Affective symptoms across the life course and resilience in cognitive function

Georgia Bell[1*], Amber John[1*], and Darya Gaysina[1]

1 School of Psychology, University of Sussex, Brighton, United Kingdom

**Joint first authors*

Correspondence to: Dr Darya Gaysina, EDGE Lab, School of Psychology, Pevensey 1, University of Sussex, Brighton, BN1 9GH, UK; email: D.Gaysina@sussex.ac.uk

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Abstract

Background

Little is known about what factors can modify the relationship between affective symptoms and cognitive function across the life course.

Aim

To investigate a number of factors that can contribute to resilience in cognitive function in relation to affective symptoms, using data from the National Child Development Study.

Methods

Adult affective symptoms were reported using the Malaise Inventory Scale (ages 23, 33, 42 and 50). Measures of immediate and delayed memory, verbal fluency and information processing accuracy (age 50) were used to derive measures of resilience in cognitive function - better than predicted cognition, when accounting for experiences of affective symptoms. Factors contributing to resilience in cognitive function were informed by a literature review and included sex, childhood cognitive ability, education, household SEP, midlife SEP, and *APOE* genotype. Linear regression and structural equation modelling approaches were used for analyses.

Results

Higher childhood cognitive ability, educational level, midlife SEP, and female sex, contributed to better than predicted cognitive function in relation to affective symptoms (i.e., resilience), with particularly consistent effects for memory. No effects on resilience were revealed for *APOE genotype*.

Conclusion

Understanding factors contributing to resilience in cognitive function in those with affective symptoms can inform interventions to promote healthy cognitive aging for those at risk.

Keywords: affective disorders; depression; anxiety; APOE; cognitive function; memory; resilience; cohort

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Data availability statement

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Introduction

With an increasing ageing population (Hayter 2017), research into healthy cognitive ageing is more relevant than ever. In addition to the association between older age and cognitive decline (Deary, Corley, Gow, Harris, Houlihan, Marioni, Penke, et al. 2009; Murman 2015), dementia is becoming more prevalent with estimates suggesting that 1 in 14 people over the age of 65 have dementia in the UK (Alzheimer's Society 2017). Therefore, research investigating risk and protective factors can have important implications identifying people who are at greater risk of cognitive decline and offering early intervention. Further, affective problems, such depression and anxiety, are highly prevalent among adults in the UK and worldwide (NICE 2011). Therefore, it is also important to understand lifetime effects of affective problems on cognitive ageing.

There is accumulating evidence for an association between affective problems and various cognitive functions, suggesting that symptoms or disorders experienced throughout the lifetime increase risk of cognitive decline and dementia in later life (Da Silva, Gonçalves-Pereira, Xavier and Mukaetova-Ladinska 2013; Cherbuin, Kim and Anstey 2015; Gulpers, Ramakers, Hamel, Köhler, Voshaar and Verhey 2016; John, Patel, Rusted, Richards and Gaysina 2018). However, less is known about what factors are associated with better than predicted cognitive function (or resilience in cognitive function), following the exposure to adverse experiences – affective symptoms across the life course (Rutter, 2012). This concept 'resilience' is different from the concept of 'cognitive reserve' or 'cognitive resilience' that refer to resilience against neurodegeneration and neuropathological damage (Stern 2002; 2009).

As little research has specifically focused on resilience in cognitive function in relation to affective problems (Gallagher, Kiss, Lanctot and Herrmann 2016), the present study aims to address this gap in the literature. First, in order to identify possible modifying

factors contributing to resilience in those with affected symptoms, we reviewed studies included in two existing systematic literature reviews on dementia (Da Silva, Gonçalves-Pereira, Xavier and Mukaetova-Ladinska, 2013) and cognitive decline (John, Patel, Rusted, Richards and Gaysina, 2018). These were selected as they both investigate associations between affective symptoms or disorders and cognitive function; excluded studies of samples with cognitive impairment at baseline; and tested modifying effects of various factors (mainly using interactive terms with affective symptoms/disorders) in relation to dementia or cognitive decline (additional information regarding the screening process and inclusion/exclusion criteria for this review can be found in the supplementary material).

To summarize results for modifying effects of sociodemographic factors (see Supplementary Table 1), significant associations between depressive symptoms and an increased risk of cognitive decline (Chang and Tsai 2015) and dementia (Fuhrer, Dufouil and Dartigues 2003; Dal Forno, Palermo, Donohue, Karagiozis, Zonderman and Kawas 2005) were shown in men only. However, four studies found no significant interaction for sex (Geerlings, Bouter, Schoevers, Beekman, Jonker, Deeg, Van Tilburg et al. 2000; Wilson, Mendes de Leon, Bennett, Bienias and Evans 2004; Dotson, Beydoun and Zonderman 2010; Lenoir, Dufouil, Auriacombe, Lacombe, Dartigues, Ritchie and Tzourio 2011), and one found a significant interaction only when the definition of depression included antidepressant medication use (Saczynski, Beiser, Seshadri, Auerbach, Wolf and Au 2010). No significant interactions were found for race (Wilson, Mendes de Leon, Bennett, Bienias and Evans 2004) or age (Bassuk, Berkman and Wypij 1998; Geerlings, Bouter, Schoevers, Beekman, Jonker, Deeg, Van Tilburg et al. 2000; Wilson, Mendes de Leon, Bennett, Bienias and Evans 2004; Lenoir, Dufouil, Auriacombe, Lacombe, Dartigues, Ritchie and Tzourio 2011), with the exception of one study suggesting that there may be an adverse impact of depressive symptoms for older individuals (75+ years) only (Dotson, Resnick and Zonderman 2008).

