model 2 additionally controls for gender, marital status, education, employment status, age and alcohol consumption.

[c] Reference class is always the class mentioned first e.g., Class 2 vs. 5 (Class 2 is the ref class).