Associations Between Objective and Subjective Socioeconomic Status and Amyloid Beta Deposition

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University of Pittsburgh, 2023

Lower socioeconomic status (SES) is associated with risk for developing Alzheimer's disease (AD). However, whether SES is related to amyloid beta (Aβ) pathology among cognitively normal individuals remains unknown. Additionally, we have yet to determine how one's self-perception of social standing may likewise relate to risk for AD. This study addressed these gaps by examining the relationships of objective and subjective SES indices with Aβ.

Data of 352 cognitively normal older adults; average age = 69.37 ($\pm$ 3.53) from Investigating Gains in Neurocognition in an Intervention Trial of Exercise were included in the current analyses. Structural MRI and PET imaging were used to measure amyloid deposition. To capture global Aβ deposition, a composite standardized uptake value ratio (SUVR) was calculated for each participant by averaging the SUVR throughout the brain. Individuals were considered positive for Aβ if their composite SUVR exceeded an a priori cutoff of 1.10. Objective SES was measured using items related to annual income, education, debt, savings, and standard of living maintenance from the MacArthur Socioeconomic Status Index. Subjective SES was measured using the US ladder from the MacArthur Socioeconomic Status Index.

Linear and logistic regression models revealed that after controlling for age and study site, objective and subjective SES were negatively associated with Aβ levels and those with lower levels of objective and subjective SES were more likely to meet criteria for Aβ positivity. Annual income was only associated with Aβ levels, while years of education was not associated

with Aβ levels nor Aβ positivity. However, when including annual income and years of education in a single regression model, annual income was no longer significantly associated with Aβ levels. Lastly, when including annual income and subjective SES in a single model, the association between annual income and Aβ levels was no longer significant; however, the association between subjective SES and Aβ levels remained significant. Similarly, subjective SES remained significantly associated with Aβ positivity even when controlling for annual income.

These findings may suggest that objective and subjective indices of SES explain significant variation in Aβ levels in cognitively normal older adults, which may help to explain disparities in AD diagnosis attributable to educational, income, and social inequalities.

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1.0 Introduction

Alzheimer's disease (AD) is a form of dementia primarily characterized by brain atrophy, severe cognitive deficits, behavioral changes, and an accumulation of Aβ and tau (Alzheimer's disease facts and figures, 2020). AD affects approximately 5.8 million people in the United States and this number is expected to rise to nearly 14 million by the year 2050 (Alzheimer's disease facts and figures, 2020). Being older, having the ε4 allele of the apolipoprotein E (APOE) gene, elevated blood pressure, excess body fat, diabetes, and engaging in lower levels of physical activity are well-established risk factors for AD (Di Battista, Heinsinger, & Rebeck, 2016;Kennelly, Lawlor, & Kenney, 2009; Profenno, Porsteinsson, & Faraone, 2010; Erickson, Weinstein, & Lopez, 2012). Additionally, emerging evidence has suggested that socioeconomic factors may be contributing to the AD crisis. Indeed, individuals of lower SES appear more likely to develop AD; however, limitations of prior studies have hampered the ability to address key questions surrounding the association between SES and risk for AD. Such limitations include: how SES is conceptualized and measured, a lack of Aβ neuropathological data and a focus solely on cases of AD that have been clinically diagnosed. The current study addresses the limitations of prior studies by examining whether SES associates with Aβ in a sample of cognitively normal (no diagnosis of AD) older adults. While these participants may not have AD-like cognitive deficits, Aβ pathology can still be found among up to 40% of cognitively normal individuals (Chételat et al., 2013; Mattson et al., 2015; Jagust, 2016). Furthermore, Aβ likely leads to later development of cognitive deficits (Jagust, 2016). As such, exploring whether SES associates with Aβ in individuals who have yet to develop the cognitive/memory symptoms of AD presents a unique opportunity to test whether measures of social stratification may be influencing levels of Aβ and contributing to higher rates of AD.

1.1 What is Socioeconomic Status?

Broadly, socioeconomic status (SES), also known as socioeconomic position, refers to an individuals' social standing based on economic, educational, and occupational factors. SES is a complex, multilevel, and multifaceted construct that requires the use of several indicators for its complete measurement (Gianaros & Manuck, 2010; Matthews & Gallo, 2012). Two ways in which indicators of SES have typically been categorized are 1) "subjective" or 2) "objective" (Adler, 2006). Objective SES quantifies standing in a social hierarchy by taking into account income, education, occupation, or a composite score of these dimensions (Winkleby, Jatulis, Frank, & Fortmann, 1992). Subjective SES refers to one's conceptualization of themselves as where they stand in a social hierarchy (Jackman & Jackman, 1973; Shaked, Williams, Evans, & Zonderman, 2016). Subjective SES is often regarded as a "cognitive averaging" of objective SES factors; in other words, it is believed that individuals consider multiple aspects of objective SES dimensions when formulating the perception of their SES (Gianaros & Manuck, 2010).

Subjective SES is often assessed using the MacArthur Scale of Subjective Social Status, which measures perceived social standing relative to others in a given society (Adler, Espel, Castellazzo, & Ickovics, 2000). There are two versions of the MacArthur Scale of Subjective Social Status; one version presents a "SES (United States) ladder", and the other version presents a "community ladder". The SES ladder, which assesses subjective SES, asks individuals to consider money, education, and occupational prestige and rank themselves relative to others in the United States (Adler, Espel, Castellazzo, & Ickovics, 2000). The community ladder, which assesses subjective social standing, asks individuals to consider their standing in the "most meaningful" community they belong to and rank their standing relative to others in their community. Subjective community ladder rankings are thought to be independent of

educational, occupational, and financial anchors for respondents. As a result, and unsurprisingly, compared to the community ladder, the SES ladder has been shown to relate more to the traditional objective indices of SES such as occupational position, education, and household income (Singh-Manoux, Adler, & Marmot, 2003). In these regards, the community ladder differs conceptually from the SES ladder such that it is able to capture perceptions of social standing relative to others in the community independently of education, income, and occupational prestige. Furthermore, as compared to the SES ladder, the community ladder may track more closely with psychosocial characteristics such as stress, depressive and anxiety symptoms (Ghaed & Gallo, 2007; Diaz, Guendelman, & Kuppermann, 2014; Zvolensky et al., 2017).

1.2 Does Socioeconomic Status Relate to Health?

Objective and subjective measures of SES associate with a variety of health outcomes such as: cardiovascular disease, hypertension, diabetes, metabolic syndrome, age-related cognitive impairment, and risk for Alzheimer's disease (Adler & Newman, 2002; Robins, Vaccarino, Zhang, & Kasi, 2005; Leng, Jin, Li, Jin, 2015; Manuck et al., 2010; Evans et al., 1997; Stern et al., 1994; Karp et al., 2004). Indeed, SES associates with health outcomes in a gradient like fashion such that risk for these conditions is inversely related to SES in a linear fashion (i.e., across declining levels of SES, risk for poorer health outcomes increases) (Adler & Ostrove, 1999). However, early work examining SES related disparities in health, evaluated SES standing based on whether income was above or below the poverty line (Adler & Ostrove, 1999).

The underlying assumption of the threshold model was that disparities in health primarily existed among those below the poverty line (Adler & Ostrove, 1999). While evidence for health disparities exists among those below the poverty line, evidence following the mid 1980s suggest that a gradient model more accurately captures the nuances in SES related health disparities that

may exist even among those above the poverty line (Adler & Ostrove, 1999). Most notably, the Whitehall study found that disparities in health exist among those with the lowest occupational grades, and also found that each step increase in occupational grades was associated with better health and reduced mortality (Adler & Ostrove, 1999; Marmot, Shipley, & Rose, 1984). Since SES appears to track a gradient, using indices of SES as continuous variables in statistical models may be most appropriate.

1.3 What are Potential Pathways Linking SES to Health?

While acknowledging disparities in health and health related outcomes across the SES gradient, it is also important to consider the mechanisms by which SES relates to health outcomes. Adler & Ostrove (1999) proposed that SES may relate to health through environmental characteristics and psychological factors such as affect and cognition (see figure 1). Environmental factors such as higher exposures to toxins, less availability of social resources (i.e., food), and greater challenges in engaging in health behaviors, all likely contribute to poorer health outcomes (Adler & Ostrove, 1999; Evans & Kantrowitz, 2002). Psychological factors (e.g., affect) might also be a mechanism such that poverty could lead to increased depressive symptoms and anxiety which in turn influence health behaviors, immune and cardiovascular function (Adler & Ostrove, 1999).

Figure 1: Model illustrating pathways that may underlie the association between socioeconomic status (SES) and health (Adler & Ostrove, 1999).
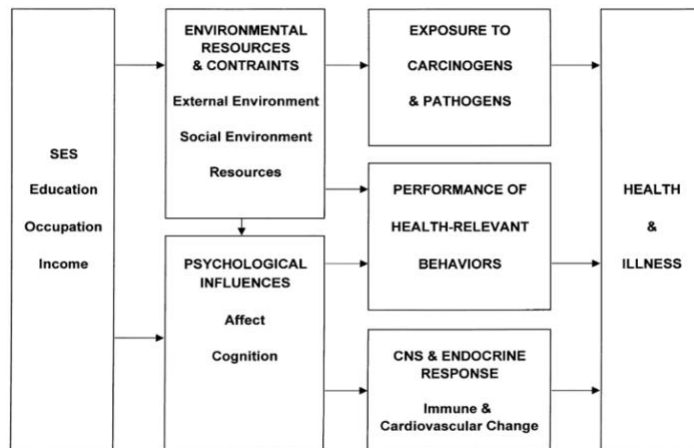
While the model by Adler & Ostrove (1999) does not consider

subjective SES and groups objective dimensions of SES (income and education) together, it is important to note that 1) different dimensions (i.e., income, and education) and types (i.e., subjective, and objective) of SES may be correlated, but they are not entirely convergent, and as such 2) different dimensions and types of SES may not affect health in the same way, nor through the same pathways.

