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The influence of demographic factors on subjective cognitive concerns and beta-amyloid

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Abstract

Background—Converging evidence suggests that subjective cognitive concerns (SCC) are associated with biomarker evidence of Alzheimer's disease (AD) prior to objective clinical impairment. However, the sensitivity of SCC reports in early AD may be biased by demographic factors. Here, we sought to investigate whether age, education, and sex influence the relationship between SCC and amyloid (A β) burden.

Methods—In this cross-sectional study, we examined 252 clinically normal (CN) individuals (57.7% females) enrolled in the Harvard Aging Brain Study, ages 63–90 years (mean 73.7 $\pm$ 6) with 6–20 years of education (mean 15.8 $\pm$ 3). SCC were assessed as a composite score comprising three questionnaires. Cortical A β burden was assessed with Pittsburgh compound B positron emission tomography imaging. A series of linear regression models assessed the potential modifying role of demographic variables with respect to A β burden and SCC. A *post-hoc* mediation model was

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Conflict of interest
None.

Description of authors' roles

S.L. Aghjayan assisted with data collection and wrote the paper. R.F. Buckley aided with carrying out the statistical analysis and with writing the paper. P. Vannini helped with writing the paper. D.M. Rentz supervised the data collection, collected the data, and assisted with writing the paper. J.D. Jackson collaborated with data collection and with writing the paper. R.A. Sperling designed the study, supervised the data collection, and assisted with writing the paper. K.A. Johnson assisted with the development of the study design, with supervising the data collection, and with writing the paper. R.E. Amariglio assisted with data collection, with carrying out the statistical analysis, and with writing the paper.

implemented to further understand the relationship between A β burden and SCC via their relationship with education.

Results—Age ($\beta = -0.84$, $p = 0.36$) and sex ($\beta = -0.55$, $p = 0.22$) did not modify the relationship between SCC and A β burden. Fewer years of education was correlated with greater SCC ($r = -0.12$, $p = 0.05$), but the relationship between A β burden and SCC was stronger in those with more education ($\beta = 1.16$, $p < 0.05$). A partial mediation effect was found of A β burden on SCC via education ($b = -0.12$, 95% CI $[-0.31, -0.02]$).

Conclusions—These findings suggest that the association between SCC and A β burden becomes stronger with greater educational attainment. Thus, SCC may be of particular importance in highly educated CN individuals harboring amyloid pathology.

Keywords

Alzheimer's disease; positron emission tomography (PET)

Introduction

Increasing evidence suggests that subjective cognitive concerns (SCC) may indicate subtle cognitive decline in clinically normal (CN) older adults that is otherwise undetected using standardized memory tests (Jessen *et al.*, 2014). Cross-sectional studies of CN older adults reveal a relationship between SCC and beta-amyloid (A β) burden, a hallmark biomarker of Alzheimer's disease (AD), further suggesting that SCC arise during the pre-clinical stage of AD (Amariglio *et al.*, 2012; Mielke *et al.*, 2012; Perrotin *et al.*, 2012; Amariglio *et al.*, 2015; Snitz *et al.*, 2015). Previous studies indicate, however, that the meaningfulness of SCC may vary depending on demographic factors, such as age and years of education (Rabin *et al.*, 2015). Thus, the sensitivity of SCC as a risk factor for AD may further increase when examined in targeted demographic populations.

Several cross-sectional, population-based studies have found that fewer years of education are associated with greater SCC (Bolla *et al.*, 1991; Derouesné *et al.*, 1993; Stewart *et al.*, 2008), whereas others have found no significant difference (Kim *et al.*, 2003; Wang *et al.*, 2004; Trouton *et al.*, 2006; Mendes *et al.*, 2008; Benito-León *et al.*, 2010). By contrast, some longitudinal studies have suggested that individuals with greater years of education endorse complaints that are more prognostic of cognitive decline than those with fewer years of education (Geerlings *et al.*, 2000; Jonker *et al.*, 2000; van Oijen *et al.*, 2007). Thus, SCC may be an appealing method for identifying highly educated individuals at risk for AD who are performing normally on standardized memory tests.

