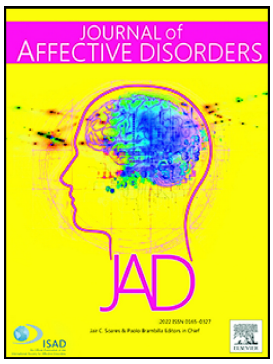

Are subtypes of affective symptoms differentially associated with change in cognition over time: A latent class analysis

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Title: Are subtypes of affective symptoms differentially associated with change in cognition over time: A latent class analysis

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Abstract

Background: In the absence of disease-modifying treatments, identifying potential psychosocial risk factors for dementia is paramount. Depression and anxiety have been identified as potential risk factors. 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.

***Methods*:** Data from participants (aged 50 and above) of the PROTECT study was used. Latent Class Analysis (LCA) was conducted on 21,684 participants with baseline anxiety and depression measures. Multiple linear regressions models, using a subset of these participants (*N* = 6,136) who had complete cognition data at baseline and at 2-year follow-up, were conducted to assess for associations between class membership and longitudinal changes in cognition.

***Results*:** The LCA identified a 5-class solution: "No Symptoms", "Sleep", "Sleep and Worry", "Sleep and Anhedonia", and "Co-morbid Depression and Anxiety". Class membership was significantly associated with longitudinal change in cognition. Furthermore, this association differed across different cognitive measures.

Limitations: Limitations included significant attrition and a generally healthy sample which may impact generalisability.

***Conclusions*:** Substantial heterogeneity in affective symptoms could explain previous inconsistent findings concerning the association between affective symptoms and cognition. Clinicians should not focus solely on total symptom scores or a *single* affective domain, but instead on the presence and *patterns* of symptoms (even if sub-clinical) on measures across *multiple* affective domains. Identifying particular subgroups that are at greater risk of poor cognitive outcomes may support targeted prevention work.

Introduction

Globally, the number of people living with dementia is expected to triple by the year 2050 (Prince et al., 2016). In the UK, dementia is currently the most common cause of mortality (ONS, 2018). In the absence of any known disease-modifying treatments, identifying modifiable risk factors that could prevent dementia is paramount. Depression and anxiety are two such possible risk factors (Gulpers et al., 2016) and several plausible mechanisms have been suggested such as 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). However, the link between depression and anxiety, and cognitive decline has been inconsistent, as some studies have found significant associations between depression and cognitive decline (Rajan et al., 2014; Chang and Tsai,

2015) and anxiety and cognitive decline (Sinoff and Werner, 2003; Gulpers et al., 2019) but some studies have not found such associations (Bunce et al., 2012; Neubauer et al., 2013; Brailean et al., 2017). Proposed reasons for these inconsistent findings include differences in study methodology, design, length of follow-up, and differences in assessment tools (John et al., 2019).

A further explanation may be due to the heterogeneity of mood and anxiety disorders, and different constellations of symptoms may be associated with differences in cognitive decline. For instance, it has been found that Repetitive Negative Thinking (RNT), but not anxiety and depression, has been associated with Tau and Amyloid pathologies, potentially indicating specific markers for cognitive decline (Marchant et al., 2020). Furthermore, such heterogeneity may be particularly salient especially when studying the older population, given that somatic symptoms, which are often measured as part of anxiety (Bártolo et al., 2017) or depression (Lamela et al., 2020) 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 and Hunsley, 2012). Put together, such heterogeneity may also account for the mixed findings in the literature, and may imply that subtypes of affective symptoms may be differentially associated with cognitive decline.

A novel approach to exploring the potential heterogeneity in affective symptoms is to identify subgroups of individuals based on different constellations of symptoms. This may be especially relevant given that depression and anxiety each cover a broad range of symptoms, not all of which are required in order to receive a clinical diagnosis, and therefore the presence of different symptoms may be associated with different cognitive profiles. Furthermore, given the number of potential co-occurring symptoms which may

make up these disorders, variable-centered approaches may struggle to model all the potential interactions between them and instead more person-centered approaches such as clustering may provide useful alternatives (Smyth et al., 2022). Clustering approaches further benefit from being able to consider multiple potentially interacting variables (such as affective symptoms), and explore differences between identified subgroups on multiple outcome variables (Saunders et al., 2020; Aiken et al., 1991). This is crucial as understanding the potential constellations of co-occurring affective symptoms across both anxiety and depression, especially considering the high degree of co-variance between anxiety and depression symptoms in older adults (Schoevers et al., 2005), might help better explain the nature of the relationship between affective symptoms and cognitive decline (with the additional benefit of identifying subgroups who may be particularly at-risk of cognitive decline). Clustering approaches such as Latent Class Analysis (LCA) have been used to identify subgroups of depression and anxiety symptoms (Rudenstine and Espinosa, 2018; Unick et al., 2009) in the general population, but not exclusively in older adults, or in order to compare subgroups on cognitive decline.

The first aim of the present study was to identify subgroups of adults over the age of 50, based on the presence of self-reported symptoms of depression and anxiety. The second aim of this study was to investigate whether cognitive decline (as measured across four cognitive domains) differs between these subgroups.

Method

Study Design and Participants

Data were taken from the ongoing PROTECT study (www.protectstudy.org.uk), launched in 2015, with the primary aim of examining age-related changes to the brain in the

context of aging (Huntley et al., 2018). Inclusion criteria for PROTECT include: being over the age of 50, living in the UK having a good understanding of English, and being 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; defined as "T0") to the 3rd wave (follow-up; defined as "T2") of data collection. Ethical approval for this study was granted by the UK London Bridge National Research Ethics Committee (Ref: 13/LO/1578)

Procedure and Data Collection

Participants were recruited via a well-publicised media campaign, GP practices and memory clinics. Participants registered interest online, and downloaded a study information sheet. Consent was requested through an approved online platform.