Indeed, subjective SES and objective dimensions of SES are moderately correlated (Cundiff & Matthews, 2017). Additionally, a meta-analysis found that subjective SES associated with physical health even when controlling for objective measures of SES (Cundiff & Matthews, 2017). Other studies have encountered similar findings (Ghaed & Gallo, 2007; Manuck et al., 2010). Lastly, one study found that subjective SES was a better predictor of changes in health over time than objective SES (Singh-Manoux, Marmot, & Adler, 2005).

More work is needed to understand the mechanisms that may be contributing to differential associations between objective and subjective SES; however, these findings suggest that it is important to consider both subjective and objective dimensions of SES when examining SES associations with health outcomes. Unfortunately, subjective and objective dimensions of SES have not been equally considered in work examining SES and risk for AD.

1.4 What is Alzheimer's Disease, Neuropathology and Symptoms?

AD is a neurodegenerative condition that primarily affects older adults (> 65 yrs) (Alzheimer's disease facts and figures, 2020). Symptoms of AD include, but are not limited to, severe declines in cognitive function across several domains such as memory, executive function, and language (Jahn, 2013; Guarino et al., 2018; Ferris & Farlow, 2013). AD has also been linked to sleep disturbances, anxiety, depression and other behavioral changes (Li, Hu, Tan, Yu, & Tan, 2014).

However, AD distinguishes itself from other forms of dementia by its two hallmark proteins, extracellular plaques (Aβ) and intracellular neurofibrillary tangles (tau).

The leading theory for the pathogenesis and etiology of AD has been the amyloid cascade hypothesis (Hardy & Allsop, 1991), which attributes AD pathogenesis to the over-production and/or impaired metabolism/clearance of Aβ (Hardy & Allsop, 1991). Aβ is produced when β- and γ-secretase cleaves the amyloid precursor protein (APP), a transmembrane protein that plays a role in neurogenesis and neuronal homeostasis (Chen et al., 2017). When Aβ is produced from APP, it can accumulate and cause other maladaptive changes to occur such as the development of tau, neurodegeneration, and impairment of cognitive capacities as observed in AD (Chen et al., 2017; Bondi, Edmond, & Salmon, 2018).

While the extent to which Aβ is the sole harbinger of AD has been called into question in recent years (Ricciarelli & Fedele, 2017; Reitz, 2012; & Karran, Mercken, Strooper, 2012), the evidence suggests that Aβ plays a critical role in the development of cognitive decline (Vlassenko, Benziger, & Morris, 2012). For instance, placing
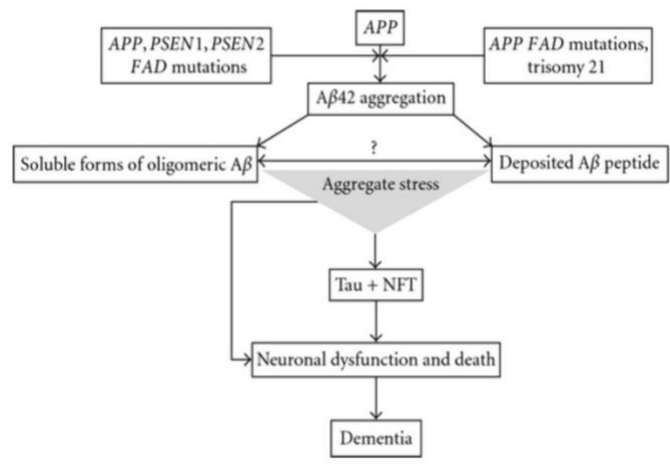
Figure 2. Hypothesized model by which Amyloid Beta (Aβ) may lead to brain atrophy, cognitive decline, in the context of Alzheimer's disease (Reitz et al., 2012).

Aβ molecules from deceased AD patients into rodent brains led to structural and functional impairments in the hippocampus (Shankar et al. (2008)). The importance of Aβ for AD has also been demonstrated in humans. For example, higher Aβ deposition measured by using positron

emission tomography was predictive of greater longitudinal declines in verbal learning and memory ((Vlassenko, Benziger, & Morris, 2012); Resnick et al. (2011)). Similarly, an initial rise in Aβ was associated with an increase in tau, which led to declines in memory function and other cognitive abilities (Hanseeuw et al. (2019).

1.5 Does Socioeconomic Status Relate to Alzheimer's Disease?

Lower SES has been related to a higher risk of numerous health conditions, including risk of AD. The following studies have defined AD based on dementia symptoms (i.e., severe impairments of cognitive function), and have focused exclusively on objective dimensions of SES. Nonetheless, lower levels of education has been associated with a higher incidence of AD (Zhang et al., 1990; Mortimer & Graves, 1993; Katzman, 1993; Ott et al., 1995; Letenneur et al., 1999; & Sharp and Gatz, 2012). Similarly, occupation and income have also been linked to AD. For example, Qiu et al. (2003) found that manual labor workers were 40 percent more likely to develop AD, relative to non-manual labor workers. Possible explanations for this association include: 1) increased exposure to environmental pollutants/toxins, 2) lower income, which may associate with poorer housing conditions and accessibility to nutritional foods, and 3) health behaviors such as a higher prevalence of smoking and alcohol consumption, and more limited psychosocial interactions (Qiu et al., 2003).

The increased risk of developing AD, related to occupation, may not be limited to manual labor work, and a combination of SES based risk factors might compound the risk of individual risk factors. Indeed, Stern et al. (1994), found that "lower occupational status" increased risk for AD, with individuals whose primary job throughout their lifetime was deemed of low status or prestige (skill/semiskilled, skilled trade or craft, and clerical/office workers) being at a greater risk than those whose primary occupation was one of high occupational status (manager

business/ government and professional/technical). Additionally, low levels of education exacerbated the effect of low occupational status on risk for developing AD such that individuals with both low occupational status and low levels of education were at a greater risk of developing AD above and beyond what was predicted from either risk factor alone (Stern et al., 1994).

Interestingly, relative to years of education and occupational status, there is limited evidence that lower income increases the risk for developing AD. Higher rates of AD have been observed among low-income and middle-income countries compared to higher income countries (Parra, Butler, McGeown, Nicholls, & Robertson, 2019); however, this association may be confounded by other characteristics of these countries which have also been found to relate to risk for AD such as air pollution (Mannuci & Franchini, 2017; Fu & Yung, 2020) and access to healthcare services (Peters, Garg, Bloom, Walker, Brieger, & Rahman 2008). Income has not been related to the likelihood of a diagnosis with AD at the individual level when controlling for other dimensions of SES (Evans et al., 1997).

Many previously mentioned studies have examined occupational status, years of education, and income separately, while others have analyzed them together. Evans et al. (1997) followed a group of older adults for approximately 4 years and found that those with fewer years of education, lower annual income, and lower occupational status were more likely to be diagnosed with AD. While only years of education remained significant when all three variables were included in a single model (Evans et al., 1997), several limitations of the study prohibit definitive conclusions. For example, the study did not consider the number of occupants living in the household when collecting data on annual income. The number of occupants in the household and whether these occupants bring income into the household provide a more accurate

description of this parameter of SES. Also, the average income for the sample was low such that the majority of the sample made less than $10,000 annually (Evans et al., 1997). A dearth of participants with higher income may have made it more difficult to detect an effect of income in the model that included all three SES indicators simultaneously.

Karp et al. (2004) followed a large sample (n = 931) of older adults for 3 years who were all cognitively normal at baseline and found that less educated individuals were 3.4 times more likely to develop AD relative to those with higher levels of education. Individuals with low occupation-based SES, based on income associated with the longest held job, were 1.6 times more likely to develop AD relative to those with high occupation-based SES. As in the case of the previous study, only years of education was significant when both predictors were included in a single model (Karp et al., 2004). Whether these findings can be replicated when using income remains unaddressed.

Despite these limitations, along with an exclusive focus on objective dimensions of SES, most studies have found that indicators of lower SES are associated with higher prevalence rates of AD. However, whether socioeconomic inequalities relate to pathophysiologic changes that underlie AD such as Aβ neuropathology remains unknown.

1.6 Does Socioeconomic Status Relate to Amyloid Beta?

Unfortunately, no study to date has explored associations between Aβ and SES. Prior work has studied SES disparities in the prevalence of AD for those exhibiting dementia symptoms (McKhann et al., 2011; Jack et al., 2018). The lack of Aβ data along with the primary use of samples with dementia/severe cognitive impairment leaves room for speculation about whether an association between SES and Aβ is detectable prior to the onset of dementia symptoms – in cognitively normal individuals or those in the preclinical stage of the disease (see Table 1).

Table 1. Abridged biomarker profile and categories

A-(N)-	Normal Alzheimer's disease biomarkers	
A+(N)-	Preclinical Alzheimer's disease/ Alzheimer's disease pathologic change	Alzheimer's continuum
A+(N)+	Alzheimer's disease	
A-(N)+	Non-AD pathologic change	

☐	**Normal Alzheimer's disease biomarkers** - Absence of Aβ pathology and neurodegeneration *rate of short-term clinical progression expected to be low*
▣	**Preclinical Alzheimer's disease/ Alzheimer's disease pathologic change** - early stage of Alzheimer's continuum, defined by Aβ pathology with no neurodegeneration
▪	**Alzheimer's disease** – Presence of Aβ pathology *rate of short-term clinical progression expected to be high*
▢	**Non-AD pathologic change** – Brain changes not related to Aβ pathology
Alzheimer's continuum – Umbrella term that refers to biomarker profiles observed across the earlier and later stages of Alzheimer's disease.	

