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Psychosocial risk factors for Alzheimer's disease in Down syndrome patients and their association with brain changes: a narrative review

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Abstract

Several recent epidemiological studies attempted to identify risk factors for Alzheimer's disease. Age, family history, genetic factors (APOE genotype, Down syndrome), physical activity, and a low level of schooling are significant risk factors. In this review, we summarize the known psychosocial risk factors for the development of Alzheimer's disease in Down syndrome patients and their association with neuroanatomical changes in the brains of people with Down syndrome. We completed a comprehensive review of the literature on PubMed, Google Scholar, and Web of Science about psychosocial risk factors for Alzheimer's disease, for Alzheimer's disease in Down syndrome, and Alzheimer's disease in Down syndrome and their association with neuroanatomical changes in the brains of people with Down syndrome. Alzheimer's disease causes early pathological changes in Down syndrome patients, especially in the hippocampus and corpus callosum. The field needs more data about the neuroanatomical changes during childhood, how they change with increasing age, and the presence or absence of psychosocial risk factors. Further neuroimaging and psychosocial assessment-focused research is needed to understand the mechanisms leading to Alzheimer's disease at an early age and create more sensitive and relevant clinical, memory, and reasoning assessments for people with Down syndrome.

Keywords
Alzheimer's disease, Corpus callosum, Dementia, Down syndrome, Hippocampus, Psychosocial Risk Factors

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Abbreviations**:** AD = Alzheimer's disease, DS = Down syndrome, MMSE = Mini-Mental State Examination, PHG = Parahippocampal gyrus

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Key Summary Points

Alzheimer's disease patients with Down syndrome show (early) degenerative alterations in specific brain areas, so Down syndrome is a suitable model for studying the early stage of Alzheimer's disease.

We searched in the literature about the common psychosocial risk factors of Alzheimer's disease in Down syndrome as age, gender, cognitive status, genetic characteristics, educational level, social standing, employment, physical activity, psychosocial activity, ethnic group, and smoking habits.

Hippocampus and corpus callosum are the most affected brain regions in Alzheimer's disease and Down syndrome patients with dementia, so they are possible biomarkers for Alzheimer's disease.

No published research specifically addressed the impact of psychosocial risk factors on the incidence of Alzheimer's disease in Down syndrome or linked them to neuroanatomical changes based on imaging data.

The study of risk factors will increase our understanding of the genetic and molecular elements that cause Alzheimer's disease and how to avoid them with different interventions.

Introduction

Since Down syndrome (DS) patients with Alzheimer's disease (AD) show (early) pathological changes in specific brain regions (1), they offer a possibility to investigate the first changes in this disease and observe its progression stage along the course of the disease. Both AD patients with and without DS will benefit from the improved diagnosis and treatment of dementia syndrome (1). Although the cause of AD in the general population remains uncertain, risk factors for AD development are known (2). Psychosocial risk factors are essential to recognize, as they can be modifiable instead of genetic factors. For example, people who were only slightly physically and cognitively active in the past and were socially involved to a limited extent develop dementia more often (3, 4). The current study focuses on the psychosocial risk factors for AD in children and adults with DS and the neuroanatomical alterations observed in these individuals using high-resolution neuroimaging (MRI imaging). The risk factors analyzed included age, gender, cognitive status, genetic factors, educational level, social status, employment, physical activity, psychosocial activity, ethnic group, and smoking habits (e.g., family members). The risk of dementia is much reduced in individuals with a high cognitive reserve and is much higher in people with low educational levels and intellectual problems. This finding results from more than 20 published studies with more than 29,000 participants and a median follow-up period of more than seven years (5). Mullins, Daly (5) concluded that demented subjects with DS and subjects with AD in the general population have significantly reduced volumes of the same brain regions and the hippocampus and other temporal lobe structures. These volume reductions have an

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association with cognitive decline in both groups. Preliminary evidence indicates that DS individuals may be more sensitive to tissue loss than others and have less "cognitive reserve" (5). Few studies used functional brain imaging to study DS (5, 6). These are characterized by small samples and using many different methods and scanning tasks with low image resolution so that the results are not easily comparable.