Participants completed a series of online self-report questionnaires annually (at each wave), which included sociodemographic (gender, age, marital status, ethnicity, education level, employment status), lifestyle (smoking history, alcohol consumption, physical activity), and mental health information (history of diagnosed depression/anxiety and current levels of depression and anxiety symptoms) and a battery of four online cognitive measures, each measuring a different cognitive domain – attention, visual working memory, spatial working memory and verbal reasoning. All cognitive measures were based on validated pen and paper versions and adapted for online use (Owen et al., 2010). They have been found to be valid (Corbett et al., 2015) and reliable (Wesnes et al., 2017). Participants were asked to attempt each cognitive measure three times over seven days, ensuring there is at least 24 hours before each trial. The scores from successfully completed trials were then averaged to compute a total summary score for each cognitive measure.

The cognitive measures took approximately half an hour to complete. Full details on the measures for depression and anxiety symptoms respectively, and the cognitive measures are provided in Table 1.

[Insert Table 1]

Statistical Analysis

Latent Class Analysis (LCA)

In the first stage of analysis, LCA was conducted on the combined 16 items of the PHQ-9 and GAD-7, using data from participants who had complete data on all these items at T0. Each of the 16 items were converted into binary indicators to reflect either symptom presence or absence (score of 0 = absence, scores of 1,2 or 3 indicate presence of symptom). This binarisation was performed for two reasons: First, 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. Second, so as to identify possible subsyndromal symptoms that are commonly missed in the older adult population, but which have been found to be associated with poorer health outcomes (Yuan et al., 2020). A number of model fit statistics were used to determine the optimal class solution, including the Vuong-Lo-Mendell-Rubin Likelihood Ratio test (VLMR-LRT; Lo et al., 2001) the Bootstrap Likelihood Ratio Difference test (B-LRT), Akaike information criterion (AIC), the Bayesian Information Criterion (BIC), sample size adjusted BIC (Vrieze, 2012) and Entropy values.

To identify the best fitting model, a number of model fit criteria were considered. Firstly, 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. 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 were taken into consideration, as recommended in the literature (Nylund et al., 2007). As a class-utility criterion, classes needed to include at least 5% of the sample (Yuan et al., 2020; Spinhoven et al., 2019). Since there was no hypothesis as to the number of classes to be identified, the analysis started with a 2-class model, and increased the number of classes whilst considering model fit information at each stage. In the case of multiple possible class solutions, model interpretability and clinical relevance would be taken into consideration, as recommended (Nylund et al., 2007). Once the optimal class solution was identified, all individuals were allocated to the class to which they had the highest probability of membership to, for use in subsequent analyses. To assess the robustness of the class solution, the sample was also randomly split in half, and LCA was performed separately on these split samples to see if the solution for the full sample was replicated between these smaller splits.

Associations between Class Membership and Cognitive Outcomes

In the second stage of analysis, changes in cognition (across all four cognitive measures) were explored between classes. Multiple linear regression models were constructed to examine whether affective symptom classes were associated with differences in cognitive change (measured by subtracting cognition scores at T0 from cognition scores at T2). Cognitive change scores were used because they improve the prediction of subsequent cognitive impairment over and above baseline cognition scores (Nation et al., 2019). This analysis therefore only included participants who had complete cognition data at T0 and T2. In order to minimise practice effects, cognitive scores were only computed for those who completed at least two (out of three) trials at T0, and only the score from the first (out of three) trial was used at T2. Furthermore, only those with a follow-up time period of between 2 years to 2 years 3 months were included in the analysis so as to ensure homogeneity in the length of time between T0 and T2. The biggest class (anticipated to be the group with the least symptoms) 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 T0 was included as a covariate. In model 2, the socio-demographic and lifestyle factors that differed between classes (assessed by chi-square tests of independence) were additionally included as covariates, as well as the total number of completed trials prior to T2 (ie. across both T0 and T1 (2nd Wave)). The analysis was conducted separately for each of the four cognitive measures. All analyses were performed using MPLUS version 8.2 (Muthén & Muthén, 2017) and R (R Core Team, 2020).

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 T0. Based on the models identified and their fit statistics (see Table 2), a number of potential solutions could be adopted. The VLMR-LRT became non-significant after running the 10-class model, which using this metric would mean that the 9-class model may be the most parsimonious model. However, 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 due to its clinical utility and interpretability. 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 Supplementary Figure 1). Furthermore, analysis on the split-half samples also indicated that the 5-class solution was the optimal solution for both these samples (full details can be found in Supplementary Figure 2 and Supplementary Table 1).

The item response probabilities, which are the probabilities of the presence of any of the symptoms conditional on latent class membership, for the 5-class model are graphically illustrated below in Figure 1 (exact probabilities can be found in Supplementary Table 2). The classes described as follows: Class 1 (*N* = 8,790; 40.5%) was labelled as “No symptoms” (Mean number of symptoms = 0.38); Class 2 (*N* = 5,845; 27.0%) was labelled as “Sleep”; Class 3 (*N* = 2,904; 13.4%) was labelled as “Sleep and Worry”; Class 4 (*N* = 2,031; 9.3%) was labelled as “Sleep and Anhedonia”; Class 5 (*N* = 2,114; 9.7%) was labelled as “Co-morbid Depression and Anxiety” (Mean number of symptoms = 11.24). The descriptive statistics of each class and the full sample, are shown below in Table 3.