Note: (Adapted from Jack et al., 2018)

1.7 What are Potential Pathways Linking SES to Amyloid Beta (Aβ)?

Inflammation may be one pathway that links SES and Aβ. Indeed, Muscatell, Brosso, & Humphreys (2020), and Gruenewald, Cohen, Matthews, Tracy, & Seeman (2009) found that lower SES was associated with greater c-reactive protein (CRP) and Interleukin 6 (IL-6). Alterations in CRP and IL-6 have also been observed among those with AD (Song, Chung, Kim, & Maeng, 2015; Cojocaru, Cojocaru, Miu, & Spira, 2011), and greater levels of IL-6 and CRP have been found to associate with greater accumulation of Aβ among cognitively normal older adults with greater levels of Aβ at baseline (Oberlin et al., 2021). Besides CRP and IL-6, alterations in microglia, the primary immune cell in the brain, and Tumor Necrosis Factor alpha (TNF Alpha) have also been observed in AD (Kinney et al., 2018).

Acute inflammation is believed to initially play a protective role against neuropathology such that it helps to clear Aβ through phagocytosis (Bolmont et al., 2008; Kinney et al., 2018).

However, this inflammatory response is often not sufficient in regulating the accumulation of neuropathology (Kinney et al., 2018). Instead, acute inflammation progresses to chronic inflammation, which further contributes to neurodegeneration (Kinney et al., 2018). While work has not tested whether inflammation is a pathway linking SES to Aβ, the co-occurrence of increased inflammation among those with lower levels of SES, and those with greater amounts of Aβ may have important implications for brain and cognitive health. Specifically, inflammation related to SES may increase the accumulation of Aβ, contribute to prolonged inflammatory responses in the brain, and work in conjunction with Aβ to accelerate declines in neurodegeneration and cognitive decline.

Pathways linking lower SES to inflammation also include engaging in unhealthy behaviors, higher prevalence of cardiometabolic alterations, and psychological dysfunction (see figure 3 for diagram). In regards to unhealthy behaviors, lower levels of SES have been related to lower levels of physical activity and access to safe places to exercise and life circumstances that permit leisure activity, less healthy diets and access to nutritious foods in underserved communities (i.e., diets low in fruit, vegetables, and fiber, and high in trans and saturated fat), and reduced sleep quality (Pampel, Krueger, & Denney, 2010). All of these unhealthy behaviors have been linked to higher inflammation (Giugliano, Ceriello, & Esposito, 2006; Meier-Ewert et al., 2004; Wirth et al., 2014).

Cardiometabolic alterations, which refer to a group of conditions that confer additional risk for cardiovascular disease (Vincent et al., 2017) such as hypertension, obesity, and diabetes, have also been linked to inflammation (Lopez-Candales, Burgos, Hernandez-Suarez, & Harris, 2017; Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017), are observed among those lower on the SES gradient (Jeffery, French, Forster, & Spry, 1991; Robbins, Vaccarino, Zhang, & Kasl,

2005; Leng, Jin, Li, Jin, 2015). Finally, the implications of low SES also extend to psychological distress such that lower levels of SES have been linked to stress, and higher depressive and anxiety symptomology (Lemstra et al.,2008; Lorant et al., 2003; Cohen, Doyle, & Baum, 2006), and psychological factors have also been closely tied to inflammation (Wirtz & Känel, 2017; Freeman et al., 2016; Lorant et al., 2003).

It is important to note that while these pathways have all been independently associated with SES and inflammation, they likely do not function in isolation. Indeed, these risk factors are interrelated such that cardiometabolic alterations are related to psychological distress (Hare, Toukhsati, Johansson, Jaarsma, 2013; Winning, Glymour, McCormick, Gilsanz, & Kubzansky, 2015). Links have also been drawn between health behaviors, psychological functioning, and cardiometabolic health (St-Pierre, Sinclair, Elgbelli, Bernard, & Dancause, 2019; Chastin, Palarea-Albaladejo, Dontje, & Skelton, 2015). Links between SES, and psychological distress, health behaviors, and cardiometabolic health may be similarly complex in that they can be bidirectional. For instance, while SES is traditionally conceptualized as a predictor of health, SES factors may likewise be augmented by alterations in cardiometabolic and psychological distress such that experiencing poorer physical and mental health may impact the ability to hold a job and pursue educational opportunities. Additionally, treatment of these conditions could have an impact on income.

The complexities of the relationship between SES, and psychological distress, cardiometabolic health, and health behaviors could be explored further; however, the focal points of the mechanisms that may underlie the association that will be tested in the current study are 1) SES may induce psychological distress, and cause poorer cardiometabolic health, and health behaviors, 2) these factors may all individually, and/or in conjunction with each other upregulate

inflammatory biomarkers, 3) greater inflammation may increase Aβ, and 4) greater amounts of

Aβ could increase risk for neurodegeneration, and cognitive decline.
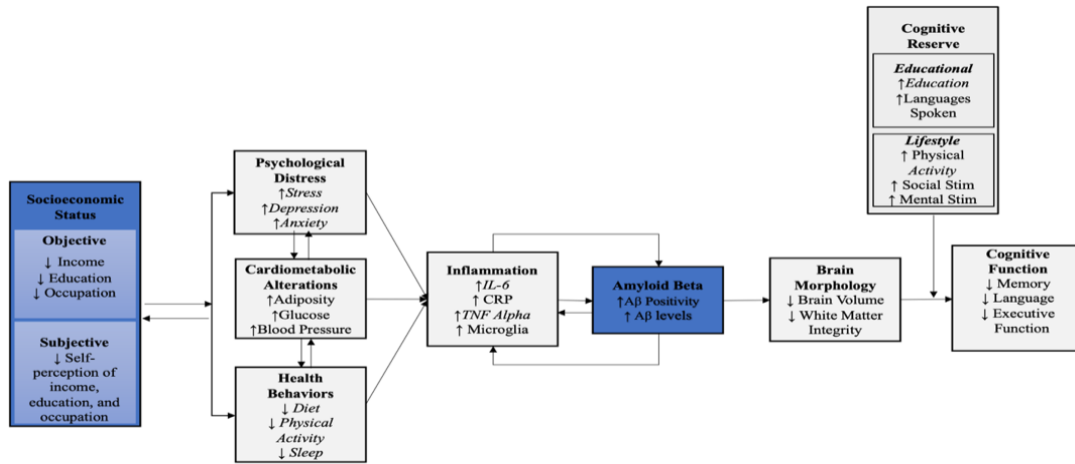
Note: "Self-perception of income, education, and occupation" refers to the SES Ladder.
The blue boxes refer to the association that will be tested in the proposal, while the grey boxes
refer to pathways that may underlie the association we are testing.

Figure 3. Conceptual schematic illustrating the mechanistic pathways by which

socioeconomic status (SES) may associate with Amyloid Beta (Aβ).

1.8 How might Brain and Cognitive Reserve affect the Potential Associations between Aβ

and Neurocognitive Health?

It is important to consider how "cognitive reserve" may impact associations between Aβ, SES,

and cognitive function. Cognitive reserve is a hypothetical construct used to explain

incongruencies between brain damage and/or levels of neuropathology (i.e., Aβ), and clinical

symptoms (i.e., level of cognitive deficits) such that maladaptive brain changes may occur

without detectable alterations in behavior or clinical declines in cognitive function (Stern, 2006;

Stern et al, 2020). Cognitive reserve cannot be measured directly; instead, it is often measured by

using metrics of education, physical activity, leisure activities, and social engagement as proxies

for the construct (Stern et al., 2020).

Debate continues about the mechanisms by which cognitive reserve allows for maintance of cognitive function in the presence of maladaptive brain changes; however, one aspect of this theory postulates that those with greater cognitive reserve may have better cognitive function prior to the accumulation of neuropathology (see figure 4) (Stern, 2009). As such, individuals with higher cognitive reserve may require greater decline in function before reaching the diagnostic threshold for cognitive impairment/dementia, and are able to function better in the face of greater amounts of neuropathology (Stern, 2009). More contemporary concepualizations of cognitive reserve speculate that it is an active and dynamic process such that individuals with greater cognitive reserve, are better at developing adaptive strategies to compensate for the maladaptive effects of the accumulation of neuropathology (Stern et al., 2020).
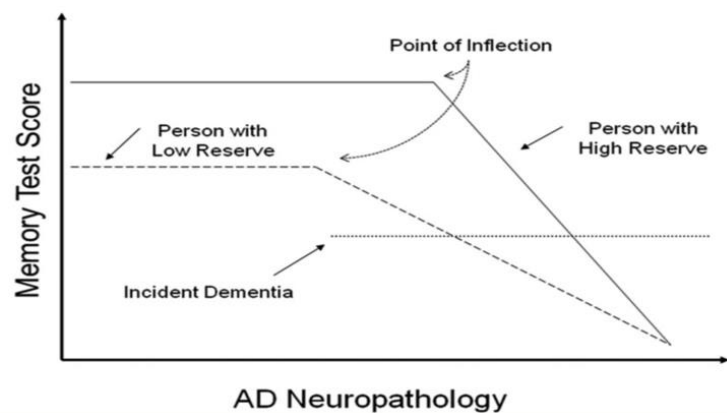
Note: Point of inflection refers to the point in which neuropathology begins to have an impact on cogntive function (Stern, 2009).
Figure 4. Theoretical illustation of how cogntive reserve may influence cognitive trajectories, and risk for Alzheimer's disease as neuropathology increases (Stern, 2009).