Additionally, previous neuroimaging studies of child development have limitations due to their coarse resolution, small group size, and limited age range (7). Previous research studies did not significantly analyze temporal lobe anomalies, parahippocampal gyrus volume, and corpus callosum changes. For instance, Rodrigues, Nunes et al. (2019) conducted a survey to assess DS neuroimaging linked abnormalities of the corpus callosum to DS, but further studies are needed to confirm this finding. This review is trying to collect data from various resources to understand this gap. We intend to provide a preliminary assessment for future examinations attempting to produce new data sets for structural neuroimaging of DS compared to AD patients in the average population and cognitive-behavioral phenotypes. Thus, we will focus on research data related to patients with DS compared neuroanatomically with the psychosocial risk factors for AD occurrence.

This review study will help us better understand the pathological and neuroanatomical linkages between AD and DS and the role of psychosocial risk factors in establishing remedies and ways to prevent AD at an early stage.

Methods

We performed a comprehensive literature search on PubMed, Google Scholar, and Web of Science. First, we reviewed articles using the search terms "Psychosocial risk factors for Alzheimer's disease" with "Risk factors, Psychosocial risk factors, Alzheimer's disease". We also used the search term "Risk factors, Psychosocial risk factors for Alzheimer's Disease in Down syndrome" with the keywords "Risk factors, Psychosocial risk factors, Alzheimer's disease, dementia, Down syndrome" for further detailed research. We found related terms such as dementia and dementia of Alzheimer's type as they are used interchangeably within the literature. We selected structural neuroimaging studies focusing on the neuroanatomical changes in DS involved in memory functions, specifically changes in regions of the hippocampus, corpus callosum, and temporal lobe in association with psychosocial risk factors related to the occurrence of AD. We searched using the keywords "Risk factors, Psychosocial risk factors, Alzheimer's disease, Dementia, Down Syndrome, Neuroimaging, Neuroanatomical changes". We did not use statistical methods but summarized related data published between 1978 and 2021 to review the recently published studies. While this study does not represent a systematic review of the literature, we selected publications and research articles for inclusion if they presented relevant outcomes related to AD and DS patient groups. Those reporting on the psychosocial risk factors of AD in DS have priority. In contrast, articles reporting on other AD risk factors in DS have no priority unless they include specific information on DS patients related to our search topic. When there were several articles on a given topic, those that contained unique information have priority for inclusion. We added more recently published publications and studies of more significant patient populations and studies with more extended follow-up periods to the list of priorities. We chose 25 articles on different topics for inclusion in the literature review (see table 1). This article is based on previously conducted studies and

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does not contain any new studies with human participants or animals performed by any of the authors.

Table 1: Number of studies (published between 1978 and 2021) reviewed in different topical areas

Topical areas	Number of studies reviewed
Psychosocial risk factors for AD	8
Psychosocial risk factors for AD in DS	12
Psychosocial risk factors for AD in DS and their association with neuroanatomical changes in the brains of people with DS	5

2. RESULTS

2.1 Psychosocial risk factors for AD

Although research data identified various neurophysiological risk factors for AD and dementia, little knowledge is available regarding psychosocial determinants (8). Previous studies identified many psychosocial risk factors for AD (see table 2). Zhang, Li (9) performed a 5- and 10-year follow-up study in Shanghai, China. The essential psychosocial risk factors for AD onset and development suggested by this study were not working (jobless or retired), no participation in community activities, analphabetism, and blue-collar status. Burke, Cadet (10) established a connection between depression, sleep disturbance, and anxiety (as individual factors and comorbid conditions) and the risk of AD development. This study, however, did not use neuroimaging to confirm the diagnosis of AD pathology (10). A survey by Burnes and Burnette (8) indicated that previous life trauma and posttraumatic stress disorder (PTSD) are good candidates as psychosocial risk factors for AD, according to the evidence presented in this research, by creating a conceptual model relating these factors to AD. Kropiunigg, Sebek (11) discussed psychosocial stress resulting from adapting to an active but ineffective work style and living with a domineering spouse as a link to an increased risk of AD. PERSSON and SKOOG (12) studied different psychosocial risk factors before the age of 70 in various age groups, such as the death of a parent, divorce of parents, growing up with one parent, different guardians, extreme poverty, death of a spouse, death of a child, serious illness in a child, shift or piece work, arduous manual labor, physical disease in a spouse, mental illness in a spouse, death of a child, severe disease in a child, death of siblings or friends, change of residence and financial status deterioration. Their findings suggest that psychosocial risk factors early in life contribute to the development of dementia later in life (12).