[Insert Figure 1]

As shown in Table 3, classes differed by cognition (on all four cognitive measures) at baseline, age, gender, marital status, education level, employment status, and alcohol consumption. These variables were therefore included as covariates in model 2. As expected, the classes also differed regarding the number of PHQ-9 and GAD-7 symptoms, total scores on the PHQ-9 and GAD-7, and history of depression/anxiety diagnosis.

[Insert Table 3]

Association between Class and Cognitive Decline

Only participants who had cognition data (on all four cognitive measures) both at T0 and T2 were included in this analysis. Of the 21,684 participants that were included in the LCA, 17,069 (78.7%) participants had complete cognition data at T0, of whom 6,507 (38.1%) participants had cognition data available at T2. Those who did not have cognition data available at T2 were more likely to be younger, non-white, GCSE/A-levels/Diploma holders, employed, have lower alcohol consumption, lower baseline scores on spatial working memory, higher rates of history of depression/anxiety diagnosis and higher average number of PHQ-9 symptoms and PHQ-9 total scores (see Supplementary Table 3). Out of these 6,507 participants, 371 participants were excluded from the final analysis because the time period between T0 and T2 was greater than 2 years and 3 months or because such information was unavailable. Therefore 6,136 participants were included in the final analysis.

The mean change scores between T0 and T2 for all five classes on all four cognitive domains were generally in the positive direction (see Supplementary Table 4 and Supplementary Figure 3), indicating improvements in cognitive performance, except on

spatial working memory, whereby declines in cognitive performance were observed. As shown in Table 4 below, after adjusting for all potential confounders, no significant differences were found between Class 1 (reference group: "No symptoms") and all other classes on attention and verbal reasoning. For spatial working memory, all classes showed significantly greater declines in cognitive performance, as compared to Class 1. For visual working memory, Class 4 ("Sleep and Anhedonia") and Class 5 ("Co-morbid Depression and Anxiety") were associated with significantly smaller increases in cognitive performance, as compared to Class 1. Exploratory post-hoc analyses were conducted to assess differences between all other classes (see Supplementary Table 5). We were particularly interested in comparing the "Co-morbid Depression and Anxiety" group with the "Sleep and Anhedonia" group and the "Sleep and Worry" group, in order to assess whether having co-morbid depression and anxiety symptoms was associated with greater cognitive risk compared to having either depression or anxiety symptoms alone. No significant differences were found between the "Co-morbid Depression and Anxiety" group and the "Sleep and Anhedonia" group on all four cognitive domains. However, the "Co-morbid Depression and Anxiety" group experienced significantly smaller increases compared to the "Sleep and Worry" group on verbal reasoning, and significantly greater declines on spatial working memory.

[Insert Table 4]

Discussion

We were the first to investigate a) whether there were distinct subgroups of participants aged 50 and over based on co-occurring depression and anxiety symptoms and b) whether these subgroups were associated with differential cognitive change and thus might confer differential risk of cognitive decline.

We found 5 classes: “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). The split sample analysis replicated the 5-class solution, supporting the robustness of the classes identified. The five classes 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 generally replicate previous findings that measured both depression and anxiety symptoms (Rudenstine and Espinosa, 2018; Unick et al., 2009) except for the identification of a “Sleep” subgroup in the present study. It may be that sleep issues in the absence of other affective symptoms is more common in adults over the age of 50, and older adults typically report more sleep difficulties (Foley et al., 2004).

We also found differential cognitive change between subgroups. Overall, there were increases in cognition scores across the sample, common in repeated neuropsychological testing (Goldberg et al., 2015) and likely a function of practice effects/repeated testing in the absence of intervention (Salthouse, 2010) except on the domain of spatial working memory where some declines were observed. A recent systematic review (Jutten et al., 2020) 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 interpreted in light of this.

The first notable finding was that while there were no significant differences between the “No symptoms” group and all four symptomatic groups on attention and verbal reasoning, there were some differences observed on visual working memory and spatial working memory. This suggests that the affective symptoms assessed in the present

study (e.g. sleep, worry, depression) were more likely to be associated with changes on working memory, rather than attention and verbal reasoning.

The second notable finding was that all symptomatic classes were associated with greater declines in cognitive performance compared to the "No symptoms" group on the domain of spatial working memory. This could have been as a result of sleep difficulties, given that it was common across all symptomatic classes. This is consistent with previous research showing sleep disturbances are associated with subsequent diagnosis of dementia (Sabia et al., 2021) and related to specific deficits in the area of working memory in younger (Peng et al., 2020) and older adults (Okuda et al., 2021).

The third notable observation was that anhedonia symptoms seemed to particularly impact performance on visual working memory. This may explain why compared to the "No Symptoms" group, the "Sleep and Anhedonia" group and "Co-morbid Depression and Anxiety" groups, but not the "Sleep" and "Sleep and Worry" groups, were found to have significantly smaller increases on visual working memory. This may also explain the finding that the "Sleep and anhedonia" group experienced significantly smaller increases on visual working memory compared to both the "Sleep" group and even the "Sleep and Worry" group. Interestingly, the "Sleep and Anhedonia" performed even more poorly on visual working memory, even when compared to the "Co-morbid Depression and Anxiety" group. One potential explanation might be that mild anxiety, serves as protective factor and counter-balance to the effects of depression (Bierman et al., 2005) specifically in the area of visual working memory.

The fourth finding was that while there was no evidence to suggest that those with co-morbid depression and anxiety symptoms were at higher risk of cognitive decline as compared to the "Sleep and Anhedonia" group, there was some evidence to suggest that

they were at higher risk compared to the "Sleep and Worry" group on spatial working memory and verbal reasoning, once again suggesting that anhedonia symptoms may be a particularly useful predictor of cognitive decline.