Another issue which has not been adequetly addressed is how to distinguish cognitive reserve from features of SES. Proxies for cognitive reserve are often overlapping with elements proposed in the conceptual framework of SES. For instance, years of education is often used as a proxy for cognitive reserve, but years of education is also a defining feature of SES.

Additionally, SES is often related to other proxies of cognitive reserve such as physical activity (Stalsberg & Pedersen, 2018; Talaei et al., 2013). As such, it is likely that individuals with higher SES will also have greater cognitive reserve; however, cognitive reserve and SES are conceptually different in some regards. Indeed, SES may associate, but it is not deterministic of other proxy measures of cognitive reserve (i.e. diet and physical activity), which may allow distinctions between the two constructs.

Nonetheless, in this context, cognitive reserve is relevant to consider for the current study, such that lower SES might also be indicative of lower cognitive reserve. These interrelated concepts will be discussed in relation to the results.

1.9 The Current Study: Aims and Hypotheses

The current study aims to extend previous research by answering the following questions: 1) does objective SES relate to Aβ neuropathology, 2) does subjective SES relate to Aβ neuropathology, 3) do the various dimensions of objective SES predict Aβ levels differentially. We hypothesize that 1) lower objective SES will predict greater Aβ neuropathology 2) lower subjective SES will predict greater Aβ neuropathology 3) various dimensions of objective SES will differentially predict Aβ neuropathology such that years of education will account for the most amount of variance in Aβ neuropathology. Addressing these questions could lead to better characterization of the relationship between SES and AD, such that if the data support our hypotheses, we will know the type (subjective or objective) and dimension (income, education, etc.) of SES most predictive of Aβ. This information could inform public health policies and produce targeted non-pharmacological interventions that help reduce SES disparities in AD, which would have an impact on the overall number of AD cases worldwide.

2.0 Methods

2.1 Participants

Cross-sectional data from Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE) will be used to test the aims. IGNITE is a 12-month, randomized clinical trial exploring the effects of physical activity on brain and cognitive health in older adults. This trial has enrolled 648 older adults between the ages of 65-80 years of age, without dementia, including AD, or mild cognitive impairment and 360 out of the 648 participants underwent PET imaging prior to the trial. IGNITE is a multisite trial, with data collected at the University of Pittsburgh (Pittsburgh), Kansas University Medical Center (Kansas), and Northeastern University (Boston); however, PET amyloid data was only collected for a few participants in Boston (n = 5). Additional subjects were excluded from the current analyses due to missing MRI and/or incomplete PET scans (n= 3). As such, 352 IGNITE participants across Pittsburgh and Kansas had data available to be included in the current analyses (see table 2 for demographic characteristics for the IGNITE sample). In addition, eligible participants were ambulatory without pain or assisted walking devices, received medical clearance by a primary care physician, were able to undergo MRI, and not have a prior diagnosis of a neurological disease.

Individuals were ineligible if they reported: 1) engagement in $\geq$20 minutes per week of structured moderate-to-vigorous intensity physical activity, 2) current diagnosis of an Axis I or II disorder including, Major Depression, 3) Type I Diabetes, Insulin-dependent Type II Diabetes, uncontrolled Type II diabetes (defined as an HbA1c level > 10), 5) Presence of metal implants (pacemaker, stents) that were MR ineligible, 6) Myocardial infarction, coronary artery bypass grafting, angioplasty or other cardiac condition in the past year , 7) Current alcohol or substance abuse or treatment for abuse in the past 5 years, 8) planning on geographical relocation outside

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of the region within 12 months, 9) Current treatment for congestive heart failure, angina, uncontrolled arrhythmia, deep vein thrombosis (DVT) or another cardiovascular event, 10) or Current treatment for cancer – except non-melanoma skin cancer (Erickson et al., 2019).

2.2 Amyloid Beta Positron Emission Tomography Acquisition and Preprocessing

Each participant underwent a 20 min PET scan (4*5 min) starting at 90 ($\pm$ 5) min after intravenous injection of 8.0 mCi $\pm$ 20% of Florbetaben F^{18} (Neuraceq), an FDA approved tracer, that has demonstrated a high sensitivity and specificity for detecting Aβ and discriminating individuals with Aβ from healthy controls (Sabri, Seibyl, Rowe, & Barthel, 2015), followed by 10 ml normal saline flush (Erickson et al., 2019). PET imaging at Pittsburgh was recorded on Siemens PET scanner and reconstructed using Order Subsets Expectation Maximization (OSEM) algorithm with 4 iterations and 24 subsets. PET imaging at Kansas was recorded on GE PET scanner and reconstructed using Fourier rebinning (FORE) algorithm with 4 iterations and 24 subsets (Defrise, Casey, Michel, & Conti, 2005). Decay, scatter, and attenuation corrections were applied on all PET scans.

PET images were motion corrected and averaged across 4 volumes. The mean PET image was co registered with individual T1 magnetization prepared rapid gradient echo (MPRAGE) image, and the transformation matrix was saved. The above steps were performed in MATLAB using SPM12. The voxel-wise standard uptake value (SUV), which takes into account an individuals' body weight and the concentration of the injected dose to estimate Aβ deposition, was calculated on motion-corrected PET images. The mean SUV image was generated by averaging the SUV values across volumes at each voxel and registered to individual T1 image using the mean PET to T1 transformation matrix. The regional standardized uptake value ratios (SUVRs) were calculated as the ratio of the averaged SUV values in the cerebral cortical regions

and the averaged SUV value of the reference region, the whole cerebellum. The whole cerebellum was used as the reference region, since it is relatively free of Aβ (Klunk et al., 2004). Lastly, to estimate global amyloid deposition, a composite SUVR was calculated for each participant using the 1) anterior cingulate cortex (ACC), 2) posterior cingulate cortex (PCC), 3) frontal, 4) parietal, 5) temporal and 6) occipital regions.

2.3 Magnetic Resonance Imaging Data Acquisition and Preprocessing

Magnetic resonance images were used for anatomical reference to identify regions with Aβ deposition from the PET imaging session. Pittsburgh used a Siemens Prisma 3T scanner with a 64-channel head coil and Kansas used a Siemens Skyra 3T scanner with a 32-channel head coil (Erickson et al., 2019). The High-resolution anatomical images were obtained using a three-dimensional MPRAGE T1-weighted brain image, which was collected with the following parameters: TR/TE/TI=2400/2.31/1060ms, FOV=256mm*256mm, 0.8*0.8mm^2 in-plane resolution, 224 sagittal slices, 0.8mm lice thickness and 8° flip angle. (Erickson et al., 2019).

Automated segmentation and parcellation were performed using Freesurfer v6.0 with default settings of "recon -all". Forty cortical brain regions and cerebellum were extracted from Desikan-Killianny-Tourville (DKT) atlas parcellation for each individual brain (Klein & Tourville, 2012). The 40 brain regions were further merged into six regions of interest (ROIs): anterior cingulate, posterior cingulate, frontal, parietal, temporal and occipital lobes, which were used to extract SUV values.

2.4 Instruments

Objective SES

Items from the MacArthur Socioeconomic Status Index were used to measure objective SES. The MacArthur Socioeconomic Status Index is an 11-item questionnaire measuring educational

attainment, occupational status, income and debt (Seeman et al., 2004). This questionnaire

captures all 3 dimensions related to objective SES and asks additional questions that may be

informative, but are not commonly included in other studies that use objective SES such as

questions related to homeownership and other assets, debt, and financial stability.

Subjective SES

To quantify subjective SES we used the MacArthur Scale of Subjective Social Status.

Participants were shown a picture of a 10-rung ladder and prompted to consider money,

education, and occupation. They were then asked, "where they think they stand, at this time of

their lives, relative to other people in the United States" and are asked to "mark an X on the rung

on the ladder" where they would place themselves. Scores range from 1 to 10, with higher scores

corresponding to higher subjective SES. Evidence suggests this scale exhibits convergent and

discriminant validity relative to measures of psychosocial factors (i.e., personality traits,

depressive symptoms, optimism, etc.) and objective indices of SES (Cundiff, Smith, Uchino, &

Berg, 2013). This scale also exhibited adequate test-retest reliability and predicted self-report

health outcomes when controlling for objective SES factors (Operario, Adler, & Williams,

2004).

2.5 Analysis

All analyses were conducted using R version 3.6.3 (R Core Team, 2020). First, a confirmatory

factor analysis was conducted, using the 'lavaan' package (Rosseel, 2012), on the 11-item

MacArthur Socioeconomic Status Index questionnaire to generate an objective SES composite

score. Using separate hierarchical linear regression models the objective composite score and the

subjective SES score were entered as predictors while global Aβ deposition was used as the

outcome of interest. Additionally, age and study site were used as covariates in both models.

Since a latent SES score derived from a factor analysis has not been commonly used in prior studies, a composite score with years of education and annual income was created to duplicate the predominant approach adopted by previous studies. Using this approach, two hierarchical linear regression models were run; one model with years of education as the sole predictor of global Aβ deposition, while the other model with annual income as the sole predictor. Our final model used years of education and annual income composite score as the predictor of global Aβ deposition. This approach allows for the identification of individual and joint contributions of years of education and annual income on AB deposition. All models controlled for age and study site.