With regards to age, several population-based studies have found that SCC steadily increase in individuals without dementia as they age over 65 years (Bolla *et al.*, 1991; Derouesné *et al.*, 1993; Kim *et al.*, 2003; Trouton *et al.*, 2006; van Oijen *et al.*, 2007; Benito-León *et al.*, 2010), although this finding is not consistent across all studies (Geerlings *et al.*, 2000; Mendes *et al.*, 2008; Stewart *et al.*, 2008). Ginó *et al.* (2010) found that different types of concerns may be more salient at different ages, and as such, may confer different meanings across the age spectrum. A prior review found that SCC in the oldest-old denoted possible

early changes associated with dementia, notably in individuals who already demonstrated signs of cognitive impairment (Jonker *et al.*, 2000). By contrast, in CN individuals, findings suggest that SCC may confer greater risk of AD in the younger-old compared to the oldest-old. Wang *et al.* (2004) conducted a longitudinal study that revealed an endorsement of SCC was associated with greater risk of developing dementia in 70 year olds versus those over 80 years. The authors suggested that SCC become more ubiquitous in the oldest-old, and so become unrelated to a specific disease pathology, which reduces the predictive effect of SCC for dementia risk (Wang *et al.*, 2004). These results were corroborated by Zwan and colleagues (2016), who found that SCC predicted greater A β burden in the younger-old compared to the oldest-old.

In terms of sex, findings have been equivocal across several population-based studies. Some studies have found that females report more SCC (Kim *et al.*, 2003; Stewart *et al.*, 2008; Tomita *et al.*, 2014), while another study found that males report more SCC (Wang *et al.*, 2004). Others have found that males and females may potentially report phenomenologically different SCC (Derouesné *et al.*, 1993), and that females use more mnemonic strategies to cope with these perceived changes in comparison with males (Bolla *et al.*, 1991). Yet, other studies found no significant sex differences (Derouesné *et al.*, 1993; Geerlings *et al.*, 2000; Jonker *et al.*, 2000; Trouton *et al.*, 2006; van Oijen *et al.*, 2007; Mendes *et al.*, 2008). It remains unclear whether SCC confer greater risk of AD in men versus women.

In this study, we sought to investigate whether education, age, and sex modify the relationship between SCC and risk for AD in CN older individuals, as measured by level of neocortical A β burden. We hypothesized that age and years of education would modify the relationship, whereby younger age and greater years of education would be associated with a stronger relationship between SCC and A β burden. As the sex literature was relatively equivocal, our analyses regarding the potential modifying role of sex on SCC and A β burden were exploratory.

Methods

Subjects

In the current cross-sectional study, a total of 252 participants were enrolled in the Harvard Aging Brain Study, a longitudinal volunteer-based study conducted at Massachusetts General Hospital. The Partners Human Research Committee approved protocols and informed consent procedures. Participants were CN, defined by a global Clinical Dementia Rating (CDR) (Morris, 1993) score of 0, an age and education-adjusted Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) score greater than or equal to 27, performance above education-adjusted cut-off scores on the Logical Memory IIa (story recall) of the Wechsler Memory Scale-Revised (Wechsler, 1987), and a 30-item Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982) score of less than 11.

All participants' statuses were confirmed to be CN and underwent a detailed review of medical history, functional performance, and a physical and neurological examination. None of the participants had a history of alcoholism, drug abuse, or head trauma; nor did they have a current serious medical or physical illness. All study staff who assessed the participants

clinically, as well as the participants themselves, were blinded to biomarker status. All assessments were conducted within a six-month window. The original sample was 274 participants, but not all participants had interpretable imaging, or received all three components of the SCC composite, which resulted in a final sample of 252 participants.

Demographic measures

Years of education and age were measured continuously. Additional measures of educational attainment and socioeconomic status were included in secondary analyses in order to determine if they demonstrated similar trends with education. These measures included the American version of the National Adult Reading Test (AMNART), a measure of premorbid intelligence (Blair and Spreen, 1989; Ryan and Paolo, 1992), and the Occupation score from the Hollingshead Two-Factor Index of Social Position (Hollingshead, A. B. (1957). Two-factor index of social status. *Unpublished manuscript.*), a measure of socioeconomic status based on educational and occupational attainment. An adjusted GDS score was computed that discarded four questions that overlapped with SCC items.

