

Stress-Related Socioeconomic Factors and Risk of Alzheimer's Disease: A Literature Review

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Abstract

Introduction: Recent studies have proposed an association between chronic stress and an increased risk of Alzheimer's Disease (AD) and other dementias. AD pathology has been linked to elevated amyloid β ($A\beta$) production and formation of $A\beta$ plaques. A key indicator of chronic stress is high cortisol levels, which have also been shown to amplify amyloid β production, thus making chronic stress a risk factor for AD. A number of risk factors for chronic stress development, including socioeconomic variables have also been suggested as potential risk factors for AD. However, the link between socioeconomic factors, chronic stress and AD incidence remains unclear. This review examines how education, income levels and occupation status may influence the relationship between chronic stress and AD risk.

Methods: We reviewed the literature examining the relationship between occupation, education, and income with stress and AD risk. We performed a thorough search of PubMed, Medline, Web of Science and PsycInfo using predefined keywords, prioritizing prospective cohort studies that primarily examined AD, but also included articles on vascular dementia.

Results: Job strain and increased mental demands at work are associated with increased AD risk. Low income is associated with multiple comorbidities, which is further associated with adverse AD. Additionally, higher education is correlated with decreased AD risk, but independently of the relationship between psychological stress and AD.

Discussion: Literature suggests that chronic stress is related to AD risk, but this relationship is complicated when considering stress-related factors including occupation, education and income. Our review demonstrates that further research must be conducted on this topic to elucidate the correlation between socioeconomic factors, chronic stress and AD risk.

Conclusion: This study will contribute to our understanding of how occupation, education level and income impact AD risk and advocate for methods in closing the health disparity through socioeconomic disparity.

Keywords: psychological stress; Alzheimer's disease; dementia; socioeconomic status; education; income; occupation; chronic stress; cognitive reserve; job strain

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disease affecting approximately 44 million people worldwide [1]. It is characterized by the progressive cognitive decline, resulting in the disruption of daily life and irreversible brain damage [2]. AD is most prevalent among older adults, and individuals with AD survive roughly 4-8 years following diagnosis [3]. The pathogenesis of AD has been linked to two main lesions: senile plaques, which are small, dense deposits of amyloid β ($A\beta$) protein that interfere with nerve signal transduction and increase the extent of neurological damage in AD patients, and neurofibrillary tangles composed of Tau protein, which hinder neural communication and prevent adequate levels of nutrients from reaching neurons [2,4].

Additional insight into how this disease develops may be observed through identification of risk factors such as age, genetics, and cardiovascular disease. Studies have also

found that susceptibility to experiencing psychological stress is a risk factor for AD [3,5]. However, there is limited research examining this relationship. Chronic stress refers to a recurring response generated from heightened emotional arousal, which can lead to the perception of a loss of control. The progressive accumulation of chronic stress is an important factor to consider in the onset of AD [6]. Stress is often measured in a clinical setting through physiological variables such as cortisol, or via self-reported questionnaires [6].

The role of stress in the pathogenesis of AD has been examined in various studies. Excessive stress can exacerbate AD progression through elevated levels of stress hormones [7]. Specifically, corticosteroids and corticotropin releasing factors were found to increase $A\beta$ production and plaque formation. In AD animal models, stress has been shown to accelerate cognitive decline. In rats and mice, stress elevated $A\beta$ peptide production and increased its deposition into amyloid plaques [7]. Another way in which stress has been

linked to AD onset is through the inflammation of microglia. Microglia are the predominant immune cells necessary in maintaining central nervous system homeostasis. These cells respond to alterations in brain homeostasis caused by chronic stress, and have been linked to neuroinflammation, which has also been causally linked to A β accumulation and Tau pathology [8].

There are a variety of socioeconomic variables that may predispose individuals to a higher number of stress-inducing events, which may contribute to increased AD risk. Socioeconomic status (SES) is a widely known determinant of health outcomes, yet research conducted in this field as it relates to AD has been sparse [9]. The American Psychological Association describes SES as the class or social standing of an individual or group [10]. This review aims to clarify whether socioeconomic factors thought to be related to stress—namely income, education, and occupation—may influence the relationship between chronic stress and risk of AD. Establishing this correlation will inform development of policies to diminish socioeconomic disparities, thus reducing the prevalence of AD.