Limitations

While this study does have several strengths including a large sample size giving high statistical power, longitudinal design allowing modelling of change over time, and the use of the PHQ-9 and GAD-7, as findings from this study can be easily applied in mental health services that routinely use these measures, such as UK Improving Access to Psychological Therapies (IAPT) services (Clark, 2018), there are also several limitations. First, the study relied on online self-report data collection which could not be easily independently verified. Second, whilst individuals with a known diagnosis of dementia were excluded, some individuals may already have underlying neuropathology that they were unaware of, given that pre-clinical dementia begins up to 15 years before symptoms are observed. Furthermore, including a measure of pre-morbid cognitive functioning might have been useful for the purposes of assessing whether cognitive decline might already have begun for some participants. Third, findings from this study should be interpreted with caution due to a possible lack of generalisability for the following reasons: Firstly, the high drop-out rate observed in this study over the 2-year period may have resulted in selective attrition. Secondly, the demographics of the sample was highly selective, primarily made up of white (98%) and female (75%) participants. Thirdly, the sample was a generally 'healthy' sample as evidenced by relatively low scores on the affective symptoms measures. Taken together, future research should examine whether these results can be replicated in other samples of differing demographics, and particularly in clinical samples. Furthermore, because of the

relatively low scores on the affective symptom measures, the item scores needed to be dichotomised. This may have possibly resulted in a loss of information. Finally, to add to the internal validity of the LCA, future research could consider randomly splitting the sample into half and comparing the LCA findings across the two halves.

Future studies could also aim to replicate the current analysis over a longer follow-up period. 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. Additionally, having multiple measurement points (rather than just two) in future research would increase the reliability of the measurement of cognition.

Conclusions

This study demonstrates that there is heterogeneity within affective symptoms experienced in a sample of adults aged 50 and above, and class membership was differentially associated with changes in cognition across different cognitive measures over a 2-year period. 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.

Given the considerable heterogeneity within affective symptoms, and that even sub-clinical symptoms, which are common in the older adult population but are often overlooked (Laborde-Lahoz et al., 2015), appear to have a longitudinal impact on cognition, clinicians should therefore be encouraged not just to focus solely on total symptom scores

on a *single* affective domain (i.e. depression *or* anxiety) that meet clinical cut-offs, but to instead look for the presence of *patterns* of symptoms (even if sub-clinical) on measures across *multiple* affective domains (i.e. depression *and* anxiety). Second, these findings could help to identify particular at-risk groups of cognitive decline. For example, given the established link between the PAL task and Alzheimer's disease (Junkkila et al., 2012), 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). Furthermore, if deficits in certain cognitive measures are found to be more predictive of certain types of neurodegenerative disease (e.g., Lewy body disease, frontotemporal dementia), then affective profiles more highly associated with those cognitive measures 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.

References

Aiken, L.S., West, S.G., Reno, R.R., 1991. Multiple Regression: Testing and Interpreting Interactions. SAGE.

Bártolo, A., Monteiro, S., Pereira, A., 2017. Factor structure and construct validity of the Generalized Anxiety Disorder 7-item (GAD-7) among Portuguese college students. Cad. Saúde Pública 33, e00212716. https://doi.org/10.1590/0102-311x00212716

Bierman, E.J.M., Comijs, H.C., Jonker, C., Beekman, A.T.F., 2005. Effects of anxiety versus depression on cognition in later life. Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry 13, 686–693. https://doi.org/10.1176/appi.ajgp.13.8.686

Bilgel, M., Koscik, R.L., An, Y., Prince, J.L., Resnick, S.M., Johnson, S.C., Jedynak, B.M., 2017. Temporal Order of Alzheimer's Disease-Related Cognitive Marker Changes in BLSA and WRAP Longitudinal Studies. J. Alzheimers Dis. JAD 59, 1335–1347. https://doi.org/10.3233/JAD-170448

Brailean, A., Aartsen, M.J., Muniz-Terrera, G., Prince, M., Prina, A.M., Comijs, H.C., Huisman, M., Beekman, A., 2017. Longitudinal associations between late-life depression dimensions and cognitive functioning: a cross-domain latent growth curve analysis. Psychol. Med. 47, 690–702. https://doi.org/10.1017/S003329171600297X

Bunce, D., Batterham, P.J., Mackinnon, A.J., Christensen, H., 2012. Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. J. Psychiatr. Res. 46, 1662–1666. https://doi.org/10.1016/j.jpsychires.2012.08.023

Chang, S.L., Tsai, A.C., 2015. Gender differences in the longitudinal associations of depressive symptoms and leisure-time physical activity with cognitive decline in ≥57year-old Taiwanese. Prev. Med. 77, 68–73. https://doi.org/10.1016/j.ypmed.2015.05.001

Clark, D.M., 2018. Realising the Mass Public Benefit of Evidence-Based Psychological Therapies: The IAPT Program. Annu. Rev. Clin. Psychol. 14, 159–183. https://doi.org/10.1146/annurev-clinpsy-050817-084833

Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., Burns, A., Howard, R., Williams, N., Williams, G., Ballard, C., 2015. The Effect of an Online Cognitive Training Package in Healthy Older Adults: An Online Randomized Controlled Trial. J. Am. Med. Dir. Assoc. 16, 990–997. https://doi.org/10.1016/j.jamda.2015.06.014

Foley, D., Ancoli-Israel, S., Britz, P., Walsh, J., 2004. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J. Psychosom. Res. 56, 497–502. https://doi.org/10.1016/j.jpsychores.2004.02.010