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Table 2: A summary of the findings from the studies (published between 1978 and 2021) that reported psychosocial risk factors for AD

Study	Psychosocial risk factors studied	Association with the risk of AD
Burke et al.	Depression, sleep disturbance, and anxiety	The study results demonstrated a substantial hazard of AD development for those reporting depression, sleep disturbance, and anxiety as independent symptoms.
X Zhang et al.	Blue-collar occupation, no job, no reading or writing, no participation in community activities, no leisure gardening, negative psychological feelings, and a lower level of education	The study concluded that these factors play a significant role in AD development without specific details.
Burnes et al.	Trauma and posttraumatic stress disorder (PTSD)	The study proposed a conceptual model relating psychological trauma, posttraumatic stress disorder (PTSD), and AD. It indicated that previous life trauma and PTSD are strong candidates as psychosocial risk factors for AD.
Kropiunigg et al.	Psychosocial stress	According to the study findings, psychosocial stress from work and lifestyle is a significant risk factor for AD.
Persson et al.	Death of a parent, divorce of parents, growing up with one parent, different guardians, extreme poverty, death of a spouse, death of a child, serious illness in a child Shift or piece work, arduous manual work, a physical condition in a spouse, mental illness in a spouse, death of a child, severe disease in a child, death of siblings or friends, change of residence and financial status deterioration.	The study results supported the hypothesis that psychosocial risk factors during earlier life contribute to the development of dementia in old age.
Wang et al.	Psychosocial stress at work	The study concluded that long-term work-related psychosocial stress, characterized by limited job control and high job strain, was linked to an elevated risk of dementia and AD in later life, independent of other known risk factors.

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He et al.	Low educational level, low cognitive function, low occupational status, lack of social interaction and leisure activities, and poor well-being	The study suggested an association between these factors and the onset and development of AD.
Bernhardt et al.	Living alone, having no intimate social connections, not participating in social or recreational activities, and never marrying	The study reviewed different living and social factors that could affect the development of dementia and AD.

AD=Alzheimer's disease

Wang, Wahlberg (13) investigated the association between psychosocial stress at work and an increased risk of dementia at a late age and found that stress conditions associated with the job contributed to a high risk of dementia and AD at a late age. Additionally, a similar study by Seidler, Nienhaus (14) studied the role of psychosocial work factors in the onset of dementia. He, Zhang (15) found that low educational level, low cognitive function, low occupational status, lack of social interaction and leisure activities, and poor well-being affect the onset and development of AD. A systemic research review by Bernhardt, Seidler (16) provided a thorough review of all reported psychosocial risk factor outcomes from controlled trials between 1994 and 2001. This review concluded that factors studied in the articles, such as living alone, having no intimate social links, not participating in social and recreational activities, and never having married, are all linked to dementia. This review suggests that AD is adversely associated with intellectual diversity and intensity and favorably associated with psychosocial inactivity, unproductive working style, living with a domineering spouse, and physical inactivity in recent studies (16).