Another approach commonly used in the literature is to treat Aβ as a dichotomized variable, which classifies an individual as Aβ positive or negative based on an *a priori* SUVR cutoff value. We used a cutoff value of 1.10 SUVR as it has been found to demonstrate high concordance in detecting amyloid positivity across various PET tracers (Cho et al., 2020). We also conducted a series of logistic regressions to predict the likelihood of an individual being Aβ positive using our objective SES factor analysis generated latent construct, subjective SES, and the composite score of years of education and occupant adjusted income, while controlling for the previously mentioned covariates. Overall this multimethod approach to address whether objective SES associates with Aβ deposition and to pinpoint which dimension of SES is most predictive of Aβ deposition will maximize comparability of findings to prior literature and construct coverage on SES, and conform with both clinical usage and epidemiological evidence for Aβ.

3.0 Results

3.1 Participants

The 352 participants included in the current analyses were, on average, 69.31 ($\pm$ 3.57) years old with 16.53 years of education ($\pm$ 2.42) (range: 10-20 years) with a broad range of highest educational attainment including Highschool/GED (16.57%), Associates degree (6.46%), Bachelor's degree (32.39%), Doctorate (4.26%), Master's degree (31.53%), Professional degree (5.68%), and Other (9.09%). Annual income ranged from <$5,000 to > $100,000, with an average of $47,608.97. Of the 352 participants 69 met criteria for amyloid positivity (SUVR >1.10), while 283 were amyloid negative. The sample was predominately White (n = 298 (84.66%)) and female (n = 253 (71.88%)). See table 1 for more information.

Of these 352 individuals, 37 were missing annual pretax income (5 responded = "Don't know", 32 responded "no response"). Missing data was also observed for total combined family income (7 responded = "Don't know", 27 responded "no response"), debt (21 responded = "Don't know", 46 responded "no response"), and for savings (21 responded = "Don't know", 42 responded "no response"). Missingness did not differ between Aβ groups or as a function of age, sex, or race/ethnicity. However, females were more likely to have missing data for annual pretax income compared to males.

Table 1. Sample Characteristics (N = 352)

Variable	Total Sample (n = 352)	Amyloid Positive (n = 69)	Amyloid Negative (n = 283)
Age	69.31 $\pm$ 3.62	70.43 $\pm$ 3.75	69.04 $\pm$ 3.55
Sex n (%)			
Male	99 (28.12)	21 (30.43)	78 (27.56)
Female	253 (71.88)	48 (69.57)	205 (72.44)
Race/Ethnicity			
White	298 (84.66)	59 (85.51)	239 (84.45)
African American/Black	44 (12.50)	8 (11.59)	36 (12.72)
Asian	3 (0.85)	0 (0)	3 (1.06)

Biracial	3 (0.85)	0 (0)	3 (1.06)
Hawaiian or Islander	1 (0.28)	1 (1.45)	0 (0)
Other	3 (0.85)	1 (1.45)	2 (0.71)
Income	$47,608.97 $\pm$ $35,655.24	$ 44,138.00 $\pm$ $31,594.24	$48,493.72$\pm$ $36,623.01
Years of Education	16.53 $\pm$ 2.42	16.62 $\pm$ 1.97	16.51$\pm$ 2.52
United States Ladder	6.19 $\pm$ 1.63	5.73 + 1.64	6.30 + 1.60
Employment Status			
Full Time	40 (11.36)	8 (11.59)	32 (11.31)
Part Time	57 (16.19)	15 (21.74)	42 (14.84)
Unemployed	3 (.85)	1 (1.45)	2 (.71)
Looking	6 (1.70)	2 (2.90)	4 (1.41)
Keeping house	7 (1.99)	2 (2.90)	5 (1.77)
Retired	254 (72.16)	45 (65.22)	209 (73.85)
Highest Degree Earned			
Highschool Diploma	58 (16.48)	7 (10.14)	51 (18.02)
Associates Degree	23 (6.53)	5 (7.25)	18 (6.36)
Bachelors	114 (32.39)	28 (40.58)	86 (30.39)
Masters	111 (31.53)	23 (33.33)	88 (31.10)
Doctorate	15 (4.26)	1 (1.45)	14 (4.95)
Professional (MD, JD, DDS, etc.))	20 (5.68)	4 (5.80)	16 (5.56)
Other	32 (9.09)	3 (4.35)	29 (10.25)
Savings			
Less than $500	11 (3.12)	3 (4.35)	8 (2.83)
$500 to $4,999	21 (5.97)	5 (7.25)	16 (5.65)
$5,000 to $9,999	12 (3.41)	3 (4.35)	9 (3.18)
$10,000 to $19,999	4 (1.14)	1 (1.45)	3 (1.06)
$20,000 to $49,999	19 (5.40)	10 (14.49)	9 (3.18)
$50,000 to $99,999	22 (6.25)	4 (5.80)	18 (6.36)
$100,000 to $199,999	41 (11.65)	7 (10.14)	34 (12.01)
$200,000 to $499,999	64 (18.18)	12 (17.39)	52 (18.37)
$500,000 and greater	95 (26.99)	17 (24.64)	80 (27.56)
Don't Know	22 (6.16)	1 (1.45)	20 (7.07)
No Response	42 (11.76)	6 (8.70)	36 (12.72)
Debt			
Less than $500	32 (9.09)	10 (13.04)	23 (8.13)
$500 to $4,999	16 (4.70)	3 (4.35)	13 (4.59)
$5,000 to $9,999	9 (2.56)	5 (7.25)	4 (1.41)
$10,000 to $19,999	9 (2.56)	2 (2.90)	7 (2.47)
$20,000 to $49,999	17 (4.83)	3 (4.35)	14 (4.95)
$50,000 to $99,999	23 (6.53)	2 (2.90)	21 (7.42)
$100,000 to $199,999	38 (10.80)	10 (14.49)	28 (9.89)
$200,000 to $499,999	55 (15.62)	11 (15.94)	44 (15.55)
$500,000 and greater	86 (24.43)	15 (21.74)	71 (25.09)

Don't Know	21 (65.97)	2 (2.90)	19 (6.71)
No Response	46 (13.07)	7 (10.14)	39 (13.78)
Standard of Living Maintenance			
Less than 1 month	14 (3.98)	4 (5.80)	10 (3.53)
1 to 2 months	35 (9.94)	11 (15.94)	24 (8.48)
3 to 6 months	40 (11.36)	6 (10.14)	33 (11.66)
7 to 12 months	24 (6.81)	5 (7.25)	19 (6.71)
More than 1 year	236 (67.05)	42 (60.87)	194 (68.55)
Don't Know	0 (0)	0 (0)	0 (0)
No Response	3 (.85)	0 (0)	3 (1.06)
Composite SUVR	1.05 ± .16	1.32 ± .19	.99 ± .05

Note: The total number of responses for some items (i.e. employment status) exceed the size of the sample given, in some instances, participants marked more than one response an item.

3.2 Missing SES Data - Multiple Imputation by Chained Equations

Using logistic regression to determine which variables associate with the odds of various indicators of SES being missing, data was determined to be missing at random (MAR), As such, to address missing data, we used multiple imputation by chained equations (MICE). MICE leverages the distribution of the observed data/variables to estimate multiple possible values for the data points (Azur, Stuart, Frangakis, & Leaf, 2011). This allows us to account for the uncertainty around the true value, and obtain approximately unbiased estimates (Azur, Stuart, Frangakis, & Leaf, 2011).

We used 10 sets of imputations, which is proportional to the total amount of missing data in the sample used in the current study (10%). All SES variables were used as auxiliary information, as well as variables included in our statistical models (age, study site, Aβ positivity, and amyloid levels). All of the imputed data were examined and determined to be within plausible ranges for each specific variable.

3.3 Structural Equation Model: Confirmatory Factor Analysis (CFA)

We conducted a confirmatory factor analysis (CFA) using items from the MacArthur Socioeconomic Status Index. We specified a two-factor model by assigning items to an objective

or a subjective SES latent construct based on how the items are discussed in the literature (Tan et al., 2020). We used diagonally weighted least squares (DWLS) as our estimator opposed to maximum-likelihood (ML) methods given deviations in normality observed among the distribution in responses of the items, and items from the questionnaire being collected ordinally (Mîndrilă, 2010). Items related to homeownership, and employment status were not considered in the CFA because of a lack of ordinal structure. Community social standing was not considered because it did not fit into theoretical conceptualization of SES in the present study. As such, 8 items remained to construct our CFA.