Next, studies that considered an interaction between education and depressive symptoms found inconsistent results. Findings from Geerlings, Bouter, Schoevers, Beekman, Jonker, Deeg, Van Tilburg et al (2000) suggest that depression was significantly associated with an increased risk of cognitive decline in participants with higher levels of education (8+ years) only, whereas Pálsson, Aevarsson and Skoog (1999) found an association in participants with lower levels of education (6 years or less) only. Additionally, one study found no significant interaction (Wilson, Mendes de Leon, Bennett, Bienias and Evans 2004). Further, a significant interaction was found for socioeconomic status (SES) (Chiao and Weng 2016), suggesting that midlife SES advantage may be a protective factor.

When considering genetic factors, there appears to be mixed evidence for the interaction effect of *Apolipoprotein E (APOE)* genotype. *APOE* is primarily involved in metabolism, transporting cholesterol and providing information to create fat-binding proteins. Polymorphisms of *APOE* include three main alleles (ε2, ε3, ε4), with ε3/3 being the most common genotype. Three studies found no significant interaction (Steffens, Plassman, Helms, Welsh-Bohmer, Saunders and Breitner 1997; Köhler, van Boxtel, van Os, Thomas, O'Brien, Jolles, Verhey and Allardyce 2010; Lenoir, Dufouil, Auriacombe, Lacombe, Dartigues, Ritchie and Tzourio 2011), suggesting that the effect of *APOE* genotype on cognitive function may be independent from and additive to the effects of depressive symptoms. Studies that reported significant interactions found that the ε4 allele acted as a risk factor for cognitive decline (Niti, Yap, Kua and Ng 2009; Rajan, Wilson, Skarupski, Mendes de Leon and Evans 2014) and risk of dementia (Irie, Masaki, Petrovitch, Abbott, Ross, Taaffe, Launer and White 2008; Kim, Kim, Bae, Kim, Shin, Yang, Song and Yoon 2010). However, the interaction found by Kim et al (2010) was only significant in men, and Irie et al's (2008) sample only consisted of male participants. Notably, as all of these studies investigated *APOE* genotype either in terms of whether the ε4 allele was present (ε2/4, ε3/4, and ε4/4) or absent (ε2/2, ε2/3,

and ε3/3) or in terms of the number of ε4 alleles present (0, 1, or 2), the possible protective effect of the ε2 allele was not considered.

Lastly, additional factors that produced significant interactions included church attendance (Reyes-Ortiz, Berges, Raji, Koenig, Kuo and Markides 2008), leisure-time physical activity (LTPA) (Chang and Tsai 2015), hypertension (Fuhrer, Dufouil and Dartigues 2003), and cardiovascular profile (Bassuk, Berkman and Wypij 1998).

The present study investigates the role of a number of factors potentially important for resilience in cognitive function in relation to affective symptoms, as informed by these two literature reviews: sex, childhood cognitive ability, education, household SEP, midlife SEP, and *APOE* genotype, using longitudinal data from the National Child Development Study (NCDS).

Method

Sample

The NCDS is comprised of over 17,000 participants from England, Scotland and Wales who were born in the same week in 1958 (Power and Elliott 2005). These individuals were followed throughout their lives, with regular data collection time-points. For this analysis, 9377 participants who took part in the biomedical survey at age 45 were included. This involved tests and self-report measures for a variety of social, medical and health factors (Fuller, Power, Shepherd and Strachan 2006). From this, participants with missing data on at least one key variable were excluded (N = 6029). Of the remaining 3348 participants, those with the *APOE* ε2/4 genotype (N = 91) were also excluded as this genotype includes both a risk allele (ε4) and a protective allele (ε2). A total sample of 3257 participants was available for the analyses.

Measures

In the NCDS, a variety of data was gathered using both qualitative and quantitative methods at ages 7, 11, 16, 23, 33, 42, 46, 50, and 55. This included information regarding social and physical development, educational and economic circumstances, health behaviours, wellbeing, and attitudes (CLS [date unknown]). The relevant measures used in this research are discussed below (CLS 2008a; 2008b; 2008c; 2012; 2014).

Affective symptoms. The Malaise Inventory scale (Rutter, Tizard and Whitmore 1970) was used to measure affective symptoms at ages 23, 33, 42 and 50. This includes 24 'yes-no' items relating to physiological and psychological symptoms, such as "Do people annoy and irritate you?" and "Do you often have bad headaches?". A score of 8 or higher was used as the cut-off to indicate the presence of affective symptoms (Hope, Power and Rodgers 1999; Sacker and Cable 2006; Lacey, Bartley, Pikhart, Stafford, Cable and Coleman 2012). At age 50, a 9-item version of the Malaise Inventory scale was administered, in which a score of 4 or higher was used to indicate the presence of affective symptoms (Bowling, Pikhartova and Dodgeon 2016). For the purpose of this analysis, participants were coded at each of the 4 time points as either having no affective symptoms present (0) or affective symptoms present (1). These were then totalled for each participant to form a lifetime affective symptoms accumulation score (John, James, Patel, Rusted, Richards and Gaysina 2019a). This accumulation score was used as the predictor variable in the initial analyses.