2.2 Psychosocial risk factors for AD in DS

Determining the risk factors is essential to assessing the risk of AD in DS patients. However, such risk factors for the occurrence risk of AD in the general population are not crucial for those developing the disease. Therefore, AD patients have no exposure to such risk factors (17). Neuropathological changes related to amyloid precursor protein (APP) contribute mainly to the first clinical signs of AD in DS (18). In autopsy, Alzheimer-type neuritic plaques and neurofibrillary tangles have been found and reported in the brains of 7.5% of people with DS in the early second decade of life, reaching 80% by the fourth decade and 100% in people over 60 years old (19). Other risk factors that can add more explanations and understanding of the mechanism of the occurrence of the predementia stage in people with DS should be studied and identified (20). The study of risk factors for dementia in people with DS faces challenges due to the lack of specific and compelling cognitive and neuropsychological status measurements in this population. We focused on psychosocial risk factors such as age, sex, mental status, education, physical activity, smoking, and other genetic and environmental factors (see table 3). Age is considered a strong common risk factor for dementia in DS, and the association between increasing age and the increased risk for dementia in DS is widely indicated (17, 20, 21). Few studies have assessed gender as a risk factor, with controversial results (20). Some evidence reports that women are at greater risk due to the low level of postmenopausal estrogen and that women

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have a higher life expectancy than men (17). A recent study by Lai, Mhatre (22) evaluated sex differences in AD risk in adults with DS. It showed no significant sex difference in the risk for AD development in adults with DS. However, they found that women with DS had a nearly 2-year duration of dementia more than males with DS from AD onset until death, although having equal mean ages at the beginning of AD. These findings (22) contrast with earlier DS research conducted on a smaller scale (23, 24). In men with DS, Schupf, Kapell (23) found a greater risk of AD, but Lai, Kammann (24) found the opposite.

In the general population, there is an evidence-based suggestion that a higher level of cognitive functioning, which has a link with a higher level of education, a higher IQ, years in an institution, and employment, is considered to be associated with a low incidence of dementia (25). This study investigated the correlation between education and other environmental factors, such as institutional years and occupation, and the occurrence of dementia in people with DS. It resulted in the theory that environmental changes can improve cognitive function, leading to the delay of the onset of dementia (25). These data led to the cognitive reserve hypothesis, suggesting that patients compensate for neuronal loss when the brain works actively to deal with neuronal damage (26). Patients with better baseline cognitive abilities can tolerate more AD pathology and neuronal loss than patients with worse baseline cognitive skills (27). Also, Zigman and Lott (17) assumed that IQ level and cognitive reserve could be possible risk factors for dementia in DS. They suggested that people with DS who function at higher levels [e.g., more excellent premorbid IQ, education, occupation, and language ability] have a reduced risk of AD dementia than their counterparts who perform at lower levels. Another decisive risk factor is a family history caused by genetic or environmental factors. The apolipoprotein E gene (APOE), encoded by three alleles, Ɛ2, Ɛ3, and Ɛ4, is associated with a risk for AD in DS (28). The apolipoprotein Ɛ4 allele is the most well-known genetic risk factor for sporadic AD, and it has a link to early symptoms and pathology in the general population (29). The APOE Ɛ4 allele is also a significant risk factor for AD in DS compared to the APOE Ɛ2 allele, which is associated with low risk and a protective role (17, 20, 28). Although an early meta-analysis of association studies revealed that dementia was higher in DS patients carrying APOE Ɛ4 (30), one case-control study in a Dutch community found no effect of APOE genotype on the incidence or onset of dementia in DS (31). The minimal number of patients studied was a critical limitation of these investigations (28).

In contrast to noncarriers, APOE Ɛ4 carriers are at increased risk for dementia in DS, with an earlier start and rapid progression, according to a recent longitudinal, large cohort study of DS patients (32). According to the available data, the evidence for a link between APOE Ɛ4 and dementia in DS is very suggestive (29). Few studies reported the effect of physical activity on cognitive function and dementia risk in DS (33). Some of these studies used the mouse model of DS (Ts65Dn mice) and found essential evidence that physical activity may help with cognition. Voluntary wheel running in mice, for example, was linked to improved performance in cognitive tasks when compared to sedentary controls, especially when considering hippocampal-mediated processes, which are essential during AD (34-36). Previous mouse model reports found that physical activity impacts gene and protein expression, neurogenesis, and brain morphology (34, 35, 37). A 12-week exercise program improved episodic memory in human studies, including people with DS (38). These studies documented improvements in executive function assessments such as inhibition (39, 40), attention shifting (41), response time (42, 43), and semantic fluency (44, 45). However,