While the chi-square statistic was statistically significant, $\chi2$ - 1177.688, p <.001, which suggests there is a discrepancy between proposed model and the observed data, the chi-square statistic is sensitive to larger sample sizes (Babyak & Green, 2010; Alavi et al., 2020). As such, we relied on other indices to evaluate model fit, and these indices converged in supporting the fit of the data (CFI - 0.998; SRMR = 0.048; RMSEA - 0.022; 90% confidence interval [CI] on RMSEA 0.000 – 0.062, RMSEA p for close fit = 0.850). Standardized loadings are presented in Table 2. Covariances between 1) years of education and highest degree earned, 2) debt and savings, and 3) annual pretax income and annual pretax income as modification indices suggest that these items were highly correlated and including the covariances between them would significantly improve model fit. The latent factor intercorrelation between the objective and subjective SES latent constructs was r =0.607, indicating a moderate to strong correlation between the objective and subjective SES latent constructs.
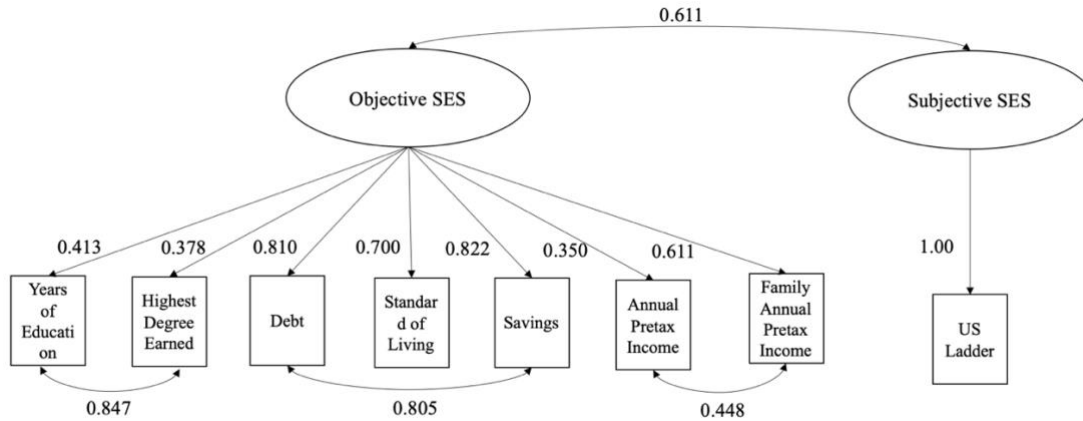
Figure 5: Confirmatory Factor Analysis of Objective SES

Table 2. Standardized Factor Loadings of Socioeconomic Status Items

MacArthur Socioeconomic Status Index Items	SES Factors	
	Objective SES	Subjective SES
1. Subjective SES: At the TOP of the ladder are the people who are the best off – those who have the most money, the most education and the most respected jobs. At the BOTTOM are the people who are the worst off – who have the least money, least education, and the least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top; the lower you are, the closer you are to the people at the very bottom. Where would you place yourself on this ladder? Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in the United States.		1.000
2. Years of Education: What is the highest grade (or year) of regular school you have completed?	0.413	
3. Highest Degree Earned: What is the highest degree you earned?	0.378	
4. Individual Annual Pretax Income: How much did you earn, before taxes and other deductions, during the past 12 months?	0.350	

5. Family Annual Pretax Income: Which of these categories best describes your total combined family income for the past 12 months?	0.611	
6. Standard of Living Maintenance: If you lost all your current source(s) of household income (your paycheck, public assistance, or other forms of income), how long could you continue to live at your current address and standard of living?	0.700	
7. Savings: Suppose you needed money quickly, and you cashed in all of your (and your spouse's) checking and savings accounts, and any stocks and bonds. If you added up what you would get, about how much would this amount to?	0.822	
8. Debt: If you now subtracted out any debt that you have (credit card debit, unpaid loans including car loans, home mortgage), about how much would you have left?	0.810	

3.4 Income and Education Composite Score

Annual income and years of education were correlated with each other at r = .28. As such, we used separate linear and logistic regression analyses using these variables as predictors of Aβ levels and Aβ positivity.

3.5 Aim 1: Does Objective SES Relate to Levels of Aβ and/or Aβ Positivity

A linear regression model, using robust standard errors, was used to examine the association between objective SES and levels of Aβ. Consistent with our hypothesis, after controlling for age and study site, a higher objective SES composite score was associated with lower Aβ (β=-.160, p=0.011). A logistic regression model was used to examine the association between objective SES, and Aβ positivity. Also, consistent with our hypothesis, after controlling for age and study site, a higher objective SES composite score was associated with a lower likelihood of meeting criteria for Aβ positivity (OR=.806, p=0.017).
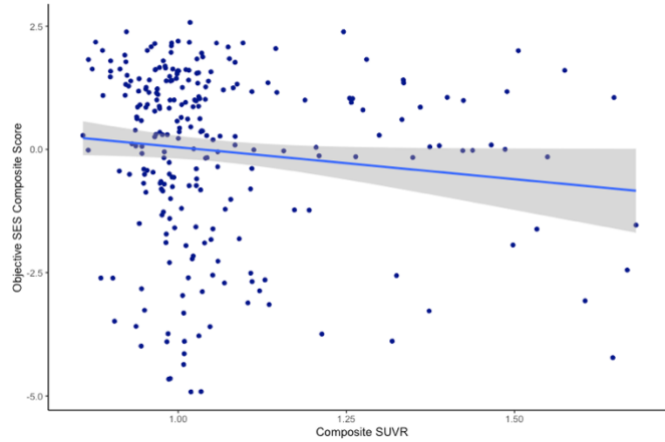
Figure 6. Association Between Objective SES and Levels of Aβ

Table 3. Linear and Logistic Regression Models of Objective SES Composite Score, Aβ

Composite Aβ SUVR, and Aβ Positivity

Variable	Observed			
	Composite Aβ SUVR		Aβ Positivity	
	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.166****	**.002**	**1.11***	**(1.02, 1.20)**
Study Site	.151	.019	**2.38***	**(1.24, 4.57)**
Objective SES Composite Score	**-.160***	**.005**	**.806***	**(.67, .96)**

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR"
refers to global levels of Aβ
*p < .05, **p < .01, ***p < .001

3.6 Aim 1a: Does Annual Income Relate to Levels of Aβ and/or Aβ Positivity

Linear regression models, using robust standard errors was used to examine the association

between annual income, and levels of Aβ. Consistent with our hypothesis, after controlling for

age and study site, a higher annual income was associated with lower levels of Aβ (β=-.112,

p=0.033). To determine whether annual income was associated with Aβ positivity, we used a

logistic regression model. Inconsistent with our hypothesis, the results of the logistic regression

indicate that annual income was not associated with the likelihood of meeting criteria for Aβ

positivity (OR = 1.00, p =0.316).

Figure 7. Association Between Annual Income and Levels of Aβ

Table 4. Linear and Logistic Regression Models of Annual Income, Composite SUVR, and Aβ

Positivity

Variable	Observed			
	Composite SUVR		Aβ Positivity	
	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.191****	**.003**	**1.11***	**(1.02, 1.19)**
Study Site	-.080	.018	1.59	(1.00, 2.80)
Income	**-.112***	**2.48e-07**	1.00	(.99, 1.00)

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR"
refers to global levels of Aβ
*p < .05, **p < .01, ***p < .001

3.7 Aim 1b: Do Years of Education Relate to levels of Aβ and/or Aβ Positivity

Linear regression models, using robust standard errors, was used to examine the association

between years of education, and levels of Aβ. Contrary to our hypothesis, after controlling for

age and study site, years of education was not associated with levels of Aβ (β=-.057, p=0.246).

To determine whether years of education was associated with Aβ positivity, we used logistic

regression. Similar to the findings of the linear regression analyses, the results of the logistic

regression do not suggest that years of education is associated with the likelihood of meeting

criteria for Aβ positivity (OR = 1.00, p =0.993).

Figure 8. Association Between Years of Education and Levels of Aβ

Table 5. Linear and Logistic Regression Models of Years of Education, Levels of Aβ, and Aβ

Positivity

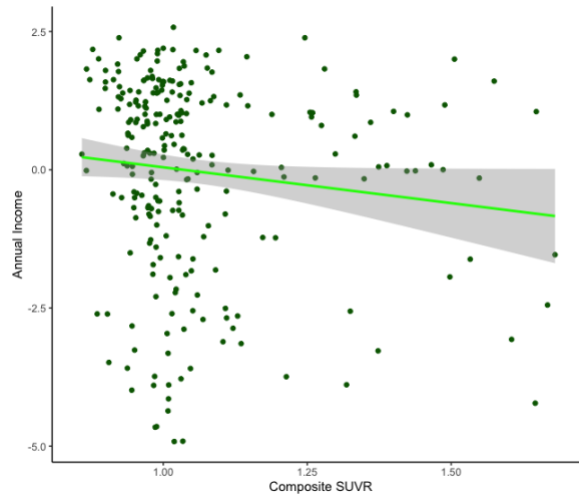| Variable	Observed			
	Composite SUVR		Aβ Positivity	
	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.204****	**.003**	**1.11****	**(1.04, 1.19)**
Study Site	.067	.017	1.53	(.89, 2.63)
Years of Education	-.057	.003	1.00	(.88, 1.12)

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR"
refers to global levels of Aβ
*p < .05, **p < .01, ***p < .001

3.8 Aim 2: Does Subjective SES Relate to Levels of Aβ and/or Aβ Positivity

A linear regression model, using robust standard errors was used to examine the association

between subjective SES, as measured by the US ladder, and Aβ. Consistent with our hypothesis,

after controlling for age and study site, higher subjective SES was associated with lower Aβ (β=-

.162, p=0.001). When including annual income in the model, the association between subjective SES and Aβ was attenuated, but remained significant (β=-.125, p=0.021). To determine whether subjective SES was associated with Aβ positivity, we used logistic regression. The results of the logistic regression suggest that higher subjective SES was associated with significantly lower odds of meeting criteria for Aβ positivity (OR = .78, p = .003). Subjective SES remained associated with the odds of meeting criteria for Aβ positivity when including annual income in the model (OR = .80, p = 0.008).