Goldberg, T.E., Harvey, P.D., Wesnes, K.A., Snyder, P.J., Schneider, L.S., 2015. Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials. Alzheimers Dement. Amst. Neth. 1, 103–111. https://doi.org/10.1016/j.dadm.2014.11.003

Gulpers, B., Ramakers, I., Hamel, R., Köhler, S., Oude Voshaar, R., Verhey, F., 2016. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. Am. J. Geriatr. Psychiatry 24, 823–842. https://doi.org/10.1016/j.jagp.2016.05.015

Gulpers, B.J.A., Oude Voshaar, R.C., van Boxtel, M.P.J., Verhey, F.R.J., Köhler, S., 2019. Anxiety as a Risk Factor for Cognitive Decline: A 12-Year Follow-Up Cohort Study. Am. J. Geriatr. Psychiatry 27, 42–52. https://doi.org/10.1016/j.jagp.2018.09.006

Huntley, J., Corbett, A., Wesnes, K., Brooker, H., Stenton, R., Hampshire, A., Ballard, C., 2018. Online assessment of risk factors for dementia and cognitive function in healthy adults. Int. J. Geriatr. Psychiatry 33, e286–e293. https://doi.org/10.1002/gps.4790

John, A., Desai, R., Richards, M., Gaysina, D., Stott, J., 2021. Role of cardiometabolic risk in the association between accumulation of affective symptoms across adulthood and mid-life cognitive function: national cohort study. Br. J. Psychiatry 218, 254–260. https://doi.org/10.1192/bjp.2020.123

John, A., Patel, U., Rusted, J., Richards, M., Gaysina, D., 2019. Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis. Psychol. Med. 49, 353–365. https://doi.org/10.1017/S0033291718001137

Junkkila J, Oja S, Laine M, Karrasch M: Applicability of the CANTAB-PAL Computerized Memory Test in Identifying Amnestic Mild Cognitive Impairment and Alzheimer's Disease. Dement Geriatr Cogn Disord 2012;34:83-89. doi: 10.1159/000342116

Jutten, R.J., Grandoit, E., Foldi, N.S., Sikkes, S.A.M., Jones, R.N., Choi, S., Lamar, M.L., Louden, D.K.N., Rich, J., Tommet, D., Crane, P.K., Rabin, L.A., 2020. Lower practice effects as a marker of cognitive performance and dementia risk: A literature review. Alzheimers Dement. Diagn. Assess. Dis. Monit. 12. https://doi.org/10.1002/dad2.12055

Laborde-Lahoz, P., El-Gabalawy, R., Kinley, J., Kirwin, P.D., Sareen, J., Pietrzak, R.H., 2015. Subsyndromal depression among older adults in the USA: prevalence, comorbidity,

and risk for new-onset psychiatric disorders in late life. Int. J. Geriatr. Psychiatry 30, 677–685. https://doi.org/10.1002/gps.4204

Lamela, D., Soreira, C., Matos, P., Morais, A., 2020. Systematic review of the factor structure and measurement invariance of the patient health questionnaire-9 (PHQ-9) and validation of the Portuguese version in community settings. J. Affect. Disord. 276, 220–233. https://doi.org/10.1016/j.jad.2020.06.066

Lo, Y., Mendell, N.R., Rubin, D.B., 2001. Testing the number of components in a normal mixture. Biometrika 88, 767–778. https://doi.org/10.1093/biomet/88.3.767

Marchant, N.L., Lovland, L.R., Jones, R., Binette, A.P., Gonneaud, J., Arenaza-Urquijo, E.M., Chételat, G., Villeneuve, S., 2020. Repetitive negative thinking is associated with amyloid, tau, and cognitive decline. Alzheimers Dement. 16, 1054–1064. https://doi.org/10.1002/alz.12116

Muthén & Muthén, 2017. Mplus user's guide: Statistical analysis with latent variables, user's guide. Muthén & Muthén. [WWW Document]. URL https://www.statmodel.com/html_ug.shtml (accessed 8.3.21).

Nation, D.A., Ho, J.K., Dutt, S., Han, S.D., Lai, M.H.C., Initiative, for the A.D.N., 2019. Neuropsychological Decline Improves Prediction of Dementia Beyond Alzheimer's Disease Biomarker and Mild Cognitive Impairment Diagnoses. J. Alzheimers Dis. 69, 1171–1182. https://doi.org/10.3233/JAD-180525

Neubauer, A.B., Wahl, H.-W., Bickel, H., 2013. Depressive symptoms as predictor of dementia versus continuous cognitive decline: a 3-year prospective study. Eur. J. Ageing 10, 37–48. https://doi.org/10.1007/s10433-012-0246-4

Nylund, K.L., Asparouhov, T., Muthén, B.O., 2007. Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. Struct. Equ. Model. Multidiscip. J. 14, 535–569. https://doi.org/10.1080/10705510701575396

Okuda, M., Noda, A., Iwamoto, K., Nakashima, H., Takeda, K., Miyata, S., Yasuma, F., Ozaki, N., Shimouchi, A., 2021. Effects of long sleep time and irregular sleep–wake rhythm on cognitive function in older people. Sci. Rep. 11, 7039. https://doi.org/10.1038/s41598-021-85817-y

ONS, 2018. Dementia and Alzheimer's disease deaths including comorbidities, England and Wales - Office for National Statistics [WWW Document]. URL https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/dementiaandalzheimersdiseasedeathsincludingcomorbiditiesengl andandwales/2019registrations (accessed 8.3.21).