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there are differences in effect sizes and findings between these studies (33). A recent survey by Pape, Baksh (33) examined the association between physical activity, regular exercise, and cognitive function in DS. The findings of this study indicated that frequent moderate and high-intensity exercise might reduce the possibility of clinically detectable mental deterioration in the DS group, with possible long-term benefits (33). No specific study from our reviewed literature correlated ethnicity as a risk factor for AD in DS, so future studies should consider this data.

Considering smoking as a risk factor for dementia in the general population is unclear (46). Research supported by the tobacco industry (conflict of interest) indicated a low risk of dementia associated with smoking (47). Nonetheless, research data with no tobacco industry affiliation (e.g., tobacco companies providing study funding, study author(s) currently or previously employed by a tobacco company) reported a significantly increased risk of AD (47). We did not find a study investigating the relationship between smoking in DS directly or passively (e.g., family members) and the risk of AD development. Many researchers who looked at potential psychosocial risk factors struggled with assessment and diagnostic challenges, making it difficult to compare results from different studies (20). Future researchers looking into the prevalence rates and psychosocial risk factors for AD in people with DS should consider these observations.

Table 3: A summary of the findings from the studies (published between 1978 and 2021) that reported psychosocial risk factors for AD in DS

Study	Psychosocial risk factors studied	Association with the risk of AD in DS
Bush and Beail	Age, gender, APOE	The study indicated that considering gender as a risk for AD in DS is contradictory. Still, it confirmed the association with age and the APOE Ɛ4 allele as a significant risk factor for dementia in DS, whereas the APOE Ɛ2 allele is protective.
Zigman and Lott	Age, sex, IQ, cognitive reserve, and APOE	The investigation demonstrated the link between growing age and the likelihood of dementia in people with DS and produced contentious findings on the role of sex as a risk factor. The study considered that IQ and cognitive reserve are risk factors for dementia in people with Down syndrome. According to the findings, APOE 4 increases the risk of dementia in individuals with DS. APOE Ɛ2 has a link to a lower incidence of dementia in people with DS.

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Lai, Mhatre et al.	Sex	The study found no sex difference in the risk of AD development in DS.
Schupf et al.	Sex	The study findings indicated that men with DS have an earlier onset of AD than women with DS.
Lai, Kammann et al.	Sex	The study found that women with DS have an increased risk of AD compared to men.
Temple et al.	Educational attainment, time spent in an institution, and employment	The study found by using a post hoc regression that cognitive function level is associated with these environmental factors and indicated that in those with DS, a better degree of cognitive functioning decreases incidences of dementia.
Verghese et al.	APOE	The study suggested strong evidence for the association between APOE (specifically Ɛ4) and the risk of dementia in DS.
Van Gool et al.	APOE	The study findings suggest that APOE Ɛ4 does not significantly affect the pathogenesis of AD in DS patients.
Prasher et al.	APOE	The study results showed a strong association between the APOE Ɛ4 genotype and risk for AD and a reduction in the age of onset of dementia. Still, in contrast to other studies, the presence of an Ɛ2 allele doesn't reduce the risk of dementia or delay the age of onset.
Bejanin et al.	APOE	The study observed an association between the APOE Ɛ4 allele and early clinical and pathological features of dementia in DS.

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Coppus, Evenhuis et al.	APOE	The study indicated an increase in the occurrence of dementia in APOE Ɛ4 carriers and concluded that APOE affects the risk of dementia in people with DS.
Pape, Baksh et al.	Physical activity	The study found that moderate and high-intensity exercise could reduce DS's cognitive decline and dementia risk with long-term benefits.