Cognitive function. Adult cognitive function measures are available at age 50 (Brown and Dodgeon 2010). This includes measures of immediate and delayed memory, verbal fluency, and information processing speed and accuracy. Memory was assessed using a word list recall test that involved 10 common words read aloud by an interviewer. Participants had two minutes to recall as many as possible (immediate memory). After a five minute interval in which other cognitive assessments were conducted, participants were asked to recall the word list again (delayed memory). Participants received scores out of 10 for each memory domain.

Verbal fluency was measured using an animal naming task, which is commonly used to assess organisation and mental flexibility. In this, participants had one minute to name as many different types of animals as possible. Information processing speed and accuracy were assessed using a letter cancellation task in which participants were presented with a page of random letters (26 rows, 30 columns) and given one minute to cross out as many Ps and Ws as possible. In total, 65 target letters were present. Participants were also instructed to underline the last letter read when the time limit was reached. From this, the total number of letters read was used to assess processing speed and the number of target letters missed (0-65) was used to assess accuracy. Data from all these tests were used as outcome measures of midlife cognitive function.

Resilience in cognitive function. In this study, measures of resilience in cognitive function were derived from the residual scores for each participant in the association between lifetime affective symptoms and cognitive function in each domain at age 50. A positive residual value for immediate memory, delayed memory, verbal fluency, and information processing speed reflects a better than expected performance (i.e., resilience), whereas a negative residual value for information processing accuracy reflects fewer mistakes made than predicted (i.e., resilience).

Factors for resilience in cognitive function. Based on the literature review, this study focusses on testing sex, *APOE* genotype, childhood cognitive ability, educational level, childhood household social economic position (SEP), and midlife SEP as factors contributing to resilience. Sex was coded as a binary variable (male, female). Blood or saliva samples collected at age 45 were used to obtain DNA that was used for *APOE* genotyping. Previous research has investigated *APOE* genotype as a risk factor for cognitive decline (Irie, Masaki, Petrovitch, Abbott, Ross, Taaffe, Launer and White 2008; Niti, Yap, Kua and Ng 2009; Kim, Kim, Bae, Kim, Shin, Yang, Song and Yoon 2010; Rajan, Wilson, Skarupski, Mendes de

Leon and Evans 2014), categorising participants as either ε4 allele present or absent. For the purpose of this analysis, categorising *APOE* genotype in this way was not appropriate to understand possible protective effects of the ε2 allele on cognitive function. Therefore, *APOE* genotype was explored in terms of risk level, with participants being categorised as either high (ε3/ε4 and ε4/ε4), medium (ε3/ε3) or low (ε2/ε3 and ε2/ε2) risk.

In order to explore the linear effect of education, this analysis defined educational level in terms of the highest academic qualification obtained by age 50. As participants included people who studied in England, Scotland or Wales, qualifications were categorised by their equivalents. These groups were no academic qualifications, GCSE level equivalent (low), A level equivalent (medium), and Degree level equivalent (high). Next, both the measures of household SEP at age 11 and midlife SEP at age 50 were categorised as either 'middle', 'intermediate' or 'working' class. In accordance with the guidelines proposed by the CLS (Elliott and Lawrence 2014), household SEP was determined by considering the father's occupation, mother's occupation, and tenure of accommodation, whereas midlife SEP reflects the participant's occupation. Lastly, childhood cognitive ability was assessed at age 11 using the General Ability Test (Douglas 1964). This was administered by teachers and included both verbal (N = 40) and non-verbal (N = 40) items. The tasks involved the child receiving a set of three related words (verbal) or symbols (non-verbal) and asked to identify from a list of five alternatives which word/symbol should fill the blank. The total score (maximum of 80 marks) from this test was used as the continuous measure of childhood cognitive ability.

Ethical considerations

Genetic data (i.e., *APOE* genotypes), were specifically requested from and approved by the METADAC committee (Reference ID: MDAC-2017-0022-01-GAYSINA. https://www.metadac.ac.uk/), who manage applications for genetic and biomedical data from

multiple longitudinal studies including the NCDS. All data was securely stored, with only the relevant persons involved in this research having access.

Analytical procedure

Using the NCDS data, analyses were conducted using the software RStudio (Studio R 2012), IBM SPSS Statistics 23 (IBM Corp. 2015), and MPlus (Muthén and Muthén, 1998-2011). First, in order to examine the effect of missing data, the sample with all data available was compared on key variables to the sample with missing data using t-tests and chi-squared tests. Additionally, key sociodemographic characteristics of the included sample were explored.

Next, the associations between lifetime affective symptoms and different cognitive domains in midlife were explored using linear regression models. For each model, the residual scores for each participant were saved to create a new variable that reflected a score of resilience for each cognitive domain.

For the next part of the analyses, the key variables of interest and childhood cognitive ability were analysed. Linear regression models were fitted to the data to investigate whether these factors explained the difference between the predicted and obtained cognitive function values (i.e., resilience scores). Additionally, each factor was explored in a combined model using multiple regression models. This was used to explore the individual effect of each factor while accounting for the effects of the other variables.