Subjective cognitive concerns measures

A SCC composite was calculated using the Everyday Memory subscale of the Everyday Cognition (E-Cog) scale, the General Frequency of Forgetting subscale of the Memory Functioning Questionnaire (MFQ), and a set of seven questions that were adapted from the Structured Telephone Interview for Dementia Assessment (STIDA), as described previously (Amariglio *et al.*, 2012). The Everyday Memory subscale of the E-Cog scale is an 8-item self-report measure scored on a Likert scale where a score of 1 = “Better or no change” and a score of 4 = “Consistently much worse.” It was specifically developed to assess cognitive abilities in older adults (Farias *et al.*, 2008). The questions are framed in the context of current performance compared to ten years ago. The General Frequency of Forgetting subscale of the MFQ (Gilewski *et al.*, 1990) is comprised of 32-items scored on a Likert scale where a score of 1 = “Serious problem” and a score of 7 = “Never a problem.” This subscale was specifically developed to assess how an individual would rate his/her memory in terms of the kinds of problems he/she has. The scale has been formally validated. The STIDA questions consist of a set of seven yes or no questions that have been used previously in large epidemiological studies to assess recent difficulty carrying out everyday activities, though it is not formally validated (Amariglio *et al.*, 2011). Answers on these questions (0 = No, 1 = Yes) were added together to create a summary score that was used for the statistical analyses. Raw scores for all three measures were converted into *z*-scores for each participant. All three *z*-scores were subsequently averaged to create a SCC composite score with higher *z*-scores indicating greater SCC. The overall distribution of SCC was slightly skewed due to a few outliers (SCC *z*-score > 2.58; *n* = 3), so analyses were run with and without outliers for comparison.

Positron emission tomography (PET)

PiB-PET was performed as previously described, with 60-minute 3D dynamic acquisition, and expressed as a mean distribution volume ratio (DVR) in a large aggregate of amyloid-vulnerable cortical regions using cerebellar reference (Johnson *et al.*, 2007). Twenty-six

percent of our sample was considered A β positive, which is the same sample previously published (Mormino *et al.*, 2014).

Statistical analyses

A series of separate linear regression models were run using A β burden, education, age, and sex as predictors of SCC. Analyses did not change significantly depending on inclusion of outliers; thus, models were run with the full sample. Covariates for the models were the remaining demographic variables not of interest in the model. For all models, the A β $\times$ demographic variable interaction term was the predictor of interest. For example, $SCC = Education + A\beta + (A\beta \times Education) + Age + Sex$. Secondary analyses were conducted to determine whether AMNART and Occupation score demonstrated similar trends as education in predicting SCC with the interaction between A β burden. We included secondary analyses with adjusted GDS scores as a covariate since this was significantly associated with the SCC composite. Finally, we ran a mediation model as a *post-hoc* test to further understand the relationship between A β burden, education and SCC. We used the Hayes *PROCESS* tool to determine whether the strength of the relationship between A β burden and SCC would be reduced after accounting for education level (Hayes, 2013). We used the Sobel test in order to measure the magnitude of the indirect effect, and presented both the direct and indirect effects in diagrammatic form for ease of interpretation. Significance was set *a priori* as $p < 0.05$. All data were analyzed using SPSS v22.0.

Results

Characteristics of the sample

The participants had an average age of 73 years (range: 63–90 years). Females made up 57.7% of the sample. Average years of education was 15.8 years (range: 6–20), average AMNART VIQ was 120.7 (range 78–132), and the average Occupation score was 2.7 (range: 1–7). While our sample tended toward higher socioeconomic status on all measures, years of education represented the most normally distributed score compared to AMNART and Occupation score. Group means and standard deviations on the SCC questionnaires, screening measures, and demographic variables are presented in Table 1.

Associations between SCC and demographic variables

Years of education was significantly correlated with the SCC composite, whereas AMNART ($r = -0.09$, $p = 0.16$) and Occupation score ($r = 0.06$, $p = 0.33$) were not. Years of education was inversely correlated with SCC, such that individuals with fewer years of education tended to report greater SCC than those with more education ($r = -0.12$, $p < 0.05$). Age was not found to correlate with the SCC composite ($r = 0.10$, $p = 0.11$), although it was at a trend level. There were no significant differences between males and females in their SCC severity ($t(251) = 0.16$, $p = 0.87$) (see Table 2).

Association between SCC and A β burden modified by age, sex, and education

The interaction between years of education and A β burden was found to significantly predict SCC, while controlling for age and sex ($\beta = 1.16$, $p = 0.045$; see Figure 1). The interaction between age and A β burden was not found to predict SCC after controlling for sex and

education ($\beta = -0.84$, $p = 0.36$). The interaction between sex and A β burden was also not found to predict SCC after controlling for age and education ($\beta = -0.55$, $p = 0.22$) (see Table 3).

Using an adjusted GDS score as an additional covariate, we found that the interaction between education and A β burden fell to trend level, although the standardized coefficient was similar ($\beta = 0.90$, $p = 0.10$). In our secondary analyses examining educational attainment and socioeconomic status, we found that neither the interaction between AMNART and A β burden ($\beta = 0.48$, $p = 0.63$), nor the interaction between Occupation score and A β burden ($\beta = -0.09$, $p = 0.85$), modified SCC.