2.3 Psychosocial risk factors for AD in DS and their association with neuroanatomical changes in the brains of people with DS

No specific study investigated DS brain areas changes related to AD, specifically the hippocampus or corpus callosum, and correlated such changes with psychosocial risk factors. Here, we correlate the results of previously published studies regarding the neuroanatomical changes related to dementia in DS with the results discussing the effect of psychosocial factors on cognitive function. All people with DS develop neuropathological features of AD by 40 years of age (1, 19, 48, 49). The aging processes in DS are associated with the deposition of senile plaques and neurofibrillary bundles (50). The build-up of these deposits, their distribution pattern in the brain, and the involvement of specific neurons are remarkably similar to the pathological changes that characterize AD (19). A better understanding of how the DS brain develops with the help of a development-oriented approach will shed light on critical neurological principles of DS in children and illuminate the basics of the phenotype in adults, particularly the increased risk of early AD (17). Therefore, DS is of interest as a model for morphological brain changes in the early stages of AD (51).

Hippocampal and temporal lobe volume reductions are typical of AD and DS patients with dementia (52-54). These volume reductions are associated with cognitive decline in both AD and demented DS groups in a study by Mullins, Daly (5). This study results showed a positive correlation in AD patients between the Mini-Mental State Examination (MMSE) score and the corrected hippocampus and temporal lobe volumes. Previous research reported a similar finding and revealed that performance on the MMSE correlates directly with hippocampal volume (55). The decline in the hippocampus and temporal lobe volumes affects their functions, which is observable by the correlation between MMSE scores and the reduced volume in these regions (5). The hippocampal structures involved in explicit memory deficits, the dentate gyrus, the essential core areas of hippocampal efferences and afferences, and the corpus callosum are crucial areas for studying structural changes related to AD. When evaluating the existing evidence of structural changes in the hippocampus in patients with AD, memory impairment was one of the first clinical signs identified (51). This symptom worsened slowly over time and took the character of personality changes, loss of language skills, and affection of the extrapyramidal motor system. Histopathological examinations show the hippocampus structure as one of the first and

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most severely affected areas by AD (51). Neurofibrillary damage and the loss of projection neurons responsible for the afferent and efferent connections of the hippocampal formation result in both disconnections of the intra-hippocampal relationships and the isolation of the hippocampus from other parts of the brain responsible for memory loss in AD (56-58). By the age of 40, the proportion of DS patients who undergo a process of cognitive impairment, such as that in AD, is observably high (59). The chronological hierarchy of symptoms begins with slowly progressing memory loss and leads to a general decline in cognitive skills accompanying dementia and emotional changes (60-63). Research-based on MRI scans indicated that hippocampal atrophy, which is significant in sporadic and DS-associated AD, can serve as a measure of allocortical neuronal degeneration (51, 57-59, 64).

Previous MRI studies proposed atrophy of the corpus callosum as a possible marker for the loss of intracortical-projecting neocortical association neurons in AD (65-69). The projecting neurons from the corpus callosum are a subgroup of the large pyramidal neurons in the association cortex's lamina III and V (70-72), which are particularly vulnerable to AD (73-75). Therefore, several studies reported atrophy of the corpus callosum in Alzheimer's type dementia (59, 76-81). Clinical symptoms of dementia in DS are memory loss, behavioral changes, language difficulties, neurological alterations, and decreased cognitive skills (82, 83).

Teipel, Schapiro (59) investigated the effect of age on volume changes in the hippocampus and corpus callosum and found a correlation between neuropsychological scores and regional volumes in DS people without dementia. This study demonstrated a decreased volume of hippocampus and corpus callosum regions with increased age and also showed a correlation between the size of corpus callosum areas and the global cognitive score, orientation, language, and visuospatial test scores in people with DS (59). Kesslak, Nagata (84), and Raz, Torres (85) found that the parahippocampal gyrus (PHG) is significantly larger in people with DS compared with normal aging and AD. Pathological and neuroimaging studies revealed that AD significantly impacts this structure, particularly its anterior portions (86, 87). Raz, Torres (85) indicated a correlation between the enlargement of the PHG and decreased total cognitive function. Mullins, Daly (5) investigated the medial temporal lobe and found a reduced volume of this region associated with cognitive decline. A study by Krasuski, Alexander (88) found that the right and left amygdala, hippocampus, and posterior parahippocampal gyrus in the DS group have a smaller volume than in the control group. These regional brain volumes were significantly associated with greater age; this association was not observable in the anterior part of the parahippocampal gyrus. The hippocampus and amygdala volumes were positively correlated with memory assessment results (88) (see table 4).