Methods

A thorough search of PubMed, Medline, Web of Science and PsycInfo was performed with the keywords listed below:

Psychological stress*, dementia*, Alzheimer*, socioeconomic, chronic stress*, employment*, income*, education*

We prioritized studies summarizing all three components of stress, socioeconomic factors, and AD risk in their results. In total, 22 articles were reviewed. Studies that specifically discussed AD were prioritized, however, articles focusing on other dementias were not excluded. If there was a lack of articles correlating all three socioeconomic measures, we included the most cited source that drew an association between two of the three components to draw inferences about how all the components were related. Observational studies were prioritized in this review, although systematic reviews were not excluded. Articles published earlier than 2000 were excluded from our search in order to include modern definitions of AD, and account for the modern conceptions of the social determinants of health.

Results

Occupation

The correlation between occupation and AD risk mediated by work-related stress has been highlighted in the available literature. Andel *et al.* published a study examining the relationship between work-related stress and dementia, vascular dementia, and Alzheimer's disease [11]. Participants were members of the Swedish Twin Registry, a population-based registry of twins residing in Sweden. In this study, occupation was measured through indicators of work-related stress derived from Karasek's job strain

model, which postulates that psychological strain is the product of job demands and range of decision-making abilities [11,12]. Job demands were defined as the workload stressors experienced, such as work schedule intensity. Job control was defined as the extent to which one exercises personal judgment in their job. Social support was defined as the possibility for helpful social interaction, and job strain was indicated by the ratio of job demands to job control [11,12]. Results from this study indicated lower job control and lower social support was associated with greater risk of vascular dementia, a condition that occurs as a result of aging of the cardiovascular system, which is linked to AD onset. Greater job strain was linked to an increased risk of vascular dementia [11].

A study in 2012 conducted by Wang *et al.* examined how high job stress during working life might lead to an increased risk of AD and non-AD dementias (NAD) later in life [13]. Healthy older adults at baseline were followed up for an average of 6 years to detect incident AD and NAD. Occupational data was collected at the first follow-up of the longitudinal study, typically through an informant who answered questions about life-span work activities. Job demands, job control, and job support were evaluated. Individuals diagnosed with dementia due to AD or other etiologies after follow-up were older, less educated, had lower job demands, and lower job control than those who did not develop dementia. Furthermore, this study indicated those who had high job strain (i.e., those in jobs with high demands and low decision latitude) were often well-educated females [13]. When Wang *et al.* controlled for work complexity, the association between passive job strain and dementia risk was weakened. It was concluded that both under stimulation and overstimulation may impact AD risk [13].

Finally, Sundstrom *et al.* examined how high mental demands at work might be a protective factor in reducing risk of dementia and AD [14]. In a prospective cohort study, healthy older adults without dementia were asked to complete an examination to determine cognitive function at baseline. At the end of the study, of the 1277 participants, 199 individuals (15.5%) developed AD, and 145 individuals (11.4%) developed vascular dementia. Occupational information was obtained through questionnaires about socioeconomic factors, such as main lifetime occupation and description of its job characteristics. Unlike the previous two studies examined, this study revealed no association between workplace mental demands and dementia or AD risk [14].

Income

Studies have indicated a correlation between income and AD-related outcomes. Income-related lifestyle factors, chronic disease, and psychological disorders were identified as main contributors to AD. However, such studies do not explicitly examine the relationship between these two variables as it relates to stress. Stepkowski *et al.* found a

negative correlation between per capita personal income and age-adjusted AD death rates such that those with higher income had lower death rate from AD [15]. Income had a significant, lifelong influence on the risk of AD development, found to be highest in the early years of life. In a cohort study by Chen *et al.* that assessed the effects of income-related insurance payments on AD survival outcomes, patients with AD and low individual payments displayed the lowest survival rate [3]. After adjusting for confounding variables, the mortality risk of patients with high income in disadvantaged geographic areas remained similar to those with high income in advantaged areas, indicating individual earnings are of greater importance regarding AD mortality.