Owen, A.M., Hampshire, A., Grahn, J.A., Stenton, R., Dajani, S., Burns, A.S., Howard, R.J., Ballard, C.G., 2010. Putting brain training to the test. Nature 465, 775–778. https://doi.org/10.1038/nature09042

Peng, Z., Dai, C., Ba, Y., Zhang, L., Shao, Y., Tian, J., 2020. Effect of Sleep Deprivation on the Working Memory-Related N2-P3 Components of the Event-Related Potential Waveform. Front. Neurosci. 14, 469. https://doi.org/10.3389/fnins.2020.00469

Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., Karagiannidou, M., 2016. World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future [WWW Document]. URL http://www.alz.co.uk/ (accessed 6.2.21).

R Core Team, 2020. R: The R Project for Statistical Computing [WWW Document]. URL https://www.r-project.org/ (accessed 8.3.21).

Rajan, K.B., Wilson, R.S., Skarupski, K.A., de Leon, C.M., Evans, D.A., 2014. Gene Behavior Interaction of Depressive Symptoms and the Apolipoprotein E ε4 Allele on Cognitive Decline. Psychosom. Med. 76, 101–108. https://doi.org/10.1097/PSY.0000000000000029

Rodrigues, R., Petersen, R.B., Perry, G., 2014. Parallels between major depressive disorder and alzheimer's disease: role of oxidative stress and genetic vulnerability. Cell. Mol. Neurobiol. 34, 925–949. https://doi.org/10.1007/s10571-014-0074-5

Rudenstine, S., Espinosa, A., 2018. Latent comorbid depression and anxiety symptoms across sex and race/ethnic subgroupings in a national epidemiologic study. J. Psychiatr. Res. 104, 114–123. https://doi.org/10.1016/j.jpsychires.2018.07.005

Sabia, S., Fayosse, A., Dumurgier, J., van Hees, V.T., Paquet, C., Sommerlad, A., Kivimäki, M., Dugravot, A., Singh-Manoux, A., 2021. Association of sleep duration in middle and old age with incidence of dementia. Nat. Commun. 12, 2289. https://doi.org/10.1038/s41467-021-22354-2

Salthouse, T.A., 2010. Influence of age on practice effects in longitudinal neurocognitive change. Neuropsychology 24, 563–572. https://doi.org/10.1037/a0019026

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. The Neuroendocrinology of Stress and Aging: The Glucocorticoid Cascade Hypothesis*. Endocr. Rev. 7, 284–301. https://doi.org/10.1210/edrv-7-3-284

Saunders, R., Buckman, J.E.J., Cape, J., Fearon, P., Leibowitz, J., Pilling, S., 2019. Trajectories of depression and anxiety symptom change during psychological therapy. J. Affect. Disord. 249, 327–335. https://doi.org/10.1016/j.jad.2019.02.043

Saunders, R., Buckman, J.E.J., Pilling, S., 2020. Latent variable mixture modelling and individual treatment prediction. Behav. Res. Ther. 124, 103505. https://doi.org/10.1016/j.brat.2019.103505

Schoevers, R.A., Deeg, D.J.H., van Tilburg, W., Beekman, A.T.F., 2005. Depression and Generalized Anxiety Disorder: Co-Occurrence and Longitudinal Patterns in Elderly Patients. Am. J. Geriatr. Psychiatry 13, 31–39. https://doi.org/10.1097/00019442-200501000-00006

Sinoff, G., Werner, P., 2003. Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. Int. J. Geriatr. Psychiatry 18, 951–959. https://doi.org/10.1002/gps.1004

Smyth, N., Buckman, J., Naqvi, S. A., Aguirre, E., Cardoso, A., Pilling, S., & Saunders, R., 2022. Understanding differences in mental health service use by men: an intersectional analysis of routine data. Social psychiatry and psychiatric epidemiology, 10.1007/s00127-022-02256-4. Advance online publication. https://doi.org/10.1007/s00127-022-02256-4

Spinhoven, P., Batelaan, N., Rhebergen, D., van Balkom, A., Schoevers, R., Penninx, B.W., 2016. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. J. Anxiety Disord. 44, 92–101. https://doi.org/10.1016/j.janxdis.2016.10.011

Therrien, Z., Hunsley, J., 2012. Assessment of anxiety in older adults: A systematic review of commonly used measures. Aging Ment. Health 16, 1–16. https://doi.org/10.1080/13607863.2011.602960

Unick, G.J., Snowden, L., Hastings, J., 2009. Heterogeneity in Comorbidity between Major Depressive Disorder and Generalized Anxiety Disorder and its Clinical Consequences. J. Nerv. Ment. Dis. 197, 215–224. https://doi.org/10.1097/NMD.0b013e31819d954f

Vrieze, S.I., 2012. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Psychol. Methods 17, 228–243. https://doi.org/10.1037/a0027127

Wesnes, K.A., Brooker, H., Ballard, C., McCambridge, L., Stenton, R., Corbett, A., 2017. Utility, reliability, sensitivity and validity of an online test system designed to monitor changes in cognitive function in clinical trials. Int. J. Geriatr. Psychiatry 32, e83–e92. https://doi.org/10.1002/gps.4659

Wu, K.-Y., Hsiao, I.-T., Chen, C.-S., Chen, C.-H., Hsieh, C.-J., Wai, Y.-Y., Chang, C.-J., Tseng, H.-J., Yen, T.-C., Liu, C.-Y., Lin, K.-J., 2014. Increased brain amyloid deposition in patients with a lifetime history of major depression: evidenced on 18F-florbetapir (AV-45/Amyvid) positron emission tomography. Eur. J. Nucl. Med. Mol. Imaging 41, 714–722. https://doi.org/10.1007/s00259-013-2627-0

Yuan, Y., Min, H.S., Lapane, K.L., Rothschild, A.J., Ulbricht, C.M., 2020. Depression symptoms and cognitive impairment in older nursing home residents in the USA: A latent class analysis. Int. J. Geriatr. Psychiatry 35, 769–778. https://doi.org/10.1002/gps.5301