Figure 9. Association Between Subjective SES and Levels of Aβ

Table 6. Linear and Logistic Regression Models of Subjective SES, Composite SUVR, and Aβ Positivity

	Observed			
Variable	Composite SUVR		Aβ Positivity	
	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.212****	**.002**	**1.12****	**(1.04, 1.21)**
Study Site	.100	.016	1.92*	(1.07, 3.41)
Subjective SES (MacArthur US Ladder)	**-.162****	**.004**	**.78****	**(.65, .93)**

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR" refers to global levels of Aβ
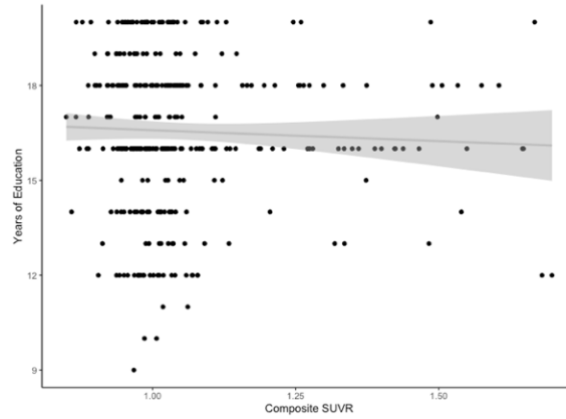
Table 7. Linear and Logistic Regression Models of Subjective SES and Annual Income, Composite SUVR, and Aβ Positivity

	Observed			
Variable	Composite SUVR		Aβ Positivity	
	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.202****	**.003**	**1.11****	**(1.03, 1.20)**
Study Site	.088	.018	2.34	(.96, 3.01)
Subjective SES (MacArthur US Ladder)	**-.125***	**.005**	**.80****	**(.67, .97)**
Annual Income	-.076	2.63e-07	.99	(.99, .100)

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR" refers to global levels of Aβ
*p < .05, **p < .01, ***p < .001

3.9 Aim 3: Do the Various Dimensions of Objective SES Predict Aβ Levels Differentially

A linear regression model, using robust standard errors was used to examine the association between years of education, income, and levels of Aβ. Inconsistent with our hypothesis, after controlling for age and study site, neither years of education, nor income was found to associate with Aβ levels (β=-.017, p=0.753) and (β=-.107;p=0.051) respectively. To determine whether income, and years of education were associated with Aβ positivity, we used logistic regression. Further, inconsistent with our hypothesis, the results of the logistic regression found that neither years of education nor income was associated with the likelihood of meeting criteria for Aβ positivity (ps >.05).

Table 8. Linear and Logistic Regression Models of Income and Education, Composite SUVR, and Aβ Positivity

	Observed	
Variable	Composite SUVR	Amyloid Positivity

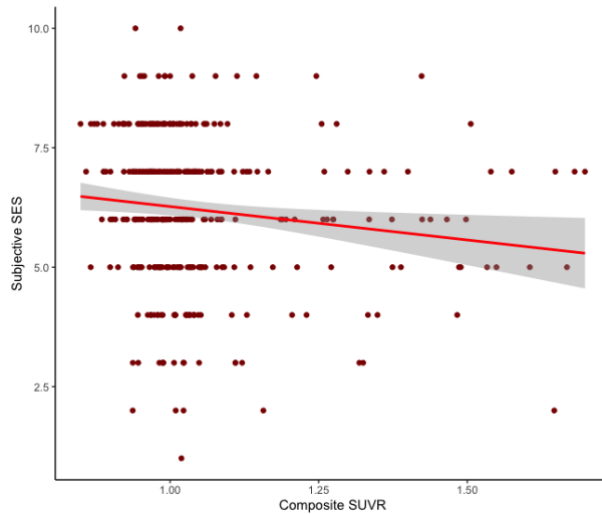|	β	*Robust SE*	*Odd Ratio*	95% CI
Age	**.190****	**.003**	**1.10****	**(1.03, 1.19)**
Study Site	.081	.018	1.79	(.99, 3.24)
Income	-.107	2.58e-07	.99	(.99, 1.00)
Years of Education	-.017	.003	1.01	(.89, 1.15)

Note: "Observed" refers to the results from the case available analyses; "Composite SUVR" refers to global levels of Aβ

*p < .05, **p < .01, ***p < .0001

3.10 Sensitivity Analyses

Using the imputed data yielded similar findings in the CFA, and the linear and logistic results

shown in tables 3, 4, 5, 6, 7, & 8.

4.0 Discussion

Previous research has found higher rates of AD among those with lower levels of SES (Zhang et

al., 1990; Mortimer & Graves, 1993; Katzman, 1993; Ott et al., 1995; Letenneur et al., 1999; &

Sharp and Gatz, 2012; Stern et al., 1994, Qiu et al., 2003; Evans et al., 1997; Karp et al. 2004).

However, whether lower SES was associated with higher levels of Aβ, particularly among

cognitively normal older adults, was poorly understood. It was hypothesized that: lower

objective and subjective SES would be associated with greater Aβ levels, and Aβ positivity. It

was also hypothesized that various dimensions of objective SES would be differentially

associated with Aβ such that years of education would account for the most amount of variance

in Aβ neuropathology.

The results of the current study are partially in support of these hypotheses. Consistent

with the hypotheses, we found that an objective SES composite score, annual income, and

subjective SES were inversely associated with Aβ levels such that those with who were lower on

these indices of SES had greater levels of Aβ. We also found that the objective SES composite

score, and subjective SES associated with the likelihood of meeting criteria for Aβ positivity. Contrary to the hypotheses, we found that years of education was not associated with Aβ levels nor Aβ positivity. As such, years of education did not account for significant additional variation in Aβ pathology when included in a model with annual income. Furthermore, including years of education in a single model with annual income attenuated the association between annual income and Aβ levels. Also, while annual income was associated with levels of Aβ in a model without years of education, annual income was not associated with Aβ positivity regardless of whether years of education was included in the model or not.

4.1 Objective SES, Aβ levels, and Aβ Positivity

In the models investigating the relationship between the objective SES composite score and Aβ pathology, we found that the objective SES composite score was associated with both continuous levels of Aβ neuropathology as well as Aβ positivity. These findings suggest that being lower on 1) annual individual income, 2) annual family income, 3) years of education, 4) highest degree earned, 5) assets, 6) standard of living maintenance and having 7) greater debt, might provoke impaired Aβ accumulation or clearance. While other studies of SES-related disparities in AD have used individual indices of objective SES and observed these indicators to be associated with risk of AD (Zhang et al., 1990; Mortimer & Graves, 1993; Katzman, 1993; Ott et al., 1995; Letenneur et al., 1999; & Sharp and Gatz, 2012; Stern et al., 1994, Qiu et al., 2003; Evans et al., 1997; Karp et al. 2004), to our knowledge, the current study is the first to demonstrate a relationship between an objective SES composite score and Aβ neuropathology.

Using a latent composite score to capture objective SES may be especially advantageous in 1) allowing us to paint a more wholistic picture across commonly interrelated, but also unique indices of objective SES 2) observing how individual indices of SES relate to one another, 3)

reducing dimensionality of SES data, and 4) examining whether indicators of SES being

aggerated to a single construct is statistically supported. Additionally, since our composite score

includes indices of objective SES related to assets, debts and standard of living maintenance

following the hypothetical loss of all current forms of income, the findings may also suggest that

other factors beyond income and education serve as risk factors for AD. In fact, we may presume

that the link observed between the objective SES composite score and Aβ may mostly be

attributed to these variables given they had the highest weights in the CFA (see table 4).

While the CFA did not model wealth as a latent variable, the three variables with the

highest factor loading from the objective SES composite score are often regarded as measures of

wealth (Cubbin et al., 2011). Compared to other objective measures of SES like annual income

that measure resources at a particular time, wealth is often regarded as a cumulative measure of

social standing (Killewald, Pfeffer, & Schachner, 2017; Cubbin et al., 2011). Wealth may be a

more comprehensive and appropriate measure of SES than annual income as many older adults

are often retired or unemployed, which may diminish associations with other variables and partly

account for the weak correlation observed between years of education and annual income

relative to other studies.

What might be mediating the association between objective SES and Aβ neuropathology?

Although the current study did not test possible mechanisms, we hypothesize that objective SES

and Aβ may be linked through various independent and interrelated pathways that span across

psychological, health, behavioral, and cardiometabolic factors (see figure 3). Furthermore, these

pathways may lead to chronic upregulation in the presence of proinflammatory biomarkers

(Kinney et al., 2018), which may be directly linked to Aβ deposition and neurodegenerative

processes (Kinney et al., 2018; Ismali et al., 2020). It is possible that certain indices of SES are

tied to a specific mechanistic pathway with Aβ. As such, in the next two sections we focus on results between income and years of education and speculate about the possible mechanisms.

4.1.1 Annual Income, Aβ levels, and Aβ Positivity

We found that lower annual income was associated with greater levels of Aβ neuropathology. However, annual income was not associated with Aβ positivity. One possible explanation for these incongruent findings is that we may not have been sufficiently powered to detect a relationship between annual income and Aβ positivity given nearly 81% of the sample included in the current analyses were Aβ negative. On the other hand, annual income may have been associated with Aβ levels, because a continuous analysis of Aβ levels may be a more sensitive, and more appropriate, measure of Aβ deposition in preclinical stages (i.e., cognitively normal individuals like the ones used in the current study) compared to individuals with MCI and AD (Jansen et al., 2022).

Yet, the findings from the current study suggest that income-related differences in Aβ pathology exist even prior to meeting criteria for Aβ positivity. This finding may allow for early detection in income-related disparities in Aβ neuropathology. It is possible that higher income affords people more opportunities to engage in behaviors that mitigate Aβ accumulation including consumption of healthier foods and engagement in physical activity.

Indeed, Kern et al., (2017) found that healthier foods cost approximately twice as much as unhealthy foods/serving size. Unsurprisingly, a lower income is associated with less healthy dietary intake (i.e. diets low in fruit, vegetables, and fiber, and high in trans and saturated fat are often more affordable) (French, Tangey, Crane, Wang & Appelhans, 2019; Mullie, Clarys, Hulens, & Vansant, 2010). Unhealthy dietary intake has been linked to overweight/obesity, and excess body fat has been linked to elevated levels of proinflammatory cytokines (Lee, Lee, &

Chou, 2013). The impact of adiposity on immune functioning extends to the brain and contributes to alterations in microglial morphology (Bocarsly et al., 2015) and functioning (Chunchai, Chattipakorn, & Chattipakorn, 2017), which may impair Aβ clearance and upregulate production.