Another study by Kumar *et al.* assessed the association between income-based disparities, chronic disease, and cognitive functioning in older adults [16]. The authors used the India dataset from the World Health Organization Study on global AGEing and adult health (SAGE). SAGE assesses older adult cognition by generating an overall cognition score, which was used in a two-level linear hierarchical model to record its association with SES at individual and community levels. Household income and community level SES were found to be positively correlated with cognition whereas multimorbidity was negatively associated with cognition. Interestingly, this paper cited that those living in deprived communities are more vulnerable to many adverse outcomes including mental disorders such as anxiety [17].

Provided that communities of lower income status are more susceptible to health problems, a connection could be bridged between a low-income environment and the development of neurodegenerative disease. In a study conducted by Huang *et al.*, data from 13,067 individuals with major depressive disorder (MDD) and 52,268 non-MDD controls were extracted from Taiwan's National Health Insurance Research Database and matched through propensity score [18]. The patients were followed up until dementia diagnosis, death, or end of 2013 to assess outcomes. The primary outcome was dementia incidence, which was further classified into an AD group and a NAD group. Compared to the non-MDD group, individuals with MDD were 4.7 times more likely to develop AD, and 3.7 times more likely to develop NAD. This indicates a correlation between low income and increased risk of adverse outcomes in AD and other dementias. In contrast with these findings, a case-control study analyzed the effects of physical and social environments on dementia incidence and found higher odds of dementia in areas with high median annual family income, although a significant relationship did not appear after further adjustment for confounding variables [19].

Education

Many correlational studies have found a negative association between years of formal education and AD risk.

The bulk of the literature considers stress and education as separate factors influencing risk of AD, and such studies have yet to explore how these two variables interact. Russ *et al.*'s meta-analysis explored how SES in early life and adulthood may be associated with dementia-related death. Psychological distress was measured as a covariate using the General Health Questionnaire. Low educational attainment was linked to a heightened risk of dementia-related death, but this relationship was only observed in women [20].

A main focus of the literature examining the relationship between education and AD is the cognitive reserve (CR) hypothesis. CR describes the use of cognitive processes to cope with the symptoms of neurodegenerative disease: for instance, switching to an alternative function when the default function is inoperable [21]. In addition to educational attainment, lifetime exposures that can increase CR include musicianship, bilingualism, and exercise [22]. Notably, Qiu *et al.* conducted a longitudinal study on older adults without dementia and found a correlation between low levels of education and increased incidence of clinical AD, which is consistent with the CR hypothesis [23]. Additionally, in a prospective cohort study by Scarmeas *et al.* examining incident AD cases over the course of 14 years, higher education was correlated with a faster rate of cognitive decline, particularly concerning executive speed and memory [24]. Researchers hypothesize that this faster rate of decline supports the CR hypothesis, as it signifies that the manifestation of symptoms in individuals of higher education occurs further along in their disease progression, when cognitive decline more sharply decreases, compared to those without higher education. Despite the plethora of research on the CR hypothesis, very few studies have explored its relationship with stress. A cross-sectional study by Cabral *et al.* found no association between measures of cortisol, self-reported stress, and CR in healthy older adults [25]. Stress and CR independently contributed to the development of AD, but CR did not modulate the relationship between stress and risk of cognitive decline [25].

Discussion

The aim of this paper was to clarify the inter-correlations between chronic stress, socioeconomic factors and AD risk. A thorough literature search was performed examining relationships between education, income, occupation, stress, and AD. The rationale behind linking socioeconomic factors to AD via stress was due to a previously established link between stress with AD risk, and socioeconomic factors with later life stress.

With regards to occupation, few studies examined how work-related stress impacted AD risk via job strain. The findings of Andel *et al.* along with those of Wang *et al.*, demonstrated that lower levels of job control are associated with an increased risk of dementia. This concept supports the CR hypothesis, in which increased mental demands at work may facilitate development of cognitive skills, such as