Finally, in order to investigate effects of each modifying factor independent of one another, a Structural Equation Modelling (SEM) approach was used. Potential modifying factors were included in the model predicting residual scores. Information processing speed was removed from the model due to a non-significant initial association between accumulation of affective symptoms and this cognitive domain. Model fit was assessed using chi-square test of model fit, CFI, TLI, and RMSEA. Standardised coefficients are presented.

In this analysis, information processing accuracy, *APOE* (coded from 1-5: ε4/4; ε4/3; ε3/3), household SEP, and adult SEP variables were all reverse coded, so positive scores always represent better than predicted cognitive function (i.e., resilience). Covariances between information processing accuracy and immediate memory/verbal fluency were not significant. These were therefore removed from the model to improve model fit. Covariances between all other cognitive domains were retained in the model. Missing data was dealt with using FIML. Finally, a sensitivity analysis was conducted, in which the multiple imputation technique was applied to the data using MICE in R (Azur, Stuart, Frangakis and Leaf 2011; Buuren and Groothuis-Oudshoorn 2010). The same procedure was used for the imputation as in previous research (John, James, Rusted, Richards, Gaysina 2019a; 2019b).

Results

Sample and missing data

Comparisons between the included (N = 3257) and excluded sample (N = 6120) revealed that the included sample had significantly higher immediate memory scores (M = 6.69, SD = 1.44, t(7188.26) = -4.80, p < .001), delayed memory scores (M = 5.57, SD = 1.78, t(7234.14) = -4.08, p < .001), verbal fluency scores (M = 22.71, SD = 6.33, t(8129) = -3.30, p = .001), and childhood cognitive ability (M = 47.25, SD = 14.60, t(7345.24) = -8.95, p < .001) than the excluded sample (immediate memory: M = 6.53, SD = 1.50; delayed memory: M = 5.40, SD = 1.87; verbal fluency: M = 22.24, SD = 6.25; childhood cognitive ability: M = 44.19, SD = 15.81). Additionally, the included sample scored lower on information processing accuracy (M = 4.14, SD = 3.87, t(7199) = 3.23, p = .001) than the excluded sample (M = 4.43, SD = 4.05). Significant differences between samples were also found for lifetime affective symptoms accumulation (X^2(4) = 53.88, p < .001), education (X^2(3) = 146.31, p < .001), and SEP at age 11 (X^2(2) = 17.78, p < .001). No significant differences were found between samples for information processing speed (p = .35), sex (p = .06), *APOE* genotype (p = .83), or SEP at age 50 (p = .43). The descriptive statistics for the included sample are presented in Table 1. From this, it appears that the male to female ratio was approximately equal (51.1% male). Further, the majority of participants had the *APOE* ε3/3 genotype (59.9%), GCSE level equivalent qualifications (54.3%), were of intermediate (38.9%) or working (38.9%) class household SEP and middle class midlife SEP (49.3%), and had not experienced any affective symptoms at any time points (81.1%). On average, this sample recalled 6.69 (SD = 1.44) words on the immediate memory word list recall test and 5.57 (SD = 1.78) words on the delayed memory recall test, named 22.71 (SD = 6.33) animals on the animal naming task, read 334.71 (SD = 88.19) words on the letter cancelation task but missed 4.14 (SD = 3.87) target letters, and scored 47.25 (SD = 14.60) marks on the General Ability Test.

Affective symptoms and resilience in cognitive function

Research from John, James, Patel, Rusted, Richards and Gaysina (2019a) has previously investigated the association between accumulative affective symptoms and different cognitive functions at midlife using the data from the NCDS 1958 birth cohort. Findings revealed significant associations for immediate memory, delayed memory and information processing accuracy, but not for information processing speed or verbal fluency. However, when trajectories of affective symptoms were considered, a significant association was found for verbal fluency for the initially high and increasing affective symptoms trajectory compared with those with no affective symptoms. For the purpose of this study, only cognitive domains with known associations with affective symptoms were considered.

A linear regression model was used to predict midlife cognitive functions using lifetime affective symptoms accumulation score. From this, the participants' residual scores for each cognitive domain were used to create measures of resilience.

Factors contributing to resilience

Model 1. Linear regression models were used to investigate whether the possible protective factors are associated with resilience in different cognitive domains (see Table 2). Results revealed that female sex was significantly associated with higher resilience in immediate (b = .34, SE = .05, $p < .001$) and delayed memory (b = .53, SE = .06, $p < .001$), but not verbal fluency (p = .41) or information processing accuracy (p = .20). Next, higher levels of academic qualification were significantly associated with resilience in immediate memory (b = .16, SE = .01, $p < .001$), delayed memory (b = .20, SE = .01, $p < .001$), and verbal fluency (b = 0.78, SE = .05, $p < .001$), but not information processing accuracy (p = .14). For childhood cognitive ability, higher scores were significantly associated with higher resilience in all cognitive domains (immediate memory: b = .03, SE = .002, $p < .001$; delayed memory: b = .03, SE = .002, $p < .001$; verbal fluency: b = .13, SE = .01, $p < .001$; information