In addition to dietary factors, income may also relate to levels of physical activity (Kari et al., 2015; Armstrong et al., 2018). Lower levels of physical activity are often found among those with lower income and this may be attributed to several factors such as 1) fewer resources to afford gym membership, 2) living in neighborhoods with fewer exercise related facilities, parks, and walkable neighborhoods (Gordon-Larsen, Nelson, Page, & Popkin, 2006), and 3) living in neighborhoods with greater crime rates, making it less safe to be outdoors (Han, Cohen, Derose, Li, & Williamson, 2018). Physical inactivity is related to increased obesity and inflammation (Fishcher, Bernsten, Perstrup, Eskildsen, & Pedersen, 2006; Abramson & Vaccarino, 2002), and inflammation may interact with and upregulate Aβ deposition to contribute to neurodegeneration and cognitive decline (Ismali et al., 2020).

4.1.2 Years of Education, Aβ levels, and Aβ Positivity

We did not find evidence suggesting a relationship between years of education and Aβ. These findings were unexpected since years of education is commonly recognized as a factor in AD risk (Zhang et al., 1990; Mortimer & Graves, 1993; Katzman, 1993; Ott et al., 1995; Letenneur et al., 1999; & Sharp and Gatz, 2012). Greater years of education has been associated with greater health literacy (Heide, Wang, Droomers, Spreeuwenberg, Radamakers, & Uiters, 2013), which may be operationalized as the extent to which people are knowledgeable on how to access, understand, and leverage health related information to make appropriate health decisions (Heide et al., 2013; Kwan et al., 2006). Furthermore, health literacy associates with engagement in

physical activity and intake of healthier foods to maintain and/or improve health (Heide et al., 2013).

However, studies observing a greater incidence of AD among those with fewer years of education did not measure AD related pathology such as Aβ. Also, while health literacy may associate with health behaviors that appear to relate to inflammation and Aβ, other factors could be limiting engagement in physical activity and intake of healthier foods independently of knowledge regarding the benefits of these behaviors and how to engage in these behaviors (i.e., limited time and/or resources to engage in physical activities and consume healthier foods).

Although the relationship between years of education and Aβ was non-significant, this does not rule out the possibility that greater years of education could have a protective effect against the impact Aβ may have on cognitive function. This finding would converge on the theory of cognitive reserve, which as previously mentioned, is a complex construct that helps to account for intraindividual differences in functioning despite age related neuronal atrophy and/or the accumulation disease related pathologies (Stern et al., 2020). While the mechanisms by cognitive reserve buffer against declines in cognitive function are poorly understood, years of education is often used as a proxy measure of cognitive reserve (Stern et al., 2020). In fact, several studies have found that those with greater years of education can remain cognitively normal despite having Aβ, compared to those with lower years of education (Roe, Mintun, D'Angelo, Xiong, Grant, & Morris, Rentz et al., 2010; Yaffe et al., 2011; Joannette et al., 2019).

Although evidence suggests that years of education may not prevent Aβ accumulation, rather it moderates the relationship between Aβ and cognitive function, the lack of a relationship between years of education and Aβ in the current study may also be attributed to a limited representation of participants with few years of education. Indeed, more than 60% of the sample

in the current study had at least a bachelors' degree and 16.53 years of education on average. However, regardless of whether the non-significant findings are due to sample characteristics or years of education having a more robust impact on the relationship between Aβ and cognitive function, the incongruency between the findings from the models using annual income and years of education highlight how using different indicators of objective SES may yield different conclusions.

4.2 Subjective SES, AB levels, and Aβ Positivity

We found that subjective SES was associated with Aβ levels and Aβ positivity. Our results suggest that individuals with perceptions of a lower social standing (based on education, occupation, and money), relative to other people in the United States, have greater Aβ pathology. While previous studies have identified SES related disparities in AD based on objective indices (Zhang et al., 1990; Mortimer & Graves, 1993; Katzman, 1993; Ott et al., 1995; Letenneur et al., 1999; & Sharp and Gatz, 2012; Stern et al., 1994, Qiu et al., 2003; Evans et al., 1997; Karp et al. 2004), this is the first study to our knowledge, to suggest that these disparities may also extend to measures of subjective SES.

Given the modest correlations between subjective SES and objective indices of SES (i.e. years of education and subjective SES, r =.30; annual income and subjective SES, r = .26), we may speculate that objective and subjective SES share similar mechanistic pathways to Aβ pathology. This idea may be further supported by the observation that the relationship between subjective SES and levels of Aβ was attenuated when including annual income and subjective SES together in a single regression model (see table 7). However, the unshared variance between these variables may also imply dissociable pathways.

One such pathway may be related to psychological distress. Indeed, while both objective and subjective SES have been individually linked to depressive symptoms (Matthews & Gallo, 2011; Lorant, Deliège, Eaton, Philippot, & Ansseau, 2003), recent evidence suggests that subjective SES has been more strongly linked to psychological factors (Sasaki et al., 2021), and may play a mediating role in explaining the link between objective SES and depressive symptoms (Hoebel, Maske, Zeeb, & Lampert, 2017). In fact, shifting self-perception of their subjective SES by either asking participants to name what separates them from those highest from the social ladder in regards to money, education, occupation, and explain how they felt disadvantaged, led to an increase in depressive thoughts (i.e., worthlessness and helplessness) (Schubert, Sussenbach, Schafer, & Eutenuer, 2016). Altogether, this suggests that subjective SES could be associated with increased depressive like symptoms, which may mediate the relationship between subjective SES and Aβ.

Research has found that greater depressive symptoms are linked to elevated Aβ pathology among cognitively normal older adults (Harrington, Lim, Gould, & Maruff, 2014). Assuming alterations in mood precede and lead to greater Aβ deposition, increased inflammation with depression might be an underlying molecular pathway (Messay, Lim, & Marsland, 2012; Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009).

It is also worth mentioning that there is some evidence suggesting that subjective SES may also modulate inflammatory gene expression (Murray, Haselton, Fales, & Cole, 2019) and associate with inflammatory markers even when controlling for depressive symptoms (Derry, Fagundes, Andrige, Glaser, Malarkey, & Kiecolt-Glaser, 2013). However, more work is needed to elucidate this pathway.

4.3 Years of Education, Annual Income, Aβ levels, and Aβ Positivity

When including years of education, and annual income in a single linear regression model, neither years of education, nor annual income was significantly associated with Aβ. While this finding is contrary to our hypothesis, it is unsurprising that years of education was not significantly associated with Aβ in a model including annual income given it was not significant when only including age and study site in the model as covariates. Additionally, while the attenuation of the relationship between Aβ and annual income when including years of education was unexpected given years of education was not found to associated with Aβ, this finding may be attributed to the shared variance between annual income and years of education (r = .28).

4.4 Strengths, Limitations, and Future Directions

The results of the current study should be interpreted in the context of several limitations. First the cross-sectional nature of these data do not allow us to determine whether there is a causal relationship between SES and Aβ. We cannot rule out the possibility that factors that lead to greater Aβ independently contribute to lower SES. Kapasi et al. (2021) found that elevated Aβ was associated with greater scam susceptibility and impaired decision-making among older adults without dementia. Impairments in decision making and greater scam susceptibility may impact measures of SES such as assets, educational decisions, and income.

The relationship between Aβ and SES may also be complicated by omission of the APOE genotype from our statistical models. Unfortunately, genetic data for IGNITE has not been processed yet. However, once these data are available, it may be an important covariate to include in our models (Di Battista, Heinsinger, & Rebeck, 2016).

These findings may also be complicated by methodological limitations and sample characteristics. First, it is worthwhile to note that the SES data were collected ordinally, which

limited the variability in the distribution of possible SES values. Here, we transformed annual income to a continuous variable. However, there was no maximum income cut off for the highest income bracket, and instead, we followed a similar approach as Gianaros, Marsland, Sheu, Erickson, & Verstynen (2013) and scaled this group scaled to 25% above the minimum value of $100,000 to give these participants a $125,000 value. Similar issues were encountered for years of education such that the highest education group did not have a maximum cutoff point, and instead we assigned individuals in the 20+ range with 20 years of education. Fortunately, in both of these instances, only a few participants fell into the highest ranges. Also, misreporting of income or SES data is also a possibility.

Finally, in regards to sample characteristics, the sample was well-educated (average = 16.53 $\pm$ 2.42 years) and most individuals in the sample identified as being white. These factors may raise questions regarding the generalizability of the current findings. Additionally, there are racial/ethnic disparities in AD (Alzheimer's disease facts and figures, 2020; Gabulal et al., 2018), which may intersect with indicators of SES that we are underpowered to explore.

<h2 style="text-align:center">5.0 Conclusion</h2>

Despite the limitations, our findings suggest that lower objective and subjective indices of SES are associated with greater Aβ levels and Aβ positivity among cognitively normal older adults. These results suggest that lower SES may increase risk for cognitive deficits due to elevated levels of Aβ. Future research would benefit from examining the possible mechanisms (i.e. inflammation) for this association and associations with cognitive functioning. Finally, examining neighborhood level SES factors, in addition to objective and subjective SES indices, could help determine whether those with lowers levels of objective and subjective SES have greater amyloid pathology due to environmental factors.

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