problem-solving and memory, that may serve as protective factors in dementia risk. However, there is an important difference between two of the studies examined with regards to how they proposed stress to interact with occupation and risk of AD [11,13]. First, Andel *et al.*, proposed a cardiovascular pathway mediated by stress underlying the relation between job control and increased dementia risk. Andel *et al.*, showed that job strain was associated with vascular dementia, a condition that arises due to accelerated aging of the cardiovascular system [11]. Thus, a cardiovascular pathway mediated by stress would account for the risk of vascular dementia proposed in this study. In addition, this cardiovascular pathway is the result of chronic stress and leads to a dysregulation of other organ systems. On the contrary, Wang *et al.* proposed a mechanism involving acute stress which would entail increasing cortisol secretion, producing short-term damage in the hippocampus. Indeed, repeated experiences of stress causes atrophy of the dendrites of pyramidal neurons in the hippocampus [11]. This mechanism is plausible in the context of Wang *et al.*'s study seeing as job strain was not associated with vascular dementia, indicating that non-cardiovascular mechanisms may be involved in the relationship. When Andel *et al.* controlled for work complexity, the association between the lack of social support at work and dementia was strengthened. This suggests that including more occupational health and wellness policies may reduce dementia risk, such as those that increase autonomy in order to increase job control, facilitate communication and social support systems, and modify job demands [11]. Wang *et al.*, on the other hand, found that both understimulation and overstimulation may impact AD risk, which suggests that a balance must be found in the workplace to ensure employees are completing fulfilling work requirements while also mitigating stress levels. This strategy may involve encouraging collaboration to reduce the workload for individuals and promoting positive relationships while accomplishing tasks with the same, or perhaps higher degree of quality [13]. Sundstrom *et al.*, highlighted some important limitations in both Andel *et al.*'s and Wang *et al.*'s work, including their small sample sizes which were subject to selection bias, and that AD prevalence was examined rather than incidence [13,14]. Sundstrom *et al.* examined a relatively homogenous population in Sweden, reducing the presence of selection bias. The discrepancy between these findings and previous ones likely lies in the variability in study design, statistical methods and adjustment for covariates. An advantage of Sundstrom *et al.* is the large sample size and follow-up time, along with its random sampling methods. However, there is a lack of detail explaining how socioeconomic factors influence the relationship between stress and dementia risk. Of the three studies, Andel *et al.* provided the most thorough investigation of the influence of each covariate, and the results were strengthened by the multiple controls utilized [11,13,14].

In terms of income, the consensus is that individuals with lower income-related SES are more likely to develop AD [3,15]. However, one study by Liu *et al.* shows that increased dementia incidence was observed in areas with high medial annual family income, although this relationship was not deemed significant after adjusting for confounding variables [19]. The studies that do establish an association do not mention how stress may mediate this relationship. Stepkowski *et al.* and Chen *et al.* found statistically significant correlations between income level and risk for both AD and non-AD dementias [3,15]. Stepkowski *et al.* postulate income-related modifiable lifestyle factors largely determine the likelihood of AD [15]. These modifiable risk factors such as smoking, physical activity, alcohol consumption, isolation, sleep disturbance, and diet need to be addressed, particularly amongst those who are financially disadvantaged. Interestingly, Chen *et al.* found that individual income is a greater determinant of AD mortality than community income [3]. This indicates that socioeconomic support should be allocated on an individual case-by-case basis rather than by community. In addition to finding an association between economic disadvantage and lower cognition, Kumar *et al.* also found that higher multimorbidity was correlated with a decrease in cognition and noted that lower-income communities are more vulnerable to health problems than higher-income communities [16]. Other studies, such as those by Vassilaki *et al.* and Villeneuve *et al.* have observed a positive relationship between multimorbidity and dementia [26,27]. Furthermore, Kumar *et al.* proposed that those with lower income are more susceptible to anxiety, and Huang *et al.* found that patients with MDD had higher risks of both AD and NAD compared to those without MDD [16,18]. Considering that multimorbidity is associated with increased risk of neurodegenerative diseases, this research paves way for future studies to establish a more concrete link between income, AD, and stress-related health problems. Therefore, stress is likely only one piece of a larger multimorbidity puzzle that bridges income and AD, as hinted by Huang *et al.* and Kumar *et al.* More research needs to be conducted to clearly establish relationships between these variables.

The relationship between education and AD risk is well established in the literature, however this link often does not account for stress. To summarize, the meta-analysis conducted by Russ *et al.* found an association between leaving full-time education earlier in life and risk of dementia-related death after adjusting for psychological distress, but only in women [20]. The study highlights the importance of intervention strategies for women, who generally have a higher risk of dementia than men [28]. The promotion of higher education in women may become an important topic in public health. Nevertheless, the effect of education on AD risk in females needs further research. Additionally, this study had the benefit of a large, well-

characterized sample that was representative of the general population of England. However, there were only 622 dementia-related deaths, since it included a wide age range of individuals 35 and older [20]. A sample with such variability in age allows for greater generalizability, but lacks specificity to AD as the age of onset for most cases is above 65 [3]. A final critique of the study is that dementia is often under-recorded as the cause of death [29]. Thus, studies that confirm dementia diagnosis through other methods may be more reliable, such as a combination of neuropsychological assessment with neuro-imaging techniques of MRI or CT scan, as seen in Scarmeas *et al.*'s study.