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Table 4: A summary of the findings from studies (published between 1978 and 2021) that identified psychosocial risk factors for AD in people with Down syndrome and linked them to neuroanatomical changes in the brains of people with DS.

Study	Psychosocial risk factors studied	Neuroanatomical findings	Neuropsychological findings related to brain changes	Association with the risk of AD
Mullins, D., et al.	Age, gender, cognitive reserve, level of education, years in an institution, and employment	Reductions in the whole brain volume, hippocampus, and temporal lobe volumes, and a significant increase in the lateral ventricle volume in AD and demented DS. Demented DS had a minor reduction in temporal lobe volume compared to individuals with AD.	There was a positive correlation between MMSE and hippocampal volume (corrected for total intracranial volume) in the AD population and between MMSE and temporal lobe volume (corrected for total intracranial volume). There was an inverse association between MMSE and the corrected lateral ventricle volume (corrected for total intracranial volume). In the DS population with dementia, there was a positive correlation between CAMCOG and the corrected hippocampal volume and between CAMCOG and the corrected temporal lobe volume.	The study indicated an association with the risk for AD, especially regarding reduced hippocampus and medial temporal lobe volume. The volumetric findings in DS patients were consistent with an AD pattern of atrophy, with a decrease in hippocampal volume. The relationship between MMSE and volume in these critical locations shows a link between reduced hippocampus and temporal lobe volumes and the affection of their functions.
Teipel et al.	Age, gender, and cognitive status	DS subjects had smaller corpus callosum areas and hippocampal volumes relative to age-matched healthy comparison groups, even after controlling age and total intracranial volume statistically.	The size of the corpus callosum areas (C3 and C4) correlates with overall cognitive test scores and orientation, language, and visuospatial test scores in people with DS.	There was an age-related decrease in the corpus callosum area (most prominent in posterior regions) and hippocampal volume in the DS group associated with AD. The study's findings pointed to an early loss of allocortical neurons in the predementia stage of DS resulting from AD-like pathology.
Kesslak et al.	Age	Hippocampal volume reduction and enlargement of the parahippocampal gyrus	Not assessed	Age-related brain changes linked to plaques and tangles, as well as the onset of dementia

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Raz et al.	Age and cognitive status	A reduced volume of brain areas, except for the parahippocampal gyrus	There was no correlation between total brain volume and cognitive scores. There is a significant inverse relationship between the volume of the parahippocampal gyrus and intelligence and language test scores.	They hypothesized that brain changes in DS do not apply to the prediction of early changes in AD.
Krasuski et al.	Age and cognitive status	The hippocampus, right and left amygdala, and posterior parahippocampal gyrus have reduced volumes.	These brain areas changes were significantly associated with greater age. There was no correlation between any regional volume and the Peabody Picture Vocabulary Test result. The study revealed a partial correlation between regional brain volume and memory tests.	The study predicted that atrophic changes in the medial temporal lobe were initially affected by AD pathology. Evaluating them might aid in identifying people in the early stages of AD.