processing accuracy: b = -.04, SE = .01, p < .001). Middle class household SEP was associated with lower resilience in immediate memory compared with working and intermediate class (Working: b = .43, SE = .07, p <.001; Intermediate: b = .11, SE = .06, p = .045). Additionally, lower household SEP significantly predicted lower resilience scores in delayed memory (Intermediate vs working: b = .18, SE = .07, p = .008; Middle vs working: b = .55, SE = .08, p < .001), and verbal fluency (Intermediate vs working: b = 1.66, SE = .25, p < .001; Middle vs working: b = 3.02, SE = .29, p < .001), but only intermediate SEP predicted resilience in information processing accuracy compared with working SEP (b = .33, SE = .15 p = .03), but middle SEP did not significantly differ from working SEP (p = .61). Similarly, lower midlife SEP significantly predicted lower resilience scores in immediate memory (Intermediate vs working: b = .53, SE = .07, p < .001; Middle vs working: b = .70, SE = .06, p < .001), delayed memory (Intermediate vs working: b = .63, SE = .09, p < .001; Middle vs working: b = .90, SE = .08, p < .001), verbal fluency (Intermediate vs working: b = .84, SE = .31, p = .007; Middle vs working: b = 2.71, SE = .29, p < .001), and information processing accuracy (Intermediate vs working: b = .46, SE = .19, p = .02; Middle vs working: b = .35, SE = .18, p = .049).

No significant associations were found for APOE genotype and resilience scores (high risk versus medium: immediate memory: p = .83; delayed memory: p = .98; verbal fluency: p = .09; information processing accuracy: p = .63; high risk versus low: immediate memory: p = .53; delayed memory: p = .16; verbal fluency: p = .76; information processing accuracy: p = .11).

Model 2. Multiple regression models were used to investigate the individual effects of each protective factor in predicting cognitive resilience in different cognitive domains, whilst accounting for the effects of the other factors (see Table 2). From the results, it appears that these models significantly predicted cognitive resilience in all cognitive domains, accounting

for 10.7% of the variance in cognitive resilience scores in immediate memory ($F(9, 3247) = 43.4$, $p < .001$, $R^2 = .11$), 12.0% in delayed memory ($F(9, 3247) = 49.4$, $p < .001$, $R^2 = .12$), 11.9% in verbal fluency ($F(9, 3247) = 48.7$, $p < .001$, $R^2 = .12$), and 2.61% in information processing accuracy ($F(9, 3247) = 9.65$, $p < .001$, $R^2 = .03$).

Female sex was significantly associated with higher cognitive resilience in immediate memory ($b = .23$, $SE = .05$, $p < .001$), delayed memory ($b = .42$, $SE = .06$, $p < .001$), and information processing accuracy ($b = -.38$, $SE = .14$, $p = .01$). Higher levels of academic qualification were significantly associated with greater cognitive resilience in immediate memory ($b = .09$, $SE = .01$, $p < .001$), delayed memory ($b = .11$, $SE = .02$, $p < .001$), and verbal fluency ($b = .39$, $SE = .06$, $p < .001$). The results for childhood cognitive ability revealed that higher scores remained significant in predicting higher cognitive resilience in all cognitive domains (immediate memory: $b = .02$, $SE = .002$, $p < .001$; delayed memory: $b = .02$, $SE = .002$, $p < .001$; verbal fluency: $b = .09$, $SE = .01$, $p < .001$; information processing accuracy: $b = .04$, $SE = .01$, $p < .001$). Next, household SEP significantly predicted cognitive resilience in verbal fluency (Intermediate vs working: $b = .65$, $SE = .24$, $p = .008$; Middle vs working: $b = 1.11$, $SE = .30$, $p < .001$) and immediate memory (Intermediate vs working: $b = -.12$, $SE = .06$, $p = .04$). Lower midlife SEP was significantly associated with lower cognitive resilience in immediate memory (Intermediate vs working: $b = .25$, $SE = .07$, $p < .001$; Middle vs working: $b = .21$, $SE = .07$, $p = .002$), delayed memory (Intermediate vs working: $b = .21$, $SE = .09$, $p = .02$; Middle vs working: $b = .26$, $SE = .09$, $p = .003$), and information processing accuracy (Intermediate vs working: $b = .47$, $SE = .21$, $p = .02$). Lastly, there was a significant effect of *APOE* genotype on resilience in verbal fluency, but only for the high risk variant vs medium ($b = .51$, $SE = .24$, $p = .04$). When models were re-run on imputed data, results were similar, though midlife SEP no longer significantly predicted resilience in immediate and delayed memory (Supplementary Table 2).