Table 1

Complete description of cognitive and affective symptoms measures

Measures	Domain	Description
Cognitive Measures		
Digit Span (DS)	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 series was one digit longer in length. If they were incorrect, the next series 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.
Paired Associate Learning (PAL)	Visual Working Memory	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 (Junkkila et al., 2012). Higher scores indicated better

		performance.
Spatial Working Memory (SWM)	Spatial Working Memory	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.
Verbal Reasoning (VR)	Verbal Reasoning	Participants are shown a sentence 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. Performance on this task was found to be strongly correlated with measures of general intelligence (Baddeley, 1968).
Affective Symptom Measures		
Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)	Depression Symptoms	PHQ-9 consisted of nine items, 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 symptoms. The PHQ-9 has been found to be a valid and reliable scale in the general population (Kroenke et al., 2001) and in the older adult population (Zhang et al., 2020).
Generalised Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006)	Anxiety Symptoms	GAD-7 consisted of seven items, 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 in the general population (Löwe et al., 2008) and in the older adult population (Wild et al., 2014).

Table 2

Fit statistics 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	36/28/12/7/6/5/4/4
9	238816	240030	239547	0.760	-119256	.002	.001	36/25/9/6/7/6/4/4/4
10	238566	239915	239378	0.755	-119114	.001	<.001	36/23/9/7/6/4/4/4/4/3

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)	1417 (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)	7.41 (1.54)	7.46 (1.50)	7.41 (1.41)	7.39 (1.43)	7.36 (1.45)	7.23 (1.36)	F (4,17064) =9.08, p <.001
PAL Mean (SD)	4.53 (0.74)	4.55 (0.74)	4.53 (0.73)	4.51 (0.75)	4.55 (0.71)	4.47 (0.72)	F (4,17064) = 5.04, p <.001
SWM Mean (SD)	7.58 (2.10)	7.66 (2.09)	7.63 (2.04)	7.50 (2.09)	7.57 (2.09)	7.24 (2.27)	F (4,17064) = 14.91, p < .001
VR Mean (SD)	32.54 (9.19)	32.23 (9.11)	32.90 (9.20)	32.48 (9.04)	32.92 (9.36)	32.62 (9.52)	F (4,17064) =4.57, 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 (4,21679) = 21961, 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 (4,21679) = 28364, p <.001
PHQ-9 total score Mean (SD)	2.67 (3.23)	0.42 (0.67)	2.64 (1.49)	2.79 (1.89)	5.87 (2.75)	8.83 (4.26)	F (4,21679) = 9779, 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 (4,21679) = 13298, p <.001
History of depression/ anxiety diagnosis							
No	13608 (71.6)	6604 (79.9)	3951 (71.6)	1546 (64.2)	1067 (61.9)	630 (46.9)	X^2 (4) = 826.77, 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 T0	10562 (61.9)	4237 (60.5)	2897 (62.5)	1385 (60.5)	998 (63.4)	1045 (65.4)	X^2 (4) = 16.32, p = .003
Cognition available at T0 and T2	6507 (38.1)	2765 (39.5)	1738 (37.5)	905 (39.5)	577 (36.6)	552 (34.6)	

* 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.

‡ p <.05 indicated statistically significant between-class differences.

Table 4

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

		Model 1*			Model 2†		
Measures	**Class Comparisons (ref class: Class 1)**	**Coeff**	**95% CI**	**p-value‡**	**Coeff**	**95% CI**	**p-value‡**
Digit Span (DS)	**1v2 ("Sleep")**	0.005	(-0.074,0.085)	.895	0.001	(-0.079,0.080)	.988
	1v3 ("Sleep & Worry")	-0.042	(-0.141,0.058)	.413	-0.061	(-0.160,0.039)	.234
	1v4 ("Sleep & Anhedonia")	0.024	(-0.095,0.142)	.696	0.016	(-0.103,0.135)	.795

	1v5 ("Depression & Anxiety")	-0.086	(-0.209,0.036)	.165	-0.091	(-0.214,0.032)	.146
Paired Associate Learning (PAL)	**1v2 ("Sleep")**	-0.017	(-0.072,0.037)	.538	-0.031	(-0.085,0.024)	.268
	1v3 ("Sleep & Worry")	-0.034	(-0.104,0.037)	.348	-0.070	(-0.141,0.001)	.052
	1v4 ("Sleep & Anhedonia")	-0.137	(-0.220,-0.053)	.001	-0.161	(-0.245,-0.077)	<.001
	1v5 ("Depression & Anxiety")	-0.058	(-0.144,0.028)	.189	-0.091	(-0.179,-0.004)	.042
Spatial Working Memory (SWM)	**1v2 ("Sleep")**	-0.128	(-0.277,0.020)	.090	-0.163	(-0.311,-0.015)	.031
	1v3 ("Sleep & Worry")	-0.154	(-0.345,0.037)	.114	-0.243	(-0.434,-0.052)	.013
	1v4 ("Sleep & Anhedonia")	-0.170	(-0.400,0.061)	.149	-0.258	(-0.489,-0.028)	.028
	1v5 ("Depression & Anxiety")	-0.472	(-0.709,-0.235)	<.001	-0.569	(-0.809,-0.330)	<.001
Verbal Reasoning (VR)	**1v2 ("Sleep")**	0.128	(-0.271,0.527)	.528	0.024	(-0.369,0.416)	.905
	1v3 ("Sleep & Worry")	0.490	(-0.015,0.995)	.057	0.217	(-0.286,0.720)	.397
	1v4 ("Sleep & Anhedonia")	-0.174	(-0.777,0.429)	.572	-0.239	(-0.840,0.363)	.437
	1v5 ("Depression & Anxiety")	-0.529	(-1.151,0.094)	.096	-0.593	(-1.218,0.032)	.063

CI = Confidence Intervals; Coeff = Unstandardised Beta Coefficients.