Furthermore, the protective association between education and AD risk was suggested through the CR hypothesis by various researchers. Qiu *et al.*'s study found an increased AD risk in those with lower educational attainment, with the effect more evident in women than in men, consistent with Russ *et al.*'s findings [20,23]. However, Qiu *et al.*'s sample included only 109 participants who were diagnosed with AD. While Russ *et al.*'s study had the issue of measuring dementia prevalence through death certificates, this study examines incident AD cases [20,22].

Another study found that individuals with AD who received higher education experience faster cognitive decline after diagnosis than individuals without higher education. The study proposes that individuals with higher education can better manage the pathological burden and mask symptoms of AD. When this population does show measurable cognitive decline, they are further along the disease progression and show faster cognitive decline than their peers with lower education, supporting the CR hypothesis [24]. However, follow-up post diagnosis in the study was relatively limited (1.8 years), so the full progression of cognitive decline may not have been captured [24]. Finally, no association was found between CR with stress in Cabral *et al.*'s cross-sectional study, which included a relatively small sample size of 145 individuals [25]. The study was conducted on healthy older adults rather than individuals with dementia-related diseases, making the findings generalizable to prodromal rather than severe AD [25]. The variability of methodologies across studies that use incident cases of AD, prevalent cases, and healthy older adults may contribute to inconsistencies in findings of how education and stress impact AD risk. Additionally, studies only accounted for the quantity of education and not quality; the difference between homeschooling, public, and private education was not researched.

Conclusions

The aim of this paper was to clarify how education level, income, and occupation influence the relationship between chronic stress and risk of AD. We hypothesized that since chronic stress has been shown to correlate with

AD, socioeconomic factors related to high levels of chronic stress will influence AD risk. Our review suggests further research, potentially in the form of prospective cohort studies, must be conducted in order to validate this correlation. For occupation, findings are mixed, as some studies suggest a relationship between mental demands at work and risk of AD, while other studies suggest that increased job strain is associated with a greater risk of developing AD. Low income was correlated with adverse AD outcomes, however, stress is not the only factor mediating this relationship—multi comorbidities may be primarily responsible. Finally, education affects AD risk through a mechanism separate from stress, with the CR hypothesis at the forefront of research. With all three socioeconomic factors, only correlational relationships could be effectively established due to the nature of the studies. Overall, SES is correlated with AD, but occupation was the only factor for which a stress-related pathway was proposed. Although stress may not be involved in the relationship between income, education, and AD, the present review suggests future directions of research in ways to mitigate AD risk. Suggested methods have included higher levels of social support at work, encouraging the pursuit of higher education, and addressing socioeconomic disparities by improving access to education and bridging health inequities. Stress reduction activities throughout one's lifetime could also promote healthy aging. Overall, more research in this field will help to gain a stronger understanding of how socioeconomic factors impact AD incidence and equip older adults with strategies and lifestyle changes to reduce their risk of AD.

List of Abbreviations Used

A β : amyloid β
AD: Alzheimer's disease
CR: cognitive reserve
MDD: major depressive disorder
NAD: non-Alzheimer's dementia
SAGE: Study on global AGEing and adult health
SES: socioeconomic status

Conflicts of Interest

The authors declare no conflict of interests.

Ethics Approval and/or Participant Consent

The study did not require ethics approval or participant consent. As a literature review, no new research was conducted, and no participants were recruited.

Authors' Contributions

SA: contributed to conducting a literature search on the topic of occupation, chronic stress and dementia, drafted the manuscript, and edited the final draft.

NL: contributed to conducting a literature search on the topic of income, chronic stress and dementia, drafted the manuscript, and edited the final draft.

TW: contributed to conducting a literature search for the topic of education, chronic stress and dementia, drafted the manuscript, and edited the final draft.

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