Model 3. The SEM fits the data well ($X^2(2) = 1.74$, $p = .42$; CFI = 1.00; TLI = 1.00; RMSEA = .000). Results are presented in Table 3. Female sex was significantly associated with resilience in immediate ($b = .08$, $SE = .02$, $p < .001$) and delayed ($b = .11$, $SE = .02$, $p < .001$) memory, and information processing accuracy ($b = .13$, $SE = .02$, $p < .001$), but not verbal fluency ($p = .89$). *APOE* genotype did not significantly predict resilience in any cognitive domain. Higher childhood cognitive function was significantly associated with resilience in immediate memory ($b = .19$, $SE = .02$, $p < .001$), delayed memory ($b = .19$, $SE = .02$, $p < .001$), verbal fluency ($b = .20$, $SE = .02$, $p < .001$), and information processing accuracy ($b = .05$, $SE = .02$, $p = .01$). Household SEP significantly predicted resilience in verbal fluency (Intermediate vs working: $b = .05$, $SE = .02$, $p = .01$; Middle vs working: $b = .08$, $SE = .02$, $p < .001$), but not in immediate memory, delayed memory or information processing accuracy. Midlife SEP was significantly associated with resilience in immediate memory (Intermediate vs working: $b = .08$, $SE = .02$, $p = .001$; Middle vs working: $b = .08$, $SE = .02$, $p = .001$), delayed memory (Intermediate vs working: $b = .06$, $SE = .02$, $p = .02$; Middle vs working: $b = .07$, $SE = .02$, $p = .002$). Belonging to the middle SEP rather than working SEP significantly predicted resilience in information processing accuracy ($b = .05$, $SE = .03$, $p = .05$), but intermediate SEP did not differ significantly in resilience from working SEP ($p = .56$). Midlife SEP did not significantly predict resilience in verbal fluency. Finally, education was significantly associated with resilience in immediate memory ($b = .14$, $SE = .02$, $p < .001$), delayed memory ($b = .15$, $SE = .02$, $p < .001$), verbal fluency ($b = .15$, $SE = .02$, $p < .001$), and information processing accuracy ($b = .07$, $SE = .02$, $p = .001$). Results from models conducted on imputed data were substantially very similar, with the main exception being that midlife SEP was no longer significantly associated with resilience in memory outcomes (Supplementary Table 3).

Discussion

This research aimed to investigate factors that contribute to resilience in midlife cognitive function cognitive in relation to lifetime affective symptoms. Overall, the results revealed that higher childhood cognitive ability contributed to resilience in all four cognitive domains. Additionally, a higher level of academic qualification appears to add to resilience in immediate and delayed memory, and verbal fluency. Results showed that higher midlife SEP and female sex may also contribute to resilience in both memory domains. Higher household SEP appeared to contribute to resilience in verbal fluency only. No effects of *APOE* genotype were found on resilience in any cognitive domains. These results remained consistent when models were re-run using imputed data, though midlife SEP was no longer significantly associated with resilience in memory outcomes.

Comparing to previous research using different approaches, these findings generally support the existing evidence on the role of these factors in cognitive function. Childhood cognitive ability was found to be one of the main predictors of cognitive resilience in all cognitive domains. Previous research that has considered the association between childhood cognitive ability and cognitive function independent of affective symptoms has also found this factor to be protective (Richards, Shipley, Fuhrer and Wadsworth 2004; McGurn, Deary and Starr 2008). In relation to education, the findings from previous research were inconsistent (Pálsson, Aevarsson and Skoog 1999; Geerlings, Bouter, Schoevers, Beekman, Jonker, Deeg, Van Tilburg et al. 2000). The present study found an association between higher levels of academic qualification and cognitive resilience in most domains. This appears to support suggestions from Pálsson, Aevarsson and Skoog (1999) for the protective role of more years spent in education. The results for SEP indicate that midlife SEP is a better predictor of cognitive resilience in different domains than household SEP. The findings for midlife SEP are consistent with those from Chiao and Weng (2016), who suggested that

midlife SES advantage may contribute to cognitive resilience and reduce late-life depressive symptoms. Findings for sex appear to be compatible with previous research that found an association between affective symptoms and cognitive decline and risk of dementia in men only (Fuhrer, Dufouil and Dartigues 2003; Dal Forno, Palermo, Donohue, Karagiozis, Zonderman and Kawas 2005; Chang and Tsai 2015). Combining these findings, it would appear that males with affective symptoms may be more at risk of cognitive decline than women with affective symptoms, and that female sex may actually be protective.

Notably, *APOE* genotype results provide no significant evidence for either the protective effect of the ε2 allele or the increased risk associated with the ε4 allele on resilience in cognitive function. Whilst this is inconsistent with previous research that found an effect of *APOE* ε4 on the association between affective symptoms and cognitive decline and risk of dementia (Irie, Masaki, Petrovitch, Abbott, Ross, Taaffe, Launer and White 2008; Niti, Yap, Kua and Ng 2009; Kim, Kim, Bae, Kim, Shin, Yang, Song and Yoon 2010; Rajan, Wilson, Skarupski, Mendes de Leon and Evans 2014), it may contribute to findings from research that did not find a significant interaction (Steffens, Plassman, Helms, Welsh-Bohmer, Saunders and Breitner 1997; Köhler, van Boxtel, van Os, Thomas, O'Brien, Jolles, Verhey and Allardyce 2010; Lenoir, Dufouil, Auriacombe, Lacombe, Dartigues, Ritchie and Tzourio 2011). Research that found no significant *APOE* interactions has suggested that the association between affective symptoms and cognitive function may be independent from the risk of the ε4 allele. Arguably, this may also be true for the protective effects of the ε2 allele, and lend some explanation for the non-significant results found in the present study. However, it should also be noted that in this research the low risk group (ε2/2, ε2/3) consisted of a relatively small number of people (N = 421) in comparison to the other risk groups. Therefore, it is possible that this sample size may have been too small to detect any protective effects of the ε2 allele. Due to the inconsistencies in the literature, it appears that more

research is needed to understand the possible moderating effect of *APOE* in the association between affective symptoms and cognitive function.