DS = Down syndrome, AD = Alzheimer's disease, CAMCOG = Cambridge Cognitive Examination; MMSE = Mini Mental State Examination

3. DISCUSSION

In this review, we discussed psychosocial risk factors for the occurrence of dementia in people with DS. An association between the DS phenotype and an increased risk of developing Alzheimer's dementia is now powerfully demonstrated (20). Previous studies indicate no significant difference between psychosocial risk factors for AD in the general population and psychosocial risk factors for AD in DS patients. This indication can provide a clue about the consideration of DS as a model for studying and understanding the clinical and pathological changes associated with the early stage of AD (1, 19, 89, 90). A rising amount of information suggests that increasing age isn't the sole risk factor to consider when determining AD development in people with DS (20). We evaluated previous reports and concluded that the APOE Ɛ4 allele is a substantial risk factor for AD in patients with DS, but the APOE Ɛ2 allele is a protective factor (17, 20). Gender as a possible risk factor has inconclusive data (20). Previous reports in DS humans and mouse models found an association between physical activity in different forms and improvement in memory and cognition (33). We did not find studies that consider ethnicity and smoking as risk factors for AD in DS, although their role in the general population is reported (46, 91). No published studies directly discussed the effect of psychosocial risk factors on the occurrence of AD in DS or related them to neuroanatomical changes depending on neuroimaging. Therefore, we assume a correlation between some of these risk factors for dementia in DS and neuroanatomical changes in brain areas related to memory and cognitive function. Aging is considered a significant risk factor for dementia in people with DS (20), in addition to genetic factors (e.g., APOE genotype) and cognitive reserve (17). Understanding the risk factors for AD in DS will help us diagnose the disease and prevent other pathological conditions (17). This review is the first study comparing the effects of

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psychosocial risk factors for AD in DS and their association with neuroanatomical changes in hippocampus and corpus callosum regions. This study's strengths include covering the most common psychosocial risk factors for dementia in DS that exist in the literature and presenting them in a summarized review considering the recently published information. Our review study also compared the relationship of these risk factors with neuroimaging biomarkers of AD, providing a clue for further research using imaging techniques to realize these results. This study's limitations include the lack of patients required to confirm our hypothesis to compare cognitive decline with neuroanatomy.

4. Conclusions

According to the National Institute on Aging (NIH) recommendations regarding AD patients in general populations, we can also suggest using these recommendations in DS patients at risk of dementia. When assessing the risk for AD, doctors and other health professionals who clinically evaluate people who have the disease should inquire about a family history of dementia and other related conditions and environmental and lifestyle factors. The difficulty in diagnosing dementia in individuals with DS faces complications by baseline intellectual disability (ID). Within the DSM 4 or ICD 10 classifications, no guidelines are available for diagnosing dementia associated with DS or any other learning disability. The study of risk factors will improve our knowledge of genetic and biological factors causing AD and how to avoid them with various measures. It is essential to perform brain studies over time in people with DS to observe and detect changes and compare them with cognitive function tests. This suggestion could be achievable through some trials and studies of biomarkers of AD. A large MRI study including people with DS with and without dementia and similar age-control groups is needed to test our hypothesis using neuropsychological assessment tests for memory and other cognitive functions. In summary, we conclude that volume reduction in regions such as the hippocampus, other medial temporal lobe structures, and corpus callosum are considered the first Alzheimer's-affected regions and are associated with age and other lifestyle factors in people with DS. This finding supports the theory that DS is of interest as a model for studying early-stage AD.

Funding

This work is part of a doctoral research project funded by the Friedrich-Naumann Foundation for Freedom (Scholar-Number: 8683/P611, 2021). The funder had no role in the design and conduct of the study, collection, analysis, and interpretation of data, preparation of the manuscript, or the review or approval of the manuscript.

Acknowledgments

We want to thank Dr. Gonzalo Alvarez-Bolado (Department of Neuroanatomy, Institute of Anatomy and Cell Biology, University of Heidelberg) for his contributions by comments and corrections during the preparation of this manuscript.

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Author Contributions

All authors contributed to the study's conception and design. Osama Hamadelseed, Thomas Skutella, and Ibrahim H. Elkhidir performed material preparation, data collection, and analysis. Osama Hamadelseed wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Disclosures

Osama Hamadelseed, Thomas Skutella, and Ibrahim H. Elkhidir declare that they have no conflict of interest.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability

This paper does not qualify for data sharing since we created no datasets or evaluated them during the research, but we reviewed data from the literature.

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