In the mediation model, we found significant direct effects of A β on education level and SCC, and of education level on SCC (see Figure 2). We also found an indirect effect of A β burden on SCC via education that reached statistical significance ($b = -0.12$, 95% CI [-0.31, -0.02]). This suggested multiple mechanisms by which A β could influence SCC. The indirect pathway exhibited, however, a relatively small effect ($K^2 = 0.03$, 95% CI [0.004, 0.07]).

Discussion

In this study, we investigated the modifying role of demographic variables on the relationship between SCC and A β burden in CN older individuals. While fewer years of education was associated with greater overall SCC, interestingly the relationship between A β burden and SCC was stronger in individuals with greater years of education than those with fewer years of education. Furthermore, follow-up analyses revealed that the relationship between A β burden and SCC is indirectly mediated by education. It is important to note that the indirect effect was small, suggesting that other factors also play a role in explaining the variance between these SCC and neocortical A β burden. These findings are consistent with previous reports demonstrating that individuals with fewer years of education endorse greater amounts of complaints (Bolla *et al.*, 1991; Derouesné *et al.*, 1993; Stewart *et al.*, 2008), yet those who are highly educated have complaints that are more prognostic of cognitive decline than those with fewer years of education (Geerlings *et al.*, 2000; Jonker *et al.*, 2000; van Oijen *et al.*, 2007). As such, individuals who are highly educated may be more perceptive of subtle memory changes that are occurring. Those that are highly educated may hold higher positions of employment, making nuanced changes in memory more apparent. Yet, those who have received greater years of education may be better able to compensate for these difficulties, concealing the risk of disease progression. This heightened perceptiveness sits in contrast to standardized objective memory measures, which typically are less sensitive in detecting pathology in individuals with more education (Stern, 2009), although this can be overcome with challenging cognitive measures (Rentz *et al.*, 2010). This suggests that SCC may be of particular importance in highly educated individuals who may be at risk for AD dementia (Rabin *et al.*, 2015).

We also investigated whether premorbid estimates of IQ (i.e. AMNART) and socioeconomic status (i.e. Occupation score of Hollingshead) modified the relationship between SCC and A β burden, but did not find an association. We may have been unable to detect these

associations due to a more restricted range in AMNART and Occupation score compared with years of education.

Greater age trended with increased SCC, although it was not a statistically significant finding. This is in contrast to several previous reports that have found greater age is associated with greater SCC (Bolla *et al.*, 1991; Derouesné *et al.*, 1993; Jonker *et al.*, 2000; Kim *et al.*, 2003; Trouton *et al.*, 2006; van Oijen *et al.*, 2007; Benito-León *et al.*, 2010), although many of these studies included a much wider age span than our more restricted sample. In general, SCC typically increase with age, as perceived memory changes become increasingly more common, but may not necessarily reflect underlying pathology (Wang *et al.*, 2004; Zwan *et al.*, 2016). This is the case, particularly for the oldest-old, for whom the meaningfulness of SCC may be quite different from the younger-old. Furthermore, age did not have a significant modifying role with A β burden and SCC. This finding is in contrast to a previous study (Zwan *et al.*, 2016) that found that SCC predict A β burden in the younger-old group (<73 years old) compared to the older-old group ($\geq$ 73 years old). In contrast with the current study, their sample was enriched for *APOE* ϵ 4 carrier status, which is known to increase the likelihood of greater A β burden and an earlier age of onset of AD symptomatology, perhaps influencing the relationship between age and SCC.

Sex was not associated with SCC, which is consistent with previous studies (Derouesné *et al.*, 1993; Geerlings *et al.*, 2000; Jonker *et al.*, 2000; Trouton *et al.*, 2006; van Oijen *et al.*, 2007; Mendes *et al.*, 2008). Additionally, sex did not play a significant modifying role with A β burden and SCC. Thus, it appears that reports of SCC in both men and women carry equal weight in its association with A β burden.

When we controlled for depression, we found that the interaction between education and A β burden was no longer associated with SCC. However, it is well-known that depressive symptoms, even sub-clinical symptoms, relate more strongly to SCC than cognition or biomarkers. While this relationship is important to explore, the strong association between these two self-report measures can obscure relationships with smaller effect sizes, such as with AD biomarkers in CN individuals. Though these effects are quite modest across a number of studies, they may be the earliest sign of change in the AD process. Thus, SCC studies should consider the role of depressive symptoms, but should not dismiss potential relationships with AD biomarkers if including depressive symptoms attenuates relationships.