The majority of the modifying factors identified in this study are environmental factors, with the exception of female sex. One possible explanation for why these factors may be protective is that they may be associated with more exposure to cognitively stimulating activities. For example, academic learning and certain types of occupations are associated with more cognitive stimulation which may contribute to cognitive reserve in later life (Le Carret, Lafont, Letenneur, Dartigues, Mayo and Fabrigoule 2003; Scarmeas and Stern 2003). Similarly, research has suggested an association between household income and children's exposure to cognitively stimulating activities within the home environment (Votruba-Drzal 2003). Whilst there has been some suggestion for the association between some of these factors, such as an indirect association between household income, parent's education and child's academic achievement (Davis-Kean 2005), this research provides evidence for the effects of these factors on cognitive resilience independently of one another. Instead, it may be that the protective effect on cognitive resilience from each of these factors is amplified with the more protective factors the person has. In other words, the protective effect of these factors may be additive with one another. Therefore, to understand this further, future research could investigate whether having more protective factors is associated with enhanced cognitive resilience.

One strength of this research is that it investigated a range of possible protective factors that were informed by evidence from the relevant literature. This was done to reduce researcher bias and investigate whether the evidence for these factors is reliable. Additionally, this research uses longitudinal secondary data that was well conducted, standardised, had a large sample, and provides a wide variety of data across multiple time points. Furthermore, the NCDS includes repeated measures of the Malaise Inventory scale, enabling the

investigation of lifetime affective symptoms accumulation. Conversely, a possible limitation of using NCDS data relates to the generalisability of the findings. As all participants were born in 1958, environmental differences including technological advancements, divorce rates, and differences in healthcare (Power and Elliott 2005) may mean that some of the data relating to environmental factors is less applicable to current and future populations.

Whilst no genetic interactions were identified, this research does contribute to evidence for the role of certain environmental factors on cognitive resilience. Possible wider implications of this may relate to the early identification of individuals who are at greater risk of cognitive decline amongst those who have experienced affective symptoms. Despite this research being unable to investigate resilience against cognitive decline in later life and risk of dementia, it is also important to understand how early these effects can be detected. Results from this research support those from John, James, Patel, Rusted, Richards and Gaysina (2019a) who found that risk of cognitive decline can be detected as early as midlife, suggesting that it may be possible to identify effects prior to the onset of clinically relevant cognitive impairment. Moreover, present findings also further understanding regarding the effects of protective factors on cognitive resilience in midlife. Identifying modifying factors associated with cognitive resilience in those who have experienced affective symptoms may have implications for early interventions aiming to reduce risk and promote healthy cognitive aging. As previously mentioned, it appears that many of the protective factors identified may be associated with more exposure to cognitively stimulating activities. Therefore, considering the evidence for the benefits of cognitive stimulation therapy (CST) for people with mild to moderate dementia (NICE 2007), perhaps recommending similar interventions at an earlier age would be beneficial for people at greater risk, particularly as this research suggests that protective effects can be seen at age 50.

In conclusion, this research contributes to the existing literature regarding the role of protective factors and cognitive resilience in the association between lifetime affective symptoms and midlife cognitive function in different domains. The present findings suggest that higher childhood cognitive ability, a higher level of academic qualification, higher midlife SEP, and female sex are all associated with cognitive resilience at age 50. However, more research is needed to understand the role of *APOE* genotype on this association.

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Disclosure of interest

The authors report no conflict of interest.

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Appendices

Tables

Table 1. Sample characteristics for the main variables

Characteristic	N (%)	Mean (SD)
Immediate memory	-	6.69 (1.44)
Delayed memory	-	5.57 (1.78)
Verbal fluency	-	22.71 (6.33)
Information processing speed	-	334.71 (88.19)
Information processing accuracy	-	4.14 (3.87)
Childhood cognitive ability	-	47.25 (14.60)
Sex		
Male	1664 (51.1)	-
Female	1593 (48.9)	-
APOE genotype (risk level)		
Low (ε2/2, ε2/3)	421 (12.9)	-
Medium (ε3/3)	1951 (59.9)	-
High (ε3/4, ε4/4)	885 (27.2)	-
Education level		
No qualifications	333 (10.2)	-
Low (GCSE level equivalent)	1770 (54.3)	-
Medium (A level equivalent)	310 (9.5)	-
High (Degree level equivalent)	844 (25.9)	-
Household SEP (age 11)		
Middle	722 (22.2)	-
Intermediate	1268 (38.9)	-
Working	1267 (38.9)	-
Midlife SEP (age 50)		
Middle	1607 (49.3)	-
Intermediate	982 (30.2)	-
Working	668 (20.5)	-
Malaise lifetime accumulation score		
No time points	2642 (81.1)	-
One time point	394 (12.1)	-
Two time points	149 (4.6)	-
Three time points	54 (1.7)	-
Four time points	18 (0.6)	-

Table 2. The association between protective factors and cognitive resilience in different cognitive domains