* Model 1 compares classes controlling for baseline cognition at T0.

† Model 2 additionally controls for gender, marital status, education, employment status, age, alcohol consumption, and total number of trials completed prior to T2 (ie. across T0 and T1).

‡ p <.05 indicated statistically significant between-class differences.

Figure 1. LCA plot* showing item response probabilities for 5-class solution (N = 21,684)

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

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Drafting of the initial manuscript: Dr Timothy Singham, Dr Rob Saunders, Dr Josh Stott
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Conflict of interest

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Dr Helen Brooker is a former employee of Wesnes Cognition, who have developed and supplied some of the tests used in this paper. She has also carried out Consultancy work for Exeter university on the development of the PROTECT Platform and owns her own cognitive tests.
Dr Adam Hampshire is the owner of Future Cognition, who helped develop some of the tests used in this paper.
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Highlights

- Latent Class Analysis identified five distinct subtypes of affective symptoms
- Class membership was significantly associated with longitudinal change in cognition
- Associations differed across different cognitive measures
- Identifying at-risk subgroups may hold the key to more targeted prevention work

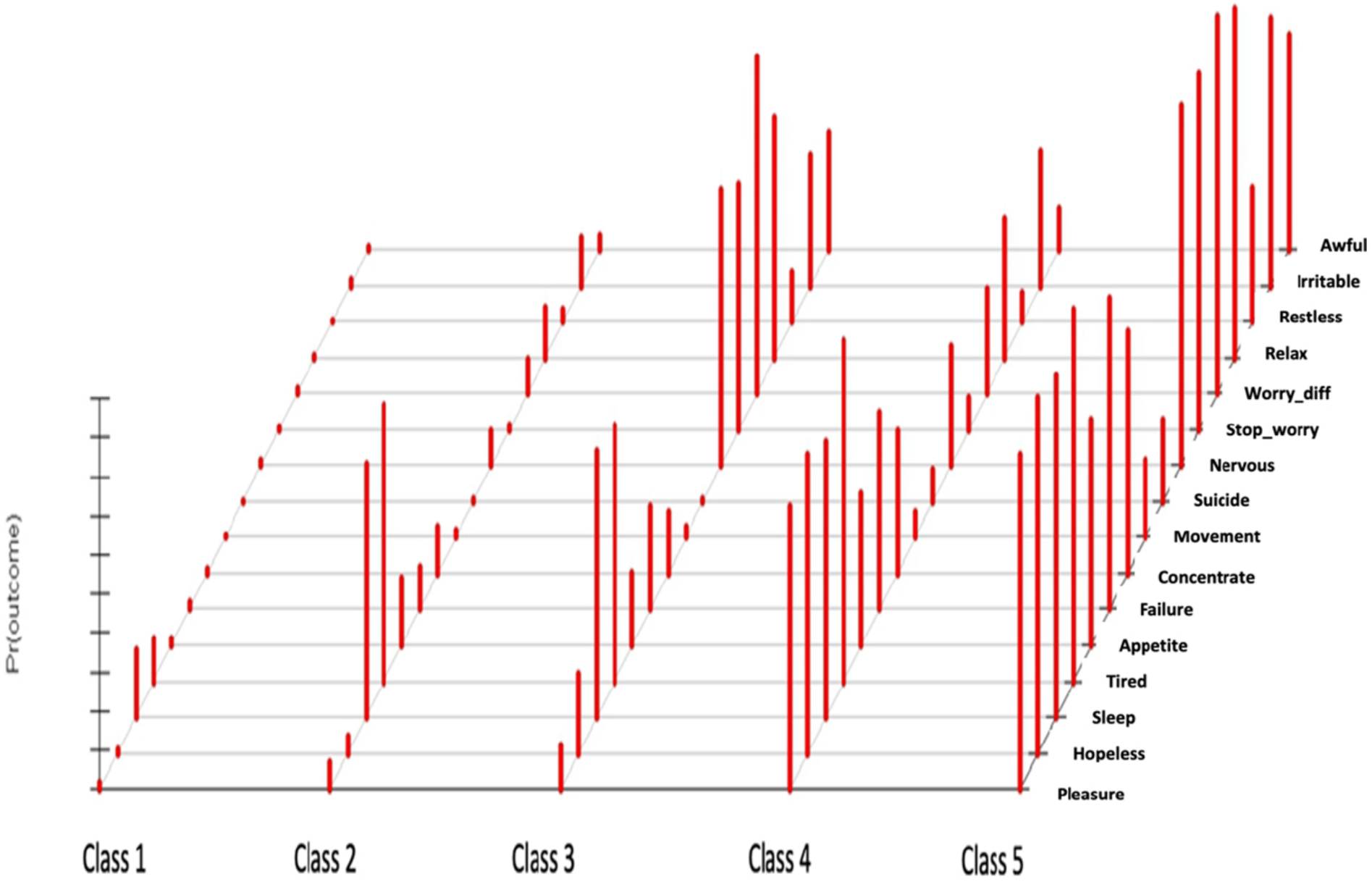
Pr(outcome)
Class 1
Class 2
Class 3
Class 4
Class 5
Awful
Irritable
Restless
Relax
Worry_diff
Stop_worry
Nervous
Suicide
Movement
Concentrate
Failure
Appetite
Tired
Sleep
Hopeless
Pleasure

Figure 1