Our analyses had several limitations. First, our sample included individuals who are highly educated; the mean level of education was a four-year college degree, which may not generalize to the population at large. Second, a composite measure was created for SCC; combining questionnaires may attenuate the influence of individual variability inherent within each SCC domain and hinder our ability to detect relationships across various aspects of memory that may differentially relate to A β burden (Amariglio *et al.*, 2015). Furthermore, it is possible that other cognitive concerns that are not memory related may also be important in the risk of AD progression.

The current study proposes that consideration of education level when interpreting SCC may improve enrichment of those likely to manifest greater neocortical A β burden. It is important

to determine the earliest point in the AD disease trajectory to intervene when a highly educated individual is concerned about memory changes, as these individuals tend to perform at ceiling on standardized measures of memory, particularly in the context of secondary prevention trials. Likewise, our findings suggest that SCC may be less useful in individuals with fewer years of education, who may report SCC that are unrelated to risk for AD. Further work will be needed to analyze the modifying role education has with SCC and A β burden over time. Ultimately, these findings have important implications in the clinical setting; that is, individuals who report concerns of memory changes but comprise an otherwise normal memory examination should not be disregarded, and should be assessed within the context of their level of educational attainment.

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Figure 1.

Scatter plot of amyloid burden by SCC modified by education group. Education was dichotomized for illustrative purposes (high > 17 : low = 16). The relationship between A β burden and SCC was stronger in individuals with greater years of education than those with fewer years of education.

Figure 2. Model of the mediation analysis of A β burden as a predictor of SCC, and mediated by education. The confidence interval for the indirect effect is bootstrapped based on 1,000 samples (Hayes, 2013).

Table 1

Sample characteristics

Age (years)	73.7 (± 6.0)
Sex (% female)	57.7
Education (years)	15.8 (± 3.0)
AMNART	120.7 (± 9.4)
Occupation	2.7 (± 1.6)
MMSE	29.0 (± 1.1)
GDS	2.3 (± 2.3)
SCC Composite	0.001 (± 0.8)
E-Cog	
MEM	1.6 (± 0.5)
MFQ	
GenFF	5.3 (± 0.9)
STIDA Sum	1.1 (± 1.2)

All values (except sex, SCC composite) represent means $\pm$ SD. SCC composite is reported as a z-score, with a higher z-score indicating higher endorsement of concerns.

Higher scores on the E-Cog refer to greater concerns. Higher scores on the STIDA sum refer to greater concerns. Lower scores on the MFQ refer to greater concerns.

Table 2

Pearson's correlations between the three measures of educational attainment, age, and sex, and the SCC composite

	AMNART	Years of Education	Occupation	Age	Sex [†]	SCC composite
AMNART		$r = 0.43$	$r = -0.30$	$r = -0.01$	$t = -0.21$	$r = -0.09$
		$p < 0.001^*$	$p < 0.001^*$	$p = 0.90$	$p = 0.84$	$p = 0.16$
Years of education			$r = -0.59$	$r = -0.08$	$t = -0.36$	$r = -0.12$
			$p < 0.001^*$	$p = 0.23$	$p = 0.72$	$p < 0.05^*$
Occupation				$r = -0.01$	$t = 1.01$	$r = 0.06$
				$p = 0.84$	$p = 0.31$	$p = 0.33$
Age					$t = -1.57$	$r = 0.10$
					$p = 0.12$	$p = 0.11$
Sex [†]						$t = 0.16$
						$p = 0.87$

* Correlation is significant at the 0.05 level.

[†] p -values are based on correlations, except for sex, where p -values are based on t -tests.

Table 3

Summary of the series of separate linear regression models for an outcome of SCC

Model 1		
Education	$\beta = -1.00$	$p = 0.02$
A β burden	$\beta = -0.42$	$p = 0.21$
Education $\times$ A β	$\beta = 1.16$	$p = 0.045^*$
Age	$\beta = 0.07$	$p = 0.29$
Sex	$\beta = 0.004$	$p = 0.95$
Model 2		
Age	$\beta = 0.46$	$p = 0.29$
A β burden	$\beta = 0.94$	$p = 0.22$
Age $\times$ A β	$\beta = -0.84$	$p = 0.36$
Sex	$\beta = 0.01$	$p = 0.93$
Education	$\beta = -0.16$	$p = 0.01$
Model 3		
Sex	$\beta = 0.55$	$p = 0.22$
A β burden	$\beta = 0.30$	$p < 0.001$
Sex $\times$ A β	$\beta = -0.55$	$p = 0.22$
Age	$\beta = 0.06$	$p = 0.30$
Education	$\beta = -0.15$	$p = 0.01$

* Statistically significant ($p < 0.05$).