	Immediate Memory			**Delayed Memory**			**Verbal Fluency**			**Information Processing Accuracy**		
	β	***SE***	***p***	**β**	***SE***	***p***	**β**	***SE***	***p***	**β**	***SE***	***p***
Model 1 (unadjusted)												
Sex	**0.34**	**0.05**	**<.001**	**0.53**	**0.06**	**<.001**	0.18	0.22	.41	-0.17	0.14	.20
APOE												
High vs medium	-0.01	0.06	.83	-0.002	0.07	.98	0.44	0.26	.09	0.08	0.16	.63
High vs low	-0.05	0.08	.53	-0.15	0.10	.16	0.12	0.37	.76	0.37	0.23	.11
Education	**0.16**	**0.01**	**<.001**	**0.20**	**0.01**	**<.001**	**0.78**	**0.05**	**<.001**	-0.04	0.03	.14
Childhood cognitive ability	**0.03**	**0.002**	**<.001**	**0.03**	**0.002**	**<.001**	**0.13**	**0.01**	**<.001**	**-0.04**	**0.01**	**<.001**
Household SEP												
Intermediate vs working	**0.11**	**0.06**	**.045**	**0.18**	**0.07**	**.008**	**1.66**	**0.25**	**<.001**	**0.33**	**0.15**	**.03**
Middle vs working	**0.43**	**0.07**	**<.001**	**0.55**	**0.08**	**<.001**	**3.02**	**0.29**	**<.001**	0.09	0.18	.61
Midlife SEP												
Intermediate vs working	**0.53**	**0.07**	**<.001**	**0.63**	**0.09**	**<.001**	**0.84**	**0.31**	**.007**	**0.46**	**0.19**	**.02**
Middle vs working	**0.70**	**0.06**	**<.001**	**0.90**	**0.08**	**<.001**	**2.71**	**0.29**	**<.001**	**0.35**	**0.18**	**.049**
Model 2 (mutually adjusted)												
Sex	**0.23**	**0.05**	**<.001**	**0.42**	**0.06**	**<.001**	-0.002	0.22	.99	**-0.38**	**0.14**	**.01**
APOE												
High vs medium	-0.00	0.06	.999	0.02	0.07	.78	**0.51**	**0.24**	**.04**	0.06	0.16	.71
High vs low	0.01	0.08	.94	-0.06	0.10	.54	0.34	0.35	.34	0.37	0.23	.11
Education	**0.09**	**0.01**	**<.001**	**0.11**	**0.02**	**<.001**	**0.39**	**0.06**	**<.001**	-0.07	0.04	.052
Childhood cognitive ability	**0.02**	**0.002**	**<.001**	**0.02**	**0.002**	**<.001**	**0.09**	**0.01**	**<.001**	**0.04**	**0.01**	**<.001**
Household SEP												
Intermediate vs working	**-0.12**	**0.06**	**.04**	-0.11	0.07	.11	**0.65**	**0.24**	**.008**	0.14	0.16	.35
Middle vs working	0.01	0.07	.88	0.01	0.08	.88	**1.11**	**0.30**	**<.001**	-0.26	0.19	.18
Midlife SEP												
Intermediate vs working	**0.25**	**0.07**	**<.001**	**0.21**	**0.09**	**.02**	-0.03	0.32	.92	**0.47**	**0.21**	**.02**
Middle vs working	**0.21**	**0.07**	**.002**	**0.26**	**0.09**	**.003**	0.54	0.31	.08	0.16	0.20	.43

Table 3. SEM model of associations between protective factors and cognitive resilience to affective symptoms

	Immediate Memory			**Delayed Memory**			**Verbal Fluency**			**Information Processing Accuracy**		
	β	***SE***	***P***	**β**	***SE***	***p***	**β**	***SE***	***P***	**β**	***SE***	***p***
Sex	**0.08**	**0.02**	**<.001**	**0.11**	**0.02**	**<.001**	0.002	0.02	.89	**0.13**	**0.02**	**<.001**
APOE												
E4/E4 vs E4/E3	0.00	0.02	.998	0.01	0.02	.75	0.03	0.02	.10	-0.01	0.02	.61
E4/E4 vs E3/E3	0.003	0.02	.87	-0.01	0.02	.64	0.02	0.02	.36	-0.01	0.02	.61
Education	**0.14**	**0.02**	**<.001**	**0.15**	**0.02**	**<.001**	**0.15**	**0.02**	**<.001**	**0.07**	**0.02**	**.001**
Childhood cognitive ability	**0.19**	**0.02**	**<.001**	**0.19**	**0.02**	**<.001**	**0.20**	**0.02**	**<.001**	**0.05**	**0.02**	**.01**
Household SEP												
Intermediate vs working	-0.04	0.02	.06	-0.03	0.02	.16	**0.05**	**0.02**	**.01**	-0.03	0.02	.13
Middle vs working	0.003	0.02	.88	-0.002	0.02	.91	**0.08**	**0.02**	**<.001**	0.03	0.02	.21
Midlife SEP												
Intermediate vs working	**0.08**	**0.02**	**.001**	**0.06**	**0.02**	**.02**	0.001	0.02	.97	0.01	0.02	.56
Middle vs working	**0.08**	**0.02**	**.001**	**0.07**	**0.02**	**.002**	0.05	0.02	.054	**0.05**	**0.03**	**.047**

* N = 3334; X2 (2) = 1.74, *p* = .42; CFI = 1.00; TLI = 1.00; RMSEA = .000